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ABSTRACTS

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Fortbildung

Lunge: Update in Diagnostik+Therapie

V12

Opportunities and challenges of molecular diagnostics in lung cancer

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With the dynamically evolving technological advances and scientific knowledge, molecular diagnostics has seen major steps forward in treatment strategies for lung cancer patients. Whilst this primarily focused on advanced non-small cell (adeno)carcinomas of the lung, broader scientific and medical engagement now also addresses novel concepts for other lung cancer entities. Moreover, not only the molecular pathology of tumor cells themselves, but also the tumor microenvironment - especially the cross talk with the immune system - are now of key molecular diagnostic and therapeutic interest. This talk will hence provide a technical, scientific and medical overview of the opportunities and challenges of molecular diagnostics in lung cancer from a molecular pathology perspective.

Disclosure: Silke Laßmann: Advisory Role: Advisory Boards: Astra Zeneca, Novartis, Roche; Financing of Scientific Research: AstraZeneca, Novartis, Roche; Expert Testimony: BMS; Other Financial Relationships: Reisekosten: AstraZeneca, Novartis, Roche

Wissenschaftliches Symposium

HPV-positive Kopf-Hals-Tumore

V19

Biology of HPV driven HNSCC

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A substantial proportion of squamous cell carcinoma of the head and neck (HNSCC) is causally linked to infections with human papillomaviruses (HPV). Specifically SCC of the Waldeyer's tonsillar ring show HPV DNA prevalence rates of 50-90% depending on the geographical region the patients live in and roughly 90% of these infections are active infections and carcinogenesis is based on the HPV infection. The prevalence rate of HPV infections in SCC of other anatomical HN locations is much lower, only about 10% seem to be active and yet, these tumors should not be neglected in studies and cost effectiveness ratios since the incidence of these tumor entities is much higher than tonsillar SCC (TSCC). Virus activity leads to (over)expression of the cellular protein p16, thus, being addressed as surrogate marker for active HPV-infections. The validity of p16 as surrogate marker has not been tested intensively throughout different populations and tumor entities throughout the world, thus, the introduction of p16 as sole marker for HPV infections in the TNM classification for oropharyngeal SCC should be interpreted with caution. HPV infections as such have been included into the TNM classification based on uniform international data from clinical studies with post hoc HPV analysis showing significant survival advantage for HPV positive cases. This survival advantage leads to the assumption that treatment of specifically HPV driven OSCC cases can be de-escalated to reduce therapy related co-morbidity. Among others own data show that the described survival advantage is fully jeopardized by a positive smoking history, not being considered in the new TNM classification or in all prospective clinical studies addressing de-escalation regimes.

Disclosure: No conflict of interest disclosed.

V22

De-Escalation of systemic treatment - Is the topic off the table?

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Human papillomavirus positive (HPV+) oropharyngeal squamous cell carcinoma (OPC) is regarded as a distinct clinical entity within the head and neck cancers mainly because of its unique epidemiology and favorable prognosis. Standard treatment consists of single modality treatment in the early stages (radiotherapy or surgery) or combined modality treatment in the locally advanced stages (LA-OPC), e.g. radiotherapy (RT) with concomitant chemotherapy (CRT) or cetuximab (Cetux-RT) or surgery followed by adjuvant RT or CRT in case of positive margins or extranodal extension (ENE).
A main factor of the quality of life after successful treatment are the observed treatment related acute and late toxicities of RT and their increased occurrence after CRT with cisplatin. Therefore, strategies to avoid or diminish these toxicities became an important objective, especially in patients with a good long-term prognosis such as HPV+OPC.
The two strategies to de-intensify treatment related toxicities include or the reduction of the RT dose, partly depending on the response to induction therapy, or the modifying or the leaving of the concomitant systemic therapy. Actual clinical studies focusing on modifying systemic treatment hypothesize that the addition of cetuximab to radiotherapy instead of cisplatin is associated with similar efficacy and at the same time with a more favorable acute and long-term toxicity profile resulting in a better quality of life. Furthermore, a subgroup analysis of the Bonner trial showed that especially younger patients with a good performance status and lower T- and higher N-stages of OPC benefited from the addition of cetuximab to RT versus RT alone. As this subgroup represents the typical HPV+OPC patient population, this suggests that cetuximab is working especially well in HPV+OPC. And indeed, a retrospective analysis of the Bonner trial showed a more pronounced advantage for the addition of cetuximab to RT in p16+OPC, a surrogate marker for HPV+OPC, versus p16-OPC. Recently, the results of two large randomized studies replacing cisplatin with cetuximab in HPV+OPC and primary RT have been published and will be discussed in the presentation.

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Wissenschaftliches Symposium

Kontroversen in der Intensivmedizin

V25

Cardiotoxicity of cancer therapies

von Bonin S.

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The prognosis of hematological patients in need for intensive care has improved in recent years. Infectious complications and respiratory failure remain the leading causes for the admission to the intensive care unit (ICU), but cardiovascular diseases (CVD) directly linked to the diagnosis and treatment of hematological malignancies also require attention. CVD mostly present as an exacerbation of a *pre-existing* (sometimes subclinical) condition, but also drug-related *de-novo* cardiotoxicity can occur. In some ways, cardiac injury in consequence of conventional cancer chemotherapy is not unexpected given the unspecific nature of the therapeutic approach. However, the age of targeted therapy has not led to the disappearance of cardiotoxicity. More selective, mechanism-based therapies are still associated with CVD due to off-target and on-target/off-tumor effects. The rapid progress in the field of targeted therapies requires interdisciplinary team-work to adequately diagnose and treat these side effects.

Disclosure: No conflict of interest disclosed.

Fortbildung

Joint Symposium (mit DGTI): Blood Banking 2019

V27

Infection safety of blood products regarding Hepatitis E Virus (HEV)

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Background: Different countries hold divergent views and have chosen different regulatory approaches to minimize the risk of transfusion-transmitted hepatitis E virus (TT-HEV) infections. Just recently, the German federal authorities have introduced mandatory testing of all therapeutic blood products beginning from January 1st 2020. Since 2015, we already perform a 100% screening of therapeutic blood products for HEV RNA voluntarily. Currently, several open issues regarding look back scheme, and re-entry of HEV positive donors are discussed.
Methods: From January 2015 to December 2018, a total of 386,307 allogenic blood donations from 69,956 individual German blood donors was screened in a minipool format of 96 samples for the presence of HEV RNA with a 95 % LOD of 4.66 IU/ml.
Results: In total, 274 HEV RNA positive donors were identified. Of these, 216 were NAT-only positive donations (78.83%). Genotyping revealed genotype 3 in all cases. The month-dependent incidence ranges from 1:719 to 1:3,781 blood donations with a peak in June and July.
Conclusions: The high number of identified HEV RNA positive donors emphasizes the need for HEV NAT screening to increase the safety of blood products. The risk and importance of TT-HEV infections by contaminated blood products is currently a controversial discussed topic in transfusion medicine. The data from the German National Blood Donor Surveillance System (Paul-Ehrlich institute [PEI]) for the years 2016/17 document, that all confirmed virus transmissions in these years were caused by HEV. In the years 2013 to 2017, 22 suspected cases of TT-HEV were reported, involving HEV RNA positive blood products: eight RBCs, three PPCs and a plasma of nine whole blood donors and 14 APCs of five donors. Our strategy for handling of positive HEV RNA donors is the re-entry at the earliest four weeks after index donation with a negative result in the individual donor (ID) NAT (LOD < 50 IU / ml). If only pool testing is performed, a provision of at least four months should be applied. The look-back screening should cover a period of six months before the HEV NAT positive donation. If the result is negative, no further analysis are required and the screening result is communicated to the PEI as part of a collective notification.

Disclosure: No conflict of interest disclosed.

Wissenschaftliches Symposium

AYA: Internationales Management

V31

Management of AYA cancer patients in Germany

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In Germany approximately 16 000 adolescents and young adults (AYA, 18-39 years) are diagnosed with cancer annually. The diagnosis in this minority of cancer patients is connected with particular challenges: nearly all components of meaningful life are in a phase of re-organisation and irritability. Risk behavior and changes in local or personal bonds are common. The "*Deutsche Stiftung für Junge Erwachsene mit Krebs*" was founded with the goal to address age-specific questions and problems in this neglected group of cancer patients. Based on the needs and input of patients and survivors different projects e.g. the portal "Young and Cancer" or the project "Rendezvous", were started. In addition, the successful efforts for the reimbursement of costs for fertility preservation by health insurance companies are of paramount importance.
In addition, the DGHO-working-party AYA-Network, a multidisciplinary interest group, has been founded to determine priorities and coordinate efforts to improve AYA cancer services and care. Last year the platform "AYApedia" was launched in order to inform AYA about different topics of supportive care in cancer treatment e.g.: fertility preservation or fatigue.
Although survival of AYA cancer patients has steadily improved over the last decades, survivors may suffer from long-term sequelae of cancer treatment and have an increased risk of premature death compared with the general population. In order to capture the incidence and outcome of sequelae among AYA survivors of hematopoietic stem cell transplantation a prospective, multicenter trial is ongoing. In addition, the program *CARE for CAYA* was designed aiming to assess the needs of cancer survivors and apply interventions. This randomized controlled multicenter trial use a novel approach with the focus on three module-interventions: physical activity, nutrition and psycho-oncology. It is currently conducted in a consortium of 15 sites in Germany.
Other groups investigate the psychosocial situation and quality of life of AYA cancer patients and their family members and launched projects like "Cancer Diagnosis - in the heart of life", "Peer-Support" or "AYA-Parents". However, although the first steps are done to lower the burden of this minority of cancer patients, a huge number of important issues are remaining. Fields of action may focus on topics like tumor biology and genome profiling, survivorship care, rehabilitation and return to work.

Disclosure: Inken Hilgendorf: Expert Testimony: Hector-Stiftung; Immaterial Conflict of Interests: Mitglied des Kuratoriums der Deutschen Stiftung für junge Erwachsene mit Krebs

Freier Vortrag

B-Zell-Lymphom, aggressiv I

V32

Updated results from a phase Ib/II study in patients (pts) with relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL) treated with polatuzumab vedotin (pola) plus bendamustine (B) with rituximab (R) or obinutuzumab (G)

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Introduction: Pola is an antibody-drug conjugate targeting CD79b, a B-cell receptor component. GO29365 is an open-label phase Ib/II study of pola+B with G or R in pts with R/R DLCBL (NCT02257567). This updated analysis reports long-term efficacy, safety and preliminary biomarker data.

Methods: Transplant-ineligible R/R DLBCL pts were enrolled in the phase Ib safety run-in (pola+BR [N=6]), phase Ib/II expansion (pola+BG [N=27]) or phase II randomization (pola+BR [N=40] vs BR [N=40]) stages. Pts were treated q3w (up to 6 cycles) with pola 1.8mg/kg + B 90mg/m2/day x 2 days and R 375mg/m2 or G 1000mg and stratified by DoR to last therapy: ≤ vs >12 months (mo). Complete response (CR) was defined by PET negativity and negative bone marrow biopsy if PET was positive (modified Lugano criteria, independent review committee (IRC)). Primary aims included safety (phase Ib) and efficacy of pola+BR vs BR at end of treatment by IRC (phase II). Other efficacy measures included DoR, PFS, OS, efficacy by cell-of-origin (COO; measured by Nanostring Lymph2x or Hans algorithm) and MYC/BCL2 double expression (DE; IHC cutoffs >40% over background and >50% with moderate to strong staining).

Results: Median follow-up (cut-off April 30, 2018) for phase Ib pola+BR, phase Ib/II pola+BG and the randomized cohort were 37.6, 27.0, and 22.3 mo, respectively. Long-term safety results were consistent with those previously described. In the randomized cohort, pts receiving pola+BR had significantly higher rates of CR (40% vs 18%; p=0.026), and significantly longer DoR (10.3 vs 4.1 mo; HR: 0.44; p=0.032), median PFS (7.6 vs 2.0 mo; HR: 0.34; p< 0.0001) and median OS (12.4 vs 4.7 mo; HR: 0.42; p=0.0023), than pts receiving BR only. Pts receiving pola-BG had a CR of 30%, DoR 28.4 mo, median PFS 5.4 mo and median OS 10.8 mo. COO analyses: 14 and 16 pts were ABC, 14 and 13 were GCB in the pola+BR and BR arm, respectively. ABC: median PFS and OS 10.5 and 13.9 mo with pola+BR vs 2.5 and 4.3 mo with BR. GCB: median PFS and OS 4.7 and 9.3 mo with pola+BR vs 1.5 and 3.2 mo with BR. Median PFS for DE was 7.0 mo with pola+BR (9 pts) vs 0.7 mo with BR (6 pts), compared with 6.3 (13 pts) vs 2.5 mo (13 pts) in non-DE. Median OS: 12.9 vs 3.8 mo for DE and 10.5 vs 3.8 mo for non-DE, with pola+BR and BR, respectively.

Conclusions: These updated analyses show that pola+BR improves responses and survival vs BR alone. Pola+BR showed a benefit over BR in all biomarker subgroups studied.

Reference: Sehn LH et al. ASH 2018

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V33

Identification of posttranslationally modified neoantigens as targets of BCRs of sporadic Burkitt lymphoma

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Introduction: Burkitt lymphoma (BL) represents the most aggressive neoplasm of mature B cells. Besides the characteristic translocation of the MYC gene with an immunoglobulin gene locus, mutations in the TCF3 and ID3 genes represent the key events. These TCF3/ID3 mutations result in tonic and antigen-independent B cell receptor (BCR) pathway activation. Additionally, chronic BCR activation by antigens might play a role in BL pathogenesis and we set out to identify such potential reactivities targeting the BCRs of Burkitt lymphoma.

Methods: BCRs were expressed as recombinant Fabs based on corresponding pairs of functional variable region heavy and light chain genes, which had been amplified from isolated genomic DNA of snap-frozen sporadic BL specimens and of Burkitt-like lymphoma (BLL) with 11q aberration. Additionally, natural Fabs and recombinant Fabs were produced of 8 established BL lines by Papain digestion and BCR expression cloning. The screening for reactivities against non-modified and posttranslationally modified human protein macroarrays. Reactivities were verified by ELISA with coated N-terminally FLAG-tagged candidate antigens, each separately for the posttranslationally modified and non-modified isoforms. Recombinant Fabs of different B-NHL entities served as controls. Functional effects on the BCR pathway activation after addition of the identified target antigens to Burkitt lymphoma cell lines with and without reactive BCRs were analyzed.

Results: Screening of BL derived Fabs resulted in sumoylated Bystin as specific BCR-antigen of CA46 and of acetylated HSP40 of BL41 line. Recombinant Fabs of DLBCL, PCNSL or MCL did neither bind sumoylated Bystin nor acetylated HSP40. Addition of the posttranslationally modified cognate antigens to respective BL cell line with the reactive BCR induced proliferation. The screening for target antigens of BLL with 11q alteration is ongoing.

Conclusions: A subgroup of sporadic BL has autoreactive BCRs with specific affinity against posttranslationally modified self-antigens, indicating a new aspect in the pathogenesis of BL. Specific secondary modifications, as sumolytation of Bystin or acetylation of HSP40 appear to evoke the immunogenicity. Future studies will focus on the functional consequences of the antigen/BCR interaction on Burkitt cells. Furthermore, the causes of these posttranslationally modified neoantigens will be investigated in more detail.

Disclosure: No conflict of interest disclosed.

V34

Targeting of lymphoma B cell receptors by using entitiy-specific epitopes of target antigens

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Background: In recent years we worked on the identification of BCR target antigens of lymphoma. Here, we want to evaluate the epitopes of various lymphoma BCR antigens for the use as capture domains of various therapeutic formats.
Methods: BCR-expression cloning was performed from DLBCL, PCNSL, BL, MCL and CLL and BCRs were screened on several types of protein arrays. Antigens were validated by immunoassays, western blots and flow. Induction of proliferation after addition of antigens was analysed. As a first step to test lymphoma-BCR-antigens for targeting lymphoma, immunotoxins comprising the epitope of the BCR antigen and a truncated form of Exotoxin A of Pseudomonas aeruginosa were recombinantly expressed in E. coli. As a second step bispecific antibody constructs of the target antigen epitope conjucated to anti-CD3 or -CD16 scFv were recombinantly expressed. To test the epitope of lymphoma BCR-antigens as ectodomains of CARs, a standard 2nd generation CD19 scFv/ CD28 CD3ζ CAR backbone will be used. Target antigen Epitopes will be compared with anti CD19 scFv.
Results: For several lymphoma entities including DLBCL, PCNSL, MCL and BL interindividually occurring and overrepresented BCR-target antigens were identified, most of them carried specific PTMs. Addition of the antigens to cell lines resulted in induction of growth. Addition of immunotoxins encompassing the epitope of the BCR target antigen fused to Pseudomonas Exotoxin A were specifically toxic to cell lines with the reactive lymphoma BCRs. Bispecific T-cell or NK-cell engager constructs with one of the identified epitope of the lymphoma BCRs resulted as well in specific toxicity against lymphoma lines with respective BCR reactivity.
Conclusions: The results provide the basis for the evaluation of lymphoma entity-specific, and frequently occuring epitopes of lymphoma BCR target antigens as ectodomains for CARs. For this reason CAR T-cells will be generated using a second generation CAR-backbone for comparission and combination of the identified epitopes of lymphoma BCR target antigens of MCL, PCNSL and systemic DLBCL with conventional anti-CD19 scFv as ectodomains of CARs. The goal of these efforts would be to generate more lymphoma-specific CAR-T cells, with the hope to reduce side effects.

Disclosure: No conflict of interest disclosed.

V35

Quantitative modelling of oncogenic signaling in B cell lymphoma

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Introduction: Aberrantly tonic or activated B-cell receptor (BCR) signaling promotes tumor proliferation in a number of aggressive lymphoma. A better understanding of proximal and distal signaling modules as well as positive and negative feedback loops is important for a more accurate derivation of molecular signatures and individualized therapies. Current literature-based networks present mostly linear signal transduction from the receptor along known pathway components. A quantitative model of these oncogenic signaling networks that can also consider nonlinear structures such as feedbacks is still missing, and would be a further step in improving our understanding of aggressive lymphoma.
Methods: Oncogenic signaling was analyzed in cell lines from Burkitt (BL) and diffuse large B cell lymphoma (DLBCL) using bead-based multianalyte profiling to detect phosphorylated signaling molecules in the presence or absence of a wide variety of pathway inhibitors. The Modular Response Analysis-based modelling approach STASNet (https://github.com/molsysbio/STASNet) was applied on this phosphorylation data set for (semi)-quantitative modelling of oncogenic signaling. Subsequently, selected signalling modules were verified by quantitative tandem mass tag (TMT) mass spectrometry analyses of the phosphopeptide-enriched fractions.
Results: In unstimulated BL cells it was shown that the inhibition of BTK, PI3K, AKT and mTOR lowered a vast majority of measured protein phosphorylations covering proximal BCR-, PI3K-, NFkB- and MAPK signalling. The αIgM stimulation increased all measured protein phosphorylations in comparison to the unstimulated control. Inhibiting MEK, in comparison, produced a less pronounced effect on the general network, instead it reduced ERK and ERK-downstream signaling and strongly increased MEK1/2 phosphorylation. Furthermore, the inhibition of MAPK14 was associated with increased phosphorylation of MEK1/2 and ERK1/2. The semi-quantitative network analysis on the perturbation data revealed a central role of the PI3K pathway and ZAP70, a negative feedback loop within the RAF-ERK pathway and an interaction between MAPK14 and MEK/ERK.
Conclusions: A generalized model of oncogenic signaling for BL and DLBCL is provided advancing the possibility to identify relevant therapeutic targets in broad and diverse groups of patients with aggressive lymphoma characterized by corresponding oncogenic pathways.

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Rituximab and Bendamustine for first-line treatment of frail or elderly patients with aggressive B-cell lymphoma: first results of the German prospective phase-II BRENDA trial

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Introduction: For patients (pts) with aggressive B-cell lymphoma immunochemotherapy with R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisolone) represents standard of care with curative intention. For elderly pts dose-reduced R-miniCHOP protocol

is feasible. For frail or old (>80yrs) pts not eligible for anthracycline-containing treatment there is no standard therapy available. Here we present the first results of the first prospective DSHNHL-phase-2 trial for old or frail pts receiving Rituximab/Bendamustin (RB) for 1st-line treatment of aggressive B-cell lymphoma.

Methods: The open-label, multicenter, prospective, non-randomized phase-II trial "Subcutaneous Rituximab and Intravenous Bendamustine in very Elderly Patients or Elderly Medically Non Fit Patients ("Slow Go") with Aggressive CD20-positive B-cell Lymphoma" (B-R-ENDA, DSHNHL 2010-1, EudraCT 2010-024004-98) included pts aged ≥81yrs or 61-80 and elevated Cumulative Illness Ratging Scale (CIRS)>6, not qualifying for CHOP, CD20+ aggressive lymphoma of any stage or IPI score and ECOG < 4 determined during prephase treatment from 51 German centers. During run-in-phase, 20 pts received prephase treatment of Prednisolone 100mg p.o. D-7 to -1, followed by Rituximab 375mg/m2 i.v. D-3. The trial-treatment consisted of 7 cycles of Rituximab 375mg/m2 i.v. on D1,q21 and 6 cycles of Bendamustine 90mg/m2 i.v. on D1 and 2,q21. After positive DSMB evaluation of the safety analysis subsequent pts received prephase treatment with Rituximab 375mg/m2 i.v. and 7 cycles of Rituximab s.c. 1400mg on D1,q21 with 6 cycles of Bendamustine 90mg/m2 i.v. on D1 and 2,q21. Primary endpoints were 2-years-progression-free survival for efficacy, and therapy-associated deaths, frequency of grade 3/4 adverse events and SAEs, adherence to the protocol, complete and partial remission rate, rate of primary progression and relapse, quality of life assessment and geriatric assessment.

Results: From 2012 to 2016, 68 pts (22 m, 46 f) were included in the trial: median age was 82 yrs (64.8-95.3), median CIRS score was 8 (1-22). Histologic subtypes were (in decreasing frequency) diffuse large B-cell lymphoma (DLBCL) not otherwise specified, centroblastic and immunoblastic DLBCL, follicular lymphoma grade IIIb and other. Observation time ended in July 2018.

Conclusions: We will present the first results of treatment safety 1st-line treatment with RB in old or frail pts with aggressive B-cell Lymphoma.

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V37

Targeted inhibition of PI3Kα/δ is synergistic with BCL-2 blockade in genetically defined subtypes of DLBCL

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Introduction: Diffuse large B-cell lymphoma (DLBCL) is a genetically heterogeneous disease that is transcriptionally classified into germinal center B-cell (GCB) and activated B-cell (ABC) subtypes. Recent study characterized primary DLBCL subsets with distinct genetic bases for perturbed BCR/PI3K signaling and dysregulated BCL-2 (*Nat Med* 2018 24:679). Cluster 3 DLBCLs (largely GCB tumors) exhibited frequent *PTEN* deletions/mutations together with *BCL2* translocations. Cluster 5 DLBCLs (largely ABC tumors) had frequent *MYD88*^{L265P} and *CD79B* mutations that often occurred together and 18q (*BCL2)* copy number gains. These findings prompted us to explore the activity of PI3K and BCL-2 inhibitors in genetically defined DLBCLs.

Methods and Results: We utilized well characterized DLBCL cell line models, a subset of which exhibited hallmark genetic features of Cluster 3 and Cluster 5. PI3K inhibitor with predominant α/δ activity, copanlisib, exhibited the highest cytotoxicity in all BCR-dependent DLBCLs. The proapoptotic effect of copanlisib was associated with DLBCL subtype-specific dysregulated expression of BCL-2 family members including HRK and its antiapoptotic partner BCL-xL, among others. Using functional BH3 profiling, we found that the cytotoxic activity of copanlisib was primarily mediated through BCL-xL and MCL-1-dependent mechanisms that might complement BCL-2 blockade.

Given the genetic bases for BCL-2 deregulation in most of these DLBCLs, we evaluated activity of BCL-2 inhibitor, venetoclax, and identified a subset with limited sensitivity to BCL-2 blockade despite having genetic bases of BCL-2 dysregulation. As these were largely BCR-dependent DLBCLs, we hypothesized that combined inhibition of PI3Kα/δ and BCL-2 would perturb BCR-dependent and BCL-2-mediated survival pathways. Indeed, we observed synergistic activity of copanlisib/venetoclax in BCR-dependent DLBCLs with genetic bases for BCL-2 dysregulation in vitro and confirmed these findings in vivo.

Conclusion: Taken together, these results provide pre-clinical evidence for the rational combination of PI3Kα/δ and BCL2 blockade and set the stage for clinical evaluation of copanlisib/venetoclax therapy in patients with genetically defined relapsed/refractory DLBCL.

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Freier Vortrag

AML I

V38

hiPSC model of stepwise leukemia development in congenital neutropenia reveals BAALC as a key mediator of leukemogenesis

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Severe congenital neutropenia (CN) is a pre-leukemic inherited bone marrow failure syndrome with a maturation arrest of granulopoiesis at the stage of promyelocytes. Recently, we reported a high frequency of co-operating *RUNX1* and *CSF3R* mutations in CN patients that developed AML or MDS (CN/AML).

To study the mechanism of leukemia development in CN, we established a model for step-wise leukemia progression in CN using hiPSC-based hematopoietic differentiation in combination with CRISPR/Cas9-mediated gene editing of hiPSCs. Using this model, we confirmed that co-acquisition of *CSF3R* and *RUNX1* mutations is necessary and sufficient to induce leukemia in CN.

We also identified BAALC (brain and acute leukemia, cytoplasmic) upregulation as a key leukemogenic event downstream of *RUNX1* and *CSF3R* mutations.

BAALC mRNA was upregulated in CN/AML blasts (n = 5) and in CD34$^+$ HSPCs generated from CN/AML iPSC clones of two CN/AML patients. Importantly, CRISPR/Cas9-mediated knockout of *BAALC* in CN/AML-iPSCs reversed defective myeloid differentiation of CN/AML blasts to the levels observed in healthy donor iPSCs. Further, an increased proliferation of CN/AML-iPSC-derived CD34$^+$ cells compared to CN was completely inhibited after BAALC KO.

Since there are no direct inhibitors for BAALC available and protein structure is not solved yet, BAALC effects can be targeted only indirectly. Using Connectivity Map analysis of RNA-Seq data of HSPCs generated from CN/AML iPSCs before and after *BAALC* knockout, we identified a small molecule inhibitor that was predicted to reverse BAALC-mediated leukemogenic gene expression signature of CN/AML HSPCs. Intriguingly, proliferation of primary CN/AML blasts, CN/AML-iPSC-derived CD34$^+$ cells and *de novo* AML blasts with high BAALC expression was decreased upon treatment with this inhibitor.

Taken together, using our hiPSC-model we confirmed the major role of BAALC in leukemia development downstream of *CSF3R* and *RUNX1* mutations in CN/AML patients and identified a potential drug to treat BAALC-high AML patients, including CN/AML and de novo AML.

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QuANTUM-R: phase 3, randomised trial of Quizartinib in patients with FLT3-Internal tandem duplication (FLT3-ITD)-positive relapsed/refractory (R/R) acute myeloid meukaemia (AML)

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Introduction: Patients with *FLT3*-ITD-positive AML have poor prognosis, increased risk of relapse and decreased response to salvage chemotherapy (SC). Quizartinib is a once-daily, oral, highly potent, selective FLT3 inhibitor with promising single agent activity and manageable safety profile.

Methods: Adult patients with R/R FLT3-ITD AML (duration of first remission ≤6 months) were randomized 2:1 to receive quizartinib (53.0 mg [26.5-mg lead-in]), or investigator's choice of preselected SC. Quizartinib and SC were given until lack of benefit, unacceptable toxicity, or hematopoietic stem cell transplant. Quizartinib-treated patients could resume quizartinib post-HSCT. Primary and secondary endpoints were overall survival (OS) and event-free survival (EFS), respectively. Predefined subgroup analyses of OS were performed. Treatment-emergent adverse events (TEAEs) included AEs ≤30 days after last dose and treatment-related AEs >30 days.

Results: 367 patients were randomized; 245 to quizartinib, 122 to SC. Median follow-up was 23.5 months. Treatment groups were balanced for baseline characteristics. OS was significantly prolonged in the quizartinib arm vs SC (HR, 0.76 [95% CI, 0.58-0.98]; stratified log-rank test, 1-sided *P*=0.0177). Median OS was 6.2 (95% CI, 5.3-7.2) vs 4.7 (95% CI, 4.0-5.5) months, with estimated 12-month OS probability: 27% vs 20% in quizartinib and SC arms, respectively. Median EFS was 1.4 (95% CI, 0.0-1.9) vs 0.9 (95% CI, 0.4-1.3) months (HR, 0.90 [95% CI, 0.70-1.16]; stratified log-rank test, 1-sided *P*=0.1071). Composite complete remission (CRc) rate was 48% and 27%; duration of CRc was 12.1 (95% CI, 10.4-27.1) vs 5.0 (95% CI, 3.3-12.6) weeks; transplant rate was 32% and 12%, all in quizartinib and SC arms, respectively. Median time to first CRc was 4.9 weeks for quizartinib vs 4.0 weeks for SC. Sensitivity analyses of OS and EFS supported benefit of quizartinib compared with SC (figure). TEAE rates were comparable, despite longer treatment duration in quizartinib vs SC arms. Most common grade ≥3 TEAEs in both arms were infections and those associated with cytopenia. Only two patients discontinued quizartinib due to grade 2 QT prolongation. QTcF>500 ms (grade 3) by central laboratory was 3% with quizartinib; no grade 4 QTcF occurred.

Conclusions: These data confirm the OS benefit and favorable safety profile observed with single agent quizartinib vs SC in patients with R/R *FLT3*-ITD AML.

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V40

The combination of Bemcentinib, a novel, oral, selective Axl-inhibitor and low-dose cytarabine yields durable responses in Aml patients unfit for intensive chemotherapy

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Background: Treatment options for AML patients ineligible for high-intensity chemotherapy are limited. Low-dose cytarabine (LDAC) monotherapy is an approved therapy for these patients yielding an ORR rate of 18%. The RTK AXL represents a novel therapeutic target promoting AML cell survival and is a negative regulator of anti-tumour immunity.
Bemcentinib is a first-in-class, highly selective, oral AXL inhibitor that has induced a 22% objective response rate in relapsed/refractory (r/r) AML and MDS patients in a Phase 1 trial.

Methods: This Phase 1/2 open label study (BGBC003) aimed to establish the RP2D when given as a monotherapy followed by a Phase II part designed to explore the safety and efficacy of bemcentinib given alone or in combination with low-dose cytarabine (LDAC) or Decitabine to patients with newly diagnosed or R/R AML unfit for intensive chemotherapy. The monotherapy dose-escalation part of the study is complete. We report here the Phase 2 results of the bemcentinib+LDAC cohort. AML patients unfit for intensive therapy received bemcentinib at RP2D (200mg daily PO) + SOC 10-day LDAC in 21-day cycles. Twelve out of 16 patients were evaluable for response assessment by BM aspirate at C2D1. Eight of the 12 patients (60%) were previously treated including 5 relapsed and 3 refractory.

Results: As of April 2019, five of 12 evaluable patients had objective responses (42%, 4 CR/CRi + 1 PR), all starting at C2D1. Responses occurred in patients with unfavourable characteristics: three previously-treated including 1 refractory, 3 unfavourable cytogenetics, and 4 ≥75 yo.
CR/CRis were durable at 9.6, 6.2, 6.2 and 0.7 months.
Three additional patients showed reduction in blast count and were stable at 6.0 (ongoing), 4.0 and 1.4 (ongoing) months.
The combination was well tolerated with expected and manageable AEs. Out of all patients treated with bemcentinib + LDAC 9 experienced TRAEs grade 1-4 (9/16; 56%), most common being diarrhoea (25%, 4/16) and ECG QTc prolongation (19%, 3/16). Three patients experienced grade 4 TRAEs (thrombocytopenia/platelet count decreased, febrile neutropenia). No tumour lysis syndrome events were reported.

Conclusions: The potential new non-intensive combination regimen, bemcentinib + LDAC, induced a response rate of 42% with durable CR/CRis lasting >6 months. Thus, bemcentinib and LDAC show additive therapeutic potential warranting further clinical development of bemcentinib in AML patients.

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Comprehensive RNA-sequencing analysis indicates a heterogeneous pathogenesis of early death events in acute promyelocytic leukemia

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Introduction: Patients with Acute Promyelocytic Leukemia (APL) show excellent long term survival in clinical studies. However, early death (ED) mortality (< 30 days upon diagnosis) remains a major clinical challenge and affects up to 29% of APL patients in population based studies. Complications due to hemorrhage and coagulopathy occur in up to 65% of all patients with APL and are the main cause of ED. We hypothesized that distinct gene expression patterns in APL blasts could identify clinically relevant molecular pathways that mediate coagulopathy and ED mortality.
Methods: We collected matched primary bone marrow mononuclear cells from 7 ED patients (median survival 4d, range 2-17) and 7 APL patients with long term survival (complete remission, CR, median FU 18 months, range 4-39) for the screening cohort and 83 samples (ED=15) for an independent validation cohort of candidate genes. RNA sequencing was performed using the Illumina TruSeq stranded total RNA kit. Differential gene expression analysis (DGE) was based on the Cufflinks package and fusion genes were detected by the FusionCatcher package. Validation was carried out by qPCR and sequencing.
Results: We could identify 164 differentially expressed genes and demonstrate mostly downregulated genes (n=144) in the ED cohort. DGE between ED and CR revealed several top differentially expressed genes e.g. *EFEMP1* (FC=42) and *S100A8/A9* (FC=0.13; 0.14). Moreover, we identified the lncRNA *XLOC* (located on chr16q42) as a yet undescribed transcript, which was underexpressed in ED. Of these, only the novel transcript retained prognostic impact in the validation cohort. Further, a DGE between ED with dedicated hemorrhagic complications (EDHC) and CR without hemorrhagic complications showed Metallothioneins (*MT1G/E)* overexpressed in patients with EDHC, which was associated with a higher rate of bleeding complications and consistent negative prognostic impact (p=0.01). Moreover, we identified TPM4-KLF2 as the most prevalent and validated fusion gene (n=10) in the screening cohort apart from PML-RARA.
Conclusions: In this comprehensive analysis of the transcriptomic landscape of ED APL we demonstrate novel potential biomarkers of ED mortality. We show novel fusion transcripts apart from PML-RARA and identified *MT1G* and *XLOC* having potential prognostic significance for OS. In summary, we present an in depth molecular analysis of APL patients, which might aid in further identification of patients at higher risk for ED.

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V42

Engineered biocompatible nanoparticles as potential therapeutics for acute myeloid leukemia

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Introduction: Acute myeloid leukemia (AML) is a malignancy associated with an unfavourable prognosis. Particularly, elderly patients suffer massively from the standard chemotherapy and have a 5-year survival of only 4%. Hence, new therapeutic agents with higher specificity and lower general cytotoxicity are urgently required.
Methods: Engineered nanoparticles were characterized by various physico-chemical methods. Cytotoxicity *in vitro* was assessed by XTT and colony-formation assays. Intracellular targets were identified by Western immunoblotting, fluorescent microscopy, flow cytometry, and various functional tests. Anticancer activity *in vivo* was analyzed by either using THP-1 xenografts on the chorioallantoic membrane of fertilized chick eggs (CAM) or primary human AML xenografts in mice.
Results: We have discovered that amino-functionalized polystyrene nanoparticles (PS-NH_2) inhibit mTOR in leukemia cells. Accordingly, PS-NH_2 inhibit proliferation and induce G_2 cell-cycle arrest in three myeloid leukemia cell lines. Besides, PS-NH_2 trigger apoptosis in leukemia xenografts *in vivo*. At the molecular level, PS-NH_2 also inhibit downstream targets of mTOR, such as Akt and p70 ribosomal S6 kinase 1, followed by overexpression of the cell-cycle regulator $p21^{Cip1/Waf1}$ and degradation of cyclin B1. In leukemia cells, PS-NH_2 elicit autophagy followed by activation of caspase 3 and subsequent induction of apoptosis. By contrast, primary macrophages did not exhibit activated mTOR signalling and proved to be relatively resistant to the PS-NH_2-induced toxicity. *In vivo*, PS-NH_2 also exhibited cytotoxicity on THP-1 xenografts on the CAM.
Similar to polystyrene particles, amino-functionalized gold nanoparticles (Au-NH_2) proved to be highly cytotoxic towards AML cell lines. Likewise, Au-NH_2 particles induce cell death in primary human leukemia cells derived from various AML patients and reduce their colony-forming potential, whereas normal hematopoietic cells remain unaffected by the treatment with Au-NH_2. In agreement with the *in vitro* data, Au-NH_2 exhibited antileukemic efficacy against primary human AML xenografted into mice. Of note, systemic Au-NH_2 treatment was not associated with any detectable adverse effects in treated mice.
Conclusions: Thus, this engineered material holds great promise as a novel nanotherapeutic for treatment of acute myeloid leukemia independent of its cytogenetic profile.

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V43

FLA-IDA salvage chemotherapy combined with venetoclax (FLAVIDA) induces high remission rates in patients with relapsed/refractory acute leukemia

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Introduction: Treatment options for relapsed and refractory (R/R) AML and ALL patients (pts) are limited and salvage chemotherapy induces remission in 20-50% of pts. Venetoclax (VEN) is a potent small molecule inhibitor of the anti-apoptotic protein BCL2, which has shown synergistic activity with hypomethylating agents (HMA) and low-dose cytarabine (LDAC). Here, we report safety and efficacy data of a novel combination therapy consisting of VEN with the salvage FLA-IDA chemotherapy (FLAVIDA) for R/R acute leukemia (AL) pts compared to FLA-IDA alone.
Methods: In this retrospective controlled study, we included pts aged 18 years or older with R/R acute leukemia previously treated with FLAVIDA. VEN was dosed orally days 1-7. Eighty-one patients treated with FLA-IDA between 2000 and 2018 for R/R AML served as control. Main outcome measure was overall response rate (ORR) defined as complete remission (CR), and CR with incomplete hematologic recovery (CRi). Safety and efficacy analyses included all patients who received one cycle of FLAVIDA.
Results: Between May 2018 and April 2019, 12 patients were treated with FLAVIDA. After a median follow up of 7.9 months, ORR was achieved in 9 of 12 patients (75%), which compared favorably with FLA-IDA (47%) (P=0.069). The median time to neutrophil recovery (≥0.5x10^9/L) in responding FLAVIDA-treated patients was 33 days (95% CI, 30-36) and 32 days (95% CI, 28-37) in the FLA-IDA control cohort (P=0.39). Median recovery times for platelet recovery (≥50x10^9/L) were 33 days (95% CI, 21-45) in the FLAVIDA cohort vs. 39 days (95% CI, 19-59) in the control cohort (P=0.13). The most common grade 3/4 all-causality event was

neutropenic fever (83%), while thrombocytopenia, anemia, and neutropenia were reported in all patients at nadir (100%).No early mortality was observed for FLAVIDA. Median overall, event-free and relapse-free survival were not reached. Six-months overall, event-free and relapse free survival were 75%, 56%, and 73%, respectively.

Conclusions: Short-term VEN can be safely administered in combination with intensive chemotherapy in younger fit adults with R/R AL with tolerable safety-profile and promising efficacy, with a high CR/CRi rate of 75%, and low early mortality providing a rationale to further evaluate this regimen in pts with acute leukemia. Longer follow up will be required to determine the impact on outcome measures. This study is registered with ClinicalTrials.gov (NCT03662724).

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Disclosure: No conflict of interest disclosed.

Freier Vortrag

Nichtmaligne Hämatologie (Anämie und Eisenstoffwechsel)

V44

Diamond Blackfan Anemia (DBA): a cancer predisposition syndrome reaching adulthood

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Diamond Blackfan Anemia (DBA) is an inherited ribosomal disorder typically presenting with hypoplastic anemia in infancy. Here, we report on outcome of 344 German DBA patients included in the GPOH/DGHO DBA registry.

As of May 2019, 344 patients had consented to participate in the DBA registry. Median age at onset of anemia was 1.7 months. Other congenital malformations were present in 67% of patients. Genetic studies performed in 279/344 (81%) patients detected a DBA-specific alteration in 67% of cases (n=188). The most common mutated genes were *RPS19* (40%), *RPL5* (18%), *RPS26* (10%) and *RPL11* (8%). Deletions involving ribosomal genes were noted in 6%, indicating the need for comparative genomic hybridization (CGH) in mutation-negative cases. Most current therapy consisted of transfusions or steroids in approximately a third of patients each. Fifteen percent of patients had been given allogeneic stem cell transplantation and 25% were without DBA-specific therapy.

At last contact, 106 of the 344 (31%) patients registered were 18 years of age or older (18 - 60 years). While there was no difference in the distribution of DBA-predisposing genetic alterations between the adult and pediatric DBA cohort, older patients were less likely to be treated with steroids (table 1).

A malignant disorder had been diagnosed in 9 patients (table 2).

Tab. 1.

	< 18y at last contact	≥ 18y at last contact	p-value
Patient number (%)	238 (69.2)	106 (30.8)	
Male/Female	115 / 123	54 / 52	n.s.
Median age at onset (days, years; range)	57.5d (-144d - 9.6y)	37d (0d - 18.6y)	0.04
Median age at last contact (years; range)	7.8y (0.2y - 17.9y)	29.05y (18.0y - 60.2y)	
Malformation (%)	167 (70.2)	64 (60.4)	0.07
DBA specific genetic alterations			
patients studied (%)	200 (84)	79 (74.5)	0.04
pathogenic variant (%)	130 (65)	58 (73.4)	n.s.
No pathogenic variant (%)	70 (35)	21 (26.6)	
DBA specific therapy at last follow-up			0.03
HSCT (%)	37 (15.9)	14 (14)	
Transfusions (%)	65 (27.9)	34 (34)	
Steroid (%)	80 (34.3)	20 (20)	
No DBA specific therapy (%)	51 (21.9)	32 (32)	
Alive / Dead at last contact (%)	230/8 (96.6/3.4)	98/8 (92.5/7.5)	0.09

Tab. 2.

Malignancy	Age at diagnosis y	Mutation	Alive/dead
MDS	4y	none detected	Alive
Osteosarcoma	6y	*RPS19*	Alive
Thyroid carcinoma	8y	*RPS19*	Alive
Breast carcinoma	38y	*RPL5*	Alive
Hepatocellular carcinoma	40y	*RPS19*	Alive
Acute myeloid leukemia	41y	not done	Dead
Lung cancer	44y	not done	Dead
Colorectal carcinoma	45y	none detected	Dead
Colorectal carcinoma	47y	*RPS19*	Alive

Of note, 6 of the 36 patients (17%) above the age of 35 years were known to suffer from malignancy. In total, 328 patients were alive, 16 had died from complications of HSCT (n=4), cancer (n=3), iron overload (n=3), pulmonary hypertension (n=1), sepsis (gram-negative n=1), catheter-related sepsis (n=1), perinatal asphyxia (n=2) or severe anemia (n=1).

In conclusion, adults with DBA have a significantly increased risk for cancer at early age. Longitudinal data in DBA registries will help to define specific surveillance recommendations.

Disclosure: No conflict of interest disclosed.

V45

Erythropoietin, linking macrophages and erythropoiesis in the erythroid niche

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Introduction: Erythropoietin (EPO) is the master regulatory hormone for red blood cell production and a widely used treatment for improvement of anemia. However, management of anemia is complex and development of EPO hypo-responsiveness together with adverse events of EPO treatment pose major problems. A better understanding of underlying pathophysiological mechanisms is warranted. Macrophages in the erythroid niche of the bone marrow support the last stages of erythropoiesis via formation of erythroblastic islands (EBI). As macrophages were reported to be a non-erythroid target for EPO, we herein investigated the role of EPO for EBI formation.

Methods: Anemia was induced in wildtype (Wt) mice via phlebotomy on three consecutive days and the bone marrow was analyzed for EBI formation (defined as $CD11b^{neg}$, $F4/80^{pos}$, $MerTK^{pos}$, $Ter119^{pos}$) over time (day 0-10) via flow cytometry. To differ between hypoxia- and EPO-mediated effects, Wt mice were injected with 10µg/kg Darbepoetin alpha. EBI formation was also analyzed in mice suffering from chronic kidney disease (CKD) caused by a diet containing adenine. Using monocyte-specific reporter mice (ROSA26-$^{tdTomatofl/fl}$Cx3cr1-^{CreERT2} mice) we studied the origin of EBI macrophages.

Results: Phlebotomy-induced anemia caused stress erythropoiesis and an appropriate increase in endogenous EPO levels. Over time, and especially in times of erythropoietic recovery, flow cytometric analysis of the bone marrow showed that EBI formation increased about 4-fold. Investigations for the ontogeny of EBI macrophages via transient labeling of monocytes revealed that EBI macrophages are monocyte-, rather than embryonically-derived and constantly recruited to the bone marrow. Next, we treated non anemic mice with Darbepoetin alpha, causing an increase in hemoglobin levels and a concomitant recruitment of monocytes to the bone marrow, leading to more EBI formation. To better dissect the importance of EBI macrophages for an appropriate response to EPO we induced CKD in genetically manipulated mice, which we found to specifically lose their EBI macrophages. While EPO treatment caused a significant anemia amelioration in Wt mice, EPO treatment was not able to induce a robust hemoglobin response if EBI macrophages were lacking.

Conclusions: EBI macrophages are monocyte-derived and continuously recruited to sites of erythropoiesis for effective erythroid output. Moreover, EBI macrophages are critical for the response to EPO during anemia.

Disclosure: No conflict of interest disclosed.

V46

Long term inhibition of complement C1s in patients with cold agglutinin disease: results from a named patient program

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Introduction: Cold agglutinin disease (CAD) results from cold-induced binding of antibodies directed against antigens on the erythrocyte surface which causes hemolysis and anemia via classical complement activation. Sutimlimab is a novel monoclonal antibody directed against the classical complement pathway factor C1s.
Methods: CAD patients treated with sutimlimab as part of a phase 1b study (Jaeger Blood 2019) were transitioned to a named patient program (NPP) to evaluate drug safety and efficacy of continuous long-term maintenance therapy (2-21 months). After a loading dose, patients received bi-weekly infusions of sutimlimab. When a patient showed laboratory signs of breakthrough hemolysis, the dose of sutimlimab was increased. The data are censored by the inclusion of those patients into an open label extension of the original sutimlimab trial.
Results: Seven patients with CAD participated in this NPP, most of whom had a prior history of multiple treatment failures and increased transfusion needs. Doses were tailored to the specific individual patient's clinical and laboratory responses. Sutimlimab infusions were well tolerated without need for premedication, and there were no relevant drug related adverse events. All 7 patients responded to the drug. Effective complement inhibition was mirrored by an increase in C4 levels and normalization of bilirubin. Sutimlimab infusions increased hemoglobin (Hb) from a mean initial level of 7.8 g/dL to a mean peak of 12.3 g/dL ($p < 0.001$). Patients maintained near normal Hb levels and inhibition of hemolysis for the duration of the study, except for few breakthrough events that were related to under-dosing and which were resolved after the appropriate dose increase. Five of the patients were eventually treated with 5.5 g of sutimlimab every 2 weeks. Of these, one had breakthrough hemolysis. This was consistent with PK/PD modeling showing a low but existent risk of decreased drug effect with this dose in certain patients, leading to a higher dosing regimen for the pivotal trials. All patients remained transfusion-free while on sutimlimab.
Conclusions: Long-term maintenance treatment with sutimlimab was safe, effectively inhibited hemolysis and significantly increased Hb levels in previously transfusion-dependent CAD patients. C1s inhibition may be an effective therapeutic target for continuous treatment of CAD patients over time. Two ongoing phase 3 trials are further evaluating the use of sutimlimab in CAD.

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V47

Blood counts in adults and elderly individuals

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Introduction: The blood count is one of the most common tests used for health assessment. In elderly individuals, selection of "healthy" reference populations is problematic due to the high prevalence of chronic morbidities, leading to uncertainty regarding appropriate reference intervals. In particular, age-specific lower reference limits for hemoglobin, which define anemia, are controversial. Here, we used a large dataset of clinical routine samples to establish reference intervals.
Methods: We examined samples from 850,013 individuals aged 20-100 years from a large laboratory service provider. We excluded samples from units/specialists with a high proportion of abnormal blood counts, samples from patients with an elevated c-reactive protein (≥ 5 mg/l) or with an unknown or decreased estimated glomerular filtration rate (< 60 ml/min $\times$ 1,73 m²), and samples with test results below the 1st or above the 99th percentile in other hematology analytes. We then used an established statistical approach (Reference Limit Estimator) to infer the distribution of physiological test results and calculated sex-specific reference intervals in 10-year age groups.
Results: After sample exclusion, 566,775-572,060 samples from different individuals were available for analysis (> 10,000 test results per analyte for each age- and sex-group in individuals < 90 years, and 9322,461 test results for individuals 90-100 years). We observed a pronounced decrease of red cell counts and hemoglobin with age in men and an increase in red cell volume with age in both sexes (Figure 1). Results were confirmed in a second dataset (198,520 individuals) .
Conclusions: We show substantial trends with age in hematology analytes´ reference intervals. Specifically, hemoglobin reference limits decline with advanced age, accompanied by increases in red cell volume, suggesting a partially physiologic cause. However, anemia is an established indicator of morbidity and mortality in the elderly, requiring exclusion of underlying diseases before consideration of a physiologic origin.

Disclosure: No conflict of interest disclosed.

V48

Seasonal patterns of anemia, hemolytic markers, healthcare resource utilization, and thromboembolic events in cold agglutinin disease

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Introduction: Cold agglutinin disease (CAD) is a rare form of autoimmune hemolytic anemia in which circulating IgM autoantibodies preferentially bind to the I antigen on red blood cells at low temperatures, resulting in chronic complement-mediated hemolysis. Patients with CAD have an increased risk of thromboembolic events (TEs). Although it is established that cold weather can elicit some of the circulatory symptoms of CAD (eg, acrocyanosis), its association with other CAD manifestations is not well understood. We therefore compared hemoglobin (Hgb), markers of hemolysis (bilirubin and lactate dehydrogenase [LDH]), healthcare resource utilization (HRU), and TE rates between seasons for patients with CAD.

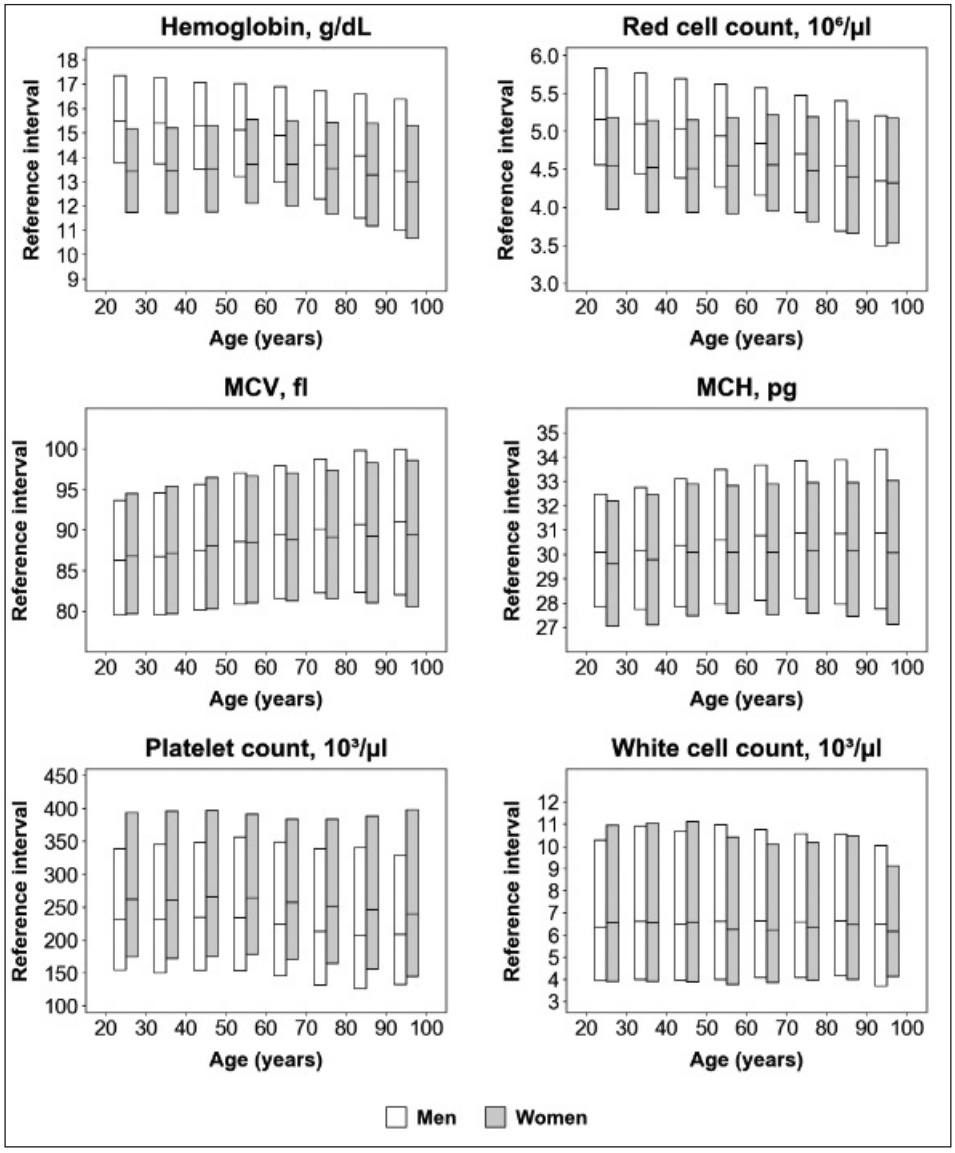

Fig. 1. Age- and sex-specific hematology reference intervals and median values for selected analytes

Methods: Patients with CAD were identified from the Optum Humedica database. Hgb, bilirubin, LDH levels, HRU measures (inpatient days, outpatient visits, and emergency room visits), and number of transfusion days were evaluated. TEs were identified using diagnostic codes. Data were compared between seasons using logistic regression adjusted for age, sex, race, region, year, Charlson Comorbidity Index, and clustering within patients.
Results: 808 patients with CAD were identified (63% female; 66% aged ≥65 years). The median minimum Hgb for winter as compared with summer was decreased by 0.54 g/dL ($P< 0.001$). The median maximum bilirubin and LDH increased by 0.12 mg/dL ($P=0.005$) and 42.1 U/L ($P< 0.001$), respectively, in winter vs summer. No significant differences in HRU measures or transfusion days were observed when stratified by season. One or more TE (n=287) occurred in 204 CAD patients (25%). Of these, 56 (19.5%) were in summer, 57 (19.9%) in fall, 79 (27.5%) in winter, and 95 (33.1%) in spring. Compared to summer, the adjusted TE risk was higher in spring (odds ratio [95% confidence interval]: 1.60 [1.09-2.33]; $P=0.016$), but not fall (1.06 [0.70-1.61]; $P=0.785$) or winter (1.42 [0.96-2.12]; $P=0.082$).
Conclusions: Patients with CAD had evidence of persistent hemolysis across all seasons. Variations in median Hgb, bilirubin, and LDH between winter and summer were not associated with differences in clinical outcomes, as there were no significant changes in HRU or transfusion days. Additionally, there was no association between colder weather and TE risk. The lack of seasonal variability in this cohort suggests that treatment considerations and monitoring of complications such as TEs in patients with CAD should be season independent.

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Catherine M. Broome: Financing of Scientific Research: Bioverativ and Alexion; Expert Testimony: Bioverativ

Wissenschaftliches Symposium

Entscheidungen am Lebensende bei onkologischen Patienten

V55
"Double awareness" in uncertain prognostic situations

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Prognostic awareness can be considered as a result of communication about the diagnosis, the course of the disease and the goals of care. Several studies have shown that a high proportion of patients in incurable stages of cancer seem to be unaware that their prognosis is limited. It may be doubted whether these studies, using simple questions or questionnaires, reflect a true lack of knowledge, or rather a sense of fear, or a socially desired response. In 2008, Rodin and Zimmerman have offered a more comprehensive approach of understanding and fostering patient understanding and coping with illness (1). According to this perspective, individuals with advanced and terminal disease are "able to sustain a ´double awareness´ of a foreshortened life, or even of imminent death, coexisting with a strong will to live and a tendency to find life meaningful". They propose that "the capacity to hold simultaneously the idea of living and dying may be the most important psychological task in those who … face the end of life." Due to recent developments in oncology, prognostic uncertainty may increase in some patient groups. How the concept of "double awareness" may also extend into other trajectories of cancer including curative situations and it may affect communication in all stages of the disease remains to be filled with experience. The concept of "double awareness" has led to the development of a standardized intervention ("Managing Cancer And Living Meaningfully", CALM) (2) which has been shown to reduce depressive symptoms and to improve coping in controlled studies (3). In day-to-day oncology, even when a standardized approach such as CALM might not be possible, the "double awareness" approach might improve communication, coping, and the integration of palliative care into oncology.

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V57
How do I deal with unrealistic hopes?

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"I am aware that this action is impossible, but it must be tried." (Raoul Wallenberg)
If one is to mention the topic of "unrealistic hope" among doctors, stories emerge about patients, who appear to be entirely ignorant of their impending futures. The Wallenberg quote and the use of the word "hope" e.g. in religious contexts shows that an easy definition is impossible, a comparison of the content of hope with a "an intersubjective standard expectation" leads nowhere. A recent review (1) and reactions to it [among others (2, 3)] outline the subject. Unrealistic optimism arises, when the probability of the desired result is grossly overestimated. Denial occurs when a person desires a certain outcome and does not face the higher probability of the unwanted outcome in some way. Self-delusion occurs when a person actively lies to himself by communicating unreal narratives of probabilities. Ignorance due to a lack of information or the ability to perceive or think can lead to unrealistic expectations.
Childers et al. (2) refer to situations in which protracted and burdensome interventions threaten without benefit. Simply repeating the factual in a confrontational way leads to nothing. It is advisable to first let the patient formulate his prognosis assessment, to let the emotion hidden in it come up. They advise to partially respond to the (not shared) prognosis assessment ("That would of course be great"). From this position, the possibility of allowing a double frame of reference can be addressed. This concept is closely related to the observation of "double awareness" (4). If this does not lead any further, the discussion might be continued theoretically and hypothetically ("I understand that you feel that it's unlikely that you will get sicker right now. I'm wondering if you could imagine what that might be like?"). This approach can allow the patient to safely express his fears and values "theoretically". The goal for the physician is to support the patient´s current coping style and see if he/she is able/willing to think about the future. Permission to speak separately with relatives can help prepare for inevitable death situations. "Before this time [of death], we would rather be helpful than be right".

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V58

Immunotherapy in the last phase of life. Until the end or finish before?

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Immunological therapeutic approaches have significantly improved the oncological treatment options in recent years. Thus, the use of immuno-checkpoint inhibitors in more and more tumor entities allows an immune-mediated tumor-directed therapy beyond the classical oncological therapy methods. Due to a completely different spectrum of side effects, the palliative medical doctor is also confronted with new symptom complexes. It is not always possible to make a clear distinction between disease-related symptoms and potentially treatable side effects of the therapy. Even though the quality of life under immunotherapies was usually better in randomized studies than under standard therapy, we must ask ourselves the critical question of how therapy delivery will influence palliative care until the end of life.
Due to the immune-mediated mechanism of action, the time to response to the therapy is sometimes weeks to months, so that the question arises in palliative care: How long should we treat? Last but not least, it is also important to discuss the economic aspects.

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Fortbildung

Hodentumore: Therapie und Management

V63

Thrombembolic complications in germ cell tumour patients: an underestimated risk?

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Introduction: Germ cell tumours (GCT) represent a unique model for a curable malignancy with an achievable cure rate of 50% to >90% even in advanced stages (IIC - III). Cisplatin-based polychemotherapy is commonly applied to treat advanced disease and is associated with immediate and mid-term side effects, including venous thromboembolism (VTE). Identifying patients at risk is important minimize such treatment-related side effects.
Methods: Based on a systematic literature search of MEDLINE and EMBASE from 2010 to 2018, VTE risk factors and potential indications for thromboprophylaxis in GCT patients are being discussed.
Results: The overall risk of VTE events has been consistently reported to increase with stage being negligible (< 1%) in localized (stage I) disease but to increase up to 20% and above in distant metastatic disease (stage III). Several clinical factors associated with development of VTE in GCT patients undergoing cisplatin-based chemotherapy have been identified. Among these retroperitoneal lymphadenopathy (RPLA) >3.5cm and a retroperitoneal primary, a history of VTE, increased lactate dehydrogenase (LDH) and central venous catheters (CVC), have been identified to substantially increase VTE risk. Few VTEs may occur even after treatment cessation.
Conclusions: VTE is a considerable disease- and treatment-related side effect among advanced GCT patients. Patients with aforementioned risk factors, if not all undergoing cisplatin-based combination chemotherapy, should be considered to receive thromboprophylaxis during treatment. Modality and duration, however, have not been defined in clinical practice guidelines.

Disclosure: No conflict of interest disclosed.

Fortbildung

Multiples Myelom: Aktuelle Therapie

V67

Primary Treatment - stratification and monitoring

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Multiple myeloma is a heterogeneous disease. In multiple myeloma many risk factors are described. In clinical practice treatment decisions are based on the degree of organ damage and biomarkers. For stratification cytogenetics and albumin plus beta2-microglobulin are used. Other factors are extra medullar disease, plasma cell leukemia and elevated LDH. Imaging is more and more important. PET-CT and MRI give information about the burden and the location of the myeloma disease.
To monitor the disease the affected M-protein, free light chain concentration (FLC) and ratio of FLC in blood are used. The quantification of light chain excretion in the urine is essential to measure the response. MRD techniques like flow cytometry, PCR techniques and next generation sequencing will be used to quantify minimal residual disease in bone marrow. Functional imaging is essential to quantify focal lesions. The combination of MRD negativity and the normalization of imaging are called "total remission". In general the patients with total remission will have the best prognosis.

Disclosure: Hartmut Goldschmidt: Advisory Role: Adaptive Biotechnology, Amgen, BMS, Celgene, Janssen, Sanofi, Takeda; Financing of Scientific Research: Art Tempi, BMS, Celgene, Chugai, Janssen, Novartis, Sanofi; Expert Testimony: Amgen, BMS, Celgene, Chugai, Janssen, Molecular Partners, MSD, Sanofi, Mundipharma, Takeda, Novartis

V68

Therapy of relapsed multiple myeloma

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Despite highly effective frontline therapy, the vast mojority of multiple myeloma patients relapse and require re-treatment. Multiple drugs and drug combinations have shown activity in these settings. The selection of treatments depends on multiple features including the biology of the disease such as genetic background and clinical course, response to and toxicity of prior lines of therapy, as well as current clinical status of the patient and the approval status and availability of drugs or combinations. The presentation reviews the clinical characteristics and biological principles of relapsed and relapsed and refractory myeloma. It then relates the available drugs and results of clinical trials to this and attempts to group therapies to these different biological and clinical categories.

Disclosure: Christoph Driessen: Advisory Role: Amgen, Janssen Cilag, Celgene, Takeda, Mundipharma

Wissenschaftliches Symposium

Aktuelle Entwicklungen in Diagnostik und Therapie von Lungenkarzinomen

V72

Integration of immune checkpoint inhibitors in the treatment of early stage lung cancer

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Antibodies directed against the immune checkpoint molecules PD-1 and PD-L1 have evolved into standard of care in patients with metastastic lung cancer of all histologies. These antibodies are either given as monotherapy or in combination with platinum-based cytotoxic chemotherapy. More recently, anti-PD-1/PD-L1 antibodies have moved to clinical exploration in curative treatment strategies for non-small cell lung cancer (NSCLC). The PACIFIC study has established 12 months of consolidation therapy with the anti-PD-L1 antibody durvalumab as the new standard in patients with PD-L1-positive NSCLC of stage III that have been curatively treated by concomitant radiochemotherapy. Current studies are underway on the role of anti-PD-1/PD-L1 antibodies given simultaneously with chemotherapy or radiochemotherapy in stage III NSCLC. Also their role in patients undergoing trimodality therapy (radiochemtherapy and resection) is explored.

Pilot studies conducted in patients with early stage NSCLC eligible for primary resection (stages I, II and resectable III A) have found that short courses of anti-PD-1/PD-L1 antibodies prior to surgery may induce dramatic histopathological responses in some patients. These effects usually do not coincide with radiological regression, and seem to be more prominent in primary tumors than in lymph node metastases. Moreover, the long-term consequences of such preoperative immunotherapies are unknown. With extensive data on safety and efficacy of anti-PD-1/PD-L1 antibodies in lung cancer at hand, these concepts open new windows for rational clinical exploration of combination therapies and development of novel risk-reducing strategies in curatively treated NSCLC.

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Fortbildung

AYA: Versorgungskonzepte Deutschland

V77

From "adolescent" to "young adult" - the Oexen AYA transition concept

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Introduction: Increasing survival rates in pediatric oncology lead to an increasing importance of medical and psycho-social rehabilitation. Therefore in Germany, rehabilitation for children and adolescents and young adults was established in 1985. Uniquely, children (< 15 years) with an oncologic illness are being rehabilitated in family-oriented rehabilitation concepts. Rehabilitation for adolescents and young adults (AYA) is performed in highly specialized centers recommended by the Society of Pediatric Oncology and Hematology (GPOH).

Methods: Adolescents 15 to < or = 18 years are being rehabilitated within their peer group. In the AYA model unit in Bad Oexen patients in the transition phase from adolescence to young adulthood are, depending on their emotional, social and cognitive development, being rehabilitated either in small groups for adolescents or - as an exception - in a family oriented rehabilitation (FOR) setting .

AYA that are 18 years or older are rehabiltated in young adults peer groups or adolescent groups dependent on their emotional, social and cognitive development, their wishes and their needs. The decision is always made on an individual basis.

ResuIts: The goal of the FOR and AYA rehabilitation is to provide support for a return back to as normal of a life as possible. Those patients who suffer from chronic illnesses due to their oncologic disease and therapy (e.g., a significant number of brain or bone tumor patients) need long-term help in various areas. AYA patients neither fit the typical pediatric nor adult oncologic profile. Topics such as physical difficulties, mental health, sexuality and fertility, career-related and financial issues are identified problem areas. There is a high, often unmet need for psychosocial support. In order to meet these needs in Bad Oexen an AYA team of pediatric and adult oncologists along with a joint psychosocial team and nursing team supports patients helping to bridge their development from childhood into adulthood. This may include topics such as school, vocational training, studying, professional career, partner and family relations, etc.

Conclusions: Age-specific AYA rehabilitation addresses the specific needs for communication about physical, emotional and psychological obstacles (e.g. after amputation in bone tumor patients) and sexuality as well as career-related issues and thus leads to a successful treatment.

Disclosure: No conflict of interest disclosed.

V78

The CARE for CAYA program - perspectives and challenges

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Background: Improved, multimodal treatment strategies increase cure rates in cancer patients. Those who survive cancer as a child, adolescent or young adult (CAYA) are at high risk for therapy- or disease-related late or long-term effects. The CARE for CAYA-Program (CFC-P) has been developed to comprehensively assess potential future problems, to offer need-based preventive interventions and thus to improve long-term outcomes in this particularly vulnerable population.

Methods: The CFC-P is designed as an adaptive trial with an annual comprehensive assessment followed by need-stratified, modular interventions, currently including physical activity, nutrition and psychooncology, aimed to improve lifestyle and/or the psychosocial situation. Patients (15-39 years) who are tumor free and in follow-up care. At baseline (and afterwards yearly) the current medical and psychosocial situation and lifestyle will be assessed by a survey compiled of validated questionnaires (e.g. EORTC QLQ C30, NCCN distress thermometer, PHQ-4, BSA, nutrition protocol) and objective parameters (e.g. BMI, WHR, co-morbidities like hyperlipidaemia, hypertension or diabetes), followed by basic care (psychological and lifestyle consultation). Depending on their needs, CAYAs will be allocated to preventive interventions in modules (physical activity, nutrition and psychooncology) over a 12-month period. After one year, the assessment will be repeated and further interventions may be applied as needed. During the initial trial phase, the efficacy of this approach will be compared to standard care (waiting list with intervention in the following year) in a randomized study. During this phase, 530 CAYAs will be included and 320 randomized. Overall, 1500 CAYAs will be included and assessed. The CFC-P is financed by the innovation fund of the German Federal Joint Committee and will be conducted at 14 German

sites. Recruitment has started in January 2018. Trial registration: DRKS-ID: DRKS00012504.
Results: The study is still recruiting. In February 340 patients were included. Only a few CAYAs (n=76) had no needs. 246 patients were randomised. Further analysis will be done.
Discussion: CAYAs are at high risk for long-term sequelae. Providing structured interventions to improve lifestyle and the psychological situation may compensate some risk factors.
In addition to the Care for CAYA program, the lecture will discuss perspectives in CAYA follow up care and the challenges.

Disclosure: No conflict of interest disclosed.

V80
Rehabilitation after cancer therapy in adolescents and young adults (AYA)

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Introduction: Only 3% of all malignancies occur in adolescents and young adults (AYAs,15-39 years). The most frequent malignancies in AYAs are melanoma, lymphoma, leukemia, breast cancer, thyroid cancer, ovarian cancer and cervical cancer. New treatment strategies with dose-intensified regimens have improved the outcome of AYAs resulting in a higher life expectancy.
Problem description: Functional impairments and therapy-related disorders may develop more frequently and physical fitness in AYAs may be more severely diminished compared to older cancer patients. Additionally to physical impairment, there might also develop insomnia, anxiety, depression, cognitive disorders, chronic fatigue, alteration of body image, social withdrawal and isolation (with impact on partnership and sexuality).
Results: These additional problems can be addressed by rehabilitation in a 4-week in-patient program within a peer group with other AYAs. Regular rehabilitation concepts for adults in Germany run over 3 weeks and include somatic therapies (exercises to improve physical condition), psychological support in groups, dietetic advice and information on maintaining and improving a healthy lifestyle. Rehabilitation concepts for AYAs go further running 4 weeks and expand psychological support by individual intervention to address the above areas. Most AYAs have not definitively concluded their professional training. Financial problems may deteriorate in case the former profession cannot be continued because of therapy-related side effects. In those cases, AYAs need to be advised on the possible alternatives and in what way they can be achieved. After rehabilitation, the physical training program should be continued for at least several months. The AYAs should be informed and motivated accordingly.
Conclusion: Rehabilitation in a 4-week in-patient program can improve somatic and psychological consequences of intensified tumor therapy as well as quality of life and return to work in AYAs.

Disclosure: No conflict of interest disclosed.

Freier Vortrag

Allogene Stammzelltransplantation I

V81
Allo-HLA-DPB1 reactive T-cell receptors with preferential recognition of hematopoietic cells can be isolated from healthy individuals for adoptive immunotherapy

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Introduction: HLA-DPB1 antigens are mismatched in about 80% of allogeneic hematopoietic stem cell transplantations (HSCT) from HLA 10/10 matched unrelated donors and were shown to be associated with a decreased risk of leukemia relapse. We recently established a reliable method to isolate HLA-DPB1 mismatch reactive T cell receptors (TCRs) from highly lytic CD4 T cell clones. TCR-modified human T cells showed eradication of primary human AML blasts engrafted into NOD/SCID/IL2Rγc$^{-/-}$ (NSG) mice. However, human fibroblasts were also recognized by HLA-DPB1 reactive T cells upon IFN-γ incubation mimicking an inflammatory condition. Here, we aimed at the isolation of TCRs recognizing mismatched HLA-DPB1 only on hematopoietic cells, which is supposed to lower their risk of graft-versus-host-disease (GvHD) reactivity.
Methods: First, we stimulated T cells from healthy donors with autologous dendritic cells expressing an allo-HLA-DPB1 allele upon transfection. We isolated different T cell clones and tested their reactivity against primary allo-HLA-DPB1$^+$ AML blasts in IFN-γ ELISpot as well as ^{51}Chromium-release assays. T cell clones were further analyzed for recognition of non-hematopoietic cells. TCRs from most promising CD4 T cell clones with preferential recognition of hematopoietic cells were further analyzed.
Results: Two CD4 T cell clones isolated from an HLA-DPB1*03:01 mismatch stimulation specifically lysed HLA-DPB1*03:01$^+$ primary AML blasts. Importantly, IFN-γ pretreated fibroblasts as surrogate target of GvHD were not recognized by one of these T cell clones. Therefore, we isolated this TCR and transferred it into CD4 and CD8 T cells from healthy donors. TCR_{DP03} re-directed T cells specifically lysed primary AML blasts from several HLA-DPB1*03:01$^+$ patients. To further increase AML reactivity, we exchanged the constant domains of the TCR with their murine counterparts. Indeed, murinized TCR_{DP03} induced higher IFN-γ levels upon recognition of AML blasts, whereas lysis was not enhanced. However, murinization also led to recognition of IFN-γ pretreated fibroblasts.
Conclusions: Our data indicate that allo-HLA-DPB1 reactive T cells with preferential recognition of hematopoietic cells indeed exist in healthy individuals. Considering relatively low polymorphism of HLA-DPB1 as well as preferential expression of class II on hematopoietic cells including leukemia, we believe that allo-HLA-DPB1 antigens are promising targets for TCR gene therapy in allogeneic HSCT.

Disclosure: No conflict of interest disclosed.

V82

Keratinocyte growth factor diminishes cytotoxic effects on human thymic epithelium induced by rabbit anti-thymocyte globulin

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Introduction: Rabbit anti-thymocyte globulin (rATG) is a polyclonal T cell depleting antibody widely used for the prevention of graft-versus-host disease (GvHD) after allogeneic hematopoietic stem cell transplantation. A delayed immune reconstitution after rATG treatment has been described repeatedly and an impaired thymic function as part of the underlying mechanism has been discussed. This study aimed at elucidating possible effects of two commonly used rATG preparations on cultured human thymic stroma cells (TSC), especially on thymic epithelial cells (TEC).
Methods: Primary TEC long-term cultures were established and challenged with rATG. Binding and cytotoxicity of two rATG preparations were assessed and compared by flow cytometry and immunofluorescence analyses. The release of several cytokines by cultured TSCs in response to rATG was analyzed via multiplex ELISA. Moreover, the protective abilities of keratinocyte growth factor (KGF) in respect of rATG effects on TECs were analyzed.
Results: rATG showed a dose-dependent binding to TECs and exerted a complement-independent, dose-dependent cytotoxicity. There were no significant differences between the two rATG preparations Grafalon® and Thymoglobulin®. rATG exposure altered the TEC cytokine secretion by reducing IL-7, IL-15 and IL-6, cytokines knowingly involved in thymic T cell development and proliferation. A pretreatment with KGF diminished rATG-induced cytotoxicity of TECs (Grafalon®: -11.44% ±4.76%; Thymoglobulin®: -6.26% ±5.71%) and restored their IL-7 and IL-15 secretion.
Conclusions: The observed rATG-induced cytotoxicity in human TECs sheds light on the underlying mechanisms of a delayed T cell reconstitution after rATG treatment. This data further supports the additive application of cytoprotective KGF when treating with rATG, in order to prevent GvHD and to simultaneously abrogate delayed T cell reconstitution due to thymic damage.

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V83

The role of CD146$^+$ mesenchymal stromal cells for the engraftment of donor hematopoiesis and relapse of myeloid neoplasia after allogeneic stem cell transplantation

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Introduction: The success of allogeneic stem cell transplantation (SCT) in myeloid neoplasia is limited by impaired hematopoiesis and relapse. Critical for engraftment of donor hematopoietic stem cells (HSC) and persistence of leukemic stem cells is the bone marrow (BM) niche. An essential part of the BM niche are multipotent mesenchymal stromal cells (MSC). As we and others have previously shown that MSC are resistant to genotoxic damage and originate from the recipient after alloSCT we hypothesize that the recipient BM niche is preserved after alloSCT and determines engraftment of donor cells and persistence of malignant cells. To gain insight into this function analysis of native niche cells is detrimental.
Methods: To investigate uncultured BM-stroma cells we isolated MSC by adherence culture from BM mononuclear cells (MNCs) but also native CD146$^+$(CD45$^-$/HLA-DR$^-$) stroma cells via our flow cytometry protocol (CD146$^+$BMSC). Total MSC and CD146$^+$BMSC of patients with acute myeloid leukemia (AML) before and after alloSCT were examined comparatively by differentiation assays, FACS and growth kinetics as well as ATAC- and RNAseq.
Results: Isolation and proliferation of cultured MSC was significantly reduced after alloSCT. CD146$^+$BMSC could be consistently isolated from BM aspirates of AML patients before and after alloSCT representing about 0.02% of the BM MNC. These CD146$^+$BMSC MSC showed CFU-F growth, typical MSC phenotype, remained CD146$^+$ for several passages and were capable of adipogenic and osteogenic differentiation *in vitro*. The CD146-negative fraction of BM MNC contained no adherent cells. Therefore, we propose that CD146$^+$BMSC represent the majority of native BM MSC. Similar to cultured MSC, CD146$^+$BMSC obtained after alloSCT showed a significantly reduced proliferation. ATAC and RNAseq analysis revealed epigenetic and gene expression alterations in paired samples before and after alloSCT. These data serve for exploring functional alterations. Here in preliminary studies, we were able to show support of viability and immature phenotype of HSC upon coculture with MSC.
Conclusions: A native uncultured CD146$^+$ stroma cell population can be isolated from BM of AML patients before and after allogeneic SCT representing the majority of the MSC in the BM. These CD146$^+$BMSC show marked reduction in proliferation and differential gene expression after alloSCT. From this, we conclude that alloSCT leads to alterations in the BM niche that may impact the outcome of SCT.

Disclosure: No conflict of interest disclosed.

V84

A single center experience in donor search for allogeneic hematopoietic stem cell transplantation (aHSCT) in patients with hematologic malignancies

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Introduction: For patients with a variety of hematologic malignancies aHSCT is a potentially curative therapy depending on diagnosis, disease risk and factors like age and comorbidities.
Methods: We retrospectively analyzed donor searches, availability, timelines and outcome in all patients (pts) for whom a search was initiated between August 2012 - August 2017 with a follow-up until 20th March 2019.
Results: For 476 pts (182 female, median age 54 yrs, range 18-74) a donor search was initiated. Diagnoses included AML 44%, ALL 7%, MDS 24%, Myelofibrosis 5%, CML 2%, NHL 7%, Myeloma 5% and others (e.g. AA) 6%. In 66 cases (21%) aBSCT with a related donor was performed. Unrelated donor search was initiated in 420 pts (88%) a median of 119 days after initial diagnosis. Median search duration was 38.5 days. For 303 pts (77%) at least 1 unrelated 10o10 and for 76 of the remaining 117 pts (65%) at least 1 9o10 donor could be identified leaving 4% of pts without a suitable donor. Median number of 10o10 and 9o10 donors per patient was 3 (1-7) and 2 (1-7), respectively. In MMUD mismatches were identified in A (52%), B (12%), C (20%), DR (8%) and DQ (8%). Median donor age was 33 years (16-68), 70% were male. Donor and recipient age (33 vs 54 yrs) differed significantly ($p< 0.005$). A donor was activated for 340 pts (71.4%) of whom 315 (92.6%) received aHSCT (MUD/MMUD: 79% vs related donor: 21%). A CMV identical donor was activated in 77%; in 13% the unfavorable constellation R+D- had to be chosen. Median time from

search initiation to activation was 66 days differing by diagnosis (AML vs AA, p= 0.049). Median time from activation to aHSCT was 41 days. The 1st activated donor donated in 86%; in 8% a 2nd and in 2% a 3rd donor had to be activated due to medical (61%), organizational (23%) or unknown (16%) reasons of donor origin. Survival after aHSCT was 66% at 2 yrs (53% at 5 yrs). Median survival was 1944 days. Mortality was treatment-related in 16% at 2 yrs (17% at 5 yrs) and disease-related in 17% at 2 yrs (20% at 5 yrs). Reasons to cancel aHSCT (n=152) were death (16%), progression (4%), comorbidities (16%), patients' decision (7%), lack of a suitable donor (3%) and others (54%).

Conclusions: A suitable unrelated donor could mostly be identified within a short time. In contrast, time from diagnosis to donor search was long even in pts with clear aHSCT indications highlighting the need for faster initiation of donor searches to improve transplant results.

Disclosure: No conflict of interest disclosed.

V85

Prognostic impact of minimal residual disease on outcome in the SORMAIN trial

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In acute myeloid leukemia (AML) the presence of an internal tandem duplication (ITD) in the *FLT3* gene is associated with a poor prognosis. Despite allogeneic stem cell transplantation (allo-SCT), relapses frequently occur and account for the main cause of death. We recently reported on the results of the randomized, placebo-controlled, double-blind phase 2 SORMAIN trial that investigated the tyrosine kinase inhibitor (TKI) sorafenib as maintenance therapy in FLT3-ITD positive AML patients in complete hematological remission after allo-SCT demonstrating a significant benefit for sorafenib in reducing relapse and death (Burchert et al. ASH 2018). Here, we evaluated the prognostic impact of molecular minimal residual disease (MRD). MRD was obtained before allo-SCT and at randomization (i.e. before starting maintenance treatment after allo-SCT). Of 83 patients that were randomized (40 in the placebo arm, 43 in the sorafenib arm) 22 patients (27%) were not MRD negative at randomization. Of the latter, 70% of patients in the placebo arm and 25% of patients in the sorafenib arm suffered from relapse (p< 0,05). The subgroup of patients not in molecular remission after allo-SCT might particularly benefit from TKI maintenance strategies (especially sorafenib) after allo-SCT for FLT3-ITD positive AML.

Disclosure: Stephan Metzelder: No conflict of interest disclosed.
Andreas Burchert: Expert Testimony: Bayer, AOP Orphan, BMS, Novartis, Pfizer

V86

The pre-treatment CD34+/CD38- burden as prognostic factor in patients (pts) with myelodysplastic syndrome (MDS) receiving allogeneic stem cell transplantation (HSCT)

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Allogeneic HSCT is the only curative treatment for MDS & of high interest in pts at high progression risk to sAML. CD34+/CD38- cells possess MDS stem cell potential & sAML clones originate from MDS disease stage. The prognostic impact of the pre-treatment MDS stem cell burden remains unknown.

We analyzed 124 MDS pts receiving reduced-intensity (44%; Fludarabine + Busulfan or Treosulfan) or non-myeloablative (56%; Fludarabine + 2Gy or 3Gy TBI)-HSCT at a median age of 61 (range 22-74) years. 59% of pts received cytoreductive therapy pre-HSCT (25% hypomethylating agents, 24% AML chemotherapy, 10% both). IPSS-R was 8% low, 30% intermediate, 23% high, 39% very high. CD34+/CD38- burden was evaluated by flow cytometry in untreated bone marrow. Using R's OptimalCutpoint package a 1% CD34+/CD38- cell cut-off was determined & divided the cohort in high (34%) or low (66%) burden pts.

Pts with a high CD34+/CD38- burden had worse IPSS-R (P=.03) risk & worse IPSS-R genetic risk (P=.02), more often an excess of blasts (P< .01) & an abnormal (P=.04), complex (CKT, P< .01) or monosomal karyotype (MKT, P< .01) & more often received cytoreductive treatment pre-HSCT (P< .01). High CD34+/CD38- burden pts had a higher cumulative incidence of relapse/progression (CIR, P< .01, Fig 1A), sAML (CIsAML, P< .01, Fig 1B) but despite separation of the curves no different overall survival (OS,P=.12). In bivariate analyses the CD34+/CD38- burden impacted on CIR & CIsAML in the context of CKT (HR 2.9, P< .01 & HR 3.2, P=.01, respectively) or MKT (HR 3.0, P< .01 & HR 3.5, P< .01, respectively). In separate analyses for IPSS-R low/intermediate & high/very high

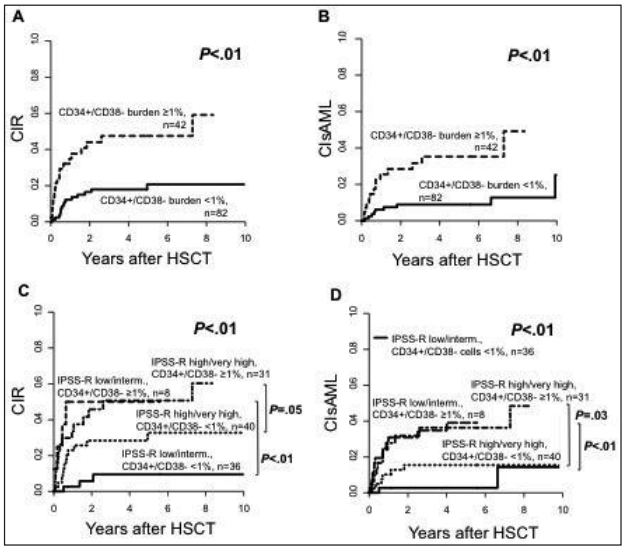

Fig. 1.

risk pts, high CD34+/CD38- burden pts had higher CIR (P< .01, Fig 1C), higher CIsAML (P< .01, Fig 1D) & by trend shorter OS (P=.07).
A high pre-treatment CD34+/CD38- burden associated with higher progression risk & by trend shorter OS after HSCT. Despite the strong correlation with high-risk MDS a high CD34+/CD38- burden remained a prognostic factor additionally to the IPSS-R & presence of CKT or MKT. The adverse prognosis is likely mediated by MDS stem cells within the CD34+/CD38- population initiating MDS relapse or progression to AML.

Disclosure: No conflict of interest disclosed.

Freier Vortrag

Chronisch lymphatische Leukämie

V87

Ibrutinib versus placebo in patients with asymptomatic, treatment-naïve early stage chronic lymphocytic leukemia (CLL): primary endpoint results of the phase 3 double-blind, placebo-controlled randomized CLL12 trial

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Introduction: So far, treatment of asymptomatic, early stage CLL patients has not been proven beneficial. Ibrutinib is a BTK inhibitor with impressive clinical efficacy in advanced or relapsed CLL. Therefore we wished to evaluate whether ibrutinib prolongs event-free survival (EFS) in early stage CLL patients with increased risk of progression defined by a recently developed score (Pflug et al., Blood 2014).
Methods: We randomly assigned treatment-naïve, asymptomatic Binet A patients with intermediate, high or very high risk of progression to receive either ibrutinib or placebo 420mg per day. The primary endpoint was EFS defined as time from randomization until occurrence of active disease according to iwCLL guidelines, new CLL treatment or death.
Results: A total of 182 or 181 patients were assigned to receive ibrutinib or placebo, respectively. At median observation time of 31 months EFS was not reached in the ibrutinib arm and was 47.8 months in the placebo arm (HR 0.25; 95%CI, 0.14 to 0.43; P< 0.0001; Figure 1). At cut-off, 6 and 5 deaths were documented in the ibrutinib and placebo group, respectively. There was no significant difference in all-grade (grade ≥3) adverse events occurring in 82.2% (43.3%) of patients in the ibrutinib group and in 84.8% (38.7%) in the placebo group. AEs of clinical interest were mostly of CTC-grade 1-2 and significantly more frequent in ibrutinib treated patients (Table 1).
Conclusions: Ibrutinib significantly improves EFS in patients with treatment-naïve early stage CLL when compared to placebo. There were no significant differences in adverse events between both study arms.

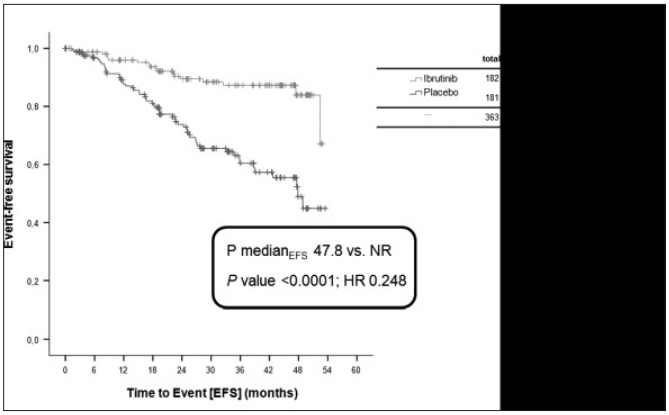

Fig. 1. Event-free survival (intention to treat)

Tab. 1. (S)AEs of clinical interest: number of patients (percent)

	ibrutinib, n=185	placebo, n=178	P-value
any (S)AE of clinical interest	106 (57.3)	71 (39.9)	0.001
diarrhea	58 (31.4)	44 (24.7)	n.s.
diarrhea, CTC ≥ 3	2 (1.1)	5 (2.8)	-
bleeding	51 (27.6)	17 (9.6)	0.000
bleeding, CTC ≥ 3	6 (3.2)	2 (1.2)	-
atrial fibrillation	33 (17.8)	13 (7.3)	0.003
atrial fibrillation, CTC ≥ 3	11 (6.5)	3 (1.7)	-
hypertensive disorders	18 (9.7)	7 (3.9)	0.04
hypertensive disorders, CTC ≥ 3	3 (1.6)	3 (1.7)	

Disclosure: Petra Langerbeins: Advisory Role: Sunesis; Financing of Scientific Research: Janssen-Cilag, Abbvie; Expert Testimony: Janssen-Cilag; Other Financial Relationships: Reisekostenunterstützung von Abbvie, Janssen-Cilag
Michael Hallek: Advisory Role: Roche Gilead, Mundipharma, Janssen, Celgene, Pharmacyclics, Boehringer; Expert Testimony: Roche, Gilead, Mundipharma, Janssen, Celgene, Pharmacyclics, Abbvie

V88

B-cell specific IRF4 deletion accelerates chronic lymphocytic leukemia development by enhancing tumor immune evasion

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Introduction: Chronic lymphocytic leukemia (CLL) is a highly heterogenous disease that is clinically and biologically highly dependent on a crosstalk of CLL cells with the microenvironment and the immune-system, in particular with T-cells. CLL derived T-cells are skewed to an antigen-experienced T-cell subset, indicating some degree of tumor recognition, but they are also mostly exhausted, thus preventing an effective anti-tumor immune response. The CLL typical T-cell shaping is directly induced by CLL tumor cells, however, the transcriptional program involved is largely unknown.
Methods: We generated and analysed Tcl1 transgenic (tg) CLL mice with conditional deletion of IRF4 (interferon-regulatory factor 4) targeted to B cells only (by CD19cre recombination) and performed analogous analyses on independent CLL cohorts based on IRF4 expression in CLL cells.

Results: Here we suggest the transcription factor IRF4 as critical regulator of T-cell activation and CLL tumor evasion based on our results in Tcl-1 tg mice, that develop a murine CLL highly similar to the human disease, with B-cell specific IRF4 deficiency. We show enhanced CLL disease progression in IRF4 deficient Tcl-1 tg mice as compared to Tcl-1 tg mice with wild-type IRF4 expression due to a severe downregulation of genes involved in T-cell activation including genes involved in antigen processing and presentation and co-stimulation which also affects T-cell subset skewing and exhaustion. These data could be verified in the human disease demonstrating inferior prognosis of CLL patients with low IRF4 expression in independent CLL patient cohorts, failed T-cell skewing to antigen-experienced subsets, decreased co-stimulation capacity and downregulation of genes involved in T-cell activation.
Conclusions: We show a novel immune escape mechanism in CLL that is based on downregulation of the antigen-presenting and costimulatory machinery and that this may be orchestrated by downregulation or loss of function of IRF4. These findings not only have prognostic but also therapeutic relevance as IRF4 expression could be manipulated by immune modulatory drugs (e.g. lenalidomide), which may decrease the immune evasion phenotype and potentially render CLL cells more prone to the elimination of tumor cells by the patients' immune system.

Disclosure: No conflict of interest disclosed.

V89

Pan-omics assessment of constitutive AKT-activation in the Eμ-TCL1 CLL-like mouse model

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Introduction: PI3K/AKT signalling is a central regulatory axis in B-cell leukaemia/lymphomas, dysregulated via pan-omic mechanisms in cancer. Based on the observation that in Chronic Lymphocytic Leukaemia (CLL) cases AKT-phosphorylation status correlated with poor risk CLL-driver genes, whilst Richter Syndrome (RS) patient biopsies expressed active AKT, we established a CLL transformed RS-like mouse model (TC-R26AKT-C) using a constitutively active AKT allele. TC-R26AKT-C mice presented with aggressive disease, diffuse large cell size and reduced overall survival. While this suggests constitutively active PI3K/AKT signalling as a mechanism of CLL to RS transformation, we wanted to further address the functional impact of constitutively active AKT on subsequent development of genomic aberrations and transformation of disease.
Methods: Mutations from spleen DNA of 23 mice (TC-R26AKT-C [n = 9], Eμ-TCL1 [n = 10], C5/Bl6^{AKT} [n = 4]) were analysed by whole exome sequencing. Human-mouse orthologs for mutated genes were filtered for CLL/DLBCL/RS using the COSMIC Cancer Browser. Single-cell RNA sequencing was conducted using the 10X Genomics 3' Single Cell Library on 10 mice (TC-R26AKT-C [n = 4], Eμ-TCL1 [n = 4], C5/Bl6 [n = 2]). Gene Ontology analysis of significant genes was conducted using GOrilla.
Results: In total, 101 mutations were identified by WES. Eμ-TCL1 mutated genes significantly associated with CLL (P = 0.003), whilst TC-R26AKT-C mice were evenly split between CLL and DLBCL (P = 0.045). In addition, a comparison to an Myd88pL252P ABC-DLBCL mouse model was conducted, showing a significant association towards DLBCL (P< 0.001). Single-cell RNA sequencing of these mice identified 12 unique B-cell clusters, 5 of which specific for TC-R26AKT-C mice (heterogeneous expression patterns), 5 for Eμ-TCL1 mice (defined by depletion of cell cycle), and 1 for C5/Bl6. Interestingly, one cluster was shared between Eμ-TCL1 and TC-R26AKT-C (defined by enrichment of cell cycle), representing a potential link for CLL to RS transformation in this model.
Conclusions: Here, we show that in TC-R26AKT-C mice that specific oncogenic signalling of constitutively active AKT in a mouse model leads to secondary accumulation of genomic mutations that correspond to human disease. In conclusion, we hypothesise that this specific genomic accumulation represents an initial transforming event, which may define the B-cell clusters observed at the single-cell level.

Disclosure: Stuart James Blakemore: No conflict of interest disclosed.
Christian Pallasch: Advisory Role: Gilead; Financing of Scientific Research: Roche; Expert Testimony: Gilead, Genzyme

V90

Unmaintained remission after discontinuation of kinase inhibitor treatment in chronic lymphocytic leukemia: an observational cohort

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Introduction: Kinase inhibitors (KI) rapidly changed treatment paradigms in CLL and ibrutinib currently enters clinical standards in previously untreated patients. In this scenario, the "treat-until-progression" concept leads to very long treatment durations or a need for drug cessation. However, explored stopping rules largely rely on MRD negativity, rarely achieved with KI. Outcomes in lineages after KI are known mostly for patients receiving immediate salvage treatment. However, in real-life many discontinuations of KI in CLL treatment happen due to toxicity and patient decisions rather than progression and may happen in MRD positive clinical remission. Their fate in a treatment-free observation setting is unknown.
Methods: We report first real-world data on CLL patients stopping ibrutinib or idelalisib in different lines of treatment due to toxicities or patient decision, after achieving measurable response. Eligible patients were in untreated observation after discontinuing the kinase inhibitor. Retrospective chart review was performed in 7 academic centres.
Results: We report 54 patients treated with either ibrutinib (n=29) or idelalisib (n=25). Median age was 74 years and the median number of treatments prior to KI was one (range 0-6). The median time on KI was 8 mo before stopping due to toxicity (n=49) or patient's decision (n=5). Responsible toxicities were as expected. Del17p/del11q was present in 33 patients. KI response was 11 CRs and 43 PRs. Median PFS after KI cessation was 9.4 mo, median TTNT was 12 mo and OS was 62% at the median observation time (27 mo). PFS and TTNT at 2a were 19 and 27%, respectively. The two drugs had similar PFS and TTNT, but idelalisib patients had better OS (median n.r. vs 20 mo, p=.002) in our cohort. PFS, TTNT and OS were not significantly different by FISH risk, while unmutated IgVH predicted earlier progression, but not OS. While the line of treatment did not affect PFS or OS, achievement of CR showed better PFS, but not OS.
Conclusion: Treatment cessation in CR or PR after kinase inhibitor treatment is associated with limited median PFS, but some patients experience prolonged treatment-free intervals. Exploratory analyses point to clinical response quality and mutational state as predictors of PFS. OS from stop of kinase inhibitor was respectable for this elderly cohort, suggesting available salvage options.

Disclosure: Alexander Egle: Advisory Role: Janssen, Abbvie, Gilead, Roche; Financing of Scientific Research: Janssen, Abbvie, Gilead, Roche
Loic Ysebaert: No conflict of interest disclosed.

V91

Second primary malignancies (SPM) in treated and untreated patients with chronic lymphocytic leukemia (CLL): an analysis of the registry of the German CLL Study Group (GCLLSG)

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Introduction: Treatment outcomes for CLL patients (pts) have markedly improved over the last decade. With longer survival, fewer pts die of CLL and SPM represent an increasingly relevant cause of death. Prior analyses have shown increased rates of SPM in CLL pts but it remains unclear whether these can be attributed to CLL-inherent immunodeficiency or effects of antineoplastic treatments. With this analysis we aim to describe the incidences of SPM in treated (T) and untreated (UT) CLL pts and assess their association with CLL therapy.
Methods: CLL pts included in the GCLLSG registry were identified and clinical data was retrieved. Time to SPM was calculated from time of CLL diagnosis and first-line therapy and evaluated by competing risk analysis considering death as a competing event.
Results: We included 3695 pts of which 1669 (45.2%) received at least one CLL treatment and 2026 (54.8%) were UT. The median observation time from CLL diagnosis was 101.5 months in the T and 42.3 in the UT group, median age at diagnosis was 63 and 67 years, respectively. First-line treatments were mostly fludarabine-(F, 28.2%), bendamustine-(B, 43.4%) or chlorambucil-based (CLB, 15.8%). We recorded 363 SPM in 315 patients, 63.9% of the cases were solid SPM (sSPM), 9.4% haematological (hSPM) and 26.7% non-melanoma skin cancer. The most common sSPM were prostate (18.5% of all sSPM), colorectal (13.4%) and breast cancer (12.5%).
Incidences of SPM were calculated from time point of CLL diagnosis. 6-year incidences (6-yi) were 7.9% and 5.5% in T and UT pts, 12-yi were 14.5% and 11.0% and 20-yi were 23.6% and 19.5%, respectively (Figure 1A). Hematological SPM occurred more frequently in T (20-yi: 2.0%) than in UT pts (20-yi: 0.6%). Within the T group, cumulative SPM incidences were 8.9% (F), 11.4% (B) and 10.0% (CLB) at 6 years and 13.5% (F), 20.3% (B) and 19.4% (CLB) at 12 years after first-line treatment (Figure 1B).
Conclusions: Compared with treated patients, the incidence of SPM appears lower in untreated patients despite the higher median age in this group. This observation might suggest an influence of CLL treatment or more advanced disease stage on the occurrence of SPM.

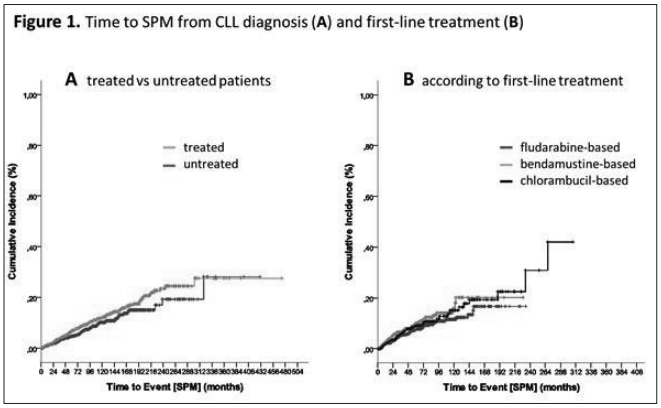

Fig. 1. Cumulative Incidence of SPM according to treatment

Disclosure: Moritz Fürstenau: No conflict of interest disclosed.
Michael Hallek: Advisory Role: Roche, Gilead, Mundipharma, Janssen, Celgene, Pharmacyclics, Boehringer; Financing of Scientific Research: Roche, Gilead, Mundipharma, Janssen, Celgene, Pharmacyclics, Boehringer; Expert Testimony: Roche, Gilead, Mundipharma, Janssen, Celgene, Pharmacyclics, Abbvie

V92

Long-time follow-up of 888 patients suffering from CLL, having been observed and cared for within the hematological supply network (WGKK)

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Introduction: Since 2013, we have developed a *hematological supply network* consisting of the 3rd Medical Department and three hematological outpatients centers, which are all members of the same institution (Hanusch KH). This resulted in a significant increase of patient frequency (from 15000 to 60000 patient contacts per year) suffering from hematological diseases or abnormal blood counts and allows us to investigate real world data in patients who were diagnosed with CLL with and without indication for specific treatment.
Methods: We performed a retrospective data analysis of *N*=888 patients suffering from CLL. These patients were either diagnosed with CLL and/or observed or treated because of their disease within our *hematological supply network* between 2012 and 2017.
Results: Epidemiological data: 52.6% of patients were male, 47.4% were female. At time of diagnosis, the median age was 67.5 years (range: 27.6-101.9 years). Median BMI was 25.5 (range: 17.6-45.5). 89.1% of patients had Binet-stadium A, 8.6% had Binet-stadium B, and 2.3% had Binet-stadium C. In 43.2% of patients, pathological lymph nodes had been observed. 7.7% of patients reported suffering from constitutional symptoms at time of diagnosis. 7.5% of patients presented with a del(17p)-mutation of ≥10%, while 57.0% of patients presented with a positive IGHV-mutation status. Comorbidities and functional status: Comorbidities were assessed using the Charlson Comorbidity Index (CCI). 29.6% of our patients suffered from cardiac comorbidities, 14.5% had diabetes mellitus, 14.0% had peripheral artery occlusive disease, 8.9% had cerebrovascular diseases and 7.9% had chronic pulmonary diseases. 99.8% of patients presented with an ECOG-status of 0 or 1.
Treatment and death: The mean time-to-first-treatment was 4.0 years (range: 0.0-31.8 years). So far, only 258 of 888 patients required therapy and received at least one therapy line (max. 6 therapy lines), whereas 70.9% of patients did not require therapy at any moment of disease history. In total, 17.3% of patients died since time of diagnosis, whereas 27.1% of patients who received treatment and 13.3% of patients who did not receive treatment died. The median age at time of death was 81.1 years (range: 41.3-103.3 years).
Conclusions: Our *hematological supply network* enables an intra- and extramural caretaking of patients suffering from various hematological and oncological diseases, and provides a basis for retrospective and epidemiological analyses.

Disclosure: Felix Keil: Financing of Scientific Research: Merck, AbbVie, Takeda, Novartis, Daiichi Sankyo, Bionorica, Celgen, Janssen, Pfizer, Roche; Expert Testimony: AbbVie, Bionorica, Janssen, Takeda, Merck
Thomas Nösslinger: Advisory Role: Janssen, Abbvie, Roche, Gilead; Financing of Scientific Research: Janssen, Abbvie, Roche, Gilead

Freier Vortrag

Gerinnung und Thrombozyten

V93

Myeloperoxidase inhibits the procoagulant activity of cell-free DNA

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Introduction: Myeloperoxidase (MPO) and DNA are main constituents of neutrophil extracellular traps (NETs) and are released in close proximity at sites of NETosis. Albeit individual NET components have been shown to promote (thrombotic) vessel occlusions in various pathological scenarios, including deep vein thrombosis, myocardial infarction or cancer, intact NETs failed to trigger coagulation in vitro in a recently published study, in which cell-free DNA via its negative surface charge, but not nucleosomes or reconstituted chromatin, activated the contact pathway of coagulation.

We have previously shown that cationic MPO is a negative regulator of phospholipid-dependent coagulation involving both the electrostatic binding and chemical modification of negatively charged phospholipids. The aim of our current study was to investigate whether MPO also exerts direct inhibitory effects on the procoagulant activity (PCA) of cell-free DNA, thus regulating DNA-induced coagulation at sites of NETosis.

Methods: We used a fluorogenic thrombin generation assay to analyze the PCA of DNA isolated from polymorphonuclear leukocytes (PMNs) in relipidated phospholipid-free plasma in the presence or absence of leukocyte-derived MPO and its substrate, H_2O_2. Isolated DNA was further characterized by MPO ELISA and gel electrophoresis.

Results: PMN-derived cell-free DNA, which was free of endogenous MPO, amplified thrombin generation in relipidated plasma in a concentration- and factor XII-dependent manner, as evidenced by the inhibitory effects of corn trypsin inhibitor (CTI) and factor XII depletion. Under these conditions, MPO alone or together with H_2O_2, which allows for generation of highly reactive hypochlorous acid, did not affect thrombin generation. However, MPO potently inhibited DNA-induced thrombin generation in a dose-dependent manner, an effect that was independent of the enzyme's catalytic activity and could be fully abolished by heat denaturation. Further, pre-incubation with MPO mitigated the ability of DNA to migrate in gel electrophoresis, indicating that electrostatic interactions between the cationic MPO and anionic DNA were involved in this process.

Conclusions: Our findings indicate that PMN-derived MPO inhibits the PCA of cell-free DNA through electrostatic complex formation and thus provide novel insights into NET biology.

Disclosure: No conflict of interest disclosed.

V94

Integrated efficacy results from the phase II and phase III studies with Caplacizumab in patients with acquired thrombotic thrombocytopenic purpura

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Introduction: Acquired thrombotic thrombocytopenic purpura (aTTP) is a rare, lifethreatening thrombotic microangiopathy, characterized by a disseminated formation of von Willebrand Factor-platelet rich microthrombi. The efficacy of caplacizumab in aTTP, in conjunction with plasma exchange (PE) and immunosuppression, was demonstrated in placebo-controlled Phase II and III studies. Here, we present the integrated efficacy results of these studies.

Methods: All randomized subjects in the two studies were included in the analysis. Subjects had a single-blind (SB) or a double-blind (DB) treatment period followed by a 30-day follow-up period. Phase III study subjects could have an openlabel caplacizumab treatment (in case of exacerbation during the DB treatment). The primary endpoint was time to platelet count response. Secondary endpoints included mortality rate; the number of PE days; the proportion of subjects with a) TTP-related death, recurrence of TTP or at least one treatment-emergent major thromboembolic event during treatment (composite endpoint); b) a recurrence of TTP; c) refractory TTP.

Results: 220 subjects were randomized, 108 to caplacizumab and 112 to placebo. Groups were well balanced except for an imbalance regarding TTP history. There was a significant difference in favour of caplacizumab in time to platelet count response ($p< 0.001$). Treatment with caplacizumab resulted in a 72.6% reduction in the composite endpoint during the DB/SB treatment period ($p< 0.0001$). Treatment with caplacizumab reduced recurrences of TTP by 84.0% during the DB/SB treatment period ($p< 0.0001$), and by 49.5% during the overall study period ($p< 0.005$). Zero vs. 7 (6.3%) subjects in the caplacizumab group had refractory TTP ($p< 0.01$). No patients died in the caplacizumab group vs. 4 in the placebo group during the DB/SB treatment period ($p< 0.05$). There was a reduction in the mean number of PE days of 3.9 days in the caplacizumab vs. placebo group.

Conclusions: This integrated efficacy analyses confirmed results from Phase II and III studies showing that caplacizumab significantly reduces time to platelet count response, and resulted in clinically meaningful and significant reductions in (i) the proportion of subjects with TTP-related death, a recurrence of TTP, or at least one major thromboembolic event; (ii) the rate of death due to TTP; (iii) refractory TTP; (iv) the mean number of PE days during the treatment period, and (v) recurrences of TTP during the study.

Disclosure: Paul Knöbl: Advisory Role: Ablynx/Sanofi; Shire/Takeda; Financing of Scientific Research: Beraterhonorare und Vortragshonorare von Ablynx/Sanofi, Shire/Takeda, Alexion
Filip Callewaert: Employment or Leadership Position: Ablynx/Sanofi Aventis

V95

Treatment of immunethrombocytopenia (ITP) with Revolade^{O} - results of the 2nd interim analysis of the German non-interventional trial RISA

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Introduction: Immune thrombocytopenia (ITP) is an acquired autoimmune disease characterized by increased platelet destruction and impaired platelet production. German guidelines recommend corticosteroids for first-line and thrombopoietin receptor-agonists (TPO-RA) for second-line therapy. The oral TPO-RA Revolade^{O} has been shown to be safe and efficient and is licensed for the treatment of patients with persistent primary ITP who are refractory to previous treatments. However, data on Revolade^{O} prescription in routine clinical practice are missing. Here we present data from the RISA-trial, an observational study of Revolade^{O} utilization in German clinical routine.
Methods: RISA is an ongoing, single-cohort, non-interventional, multicenter observational study. The individual follow-up period is approximately 24 months. Dosage of Revolade^{O} and treatment of patients follows the SmPC and the routine of treating physicians.
Results: 157 ITP-patients received at least one dose of Revolade^{O} and completed one post baseline assessment. 74,5% patients were pretreated with steroids. Median starting and daily dose of Revolade^{O} were 50.0 mg/d. Median baseline platelet count was 32,000/µl. After one month of Revolade^{O}, 71.8% of patients had platelet counts > 50,000/µl, after 6 months 81.7 %, and after one year 92.5 %. The median post-baseline platelet counts were continuously >84,000/µl. 37,6 % of patients experienced bleeding events within the last 12 months prior inclusion (29.3% WHO °I, 4.5 % WHO °II, 2.5% WHO °III, 1,3 % missing grade). The bleeding rate per patient and year was 0.68 within the first year of Revolade^{O}. 2.5% of patients experienced complete remission, 14% had completed the study regularly, and 38.9% had discontinued treatment due to insufficient effectiveness (13.4 %), adverse events (11.5 %), and non-compliance (5.1%). 77.7% of patients were reported to have experienced any adverse event (AE). Most frequent AEs were infections (24.2%), gastrointestinal disorders (14%), and fatigue (11,5 %). 9 deaths were reported that all were assessed as Revolade^{O}-unrelated.
Conclusions: The results presented here are in agreement with those of previous trials. Bleeding signs are rare and mostly mild. The vast majority of patients were pretreated with corticosteroids. Second line treatment with Revolade^{O} reduced bleeding signs and led to stable platelet counts. No additional risk factors associated with the use of Revolade^{O} could be identified.

Disclosure: No conflict of interest disclosed.

V96

Patients with abdominal vein thromboses show low allele frequencies of JAK2- and MPL-mutations: results of an ongoing study in Mecklenburg-West Pomerania

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Introduction: Abdominal vein thromboses are discussed as first manifestations of myeloproliferative neoplasms (MPN). In this context the detection of MPN related mutations in early stages is of considerable interest. Targeted next generation sequencing (NGS) / ultradeep sequencing provides a useful tool to comprehensively characterize the existence and frequency of potentially relevant mutations. Especially the existence of low and ultralow cancer associated allele frequencies is of interest as the lately identified clonal hematopoiesis of indeterminate potential (CHIP) appears to represent a pre-manifestation event in patients meeting no further criteria for hematologic neoplasms.
Methods: Herein we screened MPN relevant mutations by targeted NGS within an ongoing study analyzing patients with abdominal vein thromboses in Mecklenburg-West Pomerania (MV). Patients with a recent or past diagnosis of abdominal vein thromboses are enrolled and characterized in their clinical presentation, conventional laboratory parameters, diagnostic and therapeutic approach as well as the location of the thrombus and a possible underlying disease. Targeted sequencing analyzing the complete protein coding regions (CDS) of JAK2-, MPL- und CALR-genes was performed with a coverage of > 2000 reads.
Results: Between 02/2017 and 04/2019 in total 44 patients were included from all over MV. JAK2 V617F mutations were detected in 10/44 cases. In four of these cases allele frequencies ranged below the conventional cut off of 2%. MPL W515R was detected in 3/44 cases in low frequencies with one case showing the co-presence with JAK2 V617F (28,2%). Typical CALR type I and II mutations were not detected. Besides the hot spot mutations 170 further mutations were detected.
Conclusions: Targeted ultradeep sequencing identified in total six patients which would have been considered as molecular negative applying conventional cut off of the respective mutation and one patient showing the mutation MPL W515R additionally to JAK2 V617F. For these patients close hematological as well as molecular monitoring is warranted. Further, our findings support the currently discussed assumption that abdominal vein thromboses may represent early manifestations or even precursors of MPN.

Disclosure: No conflict of interest disclosed.

V97

The new P2Y12 inhibitor cangrelor unreliably inhibits heparin-induced platelet aggregation in the presence of HIT antibodies, an in vitro study

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Introduction: Cardiac surgery in patients with HIT puts the patient at high risk of lethal thrombotic complications if heparin is used during surgery. Two strategies exist to prevent intraoperative platelet aggregation during cardio-pulmonary bypass if anti-PF4/heparin antibodies (HIT-Abs) are present. The first is to use an alternative anticoagulant, the second is to use heparin combined with an antiplatelet agent. The new $P2Y_{12}$ inhibitor cangrelor could be an attractive candidate in this setting and several authors report its successful use. In this in vitro study we evaluated the capacity of cangrelor to inhibit platelet aggregation induced by heparin in the presence of HIT-Abs.

Methods: Platelet poor plasma (PPP) from 30 patients with functional HIT-Abs was mixed with platelet rich plasma (PRP) from healthy donors. Heparin-induced platelet aggregation (HIPA) was measured by light transmission aggregometry (LTA) after adding heparin to achieve a final concentration of 0.5 IU ml^{-1} and compared to samples with normal saline only (negative control) or cangrelor (final concentration 500 ng ml^{-1}) added prior to heparin (treatment).

Results: Heparin 0.5 IU ml^{-1} triggered platelet aggregation in 22 out of 44 PPP-PRP mixtures, with a median aggregation of 85.9 % (IQR 69.2 to 90.9). The median aggregation in the corresponding 22 negative controls was 22.1% (IQR 15.9 - 29.7) ($p< 0.001$). Median aggregation in the treatment samples was 28.5% (IQR 19.5 to 51.9): significantly lower than in HIPA positive samples ($P< 0.001$) but higher than in negative control samples ($p< 0.05$) (Figure 1). The mean percentage of inhibition of HIPA by cangrelor was 73.4 ± 34.0 %. Cangrelor reduced HIPA by more than 95% in only 10/22 samples (45%) . In 5/22 (22 %) the inhibition by cangrelor was less than 50 %, and in 3/22 (14 %) less than 10 %.

Conclusions: In this in vitro study we found that cangrelor unreliably inhibits heparin-induced platelet aggregation in the presence of HIT-Abs. We conclude that cangrelor cannot be used as a standard antiaggregant agent in combination with heparin for cardiac surgery in HIT patients, unless its efficacy has been confirmed in a functional test prior to surgery.

Disclosure: No conflict of interest disclosed.

V98

Integrated safety results from the phase II and phase III studies with Caplacizumab in patients with acquired thrombotic thrombocytopenic purpura

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Introduction: During the development of caplacizumab, safety data have been accrued from Phase I, II, and III studies in healthy subjects, patients undergoing percutaneous coronary intervention, and patients with acquired thrombotic thrombocytopenic purpura (aTTP). Given that caplacizumab blocks the interaction of the von Willebrand Factor A1 domain with the GPIb-IX-V platelet receptor, the main expected safety risk is bleeding.

Methods: The objective of this integrated analysis is to characterize the safety and tolerability of caplacizumab focusing on the pooled data from studies in aTTP. Treatment-emergent adverse events (TEAEs) and clinical laboratory evaluations were evaluated and summarized. Treatment-emergent bleeding was specified as an event of special interest. Data were analysed during the overall study including the follow-up period.

Results: Safety data for caplacizumab have been accrued in 220 aTTP patients. The median duration of exposure to study drug was 35.0 days in the caplacizumab group and 32.5 days in the placebo group. Similar percentages of subjects reported TEAEs in the caplacizumab (96.2%) and placebo (95.5%) group. Events that occurred more frequently (≥5% difference) in the caplacizumab group vs. placebo were epistaxis (29.2% vs. 5.5%; $p< 0.05$), headache (20.8% vs 13.6%) and gingival bleeding (16.0% vs 2.7%; $p< 0.05$). Events that occurred more frequently in the placebo group were TTP (35.5% vs 5.7%; $p< 0.05$), hypokalaemia (20.0% vs 12.3%), and hypertension (12.7% vs 4.7%; $p< 0.05$). Study drug discontinuation due to TEAEs occurred with similar frequencies in both groups and was mainly due to individual events with the exception of TTP. A lower percentage of subjects experienced SAEs in the caplacizumab group. The most frequently reported SAE was TTP in both the caplacizumab (5.7%) and placebo (34.5%) group. A higher percentage of subjects experienced bleeding TEAEs in the caplacizumab group (60.4% vs. 42.7%). Bleeding TEAEs were mainly mucocutaneous, most were selflimited and the majority resolved. Both treatment groups were similar with respect to laboratory values, with very few abnormalities reported as TEAEs.

Conclusions: Bleeding TEAEs (epistaxis and gingival bleeding), were the most common TEAEs in aTTP patients treated with caplacizumab. Results from laboratory tests confirmed the safety profile of caplacizumab. This integrated analysis shows that caplacizumab is well tolerated and has a favourable safety profile.

Disclosure: Paul Knöbl: Advisory Role: Ablynx/Sanofi; Shire/Takeda; Financing of Scientific Research: Berater- und Vortragshonorare von Ablynx/Sanofi, Shire/Takeda, Alexion
Filip Callewaert: Employment or Leadership Position: Ablynx/Sanofi Aventis

Freier Vortrag

T-Zell-Lymphome

V99

The ECHELON-2 trial: Results of a randomised, double-blind, active-controlled phase 3 study of brentuximab vedotin and CHP (A+CHP) vs CHOP in the frontline treatment of patients (pts) with CD30+ peripheral T-cell lymphomas (PTCLs)

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Introduction: Upfront treatment of PTCL, an aggressive form of NHL, with CHOP/CHOP-like regimens does not achieve durable remissions in most PTCL pts. Based on encouraging phase 1 results (Fanale M, et al. Blood 2018), the ECHELON-2 study was initiated to compare efficacy and safety of A+CHP vs CHOP for CD30+ PTCL treatment.
Methods: ECHELON-2 is a randomised, double-blind, active-controlled, international trial in previously-untreated CD30+ (≥10% of neoplastic cells/infiltrate by local review) adult PTCL pts (targeting 75% systemic anaplastic large cell lymphoma [sALCL] pts); ALK+ sALCL pts were required to have an IPI ≥2. The primary endpoint, PFS per blinded independent review, was analysed by intent-to-treat (ITT). Key secondary endpoints were OS, PFS in sALCL, CR rate, and objective response rate (ORR). Pts were stratified by histological subtype and IPI score, and randomised 1:1 to 21day cycles of CHOP or A+CHP for 6-8 cycles. Consolidative SCT/radiotherapy was allowed at investigator´s discretion after end of treatment.
Results: Between Jan 2013 and Nov 2016 452 pts were enrolled. Median age was 58 years (range, 18-85), pts had an ECOG PS of 0 (39%), 1 (39%), or 2 (22%); most had Stage III (27%) or IV disease (53%) at diagnosis; 78% had IPI scores ≥2 (2 [34%], 3 [29%], 4 [12%], 5 [3%]). 70% of pts had sALCL (ALK+, 22%; ALK-, 48%). As of April 2018, 449/452 pts had received ≥1 dose of study therapy; all pts had either completed therapy (82%) or discontinued due to adverse events (AEs) (7%), progressive disease (7%), investigator decision (2%), or pt decision (2%). A+CHP provided significant, clinically-meaningful improvement in efficacy in the ITT population, including OS benefits. All primary and alpha-controlled key secondary endpoints were met. Hazard ratios of PFS (0.71 [95% CI: 0.54-0.93], P=0.01) and OS (0.66 [95% CI: 0.46-0.95], P=0.02) favoured A+CHP over CHOP. ORR was 79% (95% CI: 75.4-83.1); complete response rate was 64% (95% CI: 59.1-68.2). With a median 35.2 month follow-up, 3-year PFS was 52.9% (95% CI: 47.7-57.7) and OS was 73.1% (95% CI: 68.3-77.2) for all pts. AE profiles were consistent with known brentuximab vedotin and CHOP safety profiles, including peripheral sensory neuropathy (43%). Grade ≥3 AEs in ≥10% of pts were neutropenia (33%), febrile neutropenia (17%), and anaemia (12%).
Conclusions: Frontline A+CHP was superior to CHOP for CD30+ PTCL pts, as shown by significant increases in PFS and OS, with a manageable safety profile.

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Steven M. Horwitz: Advisory Role: Seattle Genetics; Aileron Therapeutics; Innate Pharma; Forty Seven; Corvus; Mundipharma; ADC Therapeutics; Trillium; Celgene; Portola; Infinity/Verastem; Kyowa-Hakka-Kirin; Millennium Pharmaceuticals, Inc.; Expert Testimony: Seattle Genetics; Aileron Therapeutics; Forty Seven; ADC Therapeutics; Celgene; Infinity/Verastem; Spectrum; Kyowa-Hakka-Kirin; Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited

V100

PI3K-inhibition increases apoptotic priming in T-cell lymphomas and synergizes with BH3 mimetics

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Introduction: Peripheral T-cell lymphomas (PTCL) are a heterogeneous group of lymphoid malignancies with poor prognosis. Recently, inhibition of the phosphatidylinositol-3 kinase (PI3K) emerged as a promising therapeutic strategy. However, complete responses were achieved in only 20% of the patients and *in vitro*-analyses revealed broad cytostatic effects but limited induction of apoptosis.
Methods: We utilized a comprehensive set of T-cell lymphoma cell lines and assessed the cytotoxic activity of various isoform-specific PI3K inhibitors. Next, we performed dynamic BH3 profiling to functionally dissect the impact of PI3K inhibitors on the regulation of mitochondrial apoptosis. To further address the underlying mechanism, we assessed the protein abundance, phosphorylation status and binding affinities of key-players of the mitochondrial apoptosis pathway. Ultimately, we performed *in-vitro* combination testing of PI3K inhibitors and BH3-mimetics.
Results: PI3K inhibitors induced apoptosis in only a subset of PTCL cell lines. However, BH3 profiling revealed a broad and rapid enhancement of apoptotic priming in all tested cell lines. Furthermore, dynamic BH3-profiling revealed increased susceptibility to blockade of anti-apoptotic proteins, predominantly MCL1. Mechanistically, immunoblotting of pro- and anti-apoptotic BCL2-family members showed an upregulation of various pro-apoptotic proteins. Protein levels of anti-apoptotic BCL2 and BCL-xL were affected heterogeneously with downregulation of either protein in subsets of cell lines. In contrast, protein levels of MCL1 were maintained in most tested cell lines. Co-IP experiments confirmed enhanced availability of the pro-apoptotic BIM protein, but also retained binding to the anti-apoptotic protein MCL1. Based on these data, we performed combination testing of the PI3K inhibitors with BH3 mimetics. Induction of cell death by single agents and combinations was assess by flow cytometry. As predicted by dynamic BH3 profiling, we saw broad synergistic activity of PI3K inhibitors with BH3 mimetics, particularly the MCL1 inhibitor AZD5991.
Conclusions: Despite limited single-agent activity in PTCL, PI3K inhibitors induce a broad increase in apoptotic priming of PTCLs and

their dependence on anti-apoptotic BCL2-family members. While this increase in apoptotic priming does not suffice to induce apoptosis in most cases, it reasons for a combination strategy with BH3 mimetics, particularly MCL1 inhibitors.

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V101

Examining the role of CD30 in anaplastic large cell lymphoma

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Anaplastic large cell lymphomas (ALCLs) represent a heterogeneous group of T-cell non-Hodgkin lymphomas associated with a characteristic chromosomal translocation, t(2;5)(p23;35) which fuses the anaplastic lymphoma kinase (ALK) gene on chromosome 2 with the nucleophosmin (NPM) gene on chromosome 5, leading thereby to expression of the fusion protein NPM-ALK with constitutive tyrosine kinase activity. Immunophenotypic characterization of human ALCLs revealed highly CD30-positive cells of T- or Null-cell-origin. Indeed, CD30 represents an important therapeutic target for the treatment of malignant lymphomas, however its role in the pathogenesis of ALCL remains unclear. In this regard, we established a retroviral murine bone marrow transplantation model resembling human ALCL using an inducible Cre/loxP system. In this model, BM of Lck-Cre-transgenic mice is infected with a MSCV-Stop-NPM-ALK-IRES-EGFP vector leading to the expression of NPM-ALK in early T-cells. With a latency of 4-5 months, mice developed lymphomas and died from neoplastic T-cell-infiltration of BM and lymphatic organs. To investigate the impact of abrogation of CD30 signalling on the development of ALCL ALK+ lymphoma in our model, CD30 knockout mice were crossed with Lck-Cre mice. Both Lck-Cre NPM-ALK CD30 wt and Lck-Cre NPM-ALK CD30 ko recipients develop a human ALCL-like lymphoma with a pure T-cell phenotype characterized by Thy1.2+ cells infiltrating thymus and lymph node. First results from Lck-Cre NPM-ALK CD30 ko transplanted mice showed impaired disease induction and prolonged survival compared to CD30 wt animals. Moreover, secondary transplantation of NPM-ALK thymic lymphomas led to distinct deceleration of disease development upon CD30 deletion. Microarray analyses shed some light on the mechanisms underlying the delayed lymphoma progression of CD30 deleted tumors with an upregulation of inflammatory pathways and proteins being master players in inflammation and immune response. Within this new model, we are currently investigating the role of CD30 on lymphoma initiation and maintenance. Moreover, since T-Cell lymphomas are in many cases associated with dramatic alteration in "healthy" T cell subsets and profound changes in T cell activation and exhaustion states, the project may shed important light in translational strategies to use immunotherapies for patients with T-NHLs.

Disclosure: No conflict of interest disclosed.

V102

The combination of venetoclax and ibrutinib is clinically promising in relapsed/refractory T-prolymphocytic leukemia and impacts dependency on BH3-family member

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Introduction: T-cell prolymphocytic leukemia (T-PLL) is a rare and aggressive T-lymphoid malignancy with poor response to current treatment strategies and adverse prognosis. We recently demonstrated single agent activity of venetoclax in relapsed/refractory (r/r) T-PLL. Here, we report combination partners of venetoclax to overcome single-agent resistance mechanisms in T-PLL.

Methods: We applied next-generation functional testing of primary T-PLL cells of seven patients in a combinatorial screen to identify combination partners for venetoclax from 14 agents. Two late stage r/r-PLL patients were treated with the best scoring combination. Molecular mechanisms of drug combinations were evaluated by BH3-family member profiling and mass spectrometry.

Results: Pairwise combinations screen of venetoclax with candidate small molecule inhibitors on primary T-PLL cells revealed synergistic action of venetoclax with ibrutinib, idelalisib, and 5-azacytidine, whereas cisplatin antagonized the effect of venetoclax across all patient samples tested (Fig 1a). Two patients suffering from r/r T-PLL after failing at least two treatment lines including alemtuzumab were treated with the combination of venetoclax and ibrutinib resulting in significant clinical responses with substantial drops in leukocytosis, LDH and b2MiG as well as substantial clinical improvement (Fig 1b). One patient had to stop treatment due to an infectious complication; the response of the second patient is still ongoing. BH3-profiling in one patient sample showed that venetoclax enhanced overall apoptotic priming. Ibrutinib increased specific bcl-2-protein dependency indicating a synergy mechanism. This effect could be observed at venetoclax serum levels above 1µg/ml.

Conclusion: Our findings show the efficacy of combinatorial treatment of r/r-T-PLL with venetoclax and ibrutinib both *ex vivo* and in patients. Ibrutinib may further enhance the dose dependent apoptotic priming of T-PLL cells by venetoclax by increased bcl-2 dependency. These results provide the basis for an upcoming clinical study testing the efficacy of the combination venetoclax and ibrutinib in a larger cohort of T-PLL patients.

Disclosure: No conflict of interest disclosed.

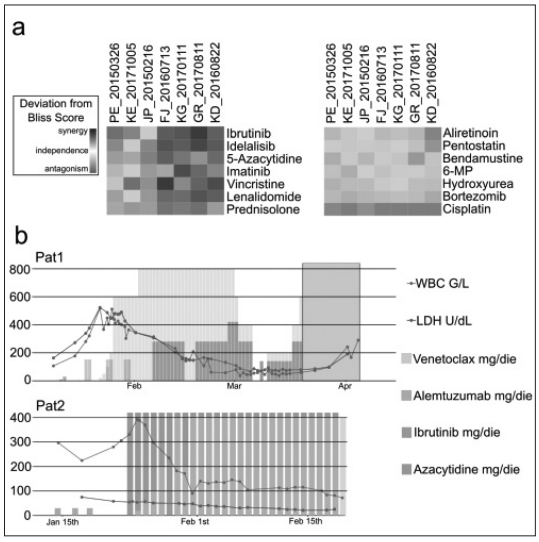

Fig. 1.

V103

Marked peripheral blood plasmacytosis as epiphenomenon of angioimmunoblastic T-cell lymphoma mimicking plasma cell leukemia

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Background: Marked plasmacytosis in peripheral blood with simultaneously increased serum protein raises the suspicion of plasma cell leukemia (PCL). However, the confirmation of the clonal origin of these plasma cells is crucial as there are various diseases associated with polyclonal plasma cell proliferation. We report a very rare case with marked plasmacytosis mimicking PCL as an epiphenomenon prior to the definitive diagnosis of an angioimmunoblastic T-cell lymphoma (AITL).
Results: In April 2019, a 70-year-old female patient was referred to our hospital for evaluation of plasmapheresis because of suspected PCL with signs of hyperviscosity syndrome as she presented with a rapid onset of dyspnea NYHA grade III. Blood values showed a moderate to severe anemia with a hemoglobin of 60 g/l, normal thrombocyte count and leukocytosis of 13.85 G/l due to an elevated plasma cell count of 29%. Additionally, elevated serum protein of 106 g/l with a low albumin fraction of 28 g/l was measured, but normal calcium and creatinine values were present. Strikingly, flow cytometric immunophenotyping of the peripheral blood revealed a polyclonal plasma cell population with a physiological marker profile and a very small clonal CD4+CD3dimPD-1+CD10+ T-lymphocyte population. Further diagnostic workup confirmed the diagnosis of an AITL Ann-Arbor stage IV with reactive plasmacytosis and consecutive hyperglobulinemia (IgG 35.5 g/l, IgA 11.65 g/l, IgM 31.7 g/l). Respiratory symptoms were attributed to the hyperviscosity syndrome and a coexisting respiratory syncytial virus infection. The patient was treated immediately with high dose intravenous corticosteroids, which rapidly led to the disappearance of the plasma cells in the peripheral blood and the decrease of serum protein as well as to clinical improvement.
Conclusions: Marked polyclonal plasmacytosis with consecutive hyperglobulinemia is a very rare first manifestation of AITL. Initial findings can lead to the suspected diagnosis of PCL and special attention should be devoted not to miss an underlying small AITL clone in flowcytometric analysis of peripheral blood samples of these patients.

Disclosure: No conflict of interest disclosed.

V104

Graft versus sezary syndrome effect in a patient with refractory disease treated with non-myeloablative allogeneic hematopoetic stem cell transplantation (HSCT)

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Introduction: Sezary Syndrome (SS) is a rare leukemic variant of primary cutaneous T-cell lymphoma. In advanced stages, cutaneous lesions may present as large symptomatic tumors with risk of secondary complications i.e. chronic septicemia, thrombosis and pain. Relapsed or refractory (rr) disease is generally considered incurable by conventional therapeutic approaches. The potential value of allogeneic HSCT has previously been described in case reports and small series showing effective graft-vs-lymphoma (GvL) effect. However, there is currently no consensus regarding the timing of HSCT or type of conditioning regimen. We present here a male patient (pt) who achieved a complete remission (CR) of primary rr SS after non-myeloablative allogeneic HSCT.
Patient: 2 years prior to HSCT, pt had been refractory to following therapies: cyclosporine, apremilast, CHOEP-based chemotherapy, interferon, extracorporal photophoresis (ECP), bexarotene. 4 months prior to HSCT a combination of ECP and brentuximab-vedotin was applied resulting in a partial remission.
Nevertheless, the patient had persistent disease with peripheral lymph node enlargements, generalized erythrodermic skin manifestations (>90% body surface) and circulating SS cells in the peripheral blood (pb). Flow cytometry of the bone marrow showed an infiltration with T-cells positive for CD5, CD4, low CD3, low CD2 and negative for CD7, CD38, HLA-DR and CD8. The trephine biopsy showed a 7% infiltration of SS cells. The CD4/CD8 ratio in pb was massively increased at 76.67, with 63.5% of white blood cells having the SS immunphenotype.
The conditioning regimen included 30 mg Fludarabine on days -5, -4 and -3 and total body irradiation with 2 Gy on day -1. The patient received $6.55x10^6$ CD34+ cells/kg body weight (bw) and $1.11x10^8$ CD3+ cells/kg bw.
Bone marrow evaluation on day 28 still showed persistent SS cells by flow cytometry. After tapering immunosuppression until day 169, the CD4:CD8 ratio in pb normalized and a CR was documented on day 169 after HSCT. CR is ongoing 312 days after HSCT.
Conclusions: We confirm that allogeneic HSCT can be a curative option for treatment refractory patients with SS. The achievement of CR after tapering of immunosuppressive therapy indicates a significant role for the GvL effect. In present treatment algorithms for patients with SS, the timing of HSCT and the intensity of conditioning should be further explored.

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Freier Vortrag

Translationale Medizin I

V105

UBQLN4 represses homologous recombination and is overexpressed in aggressive tumors

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Introduction: Each human cell is subject to thousands of DNA lesions each day. The integrity of our genome is preserved by an extensive network of DNA repair pathways. The most cytotoxic lesion is the DNA double-strand break (DSB), which is repaired by the balanced action of two main repair pathways: homologous recombination-mediated DSB repair (HRR) and non-homologous end joining (NHEJ). Defects or dysbalances

in DNA repair pathways promote genome instability that are a hallmark of both human genetic disease and cancer.
Methods: The occurrence of DNA repair defects and cancer in humans with genome instability syndromes creates a unique opportunity to identify and investigate novel DNA repair pathways. We functionally uncover uncharacterized human genome instability syndromes by screening and functional characterization of potential DNA repair defects in these patients.
Results: We identified a deleterious *UBQLN4* mutation in families with an autosomal recessive syndrome reminiscent of genome instability disorders, which we termed UBQLN4 deficiency syndrome.Loss of the proteasomal shuttle factor UBQLN4 leads to an increased sensitivity to genotoxic stress and delayed DSB repair. UBQLN4 facilitates the proteasomal turnover of ubiquitylated MRE11 to repress HRR at an early step. Thus, loss of UBQLN4 causes chromatin retention of MRE11, driving non-physiological HRR activity both *in vitro*and *in vivo*. Conversely, UBQLN4 overexpression represses HRR and favors NHEJ. Importantly, we find a correlation between poor overall survival and elevated *UBQLN4* expression in neuroblastoma, melanoma, and ovarian, breast and lung cancer. In line with a HRR defect, UBQLN4 overexpression in cancer is associated with poly (ADP-ribose) polymerase (PARP1) inhibitor sensitivity.
Conclusions: UBQLN4 curtails HRR activity through removal of MRE11 from damaged chromatin and may thus offer a therapeutic window for PARP1 inhibitor treatment in UBQLN4 overexpressing tumors. In a translational approach, we are currently generating conditional *Ubqln4* knockin mice to test the efficacy of PARP1 inhibition in *Ubqln4* overexpressing cancers *in vivo*. Furthering our understanding of DNA repair mechanisms underlying yet undiscovered genome instability syndromes will allow us to examine their crucial roles in cancer.

Disclosure: No conflict of interest disclosed.

V106

MAT2A as key regulator and therapeutic target in *MLL* leukemogenesis

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Introduction: *MLL* rearranged *(MLLr)* leukemias are associated with a poor prognosis due to limited response to chemotherapy regimens. Epigenetic dysregulation plays a pivotal role in *MLL* pathogenesis and its mechanistic understanding paves the avenue for the development of new targeted therapies. SAM is the universal methyl donor in human cells and is synthesized by MAT2A. MAT2A is already known to be deregulated in different cancer types. Recently, PF-9366 a new inhibitor of MAT2A has been developed. Here, we used our human CRISPR/Cas9-*MLLr* leukemia model mimicking faithfully *MLL* patients´ pathology with indefinite growth potential in *in vitro* culture to evaluate the role of MAT2A in *MLL* leukemogenesis and as therapeutic target.
Methods: We used CRISPR/Cas9 to induce *MLL-AF4*/*-AF9* translocations in $CD34^+$ human umbilical cord blood (huCB) cells. Transcriptomic changes were characterized by RNA sequencing (RNAseq). Publicly available patient data were screened for MAT2A expression (*oncomine.org*). Cell lines SKM-1, SEM-1, THP-1 as well as the *MLLr* model were analyzed following inhibitor treatment with PF-9366: proliferation, viability, differentiation, apoptosis, cell cycle and expression of *MLL* target genes.
Results: We performed RNAseq with our *MLLr* model and found MAT2A significantly overexpressed compared to control. We could confirm this high expression by qPCR in our model as well as in *MLLr* cell lines. Next, we reanalyzed publicly available patient data and revealed again significantly elevated MAT2A expression levels in *MLLr* leukemias as compared to other tumor entities, non-*MLLr* leukemias and healthy controls amenable to investigate the impact of MAT2A upon inhibition with PF-9366. By using non-*MLL* and *MLL* cell lines and our model, we detected a dose-dependent reduced proliferation and viability, increased differentiation and apoptosis, impairment of cell cycling and downregulation of *MLL* target genes. Interestingly, *MLLr* cell lines THP-1 and SEM-1 showed an increased response compared to the non-*MLL* cell line SKM-1 confirming its specificity towards *MLLr* leukemias.
Conclusions: Our human CRISPR/Cas9-*MLLr* leukemia model provides an experimental platform to identify molecular targets and to test new therapies. We uncovered MAT2A as a key regulator in *MLL* leukemogenesis and inhibition led to significant anti-leukemic effects. Therefore, our study paves the avenue for clinical application of PF-9366 to improve the treatment of poor prognosis *MLLr* leukemias.

Disclosure: No conflict of interest disclosed.

V107

RIG-I agonists boost the efficacy of anticancer vaccines and synergizes with immune checkpoint blockade

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Introduction: Antibody-mediated targeting of regulatory T cell receptors such as CTLA-4 enhances antitumor immune responses against several cancer entities including malignant melanoma. Yet, therapeutic success in patients remains variable underscoring the need for novel combinatorial approaches.
Methods: Here we established different vaccination strategies that combine engagement of the nucleic acid-sensing pattern recognition receptor RIG-I, antigen and CTLA-4-blockade. We used *in vitro* transcribed 5'-triphosphorylated-RNA (3pRNA) to therapeutically target the RIG-I pathway. We performed *in vitro* functional analysis in bone-marrow derived dendritic cells and investigated RIG-I-enhanced protein and cellular vaccines in different murine melanoma models.
Results: We found that protein vaccination together with RIG-I ligation via 3pRNA strongly synergizes with CTLA-4 blockade to induce expansion and activation of antigen-specific $CD8^+$ T cells that translate into potent antitumor immunity. RIG-I-induced cross-priming of cytotoxic T cells was dependent on the host adapter protein MAVS and type I interferon (IFN) signaling in dendritic cells. Furthermore, we show that activation of tumor cell-intrinsic RIG-I signaling induces immunogenic melanoma cell death that enforces cross-presentation of tumor-associated antigens by bystander dendritic cells and subsequent antitumor T-cell immunity. Using melanoma cells deficient for the transcription factors IRF3 and IRF7, we demonstrate that RIGI-activated tumor cells used as a vaccine are a relevant source of IFN-I during T cell cross-priming *in vivo*.
Conclusions: Overall, our data demonstrate the potency of novel combinatorial vaccination strategies combining RIG-I-driven immunization with CTLA-4-blockade to prevent and treat experimental melanoma. Our findings may facilitate translational development of personalized anticancer vaccines.

Disclosure: No conflict of interest disclosed.

V108

Larotrectinib efficacy and safety in TRK fusion cancer: An expanded clinical dataset showing consistency in an age and tumor agnostic approach

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Introduction: TRK fusion cancer results from gene fusions involving NTRK1, NTRK2 or NTRK3. Larotrectinib, the first selective TRK inhibitor, has demonstrated an overall response rate (ORR) of 75% with a favorable safety profile in the first 55 consecutively enrolled adult and pediatric patients with TRK fusion cancer (Drilon et al.,NEJM2018). Here, we report the clinical activity of larotrectinib in an additional 35 TRK fusion cancer patients and provide updated follow-up of the primary analysis set (PAS) of 55 patients as of 19thFeb 2018.

Methods: Patients with TRK fusion cancer detected by molecular profiling from 3 larotrectinib clinical trials (NCT02122913, NCT02637687, and NCT02576431) were eligible.Larotrectinib was administered until disease progression, withdrawal, or unacceptable toxicity. Disease status was assessed using RECIST version 1.1.

Results: As of Feb 2018, by independent review, 6 PRs in the PAS deepened to CRs. The median duration of response (DoR) and progression-free survival in the PAS had still not been reached, with 12.9 months median follow-up. At 1 year, 69% of responses were ongoing, 58% of patients remained progression-free and 90% of patients were alive. An additional 19 children and 25 adults (age range, 0.1-78 years) with TRK fusion cancer were enrolled after the PAS, and included cancers of the salivary gland, thyroid, lung, colon, melanoma, sarcoma, GIST and congenital mesoblastic nephroma. In 35 evaluable patients, the ORR by investigator assessment was 74% (5 CR, 21 PR, 6 SD, 2 PD, 1 not determined). In these patients, with median follow-up of 5.5 months, median DoR had not yet been reached, and 88% of responses were ongoing at 6 months, consistent with the PAS. Adverse events (AEs) were predominantly grade 1, with dizziness, increased AST/ALT, fatigue, nausea and constipation the most common AEs reported in 10% of patients. No AE of grade 3 or 4 related to larotrectinib occurred in more than 5% of patients.

Conclusions: TRK fusions are detected in a broad range of tumor types. Larotrectinib is an effective age- and tumor-agnostic treatment for TRK fusion cancer with a positive safety profile. Screening patients for NTRK gene fusions in solid- and brain tumors should be actively considered.

Disclosure: No conflict of interest disclosed.

V109

Metabolic regulation of T cell anti-leukemia activity: novel mechanisms and therapeutic targets

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Introduction: T cell dysfunction in B cell leukemia leads to increased susceptibility to infection and impaired anti-tumor immunity. The underlying mechanisms are poorly understood, but metabolism tightly regulates T cell function and may contribute. We hypothesized that T cell glucose metabolism and mitochondrial respiration regulate both spontaneous and therapeutic (chimeric antigen receptor supported) T cell anti-tumor response in B cell leukemia.

Methods: Samples from patients with acute and chronic B cell leukemia were obtained from the Duke University Medical Center and Amsterdam Medical Center. In addition, CD19-CAR T cells prior to infusion in CLL patients (NCT01747486 and NCT01029366) were prepared at the University of Pennsylvania. A mouse model of BCR/Abl-positive B cell leukemia was used for mechanistic studies. T cell activation, function, glucose metabolism, mitochondrial metabolism/biogenesis, and ROS production were assessed in vitro.

Results: B cell leukemia associated T cells expressed PD-1 and TIM3 and were functionally and metabolically impaired with reduced Akt/mTORC1-signaling, decreased expression of the glucose transporter Glut1 and Hexokinase 2 (HK2) and reduced glucose uptake. PD-1 was not sufficient to drive T cell impairment, as in vivo anti-PD-1 therapy on its own only modestly improved T cell function and metabolism. Importantly, impaired T cell metabolism directly contributed to dysfunction, as genetically increased Akt/mTORC1-signaling or expression of Glut1 alleviated murine T cell functional impairments, decreased TIM3 and PD-1 expression, and partially improved anti-leukemia immunity.

Similar findings were obtained in T cells from leukemia patients, which were metabolically exhausted, with defective Akt/mTOR1-signaling, reduced expression of Glut1 and HK2 and decreased glucose metabolism. Interestingly, a possible metabolic compensation resulted in increased mitochondrial respiration in human T cells from leukemic hosts, coinciding with increased ROS production and impaired mitochondrial biogenesis. Importantly, anti-CD19 CAR T cell mitochondrial metabolism prior to infusion predicted response to CAR T cell therapy in leukemia patients.

Conclusions: B cell leukemia induced inhibition of T cell Akt/mTORC1-signaling and glucose metabolism driving exhaustion, inducing mitochondrial changes and impairing T cell activation. T cell metabolic therapeutic interventions might increase immune therapy efficacy.

Disclosure: No conflict of interest disclosed.

V110

Comparison of clinical implications of targeted panel sequencing platforms versus comprehensive sequencing in precision oncology

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Background: Panel sequencing (PS) has become a widely applied diagnostic modality in precision oncology (PO). To allow for the detection of rare and ambiguous genetic alterations not covered by predefined PS, comprehensive sequencing analyses such as whole-exome (WES) and/or RNA sequencing (RNAseq) have emerged. We here report the clinical impact of targeted PS versus comprehensive sequencing assays at the Charité Molecular Tumor Board (MTB).

Methods: Patients (pts) with advanced and/or metastatic cancer with exhausted standard therapy were discussed in the MTB to i) recommend diagnostic tumor profiling and ii) guide biomarker-based therapy (BBT) options. Pts were required to be diagnosed with a rare tumor and/or be < 50 years of age to be eligible for WES/RNAseq, performed on fresh tumor samples. Ineligible patients received standard PS on archival tumor tissue. The MTB made evidence based BBT recommendations, ranked by pre-specified evidence levels and pts were followed up.

Results: Between January 2016 and February 2019, we discussed a total of 228 patients (median age 49 years, 108 female and 120 male) in the MTB. We allocated 73 and 155 pts to PS and WES/RNAseq and results were obtained for 78.1% (n=57/73) and 54.8% (n=85/155) pts, respectively. Sequencing was unsuccessful for 11 (PS; 15.1%) and 62 (WES/RNAseq; 40%) pts, most commonly due to low sample quality (n=29). At the time of analysis, sequencing was ongoing in 5 (PS) and 8 (WES/RNAseq) pts. A median of 2 BBT recommendations were made for 75.4% (43/57) of PS (range r: 1-3) and 90.6% (77/85) of WES/RNAseq pts (r: 1-6) each. 22% (n=17/77) of WES/RNAseq pts had ≥4 BBTs made by the MTB. Treatment as recommended was initiated in 30.2% (n=13/43) of PS and 40.2% (n=31/77) of WES/RNAseq pts. Clinical benefit rates (CBRs) were 23.1% (2 PR, 1 SD) for PS and 45.2% (2 CR, 3 PR, 9 SD) for WES/RNAseq pts. At the time of data-cut off, overall survival data was immature.

Conclusions: Employing WES/RNAseq is a feasible approach to perform tumor profiling in a heterogeneous cohort. We here show a higher rate of pts receiving evidence-based treatment recommendations in the WES/RNAseq group and a higher rate of treatment initiation. In the WES/RNAseq cohort, CBR nearly doubled when compared to standard PS pts, hence emphasizing the need for larger comparative studies to guide diagnostic decision-making.

Disclosure: No conflict of interest disclosed.

Plenarsitzung

Eröffnung

V116

Light microscopy in the 21st century

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Während des gesamten 20. Jahrhunderts war es eine weithin akzeptierte Tatsache: ein Lichtmikroskop, das herkömmliche Linsen verwendet und somit im optischen Fernfeld arbeitet, kann keine feineren räumlichen Details auflösen als ungefähr die halbe Lichtwellenlänge (>200 nm). In den 1990er Jahren jedoch wurde entdeckt, dass eine Überwindung der klassischen Beugungsgrenze in der Tat möglich ist und dass fluoreszente Probenstrukturen mit einer Auflösung nahe der molekularen Skala untersucht werden können.

In diesem Vortrag werden die einfachen und gleichzeitig sehr mächtigen Prinzipien erläutert, die es erlauben, die auflösungsbegrenzende Rolle der Beugung im optischen Fernfeld zu neutralisieren[1,2]. Im Kern geht es darum, Probenmoleküle, die näher beieinander liegen als der durch die Beugungsgrenze diktierte Mindestabstand in unterschiedliche (Quanten-)Zustände zu überführen, damit sie für ein kurzes Zeitintervall zur Detektion unterscheidbar gemacht werden. Im Ergebnis wird die alte Auflösungsgrenze radikal überwunden, und das Innere transparenter Proben wie zum Beispiel Zellen und Gewebe kann nun nichtinvasiv, mit fokussiertem Licht und in 3D, auf der Nanoskala abgebildet werden.

Neben den Grundlagen werden einige der neueren Fortschritte in diesem Forschungsgebiet aufgezeigt. Auch wird kurz die Relevanz der „fernfeldoptischen Nanoskopie" für verschiedene Bereiche, darunter die Lebens- und Materialwissenschaften, an Beispielen verdeutlicht.

Ein erneuter Blick auf die Grundlagen[1] zeigt, wie eine eingehende Betrachtung der grundlegenden Prinzipien der Nanoskopie zu neuen Konzepten wie MINFLUX[3], MINFIELD[4] und DyMIN[5] geführt hat. Obwohl sich diese Ansätze in einigen Aspekten unterscheiden, nutzen sie doch alle ein lokales Intensitätsminimum (eines Doughnut-Profils oder einer stehenden Welle) um die Koordinaten des/der zu erfassenden Fluorophors/-e zu bestimmen. Auf besonders eindrucksvolle Weise hat so jüngst die MINFLUX-Nanoskopie, unter Verwendung eines Intensitätsminimums von Anregungslicht für die Bestimmung der Fluorophor-Position, die ultimative (Hoch-)Auflösung erreicht: die Größe des Moleküls selbst.[3]

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Disclosure: No conflict of interest disclosed.

Fortbildung

Nierentumore: Aktuelle Therapie

V119

Treatment of the frail patient

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Treatment of metastatis renal cell carcinoma (mRCC) has become divers in recent years. Tyrosinse kinase inhibtors (TKI), mTOR inhibitors and Checkpoint inhibitors (CPI) are current representatives of its treatment landscape and may be used in seuquence. While treatment intensification is an intergral component of mRCC therapy, it may not apply to a number of patients because auf frailty or comorbidities. Treatment algorithms remain vague for this patient cohort and good quality evidence is literaly absent. However, therapy individualization is a key approach to select the most approriate therapy for these patients.

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Fortbildung

Multiples Myelom: Kontroversen

V126

Allogeneic stem cell transplantation for multiple myeloma

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Allogeneic hematopoietic stem cell transplantation is an effective and potential curative treatment option in multiple myeloma (MM) but is associated with a high therapy-related morbidity and mortality. While therapy-related mortality has decreased in the more recent years the incidence of relapse is high and has become the major reason for treatment failure. The recently published International Myeloma Working Group (IWGM) guidelines and the CIBMTR/EBMT guidelines suggested allo-SCT to be used in context of clinical trials focusing on the high-risk patients and those who relapsed early after upfront autologous stem cell transplantation. Thus, allo-SCT is now in Europe more frequently used after failure to autograft and accounts for more than 60% of the allotransplants in myeloma. However, in contrast upfront therapy prospective studies investigation allogeneic SCT in Myeloma who failed an autograft are lacking. The German Health authorities (GBA) have launched a prospective randomized trial between allogeneic SCT and conventional triple combination treatment in myeloma patient who relapsed after an autograft. This study will be conducted in Germany by the German Stem Cell Group (DAG-KBT) with more than 20 participating centers. The most frequent cause of treatment failure remains relapse. The high post-transplant relapse rate up to 60% makes the risk stratification of such patients as well as evaluation of proper post-transplant approaches one of the major practical challenges. Smaller phase I or phase II studies investigated immunomodulatory drugs, thalidomide or lenalidomide, post allogeneic stem cell transplantation as maintenance therapy. The observed activation of NK-cell activity induced by IMiDs provides an attractive rationale for its use post-transplant either alone or in combination with donor lymphocyte infusion.Donor lymphocyte infusions (DLI) are considered to be a powerful adoptive immunotherapy after allografting in MM attempting to harness T cell-mediated graft-versus-myeloma (GVM) effect in order to avoid or treat relapse or disease progression. Several reports described the use of DLI for relapsed myeloma but data of DLI to prevent relapse or maintain remission are limited. A recent published study suggest that donor lymphocytes alone or in combination with novel drugs has improved remission status after allografting up to a percentage of molecular remission.

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Fortbildung

ZNS-Tumore

V127

System therapy of glioma: state of the art

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Malignant glioma cannot be cured at this time. However, genetic markers increasingly enable prognostication and allow stratification into specific treatment groups, even if the standard histology is not distinctive.
The most widely used drug in the treatment of gliomas still is the alkylating agent Temozolomide. In addition, other alkylating agents and several experimental drugs are used within clinical trials and on a compassionate use basis. However, none of these novel substances is approved. Besides cytostatic drugs, immunotherapeutic, antiangiogenic and targeted approaches recently raised much interest and will be covered in this presentation. Another therapeutic modality uses tumor treating fields (TTF, Optune).
The development in the use of genetic markers for prognostication and therapy stratification is dynamic.Therapeutic decisions increasingly include genetic markers. The methylation of the promotor of O6-Methyl-Guanin-Methyl-Transferase (MGMT) and the codeletion of chromosome arms 1p and 19q (LOH1p1/19q) have been evaluated as predictive markers in a number of trials. They are routinely used for treatment stratification for specific sub-entities. Considering this, genetic markers are about to get more relevance for decision making in glioma therapy and will hopefully soon more thoroughly inform the treating physician about the best treatment of choice.

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V128

Neurocognitive sequelae & fitness to drive in patients with brain tumours or brain metastases: legal, ethical and medical aspects

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Neurocogntive deficits from brain tumours or their respective therapies may impair the ability to safely operate a motor vehicle. Criteria to determine fitness to drive are not clearly defined for brain tumor patients. Evidence from the literature and expert opinions will be presented as well as suggestions for a practical approach in everyday life.

Disclosure: No conflict of interest disclosed.

V130

Molecular diagnostics of tumours of the central nervous system

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The actual 2016 WHO classification of tumours of the central nervous system represents a milestone in tumour classification since it integrates for the first time histopathological grading with molecular pathology. The introduction of molecular diagnostics lead to rigorous biology-based definition of tumour entities. That particularly applies to the central group of neuroectodermal tumours, the gliomas. The most common and most malignant glioblastoma multiforme and astrocytoma/oligodendroglioma, respectively, are at least two different tumour entities based on their isocitrate dehydrogenase (IDH) mutation status. In addition, other IDH wild-type tumours can now be identified by their molecular alterations, including pilocytic astrocytomas, diffuse midline gliomas and ependymomas. The next tumour group with molecular-based subdivision are the medulloblastomas. Beyond syndromal diseases, other common neurooncological entities including meningiomas and schwannomas lack so far the genetic component of an integrated diagnosis.

A novel update system has been introduced by the International Society of Neuropathology (ISN), that is Not Official WHO (NOW). The Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy(cIMPACT-NOW) has so far published 4 updates to the actual WHO classification that will most likely be included in the next edition of the WHO classification that is expected for 2021.

The introduction of molecular data into the integrated diagnoses has raised the methodological spectrum for the investigation of the tumour probes. Briefly, single locus methods both using immunohistochemical and/or molecular techniques shape the diagnostic basis. But more comprehensive approaches are more and more in use. The two principle approaches include NGS sequencing of gene panels of different sizes and detection of the methylome thereby investigating the epigenome of the tumour tissue.

Disclosure: No conflict of interest disclosed.

Wissenschaftliches Symposium

Versorgungsforschung: Neuerungen auf dem Weg in die Routine

V131

Do organ cancer centers have a demonstrable positive impact on (the quality of) patient care?

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Introduction: Is it possible to answer this question based on the current state of knowledge? Literature research shows that numerous initiatives and activities provide useful scientific information, which can be used to answer this question. The National Cancer Plan has a great impact on the quality of cancer care.

In recent years, several evaluations focusing on quality assurance in oncology certified centers have been published. In addition to this, data from individual studies comparing certified centers and non-certified centers e.g. for breast cancer or colon cancer present a useful data source.

Methods: Literature research 2009 to date

Results: The German Cancer Society and the German Cancer Aid were actively involved in the conceptual design of the National Cancer Plan (since 2003) and the German National Cancer Decade Initiative (2019-2029) of the federal government. With the development of the quality circle, strong instruments were generated to provide nationwide coverage of high-quality oncological care for all cancer patients now and in the future. Evidence-based oncology guidelines for the most common entities covering diagnostics, therapy and after-care deliver consistent quality indicators in cancer care. The documentation of the quality of results is crucial and is becoming a standard also in regional clinical cancer registries in cooperation with the epidemiological cancer registries. By evaluating this data, it is now possible to prove that the quality of patient care has increased through the establishment of a certified organ cancer center. Nevertheless, clinical cancer registries are not yet established nationwide as standard component of oncological care.

Conclusion: A complete oncological quality reporting for each entity, cross-sectors and nationwide is not yet achieved. To answer the initial question, however, there is strong evidence that organ cancer centers provide a demonstrable positive impact on (the quality of) patient care. Significant efforts have been made to bring the established guidance into practice for a variety of entities with measurable success.

The question is why cancer service providers do not aim for certification especially if they meet the requirements?! Also, the question arises why it is still possible to earn reambursement treating cancer patients outside certified centers? And why don't cancer patients preferentially choose nationwide all over accessible certified centers.

Disclosure: No conflict of interest disclosed.

Fortbildung

MDS: Therapie und Diagnostik 2019

V134

Molecular risk profiles in MDS, demarcation to CHIP, ICUS, etc.

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The diagnosis of MDS, based on cytomorphology and histology, accompanied by cytogenetics and FISH is challenging. So far all this information is not only needed for diagnosis (according to WHO 2017) but also for prognostication (IPSS-R). Grading of dysplasia needs a lot of experience and is far away from 100 % reproducibility. Further, toxic conditions, drugs or even alcohol can mimic dysplasia. Thus, the need for molecular investigations in MDS or difficult diagnostic cases is of increasing importance. Guidelines from ELN have been published accordingly and some parts of them are already implemented in WHO Classification. To better define and delineate these respective findings in relation to clear-cut MDS, terms such as ICUS, CHIP and CCUS have been introduced. In the latter three categories dysplasia is not present and blast counts are below 5% percent in the bone marrow and 0% in the peripheral blood. However, cytopenias may occur, or clonality has been demonstrated by cytogenetics or especially molecular genetic findings. In recent years, fostered by NGS methods, several genes have been shown to be present in MDS or related disorders with different incidences. They do not only help to define diagnosis but are helpful markers for prognostication, especially in low risk MDS cases, where blast counts are below 5% percent in the bone marrow and cytogenetics shows normal karyotype. In addition, the finding for e.g. *TP53* mutation in MDS with isolated 5q- is of clinical relevance with respect to choice of treatment.

It is foreseeable that the need increased use of molecular markers (e.g. provided by panel sequencing in NGS) what will not only support the diagnosis of MDS but especially increase the quality of prognostication. It will also lead to more specific treatments (precision medicine). It seems of clinical importance to investigate all patients with MDS, for whom treatment is intended, in addition to cytomorphology and cytogenetics also with molecular genetic markers by gene panels. This information should

be included in all clinical trials, in future scores and classifications and is also helpful for individual decision-making. A lot of data has been published already or is on its way.

Disclosure: Torsten Haferlach: Employment or Leadership Position: MLL Münchner Leukämie Labor

V136

Quality of Life in MDS: Relevance for patients, physicians and stakeholders

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Patient organisations and health authorities propagate the inclusion of HRQOL in daily practice and clinical studies. Recently Haywood et al. (Qual Life Res. 2017) summarized three core values for patient engagement from an international, multiple stakeholder perspective: building relationships, improving research quality and impact, and develop best practice.

Health related quality of life (HRQOL) is multi-dimensional and reflects the physical, mental, emotional, and social wellbeing of an individual, thus provides additional information to the health status assessed in clinical routine. HRQOL scores capture these dimensions in order to allow for a patient-centred treatment approach. Evaluations and standardisation of these scores allow assessing whether a patient has restrictions in certain dimensions.

Why should HRQOL assessment be included in clinical routine? HRQOL assessments allow to more accurately predict outcome for individual patients by capturing restrictions beyond the disease specific health status. Limitations in clinical routine are lack of staff available for this task and time needed to complete the assessments. HRQOL assessment is thus often underused in clinical practice and studies.

Why are patients interested in an active patient engagement? They favor that their perspective and individual restrictions are considered in treatment decisions.

Why are physicians interested in the integration of HRQOL assessments? They need to align health care interventions with patient's individual perception assessed by standardized quality of life questionnaires.

Who are relevant stakeholders and what is their interest? Patients themselves as recipients of health research findings are the most important stakeholders. Other stakeholders include research funders, health authorities, health care industry, payers, insurers, and patient organizations/initiatives. Generally, stakeholders aim at conceptualizing and optimizing patient-centered care and patient-centered research, including clinical trials.

The ultimate aim of guiding health care interventions based on HRQOL assessments is the prevention of over- or undertreatment. For stakeholders, this increases the cost effectiveness by restricting health care interventions to patients who are more likely to benefit from a specific treatment. For patients, this allows for the best possible HRQOL supported by individualized health care interventions, thus allowing for healthier aging and increased wellbeing.

Disclosure: No conflict of interest disclosed.

Fortbildung

Geriatrische Onkologie

V137

Is fitness in elderly patients (pts) with multiple myeloma (MM) possible to be portrayed and objectified?

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Introduction, methods and results: MM has shown unprecedented advances during the past decades, moving from standard chemotherapy, radiation or palliation-induced measures to high-dose concepts, novel agents and immunotherapies. The latter approaches include proteasome inhibitors, immunomodulatory drugs, antibodies and other immunotherapies (bispecific antibodies, CAR-Ts), molecular-, microenvironment- and biology-targeting agents.

As a result, elderly pts live longer, with median survival that is 2-4-fold that of a decade earlier. However, new therapies and especially their combined application have side effects, are less used in comorbid pts, thus progress in these pts is one challenge. Another is, that - if decline of the malignant clone has been achieved with 1.-line treatment - the majority of pts relapse and require additional therapy, but 2. to further-line treatment of unfit/frail is frequently deemed impossible, albeit being required. Moreover, with our vast treatment choices today, objective assessment of biological pt fitness is relevant to avoid under- and overtreatment, quality of life decline and treatment-induced side effects. Undertreatment has been shown to be more frequent than overtreatment in MM, the latter, however, with immediate toxicity. Notably, MM pts present with infinitely heterogeneous health status, and physician judgment, age and ECOG/KPS have proven deceitful, if used alone. Reliable risk tools to obtain a true estimation of pt prognosis are therefore needed.

How ´fit´, ´unfit´ and ´frail´ in MM is defined, what tools help in daily practice, how these can be implemented into tumorboards, in and outside clinical trials (CTs), and whether comorbidity/frailty may change upon response will be discussed in this meeting. The meeting will also illustrate current frailty tools, results obtained therewith, pros and cons of their individual use, inclusion of various functional fitness tests vs. comorbidity/risk scores, and how this may be beneficially included into MM algorithms. Moreover, general considerations in frailty/comorbidity issues, frequently asked questions, when and how treatment may be effected, of retrospective, prospective, validation analyses, of single-, multicenter and CTs, with inclusion of comorbidity scores, and how this may change pt outcome, will be presented.

Conclusions: Important challenges in elderly MM care and ongoing and upcoming CTs worldwide are addressed in this symposium.

The work is supported by the German Cancer Aid (Deutsche Krebshilfe # 11424 to ME+RW), both German DSMM and GMMG study groups and international EMN, IMWG and GIMEMA study groups.

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V139

Relevance of patient-reported outcomes (PROs) in patients with cancer at advanced age

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Patient-reported outcomes (PROs) reflect the opinion, concerns and perception of patients. Based on the definition given by the FDA (U.S. Food and Drug Administration), PROs are described as any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else. Likewise, patient-reported outcome measures (PROMs) represent standardised, validated questionnaires that are completed by patients to measure their perceptions of their own functional status and wellbeing. Thus, assessment and integration of PROs provide unique information that is not captured by classic biomedical parameters or physician-reported data. PROMs frequently used in oncology include scores to assess health-related quality of life and fatigue (e.g. EORTC QLQ-C30, EQ-5D, FACT-G, FACIT-Fatigue scale, SF-36). In general, scores are classified as generic, symptom- or disease-specific. Assessment of PROs by validated scores reveals restrictions in a relevant proportion of patients and reveals differences in perception between cancer patients and treating physicians. Distinct PROMS-parameters represent valid predictors of clinical outcome. Integration of PROs improves monitoring and therapy planning. Moreover, communication between patient, physician and health-care providers is promoted, and empowerment und self-management of patients are increased. Experts, patients and stakeholders regard PROs as an essential endpoint in studies and in daily practice and appreciate their integration. Moreover, regulatory authorities including FDA and EMA (European Medicines Agency) highly recommend and appreciate PROMs as key measures and endpoints in the process of drug development. However, PROMs are so far underused in clinical trials and the implementation and integration of valid and user-friendly PROMs in cancer patients still represents a challenge. Electronic data capturing is becoming more relevant and convenient for patients and facilitates the assessment of longitudinal data. This presentation will give an up-to-date overview on the relevance and integration of PROs in clinical studies an in daily practice with focus on hematological malignancies at advanced age.

Disclosure: No conflict of interest disclosed.

Debatten

Hodentumore: Stellenwert der Strahlentherapie

V144

Stage II seminoma: Polychemotherapy or radiochemotherapy. Pros and Cons.

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Seminoma stage IIA/B can be managed by various approaches including traditional hockey-stick radiotherapy, polychemotherapy or radiochemotherapy. These diverse treatment options yield different results both in terms of cure rates and possible toxicities.
During this session pros and cons of the various approaches will be discussed based on currently available evidence.

Disclosure: Alexandros Papachristofilou: Immaterial Conflict of Interests: Coordinating investigator SAKK 01/10 & SAKK 01/18

V145

Partial tumor remission after chemotherapy: Is a consolidative radiotherapy of brain and bone metastases necessary?

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Residual disease after systemic treatment for metastatic testicular cancer with involvement of the brain and/or the bones may not be amenable to surgery. Radiation therapy has been proposed for these patients with the aim to enhance local control rates and prevent relapse. However a general consensus on its routine use has not been established.
During this session pros and cons of radiation therapy for residual lesions will be outlined.

Disclosure: No conflict of interest disclosed.

Freier Vortrag

Translationale Medizin II

V146

Metabolic reprogramming of serine synthesis confers treatment resistance to B-cell lymphomas in vivo

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Introduction: Treatment resistance is the central barrier to cure in cancer including hematological malignancies. Metabolic tumor reprogramming might simultaneously mark a pivotal contribution and cellular vulnerability to treatment resistance. Thus, identifying, functionally elucidating and effectively targeting these metabolic dependencies might become a novel layer of successful cancer therapy.
Methods: We performed a ^{13}C labeling (glucose/glutamine)-based gas chromatography-assisted mass spectrometry (GC-MS) metabolomic flux analyses using primary mouse Eμ-*myc* transgenic B-cell lymphomas. Western blotting, real-time reverse transcriptase Taqman assays and Affymetrix arrays were used for expression analysis.
Results: In about 25% of the cases, our screen of 20 different primary lymphomas identified a distinct subset exhibiting significantly elevated enrichment of glucose-derived serine/glycine labeling and increased expression of the rate-limiting enzyme of the serine synthesis pathway (SSP), phosphoglycerate dehydrogenase (Phgdh). The lymphomas were, hence, categorized based on their Phgdh expression levels as Phgdh-high and Phgdh-low. Interestingly, the Phgdh-high lymphomas demonstrated markedly reduced sensitivity to Mafosfamide (an *in vitro* Cyclophosphamide analogue) treatment *in vitro* and significantly faster time to relapse (TTR) *in vivo*. The Phgdh-low lymphomas, however, either did not relapse (*i.e.* were cured *in vivo*) or progressed much later. Importantly, restoration of SSP enzymes in Phgdh-low cells, rescued them from Mafosfamide induced cytotoxicity. Interestingly, therapy failure lymphomas (TF), representing three consecutive post-treatment relapses, expressed significantly increased levels of Phgdh and serine-glycine synthesis when compared to their treatment-naïve matched Phgdh-low counterparts. Furthermore, the Phgdh-high and TF-lymphomas were more vulnerable to conventional chemotherapy upon both pharmacological inhibition (CBR-5884) and genetic knockdown of Phgdh. In a cross-species analysis, increased PHGDH lymphoma expression of DLBCL patients significantly correlated with reduced overall survival.

Conclusions: The study unveils a novel role of the SSP in lymphoma resistance mediated by a treatment-acquired metabolic switch - from a Phgdh-low to a Phgdh-high state - as a therapeutic vulnerability exploitable in a metabolically defined subset of DLBCL patients.

Disclosure: No conflict of interest disclosed.

V147

A novel bifunctional antibody format for immunotherapy of pancreatic ductal adenocarcinoma: combining a targeting with a checkpoint blocking domain

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Antibody constructs relying on the recruitment of lymphocytes have achieved remarkable response rates. However, cellular immunotherapy is counteracted by innate and adaptive immune escape. The expression and upregulation of inhibitory checkpoint molecules (ICP) represent a well-known escape mechanism. This might be overcome by the concomitant application of checkpoint blocking antibodies, but is accompanied by severe immune-related adverse events. To address this obstacle, we developed bifunctional local inhibitory checkpoint monoclonal antibodies (licMABs). LicMABs are based on a human IgG1 and simultaneously target a tumor cell-associated surface antigen (TAA) with a high affinity and block an ICP at the immunological synapse with a low affinity. The inhibitory checkpoint molecule CD47 has been reported to be overexpressed in different hematological and solid tumors and provides a "Don't eat me signal" through interaction with SIRPα on phagocytes.

In order to identify potential TAAs and ICPs for licMAB-mediated immunotherapy of pancreatic ductal adenocarcinoma (PDAC), we performed a NanoString® gene expression analysis of 800 immune and cancer-related genes in FFPE biopsy material of PDAC patients (n=36) and healthy controls (n=12). Based on heatmap clustering and a modified version of the immunoscore, we detected an upregulation of key immune cell signaling pathways as well as elevated numbers of immune cell subsets in the tumor tissue of PDAC patients. Interestingly, within the cohort of PDAC patients, CD47 displayed the highest gene expression (PDAC=1536.44 counts vs. healthy=981.26 counts,

**p< 0.0049) among all ICPs. Additionally, due to its strong upregulation and high expression in PDAC patients (PDAC=1533.65 counts vs. healthy=62.59 counts; ***p< 0.00068), we identified mesothelin as a potential target antigen.

On the basis of these data we generated SIRPα-αmesothelin licMABs that specifically bind mesothelin and at the same time block CD47 on PDAC cells.

Preliminary data show that SIRPα-αmesothelin licMABs bind mesothelin^{high} PDAC cells with high affinity. Our data also indicate that SIRPα-αmesothelin licMABs induced enhanced antibody-dependent cellular phagocytosis (ADCP).

In conclusion this novel type of antibody format shows preclinical efficacy and has promising potential to improve the outcome of PDAC patients.

Disclosure: No conflict of interest disclosed.

V148

Implementation of a molecular tumor board in clinical decision making at the medical center University of Freiburg

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Introduction: In-depth knowledge about molecular pathogenesis of malignant diseases and rapidly increasing availability of targeted treatment options enables molecularly guided decision-making. Here, we report the 3.5-year experience of the Comprehensive Cancer Center Freiburg Molecular Tumor Board (MTB). The role of the MTB is to recommend personalized therapy for patients with cancer beyond standard-of-care treatment.

Methods: This retrospective case series includes 595 patients discussed from March 2015 through December 2018. A detailed analysis of adherence to recommendations and outcome was performed in 198 patients discussed from March 2015 through February 2017.

Results: Between March 2015 and December 2018, 1227 case discussions were conducted in 595 patients (2/patient) in 95 MTB meetings. 130 patients (22%) were referred from external cooperation partners. For the entire cohort, 513 treatment recommendations were given to 372 patients (63%; 1.4/patient), including 328 off-label recommendations (64%) and 93 recommendations for trial inclusion (18%). From March 2015 to February 2017, 198 patients were analyzed in more detail: The majority of patients had metastatic solid tumors (73.7%), mostly progressive (77.3%) after a mean of 2.0 lines of standard treatment. Diagnostic recommendations resulted in 867 molecular diagnostic tests for 172 patients (5/case), including exome analysis in 36 patients (18.2%). With a median turnaround time of 28 days, treatment recommendations were given to 104 patients (52.5%). These included single-agent targeted therapies (42.3%), checkpoint inhibitors (37.5%), and combination therapies (18.3%). Treatment recommendations were implemented in 33 of 104 patients (31.7%), of whom 19 (57.6%) showed stable disease or partial response, including 14 patients (7.1%) receiving off-label treatments.

Conclusions: Personalized extended molecular-guided patient care is feasible and effective for a small but clinically meaningful proportion of patients in challenging clinical situations. Molecular tumor boards provide access to individualized treatment strategies to a population of cancer patients with high medical need.

Disclosure: No conflict of interest disclosed.

V149

Therapeutic exploration of p53 mutant-specific sensitivity to oxidative stress in aggressive B-cell lymphoma in vitro and in vivo

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Introduction: Mutation of the *p53* gene is the most common genetic alteration among all human cancers. Aggressive B-cell Non-Hodgkin's Lymphoma (B-NHL) also frequently display p53 mutations, which abrogate p53's tumor suppressive function and may lead to gain-of-function properties that promote aggressive cancer cell properties and chemo resistance. Since p53 plays an important role in the control of cellular metabolism, including glycolysis, mitochondrial oxidative phosphorylation, glutaminolysis, lipid metabolism, and antioxidant defense, we aimed to identify the metabolic vulnerabilities of the six most frequent naturally occurring p53 "hotspot" mutants in lymphomas.
Methods: Each p53 mutant was expressed either in primary MEFs or *Eμ-myc* mouse lymphoma cells which, as previously reported, closely recapitulate human diffuse large B-cell lymphoma (DLBCL), and their impact on the sensitivity to metabolic perturbation was monitored.
Results: While other metabolic inhibitors could not discriminate between cells with different p53 mutation status, ROS-inducer treatment was found to be more effective in cells bearing the three hot spot mutants R245Q, R246S, R270H. Particularly, piperlongumine, a natural oxidative stress inducer, evoked more cell death via ROS accumulation, accompanied by the activation of p38 and JNK signaling. These three mutants inhibited piperlongumine-induced activation of $p21^{CIP1}$ and consequently attenuated the activation and function of NRF2, contributing to the massive cell death in cells harboring them. Similarly, KPT-330, a clinical inhibitor of the nucleo-cytoplasmic exporter Crm1, also caused severe cell death in $p53^{-/-}$ MEFs expressing one of the three piperlongumine-sensitive mutants. This finding implies that Crm1 might also be considered as a potential target for otherwise hard-to-treat DLBCL harboring those mutant p53.
Conclusions: Taken together, data presented in this work demonstrate that exogenous oxidative stressor Crm1 inhibition are effective in eliminating cells harboring $p53^{R248Q}$, $p53^{R249S}$ or $p53^{R273H}$ mutations with low toxicity to cells without them, suggesting oxidative stress pathways or Crm1 as potential targets in lymphomas presenting these particular mutants. Ongoing functional *in vivo*-dissection in mice and patient data analysis, with particular emphasis on the hypothesized link between mutant-specific metabolic control and Crm1 function in this context, will be reported at the conference.

Disclosure: No conflict of interest disclosed.

V150

Molecular and Immunological profile of WRN-mutated colorectal cancer

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Introduction: Werner syndrome gene (WRN) encodes a DNA helicase with an exonuclease activity that contributes to DNA repair. In cancer, WRN mutations lead to genomic instability. It is known that WRN is necessary to sustain in-vivo growth of cancers cells with microsatellite instability (MSI), including CRC. WRN is a very promising new target especially in cancers with MSI. There is still a lack of knowledge about the frequency of WRN alterations and their association with immunological and molecular phenotypes.
Methods: Tumor samples from 6854 CRC patients were analyzed using NGS (NextSEQ on 592 genes), in-situ hybridization and immunohistochemistry (Caris Life Sciences, Phoenix, AZ, USA). Tumor mutational burden (TMB) was calculated based on somatic non-synonymous missense mutations, and MSI was evaluated by NGS of known MSI loci.
Results: WRN mutations (WRN-mut) were observed in 80 of 6854 samples (1.2%). A higher prevalence of WRN-mut was detected in right- compared to left-sided CRC (2.4% vs 0.7%, p< .0001). In WRN-mut (MT) CRC, TMB (43 vs. 8.6 mutations/megabase [mut/MB], p< .0001) and PD-L1 expression (13% vs 4%, p< .0001) were higher compared to WRN wild-type (WT). A higher frequency of MSI-H was seen in cancers harboring WRN-mut (56% vs 7%, p< .0001). Also, WRN-mut was associated with a higher TMB in both MSI-H subgroup of tumors (54 vs 40 mut/MB, p=.03) and MSS subgroup (43 vs 8.6 mut/MB, p< .0001). Several differences between WRN-mut and WRN-WT CRC was observed, including TP53 (47% vs 73%), KRAS (34% vs 49%), APC (56% vs 73%), BRAF (26% vs 9%), ASXL1 (25% vs 4%), ERBB2 (9% vs 2%), BRCA1 (8% vs 1%), BRCA2 (15% vs 2%), CDK12 (10% vs 1%), (p< .01 for all). Copy number alterations (CNA) of CDX2 were seen only in WRN-WT tumors (6.4% vs 1%, p=.026) and CNAs seen more frequently in WRN-mut tumors included CD274, CALR, CRTC1, ELL, JAK3, KEAP1, LYL1, MEF2B (p< .01).
Conclusions: This is the largest profiling study to investigate the molecular and immunological landscape of WRN-mut CRCs. We show the high prevalence of MSI in WRN-mut tumors and their association with higher TMB and PD-L1 expression. Furthermore, it revealed that WRN-mut CRC is characterized by a distinct genetic profile. Our data might serve to tailor treatment in WRN-mut CRC.

Disclosure: No conflict of interest disclosed.

V151

Dual inhibition of histone deacetylses (HDACs) and growth factor receptors in gastric cancer cells

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Epigenetic regulation of oncogene expression has been delineated as a critical factor in gastric cancer. In this context, preclinical studies have defined histone deacetylases (HDAC) as potential therapeutic targets. Thus, the aim of the present study was to identify specific HDAC isoforms that are crucial for proliferation of gastric cancer cells. Furthermore, the effect of HDAC inhibition on expression of HER family receptor tyrosine kinases (RTKs) was analyzed. For this purpose, we determined antiproliferative effects of broad-spectrum and novel isoform-specific HDAC inhibitors in a panel of gastric cancer cell lines in 2D cell culture, as well as in spheroid models, and ex vivo slice cultures of primary patient tumors. Furthermore, we studied the expression of RTKs of the HER family upon treatment with HDAC inhibitors. Finally we evaluated the effect of dual HER and HDAC inhibition. Blocking HDACs in gastric cancer cell lines led to distinct effects on cell survival and apoptosis largely depending on the specific isoform targeted. Of note, a compensatory upregulation of HER receptor family members, predominantly HER1 and HER4, was found after HDAC inhibition. This adaptive oncogene upregulation upon treatment with HDAC inhibitors is per se unwanted but creates the possibility of supra additive combination therapies of HDAC and HER inhibitor. In fact, in cell lines, which were completely resistant against the HER1 inhibitor erlotinib, HDAC inhibition led to an acquired vulnerability against

HER1 inhibition resulting in a profound antitumor effect of dual inhibition. To summarize, inhibition of specific HDAC isoforms in combination with HER family receptors represents a promising therapeutic approach in gastric cancer cells. Untangling the network of affected oncogenic RTKs upon HDAC inhibition, will help to define rational strategies for combined or sequential targeted therapies.

Disclosure: No conflict of interest disclosed.

Freier Vortrag

Pankreaskarzinom

V152

Targeting aberrant SUMOylation in pancreatic adenocarcinoma

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Pancreatic ductal adenocarcinoma (PDAC) still carries a dismal prognosis with an overall five-year survival of less than 5%. Conventional treatment options confer limited long-term survival, representing a high unmet medical need and necessitating new treatment avenues. A growing understanding of the molecular drivers and the underlying disease biology based on next generation sequencing approaches has in recent years allowed to define molecularly characterized subgroups within PDAC with differential survival and distinct histopathologic features.

Patients harbouring genomic MYC amplifications exhibit an especially aggressive tumour biology with extensive resistance to conventional therapies and poor outcome. Targeting the MYC oncoprotein itself has, thus far, proven elusive. However, a growing body of literature has established the molecular dependencies that MYC-hyperactivated tumours develop and become addicted to. Over the recent years, the concept of synthetic lethality has emerged whereby non-oncogenic MYC-associated dependencies are targeted and exploited therapeutically. The aim of our study was to identify and specifically target such MYC-associated dependencies by pharmacologic means.

We analysed human PDAC gene expression datasets. Results were corroborated by the analysis of the SUMO pathway in a large PDAC cohort using IHC. A novel, high affinity SUMO inhibitor (SUMOi), currently in preclinical development, was characterized using human and murine 2D-, organoid-, and in vivo-models of PDAC to evaluate anti-tumour efficacy. SUMOi-mediated effects on apoptosis and cell cycle were assessed using flow cytometry. MYC-mediated sensitivity to pharmacological SUMO inhibition was investigated using genetically modified murine cells line stably expressing the MYC oncogene via retroviral transduction.

We observed transcriptional activation of the SUMO machinery in MYC-driven PDAC. Upregulation of components of the SUMO pathway characterise a PDAC subtype with a dismal prognosis and we provide evidence that hyperactivation of MYC is connected to an increased sensitivity to pharmacological SUMO inhibition.

SUMO inhibition could represent a novel therapeutic means for cancer therapy with broad clinical implication for PDAC patients and potentially other cancer entities. Further exploration of SUMO inhibition as monotherapy and in combination with established anti-cancer therapies is warranted to translate our promising findings into the clinic.

Disclosure: No conflict of interest disclosed.

V153

2nd-line treatment and outcome in patients with locally advanced or metastatic pancreatic cancer - data from the TPK clinical cohort study

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Introduction: Median survival after diagnosis of locally advanced or metastatic pancreatic cancer (mPC) is less than one year. The availability of new drugs - *nab*-paclitaxel (NAB) and liposomal irinotecan (nal-IRI) - has improved outcome in clinical trials. What is the impact of sequential treatment options in daily routine practice?

Methods: TPK is a prospective, multicentre, cohort study of patients (pts) with mPC receiving systemic palliative treatment. Starting in February 2014, 104 study sites in Germany have currently registered >1500 pts at the start of their 1st-line treatment who are followed until death, withdrawal of consent, loss to follow-up or end of the 2-year observation period. A broad set of data regarding pts sociodemographic and tumor characteristics, previous and ongoing systemic treatments as well as outcome data are recorded. Here, data on outcome of pts receiving 2nd-line treatment and changes of sequential treatment since approval of nal-IRI (2016) in routine practice are reported.

Results: Preliminary results from data cut-off June 2018 (1537 pts): at the start of 1st-line treatment median age was 70 years (range 39-94 years), 55% of pts were male. The most frequent 1st-line treatments were NAB in combination with gemcitabine (GEM; 43%), FOLFIRINOX (25%) and GEM monotherapy (21%). Pts characteristics differ markedly between the regimens. Before 2017 FOLFOX/OFF accounted for 27% of all 2nd line treatments which decreased to 6% thereafter. Since 2017 use of nal-IRI increased to 17%. The most frequently used sequences were FOLFIRINOX - NAB+GEM (24%) and NAB+GEM - FOLFOX/OFF (14%) but replaced by NAB+GEM - nal-IRI + 5FU/LV (13%) since the approval of nal-IRI.

43% of the pts had already reached 2nd line therapy, while 41% had died prior to receiving a 2nd-line (7% were lost to follow-up before start of 2nd-line, 9% had not yet started 2nd-line). Median overall survival (OS) was 12.7 months (95%-CI 11.8-13.6) for pts receiving a 2nd-line, while OS was 9.0 months (95%-CI 8.4-9.5) from start of 1st-line for all pts.

Results of a pre-planned data update in July 2019 will be presented (mature data of appr. 1590 pts are expected).

Conclusion: Real world data from the TPK cohort study show that newly approved treatments are quickly integrated into routine care. Merely about half of the pts are able to receive 2nd-line treatment. Those patients benefit from improved outcome, although prognosis remains poor.

Disclosure: Susanna Hegewisch-Becker: No conflict of interest disclosed. Norbert Marschner: Employment or Leadership Position: iOMEDICO; Stock Ownership: iOMEDICO; Financing of Scientific Research: Celgene; Expert Testimony: Celgene, Shire/Servier.

V154

Prolonged overall survival of pancreatic cancer patients with BRCAness germline mutations treated with DNA-damaging agents

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Pancreatic cancer is the fourth leading cause of cancer-related death in adults, with a poor 5-year survival of less than 5% in patients with metastatic disease. Newer chemotherapy regimens such as FOLFIRINOX and nab-paclitaxel/gemcitabine have demonstrated moderate improvement in survival benefit, with the sequence FOLFIRINOX followed by nab-Paclitaxel/Gemcitabine or vice versa leading to an equal outcome. However, patients with deleterious mutations in DNA damage repair genes seem to benefit particularly from platinum-based chemotherapy, prompting the question if genetic tumor testing should be performed routinely in patients with pancreatic cancer to guide therapy.
Next generation sequencing (NGS) with a panel covering 710 cancer-related genes was performed in so far 18 patients with metastasized pancreatic adenocarcinoma progressing after first-line treatment. 33% (6/18) carried pathogenic/likely pathogenic germline or somatic variants in genes encoding DNA damage repair (DDR) proteins. All patients with germline DDR gene variants (2x BRCA1, 2x NBN, 1x ATM) had received either FOLFIRINOX (4/5) or cisplatin/etoposid (1/5) as first-line treatment, while non-carriers had either FOLFIRINOX (8/12) or nab-Paclitaxel/Gemcitabine (4/12). Compared with non-carriers, patients with germline or somatic DDR gene variants had superior overall survival (OAS) with a 1-year survival of 100% versus 50%, and a 2-year survival of 82% versus 30%, respectively. Mean age at diagnosis was 65 years in non-carriers, and 58 years in germline mutation carriers; however, of the latter only a few had a striking family history regarding cancer predisposition.
Germline mutations in DNA damage repair genes can be found in a considerable fraction of patients with pancreatic cancer. Identifying this clinically meaningful subgroup by genetic testing is important since these patients seem to experience increased susceptibility to DNA-damaging agents such as platinum chemotherapy prolonging survival substantially. If this effect is also valid for patients with somatic mutations in DNA damage repair genes needs to be further investigated in a larger cohort.

Disclosure: No conflict of interest disclosed.

V155

Investigation on the significance of p-MLKL mediated necroptosis in the oncogenesis of the ductal pancreatic adenocarcinoma

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Introduction: Recent studies showed that necroptosis, an apoptosis-independent form of regulated cell death, can also impact on tumor growth and inflammation in various tissues.
This process is mediated by activation of the receptor-interacting protein kinase 3 (RIPK3) and the following phosphorylation of the mixed lineage kinase domain-like protein (MLKL) leading to a rupture of the plasma membrane.
Methods: Immunohistochemical(IHC)staining of phosphorylated (p-) MLKL was conducted on a collective of 105 paraffin tissues comprising ductal pancreatic adenocarcinoma (PDAC), chronic pancreatitis, peritumoral and healthy pancreatic tissues. The prevalence of (p-)MLKL in acini, stroma and ductal epithelium was analysed and correlated with parameters of inflammation examined in prior studies.
In vitro, supernatants were generated from the two PDAC cell lines BxPC3 and PancTu1 either left untreated or in which necroptosis was induced via TRAIL (tumor necrosis factor-related apoptosis-inducing ligand) in combination with zVAD/HHT. Afterwards, murine pancreatic myofibroblasts (PMFs) were cultured in these supernatants for 24 hours to analyse the acquisition of an inflammatory phenotype.
Results: IHC staining revealed a higher prevalence of p-MLKL in PDAC compared to other analysed tissues. Furthermore, a higher prevalence of p-MLKL in the ductal epithelium and stroma in PDAC correlated with a higher abundance of gamma-delta-T cells, CD3+, CD4+ and CD8+ T cells as well as alpha-SMA (indicative of PMFs) and was associated with longer patient`s survival and lower tumor grading.
In vitro PMFs, cultured in the supernatants of necroptotic PDAC cell lines, showed an elevated expression of VEGF-A, interleukin 6, TGF-b1 and FGF2, compared to culture in supernatants from untreated PDAC cells indicating the acquisition of inflammatory properties.
Conclusions: The in situ findings suggest that epithelial cells in PDAC tissues are more necroptotic compared to healthy pancreatic tissues which is associated with a higher inflammatory tissue reaction and a longer survival of the patients.
The *in vitro* results indicate that released factors from necroptotic PDAC cells promote an inflammatory phenotype in PMFs.
Future studies have to elucidate whether induction of necroptosis in pancreatic ductal epithelial cells promotes infiltration of immune cells promoting pancreatic inflammation or if enhanced inflammation in the pancreas leads to induction of epithelial cell necroptosis.

Disclosure: No conflict of interest disclosed.

V156

Gemcitabine versus mitomycin versus gemcitabine/mitomycin in the treatment of locally advanced and metastatic pancreatic cancer - a randomized multicenter phase II trial

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Background: There is no data available on the safety and efficacy of a combination chemotherapy regimen with gemcitabine and mitomycin as compared with gemcitabine alone in patients with locally advanced or metastatic pancreatic cancer. This is of particular interest for those patients not qualifying for intensified protocols such as FOLFIRINOX or gemcitabine/nab-paclitaxel.
Methods: A total of 130 patients with locally advanced or metastatic histologically confirmed pancreatic adenocarcinoma with an ECOG performance score of 0 to 1 were randomized to either receive gemcitabine at a dose of 1000mg per square meter day 1, 8 and 15 q4w, mitomycin at a dose of 10mg per square meter q4w or a combination of gemcitabine at a dose of 800mg per square meter day 1, 8 and 15 q4w with mitomycin at a dose of 6mg per square meter at day 1 q4w as first-line treatment. A safety and efficacy monitoring were performed after the enrolment of 23 patients into the mitomycin treatment arm, CT scans were performed every 2 cycles (8 weeks). Treatment for 6 cycles was recommended for patients responding to chemotherapy. Primary endpoint was progression free survival, secondary endpoints were overall survival, response, toxicity and clinical benefit.
Results: Progression free survival was 4.6 months in the Gemcitabine / Mitomycin arm and 3.7 months in the Gemcitabine arm, HR 0.90, 95% confidence interval [CI] 0.57 - 1.42; p=0.11. Overall survival was 8.0 months in the Gemcitabine / Mitomycin arm and 6.5 months in the Gemcitabine arm, HR 0.98, 95% confidence interval [CI] 0.59 - 1.61. The

objective response rate was 17.9% in the combination group and 20.5% in the Gemcitabine group. Adverse events were similar in both groups (any AE in the Gemcitabine arm 80.0%, any AE in the combination arm 78.3%), where as grade III/IV AE according to the CTC category were more frequent in the combination arm (50.0% versus 28.9%).
Conclusions: Gemcitabine treatment was not inferior to treatment with Mitomycin alone. The combination treatment with Gemcitabine and Mitomycin did not significantly improve progression free survival or overall survival. Overall AE were similar with nearly twice as many grade III/IV AE. Based on our findings, a combination treatment of Gemcitabine / Mitomycin for those patients not qualifying for otherwise intensified protocols such as FOLFIRINOX or Gem / nab-Paclitaxel cannot be recommended.

Disclosure: Andreas Block: Expert Testimony: ja
Carsten Bokemeyer: Advisory Role: ja; Expert Testimony: ja

Freier Vortrag

Supportive Therapie

V157

Malnutrition in cancer patients: standardized screening and intervention

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Introduction: Malnutrition is a common problem in cancer patients and is associated with an increased risk of complications of the underlying disease and decreased quality of life. However, malnutrition is still unrecognized in most cancer patients and refunding in a clinical setting is unclear, which may limit implementation.
Methods: In order to identify malnourished tumor patients as early as possible, in 2015 a prospective project was initiated to implement a standardized malnutrition screening program at the Department of Hematology and Medical Oncology, University Medical Center Goettingen. For an observation time of 6 months, with respect to the availability of the nutritionist, 210 of 425 inpatients (49.4%) were screened using the Nutritional Risk Screening NRS-2002. In total, these 210 patients were included and analyzed for malnutrition, nutritional assessment and intervention to compute the impact of coding malnutrition and/or intervention on revenues depending on Diagnosis Related Groups (DRG).
Results: 35.7% of the screened patients were identified as malnourished and treated appropriately. Determination of malnutrition and/or intervention led to an increase of revenues of 3.1%. Taking account of the costs of additional intervention (e.g. enteral or parenteral nutrition) there was still an increase of 2.5% in returns. In the setting of our clinic this amount is able to cover the additive costs of a nutritionist needed for our patients and enables implementation of screening and intervention.
Conclusions: Our data show, that a standardized screening program for malnutrition in tumor patients helps to identify malnourished patients and is able to generate additional funding to implement nutritional assessment and intervention. So, there might be a benefit in terms of optimizing medical care and also in terms of funding human resources serving our patients.

Disclosure: No conflict of interest disclosed.

V158

Analysis of real-world prescribing patterns for the management of chemotherapy-induced nausea and vomiting and antiemetic guideline adherence

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Background: Guideline-recommended antiemetic treatment can prevent vomiting in most patients (pts) receiving highly emetogenic chemotherapy (CT) (HEC). However, guidelines are often not followed leading to suboptimal CINV control. MASCC/ ESMO guidelines recommend prophylaxis with a neurokinin-1 receptor antagonist (NK_1RA), a 5-hydroxytriptamine-3 (5-HT_3) RA, and dexamethasone (DEX) for pts receiving HEC (including anthracycline-cyclophosphamide [AC]) and carboplatin-based regimens. Here, we have analyzed the use of the NK_1RA+5-HT_3RA+DEX triplet for antiemetic prophylaxis prior to HEC and moderately EC (MEC).
Methods: The data source was the Global Oncology Monitor (Ipsos Healthcare). Data were collected from patients' charts from Jan-Dec 2018. Physicians continuously report back patient record diaries based directly on medical records, collecting information such as patient demographics, diagnosis, stage, full previous and current treatment history, and supportive care. Sample bases are projected up using a proprietary projection methodology in which each patient has their own unique weight based on type of cancer, type of treatment, etc. Projected universe numbers are validated against secondary sources such as SEER, Globocan, Cancer Research UK.
The projected estimates for the prevalence of total treated pts in Germany are presented. The emetic risk of CT was classified based MASCC/ESMO guidelines.
Results: Antiemetic treatment patterns are summarized (Table). A sample of 9,135 pts treated with CT, representing a total prevalence of 353,190 pts was analysed. NK_1RAs were used in 61 %/ 69 %/ 47 % of pts receiving cisplatin-/ AC-/ carboplatin-based CT; 33 %/ 58 %/ 29 %, respectively received the guideline-recommended NK_1RA + 5-HT_3RA + DEX combination. Often, physicians' perception of the emetic risk of CT did not follow MASCC/ESMO/S3 guideline classification.
Conclusions: Analysis of clinical practice patterns revealed low adherence to antiemetic guidelines, with only 36 % of all pts (HEC/ AC/ carboplatin) receiving the recommended NK_1RA + 5-HT_3RA + DEX and more than half of the pts receiving no NK_1RA at al. New strategies to improve guideline adherence are critically needed.

Disclosure: No conflict of interest disclosed.

V159

What to do when no blood for transfusion is available? Emerging challenges in transfusion practice evoked by patients of African origin having "exotic" antibodies. Clinical cases and instruction for the practical approach

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We describe herein a patient of African origin for whom a pre-transfusion testing was performed in a practitioner setting. Crossmatch and screening for irregular antibodies was positive. After extensive diagnostic testing, an anti-U antibody was found. This antibody specificity is incompatible with all donors of European (Caucasian) origin. To provide blood supply for her, international networks had to be used and finally two (frozen) erythrocyte concentrates could be found in Paris.

Such situation is expected to occur more frequently in the future, since more patients of African origin would take part of our health system. Apart from anti-U and other rare specificities, Duffy (3) antibodies account for similar problems. This problem is aggravated by the high prevalence of haemoglobinopathy in those patients, who need blood transfusions and are accompanied by an extended prevalence of immunization against blood group antigens.
To cope with such situations, a experienced and highly specialized immunohematologic laboratory is of paramount importance. After the antibody is correctly identified, the search for compatible blood has to start.
At this point, a blood supplier with international network is needed since a search in Germany has actually a very limited success rate. This is inter alia due to the fact that African donors are excluded from our donation programs for stay in malaria regions and lack of fixed residence.
If blood donors or frozen erythrozyte concentrates, respectively have been found wherever, logistics and costs (in the range of several 1000€ for one transfusion) have to be considered as well.
Of principal relevance is the awareness of the treating physician, who should consult an experienced transfusion specialist as early as possible, when confronted with such patients as mentioned above.

Disclosure: No conflict of interest disclosed.

V160

Prophylaxis of chemotherapy-induced neutropenia (CIN) with filgrastim biosimilar Ratiograstim® - results from the prospective non-interventional study (NIS) "RatioNeu"

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Introduction: Neutropenia, associated with cytotoxic chemotherapy (CTx) in cancer patients (pts), increases the risk of infection, can be life-threatening, in particular in the manifestation of febrile neutropenia (FN), and is a frequent cause for dose reductions or delays in CTx. Filgrastim is a recombinant granulocyte colony-stimulating factor that is used to reduce duration of neutropenia and prevent FN.
Methods: Here we report the results of the German prospective, multicentre NIS "RatioNeu", in which the use, effectiveness and safety of the filgrastim biosimilar Ratiograstim® (Teva) was evaluated in a large cohort of adult cancer pts (2,410 pts in the safety sample, 2,277 pts with complete documentation in the analysis sample) under real-life conditions. Average age was 60.7 years (41.9% ≥ 65 years). The study was conducted in 230 centres in Germany, mostly oncologist practices. The primary endpoints were the rate and duration of FN and of CIN of grades 3/4.
Results: In total, 13,655 CTx cycles were documented, 8,095 of these with filgrastim support. Filgrastim application most often started on day 5 of the cycle. In 46.7% of cycles, filgrastim was applied ≤ 3 times. FN occurred in 1.5% of cycles and 4.0% of pts with filgrastim support (118 events in 91 pts, average duration 4.1 days). CIN3/4 was observed in 24.1% of cycles and more often when filgrastim was applied ≤ 3 times per cycle. 70 pts (3.1%) were hospitalised at least once due to FN or infection. Explorative analysis identified an age ≥ 65 years, low performance status and previous FN episodes as risk factors for FN development in the first cycle. High FN risk was the most significant risk factor for CIN3/4 in cycle 1. In 158 pts (6.6%), at least one adverse drug reaction (ADR) was recorded, mostly mild or moderate (CTCAE grade 1/2, 263 in total). 12 pts (0.5%) suffered from at least one severe ADR (grade 3: 30 events; grade 4: 3 events), one died of multi-organ failure (considered unrelated to filgrastim application).
Conclusions: To our knowledge, this study comprises the largest patient cohort of all filgrastim observational studies conducted so far (2,277 cancer pts undergoing CTx and 8,095 filgrastim-supported cycles). Overall, the results confirm efficacy and safety of the filgrastim biosimilar Ratiograstim® in daily clinical practise, in line with results obtained during clinical development. Filgrastim is readily given to cancer pts, but not always long enough to counteract CIN3/4.

Disclosure: Peter Jungberg: Expert Testimony: NIS RatioNeu was sponsored by Teva/ratiopharm GmbH
Jan Schröder: Expert Testimony: NIS RatioNeu was sponsored by Teva/ratiopharm GmbH.

V161

Patient reported outcomes for a fixed combination of netupitant/palonosetron (NEPA) for prevention of nausea and vomiting in patients receiving high-risk platinum chemotherapy - real life data

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Background: NEPA is the first and only fixed oral combination of a long-acting NK_1 receptor antagonist (RA), netupitant, and a pharmacologically and clinically distinct 5-HT_3RA, palonosetron. NEPA is approved for prevention of chemotherapy (ctx)-induced nausea and vomiting (CINV) in patients (pts) receiving cisplatin-based highly emetogenic ctx (HEC) or moderately emetogenic ctx (MEC). Patient-reported outcomes (PROs) during the real-world use of NEPA for the prevention of CINV were collected ina non-interventional study.Here we report interim data of the subgroup of patients receiving highly emetogenic cisplatin-based ctx.
Methods: The ongoing prospective AkyPRO study was designed to evaluate quality of life (QoL) in 2500 pts receiving NEPA for CINV prevention in single or two day MEC or HEC over 3 cycles. The primary endpoint QoL was recorded by FLIE questionnaires. Secondary endpoints were efficacy, reported by patients and physicians on a 4-point scale (very good, good, satisfactory, poor); rescue medication; and safety.
Results: At the interim cut-off date 30thNov 2017, 1997 pts had been included of which 130 received cisplatin-based HEC. This subgroup of patients included mainly pts with lung, cervical, and head-neck cancer. More than 86% of pts reported no impact on daily life due to vomiting in all analysed cycles. The percentage of pts with no impact on daily life due to nausea ranged from 60-69%. The majority of cisplatin-receiving pts (84 - 87%) reported complete control and no significant nausea (70 - 84%) in the three analysed cycles. Nearly none of the pts experienced emesis and only few had to take antiemetic rescue medication (8-13%). Effectiveness, evaluated by physicians' assessment, was rated very good/good for 86 -89% of the pts in cycle 1, 2, and 3. Comparison of patients' and physicians' perception of antiemetic treatment effectiveness showed that patients judged the effectiveness equally well. The most common treatment emergent adverse events were constipation and insomnia of mild-moderate intensity.
Conclusions: NEPA was proven highly effective in controlling both vomiting and nausea over three cycles of cisplatin-based HEC, a population at high risk for CINV. Together with its convenient administration attributes of one single dose per ctx cycle, NEPA might facilitate adherence to antiemetic guidelines and ultimately may improve CINV control.

Disclosure: Meinolf Karthaus: Advisory Role: Riemser, HELSINN; Financing of Scientific Research: Riemser, HELSINN
Joerg Schilling: Advisory Role: Riemser, HELSINN; Financing of Scientific Research: Riemser, HELSINN

V162

Mind the gap - a systematic review on medical plants used by traditional European medicine (TEM)

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Background: TEM comprises a huge variety of medical plants covering a broad spectrum of symptoms. TEM are counted among complementary and alternative medicine (CAM). It is well known that cancer patients use CAM e.g. for ameliorating oral side effects of cancer therapy.
Methods: A systematic literature research was performed on PubMed using the MESH terms [mucositis] and [herbal medicine]. Articles were screened for studies using medical plants (historically) known to TEM. As secondary end-point we assessed which medical system (e.g. TEM, Traditional Persian Medicine - TPM) initiated the clinical trial. A 2nd literature research was performed using 14 books about medical plants and herbal remedies to assess which plants were reported for treating mucositis/gingivitis or pharyngitis. If a plant was reported to alleviate oral symptoms, we recorded it as known herbal remedy. A resulting 'hit list' of medical plants was generated by recording every report per plant and book screened.
Results: The systematic literature research on PubMed yielded 33 clinical trials. 17 TEM plants were mentioned 41 times within these studies. Nearly 2/3 of all studies conducted were categorized as TPM or Traditional Japanese Medicine. Only 6.06% of studies were initiated by European study groups. Among all, Matricaria recutita/chamomilla and ginger were the most investigated medical plants. The 2nd literature research (books on TEM) yielded a total of 79 plants known to TEM. A total of 18 plants was mentioned ≥6 times and was thus included to our 'hit list' of medical plants: Arnica montana, Rubus sect. rubus, Potentilla erecta, Althaea officinalis, Quercus robur, Potentilla anserina, Vaccinium myrtillius, Tussilago farfara, Cetraria islandica, Matricaria recutita, Malva sylvestris et Malva neglecta, Agrimonia eupatoria, Calendula officinalis, Salvia officinalis et sclera, Prunus spinosus, Plantago lanceolata, Thymus vulgaris and Polygonum aviculare. When comparing the results of our two systematic literature researches we have only seen clinical trials for 12 plants out of the 79 reported remedies by TEM herbal books.
Conclusions: Despite a huge variety of medical plants for treating oral mucositis being known to TEM, only 15.2% of these were investigated by a clinical trial.

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Jens Büntzel: Advisory Role: Advisory Board Nivolumab (Bristol Myer Squibb), Advisory Board Amifostin (Clinigen); Financing of Scientific Research: Vortragshonorare Cetuximab; Immaterial Conflict of Interests: Beirat der Arbeitsgruppe PRIO

Freier Vortrag

Mammakarzinom

V163

Time for treatment and perceived constraints thereby in patients with advanced breast cancer - data from the TMK/MaLife project

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Introduction: How often do patients (pts) with advanced breast cancer (ABC) visit physicians? How much does treatment time interfere with daily and social life? The patient-reported outcome project MaLife collects data on various questions including treatment time and perceived constraints.
Methods: MaLife is conducted with the Tumor Registry Breast Cancer (TMK), a prospective cohort study of pts recruited at start of palliative 1st-line systemic therapy from >100 sites in Germany. Besides documentation of clinical data, pts receive a set of questionnaires. The questionnaire on treatment time was especially developed for MaLife and pts are asked every 3 months about the previous 3 months. Here, data on 781 pts with ABC and with ≥1 filled-in questionnaire are presented. Treatment times resulting constraints and influencing factors were analysed.
Results: Median age was 63 years, with 68% of pts having comorbidities. 1st-line treatment was 64% (n=500) chemotherapy (CT) and 36% (n=281) endocrine therapy (ET). CT was 96% intravenous and mostly 3-weekly application. Questionnaires were sent back at start of therapy (T0): 72%, 3 months (T1): 79%, 6 months (T2): 67%.
At T0, 51% of pts reported >10 medical visits in the last 3 months (median: 12 visits, including oncologist, general practitioner, home visits, etc.). Besides the oncologist, about 77% visited their general practitioner. At T1, median was 14 visits, at T2 median was 10 visits. The only influencing factor to predict frequencies of visits at T1 was the number of visits before diagnosis of ABC. The percentage of pts treated in hospital decreased over time (T0: 80%, T1: 44%, T2: 32%).
At T0, 36% of pts reported to feel no/little burden by time spent for treatment, while 35% felt constrained quite a bit/a lot. Results were similar for treatment time interfering with daily life (31% no/little, 36% quite/a lot) and social life (40% no/little, 31% quite/a lot). At T1, the percentage of pts with quite a bit/a lot constraints decreased slightly (5-7%). A multivariate logistic regression revealed that constraints by treatment time at T1 increased for younger pts, more medical visits at T1 and CT instead of ET.
Conclusions: Pts with ABC spend a lot of time with medical visits due their disease. Feeling constrained by this treatment time varies a lot between pts and increases for younger pts, more medical visits and chemotherapy. Treatment time should be considered as a patient-relevant factors upon decision making.

Disclosure: Sandra Linke: No conflict of interest disclosed.
Norbert Marschner: Employment or Leadership Position: iOMEDICO; Advisory Role: Roche, Mundipharma, Lilly; Stock Ownership: iOMEDICO; Expert Testimony: Oncovis, Roche, Pfizer, Mundipharma, Lilly

V164

First data on overall survival of metastatic breast cancer patients in Austria according to breast cancer subtype: results from the AGMT MBC Registry

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Background: In recent years, major progress has been made in the treatment of metastatic breast cancer (MBC), especially for hormone receptor (HR) positive and HER2 positive MBC. In contrast, for most triple-negative breast cancer (TNBC) patients no targeted treatment options are available. This fact and known differences in tumor biology suggest substantial differences in prognosis between different breast cancer subtypes. Population-based data on overall survival (OS) of MBC are scarce and were totally missing for the Austrian population. Here, we present the overall survival (OS) results according to breast cancer subtype of patients included the MBC registry of the Austrian Study Group for Medical Tumor Therapy (AGMT).

Patients and methods: The AGMT MBC Registry is an ongoing multicenter registry for MBC patients in Austria. Unadjusted, univariate survival probabilities of OS were calculated by the Kaplan-Meier method. Multivariate hazard ratios were estimated by Cox regression models. Patients with available HR, HER2 and Ki-67 status and sufficient outcome data were included in this analysis.

Results: As of 31/01/2019, 1,253 patients were enrolled into the AGMT MBC Registry. Overall median OS of was 32.9 months (95% CI 29.7-35.7; n=1,219). According to breast cancer subtype, median OS was 40.6 months (95% CI 34.9-44.3) for luminal A like (HR+/HER2-,G1-2 and Ki-67 ≤ 20%; n=390), 35.5 months (95% CI 32.3-40.2) for luminal B like (HR+/HER2-,G3 or Ki-67 > 20%; n=297), 49.6 months (95% CI 40.4-58.5) for luminal HER2+ (HR+/HER2+; n=157), 26.4 months (95%CI 22.6-35.8) for HR-/HER2+ (n=102) and 15.2 months (95%CI 11.8-18.5) for triple-negative tumors (n=203), respectively. Five year survival estimates were 28.6% (95%CI 25.6-31.8) in the overall cohort, 32.2% (95%CI 26.7-37.8) for luminal A like, 28.4% (95%CI 21.9-35.2) for luminal B like, 37.0% (95%CI 27.3-46.7) for luminal HER2+, 27.6% (95%CI 18.0-37.9) for HR-/HER2+ and 10.1% (95%CI 6.1-15.3) for triple-negative tumors, respectively. In multivariate analysis a disease free survival ≥ 24 months or *de novo* MBC, age at diagnosis of MBC < 60 years, metastatic spread at diagnosis to only one site, non-visceral disease at diagnosis, and non-TNBC were significantly associated with a longer survival.

Conclusions: Best prognosis was associated with luminal HER2+ and luminal A like tumors reflecting the availability of novel treatment options for these tumors in recent years. TNBC was associated with the worst prognosis.

Disclosure: Gabriel Rinnerthaler: Advisory Role: Roche, Pfizer; Financing of Scientific Research: Roche, Pfizer; Expert Testimony: Roche; Other Financial Relationships: Roche, Pfizer.
Richard Greil: Advisory Role: Roche; Financing of Scientific Research: Roche, Pfizer; Expert Testimony: Roche, Pfizer; Other Financial Relationships: Roche.

V165

Interplay of poly (ADP-ribose) polymerase 1 (PARP-1), histone H1 and sirtuin 1 (SIRT1) as a new key mechanism for breast cancer related aromatase promoter I.3/II regulation

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Introduction: Paracrine interactions in estrogen receptor positive (ER+) breast cancers between malignant cells and breast adipose fibroblasts (BAFs) are essential for estrogen biosynthesis by aromatase in BAFs. We previously identified a SNV (NC_000015.10:n.51243270T>C) in breast cancer-related aromatase promoter I.3/II, which reduced promoter activity by 70%. Here, we identified SNV-dependent DNA-binding proteins and their functions in breast cancer-relevant aromatase promoter I.3/II regulation.

Methods: DNA-binding proteins were identified by LC-mass spectrometry after oligonucleotide-coupled magnetic bead purification from 3T3-L1 cells used as a model for BAFs. DNA-binding was verified *in vitro* by electrophoretic mobility shift and immunoprecipitation (IP)-based assays, respectively, and in cells by chromatin IP. Luciferase reporter gene assays, overexpression and inhibitor experiments were performed in 3T3-L1 cells and MEFs (PARP-1 knock-out and wildtype). Inhibitors were also tested in human BAFs. Effects of inhibition of PARP-1, HDACs or specifically SIRT1 by PJ34, panobinostat or selisistat, respectively, on aromatase gene expression, activity or NAD^+/NADH-ratio in BAFs were measured after forskolin stimulation.

Results: PARP-1 bound and activated the aromatase promoter I.3/II SNV-dependently. It functionally interacted with histone H1, SIRT1 and other class I/II HDACs. PARP-1 parylated histone H1 and competed for DNA-binding with histone H1, thereby inhibiting its gene silencing action. SIRT1 also competed for DNA-binding with PARP-1 and activated the promoter I.3/II. In functional assays PARP-1-mediated induction of the aromatase promoter showed a bi-phasic dose-response in over-expression and inhibition experiments, respectively. The HDAC-inhibitors panobinostat and selisistat inhibited promoter I.3/II-mediated gene expression. Furthermore, inhibition of both, PARP-1 and SIRT1, increased the NAD^+/NADH-ratio in BAFs.

Conclusions: Stimulation of BAFs leads to increased occupancy of the breast cancer associated aromatase promoter I.3/II by PARP-1. Its complex interactions with histone H1 and SIRT1 fit best to an interplay of parylation and acetylation/de-acetylation events, which strongly depends on the cellular NAD^+/NADH-ratio. Lower NAD^+/NADH-ratios like in case of a reverse Warburg effect in BAFs most likely promoted PARP-1-activation and DNA-binding. Therefore, PARP-1 could be a new therapeutic target in the treatment of ER+ breast cancers.

Disclosure: No conflict of interest disclosed.

V166

Patient preferences for palliative treatment of locally advanced or metastatic Breast Cancer: an adaptive choice-based conjoint analysis study from Germany

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Introduction: Patients with different types of metastatic or advanced cancer will likely have cancer-specific attitudes, needs and expectations regarding treatment. Patient preferences should be considered in the regulatory approval process. This study aimed to gain insights into lives of patients with metastatic Breast Cancer (mBC), to identify preferences related to potential cancer treatment characteristics, and to reveal the relative importance of gained lifetime (OS) and gained time to progression (PFS) in relation to quality of life (QoL) and side effects associated with cancer therapies.
Methods: Female post-menopausal patients with HR+/HER2- metastatic or locally advanced mBC (relapsed after adjuvant treatment or de novo), receiving active 1st or 2nd line treatment, were recruited in Germany. Attributes and levels relevant for the defined population in assessing cancer therapy were collected stepwise. A cross-functional team reviewed items and developed a list of most important attributes and appropriate levels (three per attribute). A draft conjoint matrix was developed, validated and refined using two pre-tests with mBC patients (n=9). The final conjoint matrix consisted of 2 attributes for therapy goals (OS, PFS), 4 for dimensions of health-related QoL and 6 for side effects. It formed the basis of the subsequent quantitative survey using adaptive choice based conjoint methodology, implemented as the core of an online questionnaire.
Results: 104 mBC patients, classified into 2 groups (1st line (n=67), 2nd line (n=37)), participated in the quantitative survey. QoL ('physical mobility and flexibility') received the highest value (19.4%), followed by treatment goals (OS 15.2%, PFS 14.4%). Therapy-related side effects were considered less important. 'Nausea and vomiting' (9.3%) were the most relevant side effects, followed by infection risk (6.4%). Diarrhea (2.9%) and mucosal dryness (1.2%) were considered least important side effects. No significant differences were found between 1st vs 2nd line patients. McFadden pseudo R^2 (0.805), Root-Likelihood (0.864) and Chi-square test (2809.041, highly significant ($p< 0.0001$)) demonstrated excellent statistical quality.
Conclusions: The study shows that in the context of mBC treatment decisions, patient preferences, independent of treatment experience, mainly focus on QoL and therapy goals such as OS and PFS. Patients seem to tolerate side effects to a certain level provided QoL,OS and PFS goals are achieved.

Disclosure: Thorsten Otto: Employment or Leadership Position: Is an employee of Eli Lilly and Company.; Stock Ownership: Owns stock in Eli Lilly and Company. Elke Weidling: Employment or Leadership Position: Is working (part-time) on behalf of Eli Lilly and Company as a contractor

V167

Monitoring therapy response and assessing prognosis by untargeted FAST-SeqS of circulating tumor DNA in metastatic breast cancer patients

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Background: The objective of this study was to explore the clinical benefit of monitoring plasm a tumor fractions using an untargeted FAST-SeqS approach during systemic treatment of metastatic breast cancer patients.
Patients and methods: Blood samples were obtained from 29 patients with metastatic breast cancer. Samples were analyzed at first diagnosis of metastases, during several lines of treatment, and/or at every further moment of progression/development of new metastases. We assessed tumor fractions in plasma using an untargeted mFAST-SeqS method. Resulting ctDNA z-scores were compared to tumor fractions established with the recently published ichorCNA algorithm and associated with the clinical outcome.
Results: We observed a strong correlation between mFAST-SeqS z-scores and ichorCNA ctDNA quantifications. Patients with mFAST-SeqS z-scores above three (34.5%) showed significantly worse overall (p=0.014) and progression-free survival (p=0.018) compared to patients with lower values. Elevated z-score values were clearly associated with radiological proven progression. In contrast, CEA, and CA15-5 had no prognostic impact on the outcome of patients in the analyzed cohort.
Conclusions: ctDNA levels detected with mFAST-SeqS holds great promise as a very fast and cost-effective minimally invasive and clinically relevant biomarker to assess the ctDNA fraction without prior knowledge of the genetic landscape of the tumor.

Disclosure: No conflict of interest disclosed.

V168

Exploring real world data treatment patterns and outcomes in participants with HER2+ unresectable LA/mBC - Austrian participation in the prospective European registry SAMANTHA study

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Introduction: Currently available treatment options for HER2+ breast cancer patients include trastuzumab, pertuzumab, trastuzumab-emtansine as well as lapatinib. The used drugs as well as the sequence in which they are used may vary between countries.
Efficacy of regularly used treatment options has been established in various randomized controlled clinical trials (RCT). RCT usually include patients with a rather narrow patient profile and a good performance status. Therefore, there is an unmet need for Real World Data (RWD) from the daily clinical practice concerning the treatment of HER2+ unresectable LA/mBC in order to evaluate whether and to what extent results from RCT can be applied to a broader patient spectrum. The SAMANTHA Study collects RWD from 5 different European countries and is also part of a global umbrella study. Real World Evidence from the SAMANTHA study may help to understand current treatment patterns and outcomes in HER2+ unresectable LA/mBC. A descriptive analysis may identify possible associations between patient characteristics, treatments and outcomes. Possible differences between countries will also be examined. The up to eight-year observation period in the study offers a unique chance to include data from novel treatment options, which may be available in the future.
Patients and methods: Study population: 635 planned patients ≥ 18 years initially diagnosed with HER2+ unresectable LA/mBC no more than 6 months prior to enrollment. Participants will receive treatment and clinical assessments as determined by their treating physician, according to

the standard of care and routine clinical practice at each site. After a 3 year recruitment period patients will be followed for 5 more years. Primary outcome measures are progression-free survival per anti-cancer treatment regimens assessed according to site-/country-specific medical practice and percentage of participants by different anti-cancer treatment regimens and treatment sequences.
Results: An update of the baseline data from the 2nd interim analysis including baseline demographics and treatment regimens used in 1st line will be presented.
Conclusions: The SAMANTHA study aims to provide health care professionals with extensive RWD data that may help to answer question of clinical practice in the treatment of HER2+ unresectable LA/mBC.

Clinical Trial Identification: NCT02913456, EUPAS22426, MO39146
Legal entity responsible for the study: F.Hoffmann-La Roche Ltd.

Disclosure: Günther Steger: Other Financial Relationships: has received honoraria and travel support by Roche Austria
Nicolas Lindegger: Employment or Leadership Position: is an employee of F.Hoffmann-La Roche

Fortbildung

B-NHL aggressiv: Therapeutische Algorithmen

V173

Strategies of therapy reduction in DLBCL patients with very good prognosis

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Outcome of patients (pts) with diffuse large B cell lymphoma (DLBCL) and favourable prognosis has significantly improved in recent years. Results of the MinT study have demonstrated that young (18-69 years) pts with aggressive lymphoma without risk factor according to IPI or bulk (single or conglomerate tumour ≥7.5 cm) have an excellent prognosis [Pfreundschuh et al., Lancet Oncol 2011; 12: 1013-22]. After chemotherapy plus rituximab their 6 years event-free survival (EFS) was 84.3%, progression-free survival (PFS) was 89.6%, overall survival (OS) was 94.9%. Similarly elderly pts (61-80 years) in the RICOVER trial with favourable prognosis defined as IPI=1 (age), no bulk (max. tumour diameter ≤7.5 cm) showed a 2-year PFS of 90% and OS of 91% [Pfreundschuh et al., Lancet Oncol 2008; 9: 105-16]. Therefore it can be hypothesized that a large proportion of pts receiving 6 cycles R-CHOP are cured but potentially "overtreated".
This has already been shown in the FLYER trial for young pts with favourable prognosis (IPI=0, no bulk). After 66 months median observation time 3-year PFS after 4x R-CHOP+2xR was 96% vs. 94% after 6x R-CHOP. 3-year EFS was 89% in both treatment arms, OS was 99% after 4x R-CHOP+2xR vs. 98% after 6x R-CHOP. Therefore outcome after 4x R-CHOP-21+ 2xR was non-inferior compared to the previous standard 6x R-CHOP-21. Chemotherapy can be spared without compromising prognosis in this population [Poeschel et al., Blood 2018; 132:781].
A registry study of 50 pts with no risk factor other than age (median 67 years) and no bulky disease showed that pts with limited-stage DLBCL who are PET-negative after 3 cycles R-CHOP can be effectively treated with abbreviated chemoimmunotherapy alone (4 cycles R-CHOP) [Sehn et al., Blood 2007; 110:787].
In elderly pts with very good prognosis the concept of a controlled reduction of treatment intensity is currently prospectively investigated in the OPTIMAL>60 trial (EudraCT: 2010-019587-36). Pts with a negative PET after 4x-R-CHOP/R-CHLIP-14 complete the remaining 4xR, while PET-positive pts in addition receive 2 additional CHOP/CHLIP-14 + ISRT (39.6 Gy) to originally involved sites. Results of the first 120 pts treated according to this PET guided treatment strategy showed that it allows sparing 2 cycles chemotherapy in 82% of pts without compromising their outcome [Pfreundschuh et al., Blood 2017; 130:1549]. However these are preliminary results and the final analysis of 288 favourable pts is not available yet.

Disclosure: Viola Poeschel: Advisory Role: Hexal; Other Financial Relationships: Reisekostenunterstütung: Roche, Amgen, Abbvie

V174

Therapeutic strategies in high-risk DLBCL patients

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Despite the therapeutic advances in the last years, there are subgroups of patients with diffuse-large B-cell lymphoma (DLBCL) with a poor prognosis. Relapsed patients have an inferior outcome, particularly patients with relapse within the first years after diagnosis or primary refractory patients. There is a plentitude of factors anticipating a poor outcome before or during the first line treatment as e.g.: (1) clinical risk factors like the International prognostic Index and its modifications as well as the presence of a bulky disease (lymphoma diameter > 7.5cm). (2) biological risk factors, particularly the differentiation between „GCB" (germinal B-cell like) and „ABC" (activated B-cell like) as well as the „double hit"- and „double expressor" status, which is now part of the routine diagnostic; (3) the early response evaluated by interim-positrone emission tomography (iPET) or by minimal residual disease by NGS (next generation sequencing) based technologies; (4) patient related factors like age and comorbidity.
In contrast to the amount of prognostic factors, therapeutic strategies are still limited. Many new concepts in randomized phase 3 trials failed to replace the standard immunochemotherapy with Rituximab and CHOP. Eight cycles of R-CHOEP-14 are considered as standard treatment in younger patients in Germany, however, the treatment was not tested against the standard R-CHOP. Clinical trials on dose escalation in patients with a positive iPET show some controversial results. Ibrutinib might have an efficacy in younger patients with non-GCB lymphoma and venetoclax might improve the prognosis of patients with Bcl2 overexpression, however, both results have to be reevaluated in larger phase-III trials. Antibody- or cell-based immunotherapies are still experimental in first-line treatment. Taking together a more exact definition of "high risk" DLBCL patients and the increasing therapeutic options, a substantial improvement of the outcome is expected within the next few years.

Disclosure: Andreas Viardot: Advisory Role: Amgen, BMS, Roche, Kite/Gilead, Pfizer; Financing of Scientific Research: Pfizer, Amgen, Roche, BMS; Other Financial Relationships: Reisekostenerstattung: Roche, Celgene, BMS, Abbvie, Janssen, Kite/Gilead

Wissenschaftliches Symposium

Kopf-Hals-Tumore: I/O in Rezidiv und Metastasierung

V182

Challenges in Supportive Care of Patients Undergoing Treatment for Head and Neck Cancer

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Patients undergoing treatment for head and neck cancer often require a combined modality treatment approach. During treatment patients face multiple physical and psychosocial challenges due to disfigurement, emotional suffering, and social isolation that can be demoralizing and ideally require the attention of a multidisciplinary care team.
In addition, severe acute toxicities can impair treatment adherence and result in increased morbidity and mortality. Acute treatment toxicities

may lead to airway issues, speech difficulties and severe nutritional deficits through swallowing impairment. Some of these treatment side effects can result in long-term morbidity that significantly decreases patient's quality of life.
This presentation will describe pathology and assessment of toxicities for patients with head and neck cancer and provide guidance for supportive-care measures to reduce acute and late effects.

Disclosure: No conflict of interest disclosed.

Wissenschaftliches Symposium

Kontroversen in der Therapie des frühen Mammakarzinoms

V195

Who still needs chemotherapy in HR+ HER2- early breast cancer?

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Tumorbiologie und Tumorlast sind die wichtigsten Kriterien für die Chemotherapieindikation beim hormonrezeptor (HR)-positiven, HER2-negativen frühen Mammakarzinom (EBC). Ein hoch hormonrezeptorpositiver Tumor mit niedriger Proliferationsrate (luminal A) benötigt bei bis zu drei befallenen Lymphknoten nicht zwingend eine Chemotherapie, luminal B Karzinome mit hoher Proliferationsrate in der Regel immer. Ab vier befallenen Lymphknoten ist eine Chemotherapie in der Regel immer indiziert. Neben den klassischen histopathologischen Kriterien können heute Genexpressiontests helfen, die Indikation zur (neo-)adjuvanten Chemotherapie zu stellen. Oncotype DX® und MammaPrint® wurden prospektiv in klinischen Studien evaluiert (TAILORx. PlanB, MINDACT), EndoPredict® und Prosigna® prospektiv-retrospektiv an bereits vorhanden Tumorbanken von Phase III Studien. Aus den prospektiven Studien geht hervor, dass Patientinnen mit einem Niedrig-Risiko Gentestergebnis und bis zu 3 befallenen Lymphknoten sehr gute Heilungschancen haben und von einer zusätzlichen Chemotherapie kaum oder gar nicht profitieren würden. TAILORx zeigt dies ebenfalls für Patientinnen mit einem mittleren Risiko im Oncotype DX®. Der Einsatz dieser Genexpressionstests im klinischen Alltag ist umstritten, da keine eindeutige Regelung zur Kostenübernahme in der Regelversorgung besteht - eine rasche Lösung im Sinne der Patientinnen wäre hier sehr wünschenswert.
Die kurzeitige endokrine Therapie (2-3 Wochen) vor der Operation ist eine validierte Möglichkeit, die endokrine Sensitivität besser einzuschätzen, da hier neben den statischen Biomarkern bei der Erstdiagnose noch zusätzlich ein dynamischer Marker evaluiert wird. In der WSG-ADAPT Studie konnten Patientinnen mit einem intermediate-risk Recurrence Score und gutem endokrinem Ansprechen auf eine Chemotherapie verzichten - die Studie wird im Sommer 2019 fertig rekrutiert sein. In der Nachfolgestudie ADAPTcycle werden die Tumoren wieder anhand des endokrinen Ansprechens auf die präoperative endokrine Therapie charakterisiert. Tumoren mit einem mittleren Recurrence Score und schlechtem endokrinen Ansprechen oder solche mit gutem endokrinen Ansprechen aber hoher Tumorlast werden zwischen Standardchemotherapie und endokrin-basierter Therapie mit AI und dem CDK 4/6 Inhibitor Ribociclib randomisiert (*www.wsg-online.com*).
Insgesamt sind die Heilungschancen für Patientinnen mit HR+ HER2- EBC heute sehr gut. Genexpressionstest können bei unklarer Indikation anhand der klassischen histopathologischen Faktoren eine weitere Abschätzung des Rückfallrisikos erlauben *(www.ago-online.de).* Eine De-eskalation der Systemtherapie mit Verzicht auf (neo-)adjuvante Chemotherapie sollte angesichts der guten Heilungschancen mit der Standardtherapie nur evidenz-basiert oder im Rahmen von Studien erfolgen.

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Debatten

Slim CRAB-positives frühes Multiples Myelom:
Richtlinien vs. Klinische Entscheidungsfindung

V200

„Slim CRAB positive early Myeloma: Guidelines versus clinical decision making: A pro and contra debate. *Pro: Early therapy avoids complications and open the road to long-term remissions*

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Introduction: In 2014 the International Myeloma Working Group (IMWG) revised the criteria for diagnosis and treatment indications in Multiple Myeloma. The revised IMWG criteria allow, in addition to the classic CRAB features, three myeloma defining events (MDEs). The presence of at least one of these markers is considered sufficient for a diagnosis of multiple myeloma, regardless of the presence or absence of symptoms or CRAB features. Each of these markers has been shown to be associated with an approximately 80% or higher risk of developing myeloma-related organ damage within two years. These three MDEs are: 1. 60% or greater clonal plasma cells on bone marrow examination. 2. Serum involved / uninvolved free light chain ratio of 100 or greater, provided the absolute level of the involved light chain is at least 100mg/L . 3. More than one focal lesion on MRI that is at least 5mm in size**.** Patients presenting with at least one of the MDEs are called *"Early Myelomas"* and qualify for treatment.
Rationale: Initiating MM treatment according to IMWG criteria may result in several potential benefits for patients: **1.** Avoiding catastrophic first manifestations of MM (renal failure, spinal compression, severe bone disease) that may impede adequate subsequent therapy **2.** Better tolerability of therapies due to younger age, less tumor burden, and a better hematopoietic capacity. **3.** Initiating treatment in a disease state with less genetic complexity and drug resistancies**. 4.** Higher potential to induce deep responses and long lasting remissions. Two strategies are under evaluation with respect to early treatment of MM: **A.** Low intensity interventions aimed at re-instating a MGUS-like state of the disease **. B.** "All-in" intensive therapies aimed at disease eradication and ultimately cure of MM
Evidence: While clinical trials supporting strategy A (e.g. the QUIREDEX trial) have been published demonstrating both time-to-progression, as well as an overall survival benefit, results for trials with a "curative" intent are preliminary, although highly promising (e.g. the GEM-Cesar trial).
Outlook: With the integration of immuno-oncologic strategies and population based screening for paraproteinaemias (Black Swan Initiative) early treatment of MM holds the potential to induce long lasting deep remissions (operational cure) and furthermore may help to avoid the development of debilitating complications of this dreadful disease in a majority of patients.

Disclosure: Wolfgang Willenbacher: Employment or Leadership Position: Oncotyrol; Advisory Role: AMGEN, BMS, Celgene, Gilead, Janssen, Novartis, Merck, Pfizer, Roche, Sandoz, Sanofi, Takeda; Financing of Scientific Research: AMGEN, Abbvie, BMS, Celgene, Fujimoto , Gilead, Janssen, Myelom- und Lymphomselbsthilfe Österreich, Novartis, Pfizer, Roche, Sandoz, Takeda; Expert Testimony: AMGEN, BMS, Celgene , Janssen, Novartis, Roche, Takeda,European Commission (FP7 - OPTATIO), Bundesland Tirol Programm: „Translational research; Immaterial Conflict of Interests: Steering Board DSMM, Amgen, Celgene
Ella Willenbacher: No conflict of interest disclosed.

Freier Vortrag

Myelodysplastisches Syndrom I

V201

Comparison of different humanized hematopoietic niche xenotransplantation models to investigate myelodysplastic syndromes

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Introduction: Xenograft models of Myelodysplastic Syndromes (MDS) in NSG mice have emerged as versatile preclinical platforms for investigation of functional pathomechanisms in myeloid neoplasms ([1] Medyouf et al., 2014, [2] Rouault-Pierre et al., 2017). The low engraftment of patient-derived $CD34^+$ hematopoietic stem cells (HSCs) from low-risk MDS bone marrow (BM) aspirates is the limiting factor for these models. Efficient humanized 3D scaffolds in immune-compromised mouse models have been established, enabling to increase engraftment rates of normal and malignant hematopoiesis ([3] Reinisch et al., 2016, [4] Abarrategi et al., 2017). Therefore, we evaluated engraftment ability of low-risk and int-1-risk-patient samples, which were not able to engraft in our previously established model, in four different 3D scaffolds.
Methods: Currently, samples from n=5 MDS patients have been parallelly xenografted into NSG mice by intrafemoral co-injection of $CD34^+$ HSCs and MSCs according to [1] or by subcutaneous implantation of 3D scaffolds. Gelfoam and Bio-OSS were used as described in [4], Matrigel ossicles were generated according to [3] and human bone was isolated after hip replacement, inserted with Gelfoam, preseeded *in vitro* with MSCs and MNC and injected *in vivo* with $CD34^+$ HSCs 8 weeks after implantation (human bone ossicles). Ossicles, bone marrow (BM), peripheral blood and spleens were analyzed 12 weeks after implantation.
Results: Flow cytometric analysis revealed higher $hCD45^+$cell engraftment in Gelfoam and human bone ossicles. Engraftment in human bone seems to be similarly robust but with Gelfoam higher engraftment levels could be observed ranging from 0% to 70% compared to human bone ossicles ranging from 0.05% to 27%. We found $hCD45^+$cells especially in the BM, peripheral blood and spleen of mice with human bone ossicles. Another set of experiments with human bone ossicles showed that colonization of the scaffold is the same with $CD34^+$ cells + MSCs, MNCs+MSCs or just MNCs, but systemic engraftment could be just observed through the application of MNCs.
Conclusions: $hCD45^+$cells and MSCs from MDS BM, which could not engraft in NSG mice through interfemoral injection, were able to colonize humanized scaffolds. Therefore, Gelfoam and human bone ossicles are promising novel methods for improved MDS xenograft models. For systemic engraftment, application of MNCs seems to be necessary. Histological and molecular analyses are ongoing.

Disclosure: No conflict of interest disclosed.

V202

Adherence to treatment recommendations from a referral center for myelodysplastic syndromes (MDS)

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Introduction: Adherence to expert recommendations for therapy has not yet been evaluated in patients with myelodysplastic syndromes.
Methods: In a prospective analysis of 381 patients, who were followed for a median time of 14 months, we documented place of residence, IPSS-R, MDS-CI and HCT-CI, as well as treatment recommendations, including watchful waiting (ww), best supportive care (BSC), epigenetic treatment (HMA), induction chemotherapy and low dose chemotherapy, lenalidomide, and allogeneic stem cell transplantation (alloSCT). Information regarding adherence to the treatment recommendation was obtained by searching medical files and contacting primary care physicians.
Results: Median time from diagnosis to first presentation was 5 months (0-286). Median age at diagnosis was 64 years (23-88), 62.2% of pts were male, 2.4% were diagnosed with MDS-SLD, 27.6% had MDS-MLD, 3.9% MDS-RS-SLD, 8.1% MDS-RS-MLD, 4.5% MDS-del(5q), 10.5% MDS-EB-1, 13.9% MDS-EB-2, 11.3% CMML, 4.2% sAML, 7.1% MDS-U, 1.6% RARS-T, and 5% MDS-NOS. Distribution among IPSSR risk groups was: 10.8% very low, 31.2% low, 12.9% intermediate, 18.4% high and 13.8% very high risk. Applying the MDS-CI at least one comorbidity was present in 43.8%, with cardiac comorbidities and solid tumors being most frequent (26.2% and 18.9%). Patients living > 100 km away were younger (p=0.038), had less comorbidities (p=0.006), and belonged to lower IPSS-R categories (p=0.006). Ww was recommended in 22.3%, BSC in 26.2%, HMA in 13.9%, lenalidomide in 3.4%, chemotherapy in 4.2%, alloSCT in 25%, and other individualized approaches in 5%. In 5.2% of the pts a comprehensive follow-up was not possible. In 67.5% of cases the recommendation was implemented within 4 months. 10.2% of the pts did not receive any treatment throughout the observation period including the time from diagnosis to first presentation. 21.2% of those who were recommended to be under ww received active treatment instead. Non-adherence to the recommendation of HMA was 28.8%. Non-adherence to the recommendation of alloSCT was 29.2%. Major reasons for non-adherence were comorbidities assessed during follow-up (44%), patient decision (28%), and non-availability of a donor (16%).
Conclusions: Patients seen in our MDS referral center are younger, have less comorbidities and belong to higher IPSS-R risk categories as compared to patient populations in large MDS registries. Non-adherence to our treatment recommendations was found in 33% of the patients.

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V204

Transcriptional regulation of the HOXA cluster in ASXL1-mutant chronic myelomonocytic leukemia

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Introduction: Truncating ASXL1 mutations are adverse prognostic factors in myeloid malignancies and occur in 40% of patients with chronic myelomonocytic leukemia (CMML). These mutations are associated with a proliferative disease phenotype, thought to be driven by epigenomic mechanisms such as PRC-mediated loss of H3K27me3. We studied the

transcriptome and epigenome of patients with CMML to elucidate potential regulatory mechanisms.

Methods: We performed targeted next generation sequencing of DNA (NGS), whole transcriptome shotgun sequencing (RNA-seq), chromatin immunoprecipitation (H3K27me3, H3K4me1) followed by sequencing (ChIP-seq), and an assay for transposase-accessible chromatin followed by sequencing (ATAC-seq) on bone marrow mononuclear cells from 12 patients with CMML. After quality control, sequencing was performed on an Illumina HiSeq, reads were aligned to the genome, and analyzed using an established bioinformatics pipeline.

Results: Five patients were ASXL1-mutant (ASXL1mt), 7 were ASXL1-wildtype (ASXL1wt). All ASXL1 mutations were truncating (C605Dfs*10 VAF 47%, G646Wfs*12 VAF 39%, G646Wfs*12 VAF 42%, Q695Nfs*24 VAF 37%, and L775* 48%). The spectrum of co-mutations was typical for CMML, involving spliceosome components, epigenetic regulators, chromatin regulators, and cell signaling molecules. There was predominant up-regulation of gene expression in ASXL1mt patients (versus ASXL1wt): 124 genes up- and 73 genes down-regulated (FDR < 0.05). The up-regulated genes included several HOXA family members (HOXA3, HOXA6, HOXA7, HOXA9, and HOXA10). There was no decrease in H3K27me3 occupancy at the HOXA cluster. There was an increase in H3K4me1 occupancy along with a predominantly intergenic increase in chromatin accessibility.

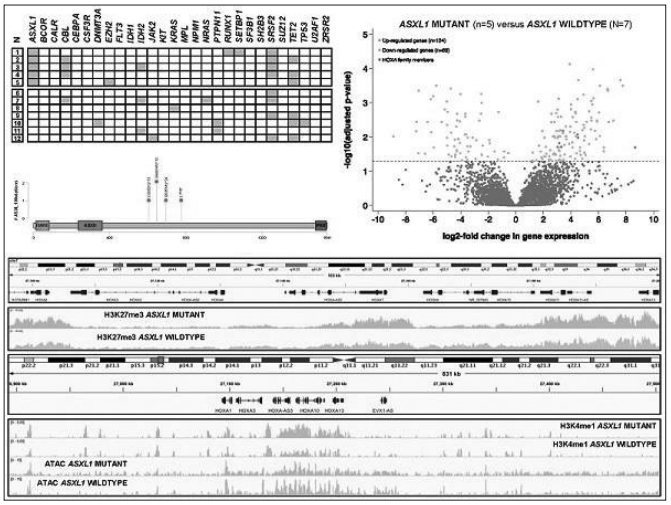

Fig.1. Mutational spectrum, differential gene expression, and epigenomic findings at the HOXA cluster

Conclusions: There was up-regulation of several HOXA genes in ASXL1mt CMML, several of which have been implicated in myeloid transformation and leukemogenesis. There was no decrease in H3K27me3 occupancy explaining the increased transcriptional activity at the HOXA cluster. Intergenic increases in H3K4me1 and chromatin accessibility point towards alternative regulatory mechanisms such as enhancer elements that need further exploration.

Disclosure: No conflict of interest disclosed.

V205

In vivo impact of Azacitidine on complex aberrant and TP53-mutated cell clones in MDS and AML

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Introduction: Mutations in *TP53* (*TP53*^{mut}) are associated with complex aberrant karyotypes (CK) and poor prognosis in pts with MDS and AML. Therapy refractoriness is highly probable. Even the outcome of allogeneic stem cell transplantation (SCT) is dismal (Lindsley, 2017). Regarding hypomethylating agents (HMA) it was assumed that pts with *TP53*^{mut} respond to decitabine only (Welch, 2016). Recently, however, a response to azacitidine (AZA) has also been reported in AML (Döhner, 2018). The aim of our study was to collect real-life longitudinal data to prospectively investigate the response to AZA in pts with *TP53*^{mut} and with/without CK.

Methods: To date, we have analyzed 34 MDS and AML pts using banding analysis, FISH (10 probes) and NGS (54 genes). The cohort consisted of pts with (N=16) and without *TP53*^{mut} (N=18). Frequent genetic follow-up during AZA was performed in 6 pts with and in all 18 pts without *TP53*^{mut}. The median observation time was 429 days (range: 91-905) and the median number of sequential genetic analyses for each patient was 7 (range: 2-11). Genetic response was defined as at least 50% reduction in FISH clone size or variant allele frequency.

Results: Clones with *TP53*^{mut} responded to AZA in all 6/6 pts with *TP53*^{mut} and genetic follow-up. In contrast, only 10/18 pts (56%) without *TP53*^{mut} responded with at least one clone to AZA. The following aberrations were responsive: mutations of *ASXL1*, *IDH2*, *RUNX1*, *SF3B1*, *SRSF2*, *TET2*, *U2AF1* and +1, t(3;3), 5q-, -7, i(12q), 17p-, 17q- and 20q-. The 6 pts with reduction in the *TP53* clone had a median overall survival (OS) of 432 days. Pts without *TP53*^{mut} and with genetic response of other genetic aberrations showed a significant longer median OS of 682 days (P=0.02). The 10 pts with *TP53*^{mut} but without genetic follow-up due to SCT (1x), death (5x), or loss to follow-up (4x) had a med. OS of just 266 days (P=0.04).

Conclusions: Although pts with *TP53*^{mut} have an unfavorable prognosis even when treated with AZA, they benefit from therapy. In our cohort, we detected a high response rate of *TP53*^{mut} clones (6/6 pts). Our observation suggests that pts with *TP53*^{mut} respond not only to decitabine but also to AZA and thus, generally *TP53*^{mut} seems to be a responsive target for HMA. Although the response is non-persistent, treatment with AZA may prolong survival, delay progression, bridge the time to transplantation, and thus generate substantial benefit for pts with *TP53*^{mut}.

Disclosure: Christina Ganster: No conflict of interest disclosed.
Detlef Haase: Expert Testimony: Forschungsförderung Celgene

V206

Characterization of disease progression of patients with myelodysplastic syndromes

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Introduction: The prognosis of patients with myelodysplastic syndromes (MDS) is depending on several disease characteristics as cell counts in the peripheral blood, cytogenetic findings or the bone marrow blast count, respectively. These parameters have a clear association with overall survival rates and the rates of AML progression. However, data on progression characteristics to an unfavorable MDS subtype are sparse.

Methods: On the basis of the Düsseldorf MDS registry, we retrospectively analyzed the course of disease of 1141 MDS patients that did not receive any disease modifying treatment with regard to WHO subtype and IP-SS-R risk category in follow-up examinations of the bone marrow.
Results: After a median follow-up of 27 months (range 1-390 months), in 282 patients (25%) a progression to a higher risk was documented. An AML evolution occurred in 379 patients (33%), whereas in 316 patients the AML occurred directly without prior MDS progression. Median time to MDS progression was 16 months and median time to AML 10 months, respectively.
Beside AML evolution, a progression of the MDS had a significant impact on prognosis with a median OS of 41 months in comparison to 54 months without progression (p< 0.0001). However, looking at the impact of MDS progression on the prognosis of low- and high-risk patients defined by < 5% and >5% medullary blasts separately, in low risk patients, the prognosis with progress was significantly inferior in comparison to patients without disease progression (45 vs. 64 months, respectively, p< 0001). In contrast, in high risk patients with a medullary blast count >5%, a progression of the MDS towards an inferior subtype had no influence on prognosis (30 vs. 33 months, p=0.7). The cause of death was known in 563 patients. Fatal infections were the most frequent cause of death in patients without as well as with MDS progression (46 and 42%, respectively). In those patients without MDS progression, with 21% the highest amount of not-disease-related causes of death were found, among them, in 10% therapy refractory heart failure.
Conclusions: A progression of MDS towards an inferior subtype occurs frequently and affects the prognosis, especially in low risk patients. The prognosis of high risk patients is worse per se, so that a disease progression with an increase of medullary blast count has no additionally impact on the survival probability.

Disclosure: No conflict of interest disclosed.

Freier Vortrag

Prostatakarzinom

V207

Investigations of the anticancer activity and mechanism of action of derivatives of the marine alkaloid Ascididemine

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Introduction: In the last decades, marine organisms have served as a source for new potent anticancer drugs. Marine natural compound Ascididemine, a pentacyclic aromatic marine alkaloid, exhibits promising activity in different models of human cancer *in vitro*. Consequently, a family of Ascididemine derivatives was synthesized in order to improve the anticancer and physic-chemical properties of the molecule.
Methods: We performed screening of 24 synthetic derivatives of the marine alkaloid Ascididemine in order to determine the cytotoxicity and selectivity in human drug-resistant prostate cancer (PCa) cells in comparison with non-cancer cells *in vitro*. For the most active compounds the mechanism of action, including the effects on proteome and kinome, as well as the effect in combination with established drugs were examined in androgen- independent and docetaxel resistant PC3 cells and AR-V7-positive, BRCA2- mutated 22Rv1 cells.
Results: We identified two derivatives to be able to selectively inhibit human drug-resistant PCa cells, while non-malignant cells were less affected. The compounds primarily targeted mitochondria, induced ROS production and a mitochondrial membrane depolarization, followed by caspase-3 and -9 mediated apoptosis. Downregulation of AR-V7 expression and PSA decline were detected in 22Rv1 cells. When applied in combination with the PARP-inhibitor Olaparib, both compounds exhibited strong synergism in BRCA2-deficient prostate cancer cells. Analysis of the kinome and proteome revealed an upregulation of the katalytic activity of multiple kinases, specifically affecting the PI3K-Akt-Pathway as well as the PIM1 kinase. In line with this, a combinational treatment with specific Akt-inhibitors showed highly synergistic effect. Moreover a moderate to high synergism in drug-resistant PCa cells was found for abiraterone, enzalutamid and docetaxel, indicating a resensitization for the drugs by the marine compounds.
Conclusions: In conclusion, we were able to identify two marine-derived substances with potent anticancer activity and high potential to overcome resistance mechanisms alone as well as in combination with established drugs in castration- resistant PCa, therefore filling a medical demand. The suggested mechanism of action includes the induction of mitochondrial damage, ROS induction and caspase-dependent apoptosis. Further *in vitro* and *in vivo* examinations are ongoing.

Disclosure: Moritz Kaune: No conflict of interest disclosed.
Gunhild von Amsberg: Advisory Role: Roche, BMS, Astellas, Sanofi, MSD; Financing of Scientific Research: Roche, BMS, Sanofi, Astellas, Ipsen, EISAI, Pierre Fabre, MSD und Astra Zeneca; Expert Testimony: Roche, BMS, MSD, Astra Zeneca, Sanofi, Bayer (Durchführung klinischer Studien)

V208

The role of the mediator complex subunits CDK8 and CDK19 in prostate cancer progression

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Objectives: The Mediator complex is a multi-protein complex serving as an integrative hub for the transcription machinery. Recently, we identified the Mediator subunits CDK8 and its paralogue CDK19 to be overexpressed in advanced prostate cancer (PCa) and to promote invasive properties in vitro. Aim of our study was to comprehensively characterize CDK8 and CDK19 in PCa tissues and to proof their prognostic potential as well as to mechanistically understand CDK8/19 mediated pro-metastatic features.
Material and methods: We performed immunohistochemistry (IHC) for CDK8/19 on needle biopsies from 202 patients, 799 primary tumor foci of radical prostatectomy specimens from 415 patients, 120 locally advanced tumor foci obtained by palliative transurethral resection, 140 lymph node metastases, 67 distant metastases and 82 benigns. Primary endpoint was disease-recurrence-free survival (DFS). Cells were treated with various small molecule inhibitors against CDK8/19 followed by proliferation, migration and adhesion assays. Pamgene phosphoarray was used to identify substrates for CDK8/19 mediated phosphorylation.
Results: Nuclear CDK19 and CDK8 expression increases during progression showing highest intensity in metastatic and castration-resistant tumors. High CDK19 expression on primary tumors correlates with DFS independently from Gleason grade and PSA. CDK19 correlates with Gleason grade and T-stage. CDK8/19 inhibition decreases migration and increases adhesion as well as phosphorylation of oncogenic signaling molecules such as AKT, GSK3ß and STAT1.
Conclusions: Therapeutic options for metastatic and castration-resistant PCa remain limited. In the current study, we confirmed an important role of the Mediator subunit CDK19 in advanced PCa supporting current developments to target CDK19 and its paralog CDK8. By its kinase activity, CDK8/19 are mechanistically linked to pro-metastatic pathways such as

Wnt/ßCatenin, AKT and STAT1 signaling. Furthermore, CDK19 protein expression has the potential to predict disease recurrence independently from established biomarkers thus contributing to individual management for PCa patients.

Disclosure: No conflict of interest disclosed.

V209

Expression of prostate-specific membrane antigen (PSMA) on biopsies is an independent risk stratifier of prostate cancer patients at time of initial diagnosis

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Objectives: Stratifying PCa patients into risk groups at time of initial diagnosis enabling a risk-adapted disease management is still a major clinical challenge. Existing studies evaluating the prognostic potential of PSMA for PCa were performed on radical prostatectomy specimens (RPE), i.e. decision making for disease management was already completed at time of sample analysis. Aim of our study was to assess the prognostic value of PSMA (prostate-specific membrane antigen) expression for prostate cancer (PCa) patients on biopsies at time of initial diagnosis.
Materials and methods: PSMA expression was assessed by immunohistochemistry on 294 prostate biopsies with corresponding RPE, 621 primary tumor foci from 242 RPE, 43 locally advanced or recurrent tumors, 34 lymph node metastases, 78 distant metastases and 52 benign prostatic samples. PSMA expression was correlated with clinico-pathologic features. Primary endpoint was recurrence free survival. Other clinicopathologic features included WHO/ISUP grade groups, PSA serum level, TNM-stage, and R-status. Chi-square test, ANOVA-analyses, Cox-regression and log-rank tests were performed for statistical analyses.
Results: High PSMA expression on both biopsy and RPE significantly associates with a higher risk of disease recurrence following curative surgery. The 5-year-recurrence free survival rates were 88.2%, 74.2%, 67.7% and 26.8% for patients exhibiting no, low, medium or high PSMA expression on biopsy, respectively. High PSMA expression on biopsy was significant in multivariate analysis predicting a 4-fold increased risk of disease recurrence independently from established prognostic markers. PSMA significantly increases during PCa progression.
Conclusions: PSMA is an independent prognostic marker on biopsies at time of initial diagnosis and can predict disease recurrence following curative therapy for PCa. Our study proposes the application of the routinely used IHC marker PSMA for outcome prediction and decision making in risk-adapted PCa management on biopsies at time of initial diagnosis.

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V210

Activity of two routine cabazitaxel treatment sequences in patients with metastatic castration-resistant prostate cancer (mCRPC) - Interim analysis of the non-interventional SCOPE study

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Introduction: Cabazitaxel (CAB) and new hormonal therapies (HT: abiraterone or enzalutamide) have demonstrated a survival benefit in the post-docetaxel setting. Optimal sequencing of these agents is unknown. SCOPE is the first multinational, non-interventional study evaluating prospectively the activity of CAB according to different sequences. The study is supported by Sanofi-Aventis Germany.
Methods: SCOPE is aimed at recruiting 900 patients (pts.) starting a treatment with CAB in daily practice. Medical history, previous life-extending therapies received and outcome during CAB therapy (PSA response, clinical benefit, pain relief, tumor response as per RECIST) are collected. Patients are followed for up to 24 months after start of CAB therapy. Treatment outcomes (PSA, clinical including pain or radiological) are collected. For the current interim analysis (cut-off FEB 04, 2019) preliminary treatment outcomes of 2 sequences of therapies (Doc→CAB→HT and Doc→HT→CAB) are provided.
Results: Out of 734 enrolled pts., 273 pts. have currently completed CAB therapy and are included in this interim analysis. Of them, 150 pts. (55%; median age 70 yrs) received Doc→CAB→HT and 123 received Doc→HT→CAB (45%, median age 73 yrs). Of these 273 pts, 146 (53.5%) responded to CAB (Doc→CAB→HT, n=87; Doc→HT→CAB, n=59), 76 (27.8%) had no response and outcome was missing for 51 (18.7%). Responses to CAB (n=146) documented by investigators were mainly a PSA decrease (≥30% and ≥50% in 92 and 63 pts, respectively) but also clinical responses (n=36), pain relief (n=18) and RECIST responses (n=13; PR n=6 and SD n=7). Median progression-free survival with Cab was 4.9 months (95% CI 4.0-5.5) with Doc→CAB→HT and 4.6 months (95% CI 3.9-5.4) with Doc→HT→CAB (p=0.24). Overall survival data are not yet mature. Treatment emergent adverse events (TEAE) were observed in 141 pts. (51.7%). Main adverse events of CAB ≥ 5% were nausea (7.3%), fatigue (6.3%), anemia (5 %) and diarrhea (4.7%).
Conclusions: Preliminary results of SCOPE prospective registry suggest that under routine conditions, CAB is active (even after new HT) and shows manageable tolerability.

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Jürgen E. Gschwend: Employment or Leadership Position: nothing to disclose; Advisory Role: Amgen, Bayer, Janssen, MSD, Pfizer, Roche, Sanofi; Stock Ownership: nothing to disclose; Honoraria: nothing to disclose; Financing of Scientific Research: Amgen, Bayer, Janssen, MSD, Pfizer, Roche, Sanofi; Expert Testimony: nothing to disclose; Other Financial Relationships: nothing to disclose; Immaterial Conflict of Interests: nothing to disclose

V211

Successful targeting of the Warburg effect in prostate cancer by glucose-conjugated marine compounds

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Introduction: The Warburg effect describes the ability of cancer cells to consume larger amounts of glucose compared to normal tissues. Increased glucose uptake in prostate cancer is mediated by overexpression of glycolytic enzymes and insulin-independent glucose transporters such as GLUT-1. Marine compounds have been identified as valuable source for novel anticancer drugs characterized by unique mechanisms of action. In order to further increase selectivity and efficacy of the certain marine compounds we synthesized its glucose-containing conjugates.
Methods: We investigated the anticancer activity and selectivity of 28 synthetic sugar-conjugated derivatives containing a structure element of biologically active pigments of sea urchins. These compounds possess a

1,4-naphthoquinone moiety and a glucose residue, conjugated to the core "warhead molecule" via non-glycoside bond. Mechanism of action for the most effective conjugates was examined.
Results: We have identified four molecules showing the highest selectivity towards human drug-resistant prostate cancer cells. Prostate cancer cells have exhibited a higher expression of GLUT-1 in comparison with non-cancer cells and the cytotoxicity of the compounds strongly correlated with the GLUT-1 expression. Moreover, the substances were able to inhibit the glucose uptake, which suggested its concurrent uptake by the cells via the same system (GLUT-1) as glucose. The compounds were able to induce pro-apoptotic signs such as DNA fragmentation, cleavage of caspase-3, -9 and PARP, as well as phosphatidylserine externalization. The evidences of inhibition of such pro-survival processes as autophagy and AR-signaling have also been observed. The global proteome screening has suggested a mitochondria targeting by the synthesized derivatives. This has been validated by functional analysis: in fact, mitochondria depolarization, elevated level of cytotoxic ROS, an incensement of Bax/Bcl-2 ratio as well as release of mitochondrial proteins such as AIF and cytochrome C to cytoplasm were observed.
Conclusions: In conclusion, synthetic glucose-conjugated 1,4-naphthoquinone derivatives show potent activity and selectivity in human prostate cancer cells resistant to current standard therapies by targeting the Warburg effect. The cytotoxic activity of these compounds was associated with mitochondrial deterioration leading to the apoptotic death. Further *in vitro* and *in vivo* examinations are ongoing.

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Gunhild von Amsberg: Advisory Role: Roche, BMS, Astellas, Sanofi, MSD; Financing of Scientific Research: Roche, BMS, Sanofi, Astellas, Ipsen, EISAI, Pierre Fabre, MSD, Astra Zeneca; Expert Testimony: Roche, BMS, MSD, Astra Zeneca, Sanofi, Bayer (Durchführung klinischer Studien)

Freier Vortrag

Versorgungsforschung I

V212

Patients' reporting on cancer treatment information in oncology practices concerning risks, side effects, and medication

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Introduction: Information on risks and side effects of cancer therapy as well as information on medication are important aspects of patient competence and patient safety. Thus, it is crucial that doctors and practice staff provide such information to their patients. This presentation deals with patients reported experiences with information provided in oncology practices.
Methods: WINHO offers its partner practices to conduct patient surveys on an annual basis. The paper-based survey includes questions about patients' experiences with different aspects of the practice structure, conversation with the doctor, and socio-demographic factors. The survey is anonymous and conducted in the practices. Each practice receives 60 questionnaires per doctor. Data are analysed using SPSS 22 and Excel 2016. Only cancer patients are included in this analysis.
Results: 11,829 patients participated in the survey; 71% (n=8,447) stated that they visit the respective practice due to a cancer disease. Of these, 84% confirmed that they got a reasonable explanation and discussion of risks and side effects of their treatment, 13% confirmed this in parts, and 3% denied it. 72% remembered that it was shown or explained to them how to react in the case of side effects, 19% stated that it was only shown or explained in parts, and 10% stated it was not shown or explained at all. Regarding medication, 90% affirmed, 6% affirmed in parts, and 4% denied that the doctor or staff asked them about all medication they take. Having received a written note about the use of their medication was reported by 71%, confirmed in parts by 7%, and denied by 22% of the patients. 61% confirmed, 14% confirmed in parts, and 25% denied that they received written information about their disease and related topics. These results vary between practices, and in some cases within practices.
Conclusions: The vast majority of cancer patients received at least some information about risks, side effects and their medication. However, there seems to be room for improvement, esp. regarding written information about the use of medication. The results may be biased because they are retrospective reports by patients. The experienced burden of a disease like cancer is high and processing information difficult during the time of diagnosis and treatment. Hence, additional support, e.g. by specially trained nurses, and providing medication lists could be helpful ways to better inform patients.

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V213

Assessing obstacles for better vaccination coverage of oncological patients: the oncologist perception

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Introduction: The German Standing Committee on Vaccination (STIKO) clearly recommends vaccinations for oncological patients under systemic antineoplastic therapy. Nonetheless, health insurance data only show coverage of about 5% for oncological patients.(Schmedt *et al*, 2017) Reasons for this short-coming have not yet been thoroughly investigated.
Methods: We contacted all medical oncologists in Berlin requesting to fill out a paper pencil questionnaire. Addresses were taken from the Association of Statutory Health Insurance Physicians (Kassenärztliche Vereinigung).
Results: Fourty medical oncologists of the city of Berlin have been contacted, 31 (77.5%) returned completed questionnaires. Answers are presented in table 1.
The Majority (96.8%) place the responsibility for vaccination of oncological patients on the family doctor, but 74.2% also as their own liability. Almost half (48.4%) of oncologists indicated to perform vaccinations often in their routine clinical practice. In this regard, 22.6% check the vaccination card regularly before start of chemotherapy and 51.6% occasionally, but 25.8% never. The major problem perceived in vaccinating oncological patients were a) expected insufficient immunological response (74.2%) and b) logistic restrains (29.0%). Reason not to perform vaccination oneself were numerous (e.g. lack of time, experience, interest, and logistics), but 61.3% did not see any obvious obstacle. The mean estimated vaccination rate of their own patients according to the STIKO recommendations was 50.1%, while 90.3% indicated to be aware of the recommendations.
Conclusions: Medical oncologists are less concerned about their own ability to supervise and conduct vaccinations. Main concern stated is an insufficient immune response under cytostatic treatment. Estimated vaccination rate of the own patient population according to STIKO recommendations was surprisingly high with regard to the published data. More real-life data of actual vaccination rates and immunological response in this treatment setting is urgently needed to identify this need and address concerns. Easy-to-apply vaccination strategies for oncological patients should be developed.

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V214

Financial burden of oncological patients from a social services perspective

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Introduction: In addition to physical, psychological and social effects, the economic effects of a cancer disease may also gain in importance during longer disease progressions. This can lead to a severe financial burden for patients. In oncology, counselling by social services plays a major role in coping with this burden. Due to low evidence regarding the financial burden of oncological patients in Germany and the effectiveness of counselling in this regard, the aim of the study is to investigate the social services perspective with respect to individual financial burden of cancer patients and to collect information for the improvement of appropriate counselling services.
Methods: Using an e-mail distribution list of the DVSG (Deutsche Vereinigung für Soziale Arbeit im Gesundheitswesen) about 650 people employed in social work in oncology were invited to take part in an online survey, of whom n=145 completed the questionnaire. The online survey contained 16 items on the subjective perception of financial burden for cancer patients in everyday counselling, changes in the relevance of the topic, risk factors and the current counselling practice with regard to financially burdened tumour patients.
Results: Overall, 117 (80.7%) of all respondents stated that financial difficulties as a consequence of a cancer diagnosis are a relevant topic in their daily counselling routine for at least half of the patients. 79 (54.6%) mentioned that this topic has gained in importance over the last years. Accordingly, the provided rationale for that development were especially the higher chance of survival, an increased number of younger patients and changes in life-style as well as poorer social security and working conditions. Risk factors for financial difficulties most commonly stated were a long disease duration (97.5%), being a single-parent (94.1%) or living alone (91.6%) as well as an being aged between 31 and 60 years (89,1%), being self-employed (85.7%) or being female (79%).
Conclusions: Despite comprehensive insurance coverage, the financial burden of cancer patients has gained in importance and thus needs to be addressed by the day-to-day counselling of social services in Germany. Due to the numerous risk factors and the multilayered reasons for the financial burden, further research is necessary in order to develop suitable measures for improvement.

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V215

Is long-term adjuvant endocrine therapy for breast cancer an over-treatment?

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Introduction: In breast cancer (BC), the duration of endocrine adjuvant therapies (AT) has been extended continuously. Guidelines already recommend a treatment of 10 years. But so far there is no convincing rationale for the improvement of survival.
Methods: The presentation is based on a review of pertinent randomized controlled trials and population-based data. Three types of results are reviewed: First, the effects of chemoprevention, neoadjuvant and adjuvant trials, latter also delayed and extended. Secondly, data for initiation and growth of BCs and their metastases (MET) is considered. Thirdly, population-based data of the Munich Cancer Registry is compiled for MET-free survival, time trends of MET pattern and survival achieved by improved ATs. From these data, principles of MET and the effects of AT are derived that explain the results of extended ATs (EAT).
Results: Endocrine ATs that continue after 1, 2, 5, or 10 years reduce mortality only slightly compared to the risk at diagnosis. The effect is shiftable, constant despite decreasing MET risks and occurs delayed after almost 6 years. Therefore, dormant tumor cells cannot be clinically relevant and EATs do not affect the prognosis of 1stBCs. They eradicate as neo-ATs ipsi- and contralateral 2ndBCs which were initiated after the diagnosis of the 1stBC and with them their future life-threatening METs. The growth time of BCs explains the effect shift. In particular, the trials on EATs show with the effect shift that initiation of hormone receptor positive BCs and their METs are unlikely within 3-4 years. Because chemoprevention can eradicate BCs from the smallest clusters to almost the detection threshold, ATs can be temporarily suspended. Equivalent results to EATs should be achieved by 12-18 months of AT of the 1stBC and by repeated neo-AT for the lifelong developing 2ndBCs, probably equally long-lasting. The available evidence suggests that a 70-80% reduction of EAT might be functionally equivalent.
Conclusion: The EAT trials prove a causality, which is only to be interpreted differently. Initiation, growth of tumors and known effects of preventive and ATs suggest that intermittent endocrine ATs may achieve the same results and significantly reduce over-treatment. Quality of life and survival of millions of patients could be improved because of fewer side effects and better compliance. The challenge for further developments of ATs is not how long is long enough but how short is short enough.

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V216

CDx report program - a pilot project of the current reporting practice for hemato-oncology companion diagnostics (CDx) markers in Germany

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In the era of personalized medicine, CDx becomes the basis for optimal patient care. While technical aspects of a CDx assays' performance is audited regularly by participating in external quality assessment (EQA) programs, the reporting of these CDx markers is rarely scrutinised. The aim of this CDx report program is to get a detailed picture of hemato-oncology CDx marker reporting in Germany.
Eleven clinical labs provided information for 7 biomarkers used for treatment decisions in hemato-oncology. The 7 CDx markers covered in this first CDx report program are: *BCR-ABL1* in CML (diagnosis), *BCR-ABL1* in CML (MRD), *IDH1/2* in AML, *FLT3*-ITD in AML, *FLT3*-TKD in AML, *IGHV* in CLL, *TP53* in CLL. The information requested included two anonymized or blank reports: one report with a mutant result and one with a wild type result. The received anonymized reports were reviewed by experienced experts according to pre-agreed review criteria. In addition, labs participated in a short online survey. The online survey covered test volumes, turnaround time (TAT), positivity rates, participation in an EQA program, accreditation status, and reimbursement situation. The results of the questionnaires were forwarded as anonymized and aggregated data to reviewing experts.
Overall, we received 63 survey datasets and 58 sets of anonymized reports from 11 labs. The review of the anonymized reports according to pre-defined criteria revealed differences in the way how CDx results are represented and interpreted in clinical reports. Since not all markers covered

in this program were performed by all participating labs the number of survey datasets per CDx marker ranged from 7 to 11 (*BCR-ABL1* (diagnosis): 11 datasets, *BCR-ABL1* (MRD): 11, *FLT3*-ITD: 9, *FLT3*-TKD: 9, *IDH1/2*: 9, *IGHV*: 7, *TP53*: 7). The 63 survey datasets represented approximately 4,000 tests per months with an average TAT across all markers of 5 days. In 43/61 (70%) datasets labs participated in EQA programs while in 18/61 (30%) datasets labs did not participate in an EQA scheme. For 40/60 (67%) datasets labs were accredited according ISO15189, in 5/60 (8%) datasets labs were CAP accredited and in 15/60 (25%) datasets labs were not accredited.
An identical CDx report program is currently conducted in 10 other countries including US, UK and China. The anonymized and aggregated data generated provides the basis for other initiatives and might support guideline updates and the international harmonisation of CDx reporting.

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V217

Implementation of a molecular tumor board -two year`s experience at the Cancer Center Heilbronn-Franken

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Background: To improve interpretation of genomics-guided cancer therapies, a Molecular Tumor Board (MTB) and supporting IT-frame work have been established at the Cancer Center Heilbronn-Franken and the MOLIT Institute for personalized medicine. Since its establishment in 2017 we have been consistently working on improving the potential of the MTB. Here, we report recent advances made in development and implementation.
Results: Between 2017 and 2018 we almost doubled our patient`s number (~37 vs. ~65) and we expect the cases to have doubled again until December 2019. So far more than 130 cases have been evaluated by our interdisciplinary team comprising oncologists, genetic counselors, basic scientists and a MTB coordinator, responsible for scientific management and administrative organization. External experts and interested clinicians can join the MTB via video conferencing. To assist treating physicians in interpreting genetic profiles, an individual report is generated within seven working days.
Main criteria for applying NGS profiling were young age of onset, rare cancer type or lack of standard treatment options. About half of the cases have been diagnosed with GI or pancreatic cancer. In about 21% of patients a germline mutation in a cancer susceptibility gene was identified, with most of the aberrations affecting DNA damage repair genes. In 50% of the cases, a molecular stratified treatment based on tumor genetic profile was recommended. 17% were subsequently treated with MTB-recommended personalized targeted agents, and for another 15% targeted agents serve as an option in case of future progression. Inclusion in a clinical trial was possible for 3% of the patients. Most common reasons that MTB-recommended therapy was not administered were very late stage disease or lack of drug access due to off-label use not covered by the insurance.
Conclusions: Comprehensive molecular characterization of patient tumors is feasible in the routine setting and provides a good solution especially for detecting rare mutations. However patient-centered interpreting of variants still remains a challenge since most clinicians are only limited trained in genomic profiling. The implementation of a molecular tumor board is therefore of central importance and will be crucial to further advances of personalized treatment. As technology envolves novel decision support tools and data sharing efforts may help us to fully realize the potential of the MTB in the future.

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Wissenschaftliches Symposium

MDS: Grundlagen

V224

Pre-clinical models of MDS

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Myelodysplastic Syndromes (MDS) are heterogeneous malignant clonal diseases of myeloid hematopoiesis. Clinically, MDS are characterized by dysplastic hematopoiesis with disturbed differentiation and production of mature blood components such as erythrocytes, leukocytes and platelets. In the past years a large number of MDS associated acquired molecular lesions have been discovered with next generation sequencing techniques. Nevertheless, translation of this abundance of possible molecular targets into new therapeutic strategies has been lagging behind in comparison to other hematologic malignancies. In part, this is due to a lack of functional experimental models of MDS in which new hypotheses could be evaluated pre-clinically. It has not been possible to develop MDS cell lines. In vitro cultivation of primary MDS cells is technically challenging, frequently completely futile or of limited duration. Some transgene mouse models have been developed, which present with MDS like phenotypes. However, these models are not able to replicate the molecular and clinical heterogeneity of human MDS. Establishment of MDS patient derived xenografts (PDX) in immunocompromised mice has also been difficult, especially for lower risk entities. Only recently, with the availability of improved mouse strains such as NSG, NSGS, NSGW41 or MISTRG, orthotopic injection routes and support by bone marrow derived stromal cells it has been possible to establish stable long term MDS xenografts with sufficient engraftment in order to validate the molecular profiles of the primary patient samples and perform functional assays. With increasing evidence for the importance of interaction between the hematopoietic and the stroma compartment, new techniques to further improve MDS PDX models by establishing fully humanized ectopic matrix supported niche units are currently being developed.

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V225

Metabolic pathways as therapeutic Targets in MDS

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Metabolism is being increasingly recognized as a therapeutic target in myeloid malignancies. Mutations in IDH1 and IDH2 have directed our attention to the tricarboxylic acid cycle that provides a platform for the synthesis of fatty acids and macromolecules. The TCA cycle receives its input from two sides: acetyl-CoA enters the TCA cycle on the one hand, and glutamine enters it on the other hand. The TCA cycle and the electron transport chain are the main functions of the mitochondrion that is responsible for bioenergetics, biosynthesis and redox balance of the cell. Recently, two drugs that target mitochondrial metabolism have been approved for AML patients: The IDH2 mutant-specific inhibitor enasidenib directly targets aberrant mitochondrial metabolism in MDS and AML cells. The BH3-mimetic venetoclax acts on mitochondrial metabolism by membrane stabilization and requires BIM-primed BCL-2 receptors to lower the apoptotic threshold of the mitochondrion below a critical level. Currently, other approaches to target aberrant metabolism are being developed. Cancer cells have a high demand of carbon backbones that are channeled into the TCA cycle by the rate-limiting enzymes pyruvate dehydrogenase (PDH) and α-ketoglutarate dehydrogenase (KGDH). These two enzymes can now be inhibited by the inhibitor CPI-613. This inhibitor showed clear signs of efficacy in AML patients and is now being developed in MDS and AML patients. To more specifically inhibit glutamine uptake, the glutaminase inhibitor telaglenastat (CB839) has been

developed. This inhibitor is now in clinical development. Arginine is an essential amino acid, which plays a role in pyrimidine and polyamine synthesis. The arginine-metabolizing enzyme arginase has been found increased in tumor cells, while arginine levels were reduced in plasma from cancer patients. An arginase inhibitor, which has shown anti-tumor activity, provided the rationale for further clinical development. Starting from the amino acid aspartate, dihydroorotate (DHO) is metabolized to orotate by dihydroorotate dehydrogenase (DHODH). This metabolism is the basis for pyrimidine synthesis and therefore essential for DNA replication. DHODH inhibitors are now being developed in myeloid malignancies, after preclinical data have shown an inhibitory effect in AML cells in vitro and in vivo. Thus, metabolism is coming into focus of targeted treatment approaches for patients with myeloid malignancies.

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V226

Impact of the inflammasome and immunological alterations in MDS

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In the past decade, aberrant innate immune activation and pro-inflammatory signaling within the malignant clone and the bone marrow microenvironment were identified as key drivers of myelodysplastic syndromes (MDS). Heterozygous deletion of chromosome 5q (del(5q)) is the most common cytogenetic abnormality in MDS. Dysregulation of the innate immune signaling is a featured signature of MDS with del(5q). Thus, del(5q) MDS represents an optimal model system to dissect the influence of genetic alterations on the hematopoietic stem cell function (HSCs; HSC-intrinsic effects) and to analyze the interaction of the 5q- hematopoietic clone with the microenvironment (HSC-extrinsic effects). Many genes that are involved in the innate immune signaling are located in or in close proximity to the common deleted regions of chromosome 5q.
RPS14, CSNK1A1 and microRNA (miR)-145 are universally co-deleted in the 5q- syndrome and each has been shown to drive distinct clinical features of del(5q) MDS in murine models.A novel mouse model for del(5q) MDS combining haploinsufficiency for these three alleles using mice with genetically engineered, conditional heterozygous inactivation of *Rps14*and *Csnk1a1* and stable knockdown of *miR-145*/*miR-146a* showedhigh fidelity to human MDS and recapitulates the del(5q) MDS phenotype.
The bone marrow microenvironment is abnormal and inflammatory in MDS, but whether this is a direct consequence of changes in hematopoietic cells or instead independent of the disease remained elusive for a long time. Increased expression of the alarmins S100A8/S100A9 in MDS-derived macrophages induces alarmin expression in neighboring mesenchymal stromal cells. Alarmin-expression in stromal cells leads to loss-of their hematopoiesis-supporting capacity. These data indicate that intrinsic defects of the del(5q) MDS hematopoietic stem cell directly alter the surrounding microenvironment, which in turn negatively affects hematopoiesis as an extrinsic mechanism.
Recent investigations have shown that activation of the NLRP3 inflammasome complex has more broad reaching importance, particularly as a possible disease-specific biomarker for MDS, and mechanistically, as a driver of cardiovascular morbidity/mortality in individuals with age-related, clonal hematopoiesis. Recognition of the mechanistic role of aberrant innate immune activation in MDS provides a new perspective for therapeutic development that could usher in a novel class of disease modifying agents.

Disclosure: No conflict of interest disclosed.

Fortbildung

Amyloidose

V227

Outpatient treatment of AL Amyloidosis in the hematology and onocology practice

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Amyloidoses are rare disorders characterized by misfolding of different kinds of precursor proteins leading to amyloid fibril formation and deposition causing progressive organ dysfunction. Treatment depends on the underlying disease. One of the most frequent forms is systemic light chain (AL) Amyloidosis where misfolded monoclonal free light chains deposits impair organ function especially of the heart and the kidney but also of liver, soft tissue, peripheral nervous system, autonomous nervous system and GI tract. To date effective approaches to clean the organs of amyloid is still in research, so the treatment goal is to interrupt production of monoclonal light chains by plasma cell directed chemotherapy. Interdisciplinary care of patients is necessary because of the disease pattern with involvement of multiple organs.
On the one hand due to the rarity of the disease, reference university centers are important but on the other hand, nearly all parts of diagnostics and the usually long lasting therapy are possible to be done outpatient so the hematology and oncology practice becomes an important role in this setting, too.
This talk gives a short overview about AL Amyloidosis and treatment options combined with corresponding case reports of the everyday practice.

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Wissenschaftliches Symposium

ALL: Perspektiven der Optimierung

V231

Antibody engineering: Room for improvement?

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Therapeutic antibodies have significantly improved the treatment options of leukemia and lymphoma patients, but a significant number of patients do not benefit from antibody therapy. Therefore, rational design of more potent antibody molecules represents a major goal in translational research.
A better understanding of the mechanisms of action triggered by monoclonal antibodies allowed the development of engineering approaches to improve antibodies´ natural effector functions. Antibody dependent cell-mediated cytotoxicity (ADCC) and phagocytosis are considered to play an important role in antibody-based immunotherapy. Therefore, strategies in improving these effector functions by Fc-engineering have been evaluated and with obinutuzumab were clinically translated in lymphoma therapy. By applying these approaches, also other promising target structures in ALL like CD19 can be addressed, which in the past were regarded as unfavorable targets for non-engineered antibodies. Besides engineered conventional antibodies a large number of antibody derivatives designed to potently engage immune effector cells are in different stages of clinical development. With the approval of blinatumomab in ALL, especially T cell-engaging bispecific antibodies have regained great attention, but also alternative antibody formats designed to potently activate NK cells via engagement of FcγRIIIa or NKG2D may represent promising agents.

While conventional antibodies and effector cell recruiting bispecific antibodies such as blinatumomab act via engagement of the patient´s immune system to trigger anti-leukemia activity, antibodies may also be used to directly deliver cytotoxic compounds. With inotuzumab-ozogamicin a prototypic antibody drug conjugate has recently been approved in ALL treatment and a variety of next generation agents entered clinical development. The design of antibody drug conjugates or cytotoxic fusion proteins (e.g. immunotoxins) requires special considerations since potent anti-tumor activity may only be obtained when the toxic payload is efficiently routed to a specific intracellular compartment.
In conclusion, a large panel of antibody engineering strategies have been developed allowing the rational design of next generation antibodies with tailor-made unique effector functions. Established and emerging antibody engineering concepts will be presented and discussed.

Disclosure: No conflict of interest disclosed.

V232
MRD: when and how in times of new treatment modalities?

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During the last couple of years innovative targeted therapies became available that led to high remission rates even in relapsed or refractory ALL. However, these treatment elements partly induce leukemia escape mechanisms with considerable changes in the leukemic genotype and phenotype that potentially influence the sensitivity and specificity of current methods to monitor MRD. In particular CD19 directed treatment drives extreme escape strategies by the leukemic cells. They are all characterized by the apparent loss of CD19 on the surface of the leukemic blasts hampering classical methods to identify MRD: usage of CD19 as backbone marker might lead to false MRD negativity, and addition of further B-cell-, precursor- and/or monocytic lineage markers are needed to unambiguously identify MRD cells by flow cytometry (FCM). Besides, optimal time-points to assess MRD in the setting of CD19 therapy still have to be defined. Also CD20 directed therapy is increasingly included into the upfront treatment protocols. Within the current GMALL 08 protocol Rituximab is applied to all Philadelphia chromosome (Ph)-negative BCP-ALLs, and CD20 expression is assessed at diagnosis and after prephase immediately prior to Rituximab application. We measured a significant increase in leukemic CD20 expression after prephase challenging the conventional eligibility criteria for CD20 targeted treatment and arguing in favour of an FCM-based characterization of the MRD population immediately prior to Rituximab application. Whereas MRD is accepted as most important prognostic factor in Ph-negative ALL, the utility of MRD assessment in Ph+ ALL is less defined. Within the GMALL we compared BCR-ABL1 and IG/TR based MRD analysis which uncovered significant discrepancies between both methodologies. This might be related to a multilineage involvement of the BCR-ABL1-positive clone suggesting that Ph+ ALL might resemble a CML-like disease manifesting in "lymphoid blast crisis" in a subset of Ph+ patients. It appears that in these patients IG/TR and BCR-ABL1 MRD may provide distinct insights in MRD kinetics of different leukemic subpopulations, potentially allowing for separately monitoring the response of the "CML-part" and the "lymphoid blast clone" with their potential differences in sensitivity against chemotherapy, tyrosine kinase inhibitors, stem cell transplantation and possibly also immunotherapies.

Disclosure: Monika Brüggemann: Advisory Role: Amgen, Incyte; Financing of Scientific Research: Amgen, Incyte, Roche, Pfizer; Expert Testimony: Amgen

V233
Antibodies versus CAR T cells in ALL

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Cellular therapy with chimeric antigen receptor gene-modified T cells (CAR T cells) directed against B lineage antigens is a major innovation in the treatment of B cell malignancies. Bispecific T cell engagers and immunotoxins provide alternative B-lineage targeting therapies and are also highly effective to induce remissions in patients with chemorefractory disease. In contrast to CAR T cells, which require complex and expensive patient-individual manufacturing, T cell engagers and immunotoxins are available off-the-shelf. The conceptual advantage of CAR T cells is their ability to induce long-term immune control of the disease by in vivo persistence of memory populations of the CAR T cells, leading to durable remissions even as stand-alone therapies. Moreover, in contrast to antibody fragments and immunotoxins, CAR T cells effectively penetrate endothelial barriers and clear CNS disease and other extramedullary disease manifestations.
Whereas alternative B-lineage targeting agents are currently considered effective options to bridge patients with relapsed and/or refractory disease to potentially curative subsequent allogeneic stem cell transplants, CAR T cell therapy could also serve as alternative to current therapies, with the goal to prevent the significant late effects associated with intensive chemotherapy and stem cell transplant.
To establish the optimal role of antibody-based therapies also in the first and second line therapy of ALL, we need to perform comparative phase III multicenter trials in the well-established national and international consortiums that allow to randomize large numbers of patients. To include CAR T cell therapy into future studies, reliable and affordable access to standardized and highly comparable CAR T cell products in all the countries that participate will be needed.
A limitation to all types of antibody-based therapies is relapse by emergence of antigen-negative escape variants of the disease. Thus, combinatorial targeting approaches will be needed to fully exploit the potential of these treatment modalities in the future.

Disclosure: Claudia Rössig: Financing of Scientific Research: Pfizer, Celgene, Amgen, Roche, EUSA Pharma, Novartis

Wissenschaftliches Symposium

Entzündung und Fibrose bei MPN

V239
Dissecting mechanisms in the initiation and progression of bone marrow fibrosis

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Bone marrow (BM) fibrosis is associated with a variety of malignant hematopoietic disorders and is a central pathological feature of primary myelofibrosis (PMF). Although the somatic mutations that drive the development of MPN have been largely defined, the cellular targets of bone marrow fibrosis still remain obscure. In MPN, mesenchymal stromal cells (MSCs), key components of the HSC niche, have recently been shown to acquire a secretory, extracellular matrix remodelling phenotype and lose their hematopoiesis-supporting capacity. It was demonstrated in a knock-in Jak2V617F MPN mouse model that MPN progression in the bone marrow creates neuropathic changes in the BM niche, which affect the activity of perivascular MSCs and alter the function of the HSC niche.
We demonstrated using genetic fate tracing in two murine models of PMF and patient samples that 1) Gli1^{+}mesenchymal stromal cells (MSC) are

fibrosis-driving cells in PMF, 2) that their frequency correlates with fibrosis severity in patients, and 3) that their ablation ameliorates BM fibrosis (3). Our data in patient samples and in murine models thus indicate that targeting Gli/Hedgehog (Hh)-signaling is an attractive strategy for the treatment of PMF. We now sought to determine the underlying mechanisms for the fibrotic transformation of sort-purified Gli1+ cells in bone marrow fibrosis and homeostasis using RNA sequencing and also single cell RNA sequencing using an unbiased approach for the purification of stromal cells. Differential gene expression analysis demonstrated that megakaryocyte-associated genes were significantly enriched in the fibrosis-driving cells, in particular the chemokine Cxcl4, also called platelet-factor 4 (PF4). Using in vitro co-culture assays and genetic knockdown experiments, we now demonstrate that Cxcl4 plays a central role in the activation of Gli1^{+}stromal cells and their myofibroblastic differentiation. Our data demonstrate that CXCL4 plays a central role in the fibrotic transformation of Gli1+ cells in PMF and is a potential therapeutic target. We also elucidated fibrosis-driving subpopulations in the bone marrow in fibrosis and mapped their transcriptional reprogramming during pre-fibrosis and fibrosis. Understanding the mechanisms that lead to fibrosis initiation and progression is crucial to ultimately identify novel curative targeted therapies.

Disclosure: No conflict of interest disclosed.

Fortbildung

Melanom: Therapie des metastasierten Melanoms

V248

Melanoma: treatment of metastasized melanoma

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Im letzten Jahrzehnt sind in der Behandlung des metastasierten Melanoms erhebliche Fortschritte erzielt worden. Dank neuer Immuntherapien in Form von Checkpoint-Inhibitoren, welche mittlerweile auch bei anderen, soliden Tumoren etablierte, klassische Chemotherapeutika in diversen Therapielinien ablösen konnten, aber auch dank zielgerichteter Therapien (BRAF-, MEK-Inhibitoren). Die Erweiterung unseres Armamentariums birgt jedoch auch Fragen für die Klinik. Als Beispiel kann die Auswahl der besten Behandlungssequenz in Abhängigkeit des klinischen Settings genannt werden. Das Toxizitätsprofil, die Ansprechrate und Dauer des Therapieansprechens sind wichtige Faktoren die Auswahl der Therapie betreffend; die Tumorlast, die Lokalisation der Metastasierung und die Proliferation der Erkrankung, zu berücksichtigende Faktoren die Erkrankung betreffend. Diese Faktoren sollten, angepasst an die Komorbiditäten, dem Alter und den Allgemeinzustand der Patienten, in den Therapieentscheid integriert werden.

Disclosure: No conflict of interest disclosed.

Freier Vortrag

Kolon-/Rektumkarzinom

V253

Final results of the randomized phase II VOLFI trial (AIO-KRK0109): mFOLFOXIRI + Panitumumab versus FOLFOXIRI as first-line treatment in patients with RAS wild- type metastatic colorectal cancer (mCRC)

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Introduction: This trial evaluated activity and safety of mFOLFOXIRI + panitumumab (P) vs FOLFOXIRI in ECOG 0-1, primarily non-resectable mCRC patients. The primary endpoint was initially presented at ASCO and ESMO 2018. Now we report the final results including central radiology review.

Methods: Prospective 2:1 randomized, controlled, open label phase II trial comparing mFOLFOXIRI + P (arm A) with FOLFOXIRI (arm B), both arms q2w. Stratified cohort 2: chance of secondary resection of metastatic lesions (n=31). Primary endpoint was ORR, secondary endpoints were secondary resection rate, PFS, OS, toxicity. Radiologic images from the study were centrally examined according to RECIST 1.1: ORR, early tumor shrinkage (=ETS: 20% shrinkage at first re-assessment) and depth of response (DpR). Financially supported by an unrestricted grant from Amgen.

Results: A total of 96 patients were randomized (63 arm A, 33 arm B). Images were available for 88 of 96 patients (91.7%). According to central and investigator review, objective response rates were 89.2% and 87.3% vs 66.7% and 60.6% with FOLFOXIRI plus P vs FOLFOXIRI alone, respectively (P=0.02 and 0.004). ETS was also significantly more frequent (85.7% vs. 60.0%; P=0.01) and DPR (58.9% vs. 40.9%, P= 0.004) significantly greater with P as compared to chemotherapy alone. Secondary resections of metastases in the ITT population and cohort 2 were observed in 33·3% (arm A) versus 12·1% (arm B) (p=0·029) and 75% (arm A) versus 36.4% (arm B) (p=0.05), respectively. Median PFS was similar in the study arms (9.7 mo in both arms, HR 1.071). OS showed a strong trend in favour of the P-containing arm with a median OS of 35.7 mo compared to 29.8 mo in arm B (HR: 0·67; 95%-CI 0.41-1.11, P=0·12). mOS was 52.0 mo versus 41.7 mo in cohort 2 (HR 0.413; 95%-CI 0.15-1.12, p=0.07). Further results regarding to sidedness and BRAF mutational status will be presented.

Conclusions: The addition of panitumumab to a mFOLFOXIRI regimen in patients with RAS wildtype metastatic colorectal cancer significantly improved objective response rate both investigator and centrally assessed as well as the rate of secondary resection of metastases. Although PFS was comparable, there was a strong trend towards improved OS in the panitumumab arm. Therefore, intensive upfront therapy with modified FOLFIRINOX+P represents a valuable treatment option in patients with the need of a highly active 1st-line therapy.

Disclosure: Michael Geißler: Advisory Role: AMGEN, Merck, Lilly, MSD, Sanofi; Financing of Scientific Research: AMGEN, Merck, Lilly, MSD, Sanofi; Expert Testimony: AMGEN
Dominik Modest: Advisory Role: AMGEN, Merck, Roche; Expert Testimony: AMGEN, Merck, Roche

V254

Quality of life during 1st-line FOLFOXIRI+/- Panitumumab in RAS wild-type metastatic colorectal cancer: results from the randomized VOLFI trial (AIO KRK-0109)

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Introduction: This trial evaluated activity and safety of mFOLFOXIRI + panitumumab (P) vs FOLFOXIRI in ECOG 0-1, primarily non-resectable mCRC patients. Here, we report the quality of life data.
Methods: Prospective 2:1 randomized, phase II trial comparing mFOLFOXIRI (Ox 85 mg/m2, Iri 150 mg/m2, 5-FU 3000mg/m2 cont. 48h, LV 200 mg/m2) + P 6 mg/KG (arm A) with FOLFOXIRI (Ox 85 mg/m2, Iri 165 mg/m2, 5-FU 3200mg/m2 cont. 48h, LV 200 mg/m2; arm B), both arms q2w. Cohort 1: irresectable mCRC; cohort 2: chance of secondary resection of metastatic lesions. Primary endpoint was ORR, secondary endpoints were secondary resection rate (cohort 2), toxicity, quality of life (QoL, QLQ-C30). Between-treatment differences in QoL were assessed from baseline to disease progression, and to discontinuation of 1st-line treatment, using analysis of covariance (ANCOVA).
Results: A total of 96 patients were randomized (63 arm A, 33 arm B). There were significantly higher ORR (87.3% vs. 60.6%, p=0.004), ETS (85.7% vs 60.0%, p=0.01) and DpR (58.9% vs. 40.9%) in the P arm compared to FOLFOXIRI alone. QoL analyses was performed in 51 patients in arm A and 26 patients in arm B. There were no statistically significant differences between treatment arms from baseline to progression or to discontinuation. Although significantly more secondary resections of metastases were achieved in the P arm of cohort 2 (75.0% vs. 36.4%, p=0.05), QoL was not different between cohorts 1 and 2 and the treatment arms, respectively. Toxicity or patient wish as the reason for end of therapy were not different between the treatment arms A and B (12.7% vs. 21.2% and 0% vs 6.1%, respectively). Grade III/IV toxicities were numerically higher in the P arm (81.3% vs. 66.7%). This increase was mainly due to toxicities such as diarrhea (25.0% vs 12.1%), mucositis (9.4 vs. 0%), rash (14.1% vs. 0%), and fatigue (7.8% vs. 0%). Hematological toxicity was not increased in the P arm, although more G-CSF was administered in arm A (30.3% vs. 18.2%).
Conclusions: mFOLFOXIRI plus P results in significantly higher response rates compared to FOLFOXIRI in RAS wild-type mCRC. Although toxicity was increased, QL reporting was similar in both arms. Therefore, intensive upfront therapy with modified FOLFIRINOX+P represents a valuable treatment option in patients with the need of a highly active 1st-line therapy.

Disclosure: Michael Geißler: Advisory Role: AMGEN, Lilly, Merck, Bayer, MSD; Financing of Scientific Research: AMGEN, Lilly, Merck, Bayer, MSD; Expert Testimony: AMGEN
Dominik Modest: Advisory Role: AMGEN, Roche, Merck; Financing of Scientific Research: AMGEN, Roche, Merck; Expert Testimony: AMGEN, Roche, Merck

V255

The predictive role of ctDNA for response to neoadjuvant chemoradiotherapy in locally advanced rectal cancer (NEORECT trial)

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Introduction: Stage II or III locally advanced rectal cancer is treated with neoadjuvant chemoradiotherapy (nCRT) followed by total mesorectal excision (TME). Complete pathologic remissions (pCR) are observed in 20-30% of patients (pts) undergoing nCRT. Several studies and case series comparing TME and "watch and wait" strategy after nCRT have reported similar excellent outcome. Thus, non-surgical treatment for locally advanced rectal cancer might constitute a treatment option for selected pts. However, reliable (bio-)markers predicting pCR are missing. Circulating tumor DNA (ctDNA) is suitable for monitoring treatment response and detecting minimal residual disease (MRD). We hypothesized that monitoring ctDNA changes in pts with rectal cancer undergoing nCRT might facilitate identifying pts reaching pCR and thereby prospectively guiding therapy.
Methods: We have conducted a prospective single center study in pts with stage II and III rectal cancer subjected to nCRT and TME. Plasma samples were collected before, during and after nCRT and before TME. Circulating free DNA was extracted from 4 ml plasma. Informative somatic mutations were identified initially in rectal biopsies by NGS (Thermo Fisher Oncomine HotSpot Panel) and subsequently used for ctDNA quantification by dPCR (Thermo Fisher QuantStudio 3D Digital PCR System).
Results: By the current interims analysis, 30 pts were included in the trial. Median age was 67 years (range 49-81), 60% were male. 10 pts who completed the protocol and reached TME had ctDNA samples available for analysis. Of these, 6 pts had detectable ctDNA prior to therapy. Lower detection limit for dPCR on plasma from rectal cancer pts was 0.1%. In 6 out of 6 pts, decrease of ctDNA was observable during nCRT. pCR was reached in 4 pts without detectable ctDNA and in 2 out of the 6 pts with decreasing ctDNA. One patient showed a continuous decline of ctDNA during nCRT (1.15%, 0.9% and 0.55%). Directly before TME, a 10-fold steep rise of mutant alleles (5.5%) accompanied by new hepatic metastases was observed followed by direct decrease of mutant alleles after resection of metastases. Our preliminary results indicate an interrelation between absence or early decrease of ctDNA and remission after nCRT.
Conclusions: ctDNA is detectable in pts with stage II and III rectal cancer undergoing nCRT. Monitoring ctDNA levels and dynamics during nCRT is a feasible approach to be further developed as predictive marker for achieving pCR.

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Rainer Claus: Advisory Role: AbbVie, Roche, Janssen Cilag, Gilead, Celgene; Stock Ownership: Beigene

V256

Quality of life (QoL) in patients with aflibercept (AFL) and FOLFIRI for metastatic colorectal cancer (mCRC) - interim analysis with focus on mutational status of the non-interventional study QoLiTrap (AIO-LQ-0113)

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Introduction: The anti-angiogenic fusion protein AFL targets VEGF-A, VEGF-B and PlGF. It is approved in combination with FOLFIRI for treatment of mCRC that is resistant to or has progressed after oxaliplatin-containing therapy.
Methods: QoLiTrap is an ongoing non-interventional study conducted in the DACH region to evaluate Quality of Life in 1500 mCRC patients treated with AFL+FOLFIRI using the EORTC-QLQ C30 questionnaire at baseline and before every cycle.
Results: For this interim analysis (cut-off: 02 Jan 2019) 839 patients (mean age: 64.7 ± 9.8 years; 64.4% male, 50.9% with documented RAS mutation, ECOG 0-1: 86.0%) who completed the baseline and at least 2 post-baseline EORTC-QLQ C30 questionnaires were evaluated.
AFL was administered for a median of 7 cycles to RAS-wild-type (wt) (range: 1-61) and RAS-mutated (mut) (range 1-44) patients. Of those 772 patients with a previous therapy, 56.7 % received bevacizumab (BEV), 15.3% anti-EGFR antibodies (cetuximab and/or panitumumab) and 14.6 % both agents. 42.1% of RAS-wt and 56.7% of RAS-mut patients received AFL in second line setting.
Median global health score at baseline was 58.3 and decreased moderately (mean change -3.4%, p< 0.0001) within the first 12 weeks of therapy. Reduction was greater in RAS-mut compared to RAS-wt (mean change -5.1% vs. -1.1%).
Among evaluable patients receiving AFL in second line after anti-EGFR or BEV, 25.0% exhibited CR+PR and 51.6% had SD as best response. RAS mutational status had an impact on the rate of disease control in these patients (85.7% disease control in RAS-wt vs. 69.8% in RAS-mut; p= 0.0242). Median PFS in these patients was 7.6 months (95% CI 6.3- 12.4) for RAS-wt patients and 8.2 months (95% CI 5.9- 9.0) for RAS-mut patients.
Toxicity was in line with the known safety profile.
Conclusions: The current interim analysis suggests that FOLFIRI + AFL administered in routine conditions after either BEV or anti-EGFR is an active second-line therapy. Both RAS-wt and RAS-mut patients benefited from this combination. No clinically relevant decrease in global health status was observed during study treatment.

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Ralf-Dieter Hofheinz: Advisory Role: Amgen, Roche, Merck, Sanofi, Bayer, Ipsen, BMS, MSD, Deutsche Krebshilfe; Financing of Scientific Research: Amgen, Roche, Merck, Sanofi, Bayer, medac, MSD, Boehringer, BMS, Celgene, Ipsen, Saladax,; Expert Testimony: Amgen, medac, Merck, Roche, Sanofi

V257

Circulating tumor DNA for detection of recurrence in colorectal cancer

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Introduction: In malignant diseases, plasma cell-free DNA (cfDNA) is enriched with circulating tumor DNA (ctDNA) that carries tumor-derived genetic aberrations. As the release of ctDNA from tumor cells may vary owing to cancer progression, the detection of ctDNA has potential to serve as a liquid biopsy for early assessment of recurrence. In order to accurately detect plasma ctDNA for diagnostic purposes, we performed a detailed evaluation on the efficacy of different cfDNA preservation and extraction approaches. To test the feasibility of ctDNA for early detection of recurrence, we retrospectively analyzed follow-up samples of patients with advanced colorectal cancer (CRC). Time to relapse was compared between the detection of ctDNA and routine imaging-based staging.
Methods: To monitor ctDNA stability, blood of a KRAS c.38G>A positive patient was incubated (22°C/4d) using different collection tubes (EDTA, Streck) and processed at 0h-96h. Extraction yields and ctDNA detection were compared for extraction kits from Analytik Jena (AJ), Qiagen (Q) and Zymo Research (ZR). To test the usability of ctDNA in clinical settings, serial plasma samples from 14 CRC patients with relapse during adjuvant treatment were analyzed for the detection of known mutations. Target regions were amplified using 5 ng cfDNA and sequenced on an Ion Torrent PGM/S5 XL with a median coverage of 64315 reads.
Results: Yields of cfDNA were significantly (p>0.05) higher using procedures by ZR and Q (5.6-5.3 ng) compared to the protocol of AJ (2.8 ng). ctDNA levels in Streck tubes were stable compared to EDTA tubes for up to 96h. Using optimized conditions, tumor-specific variants were detected in matched cfDNA of CRC patients with a sensitivity of 92%. Generally, concentrations of plasma cfDNA correlated with the burden of mutant alleles. Rates of plasma ctDNA accumulation increased progressively prior to clinical relapse (up to 0.012% ctDNA d-1). Highest concentrations of ctDNA were detected at the time of imaging-based relapse with a median VAF of 0.38% (range 0.18-5.04%). The median delta between imaging- and ctDNA-based detection of recurrence was 112 days (0-226d).
Conclusion: Yields of plasma cfDNA and the detection of ctDNA can be enhanced by the choice of adequate preservation and extraction protocols. The NGS-based detection of relapse in CRC patients using plasma ctDNA is feasible with excellent sensitivity and reproducibility and superior compared to imaging based diagnostics.

Disclosure: Sebastian Stasik: No conflict of interest disclosed.
Christian Thiede: Employment or Leadership Position: CEO and co-owner of AgenDix GmbH, a company performing molecular diagnostics.

V258

Impact of NGS panel size on potential treatment options in metastasized colorectal cancer

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Background: In routine clinical cancer care, next-generation sequencing (NGS) panels are already widely used for defining tumor mutation profiles and determining treatment approaches. However, established panels often vary considerably in size. While some cover only hotspots and targeted regions of less than 20 cancer-related genes, others comprise several hundred genes that may contribute to tumorigenesis. For most oncologists, balancing the extent of available data against costs and limited resources remains a challenge. We evaluated, if in metastatic colorectal cancer (mCRC) patients a large-scale NGS approach has the potential to impact

therapeutic decisions by identifying additional mutations of known or potential clinical significance.
Methods: Since RAS (KRAS and NRAS) status is a pre-requisite for the use of anti-EGFR agents for mCRC patients, a targeted colorectal cancer NGS panel of 30 genes (mainly components of the oncogenic MAPK or WNT/β-Catenin signaling pathways) is now routinely utilized in our hospital. In 23 patients with either lack of further standard treatment options or early onset of disease, a comprehensive multi-gene panel covering 710 cancer-related genes and selected chromosomal translocations was used. Both panels report copy number variants (CNVs). However, Tumor Mutational Burden (TMB) was only provided by the large-scale NGS panel. All genetic analyses were performed in certified laboratories.
Results: Using the large-scale NGS panel, driver mutations in 38 different oncogenic genes were identified in 22 of 23 patients. Most commonly muted genes were APC, KRAS, TP53 and BRAF, which are part of both panels. However, 26 oncogenic driver mutations would have been missed with the targeted colorectal cancer panel approach, including four germline mutations in genes involved in DNA repair pathways. Molecular stratified treatment was recommended in 6 of 22 patients (including one referral to a clinical trial) with four of the druggable alterations covered only by the large-scale NGS panel.
Conclusions: Comprehensive NGS-based genetic testing is able to provide additional molecularly stratified treatment options beyond standard therapy in a considerable amount of patients with mCRC. However, if these options are eventually adopted into clinical care of the individual patient and translate into clinical benefit remains to be elucidated.

Disclosure: No conflict of interest disclosed.

Freier Vortrag

Kopf-/Hals-Tumoren

V259

Prognostic impact of molecular subtypes of head and neck cancer

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Background: The CEFCID trial was a randomized, multi-centre phase II trial in Germany for recurrent/metastatic head and neck cancer (HNC) which evaluated treatment intensification by the addition of docetaxel to platinum, 5-FU and cetuximab. Molecular subtypes of head and neck cancer were assessed by gene expression analysis to evaluate the feasibility of working with long term stored FFPE tissue and explore the prognostic and predictive value of molecular subtypes in this setting. In preclinical models, we observed a statistical significant correlation of cetuximab treatment failure and inflamed/mesenchymal subtype.
Methods: The 228 strongest subtype defining genes, based on previous analysis (1) were chosen for a nanostring panel design. RNA was micro-dissected from FFPE embedded tissue after identification of tumor on hematoxylin/eosin stained slides by board certified pathologists. From the 180 patients treated within the trial, 96 had sufficient RNA extracted from their tumor block, which passed quality control for nanostring analyses. For computational analysis R and SPSS v21 was used.
Results: By assigning 92 of 96 (95,8%) samples with statistical significance to either basal, classical or inflamed/mesenchymal subtype, the designed nanostring panel proved feasible to determine the molecular subtypes of head and neck cancer. No correlation of molecular subtype and treatment response to PFC or D-PFC, gender, smoking habits, cetuximab maintenance treatment and age was detected. Evaluation of the prognostic value of molecular subtypes showed a significant survival benefit for patients with basal subtype compared to inflamed/mesenchymal; 64.08 months vs 28.5 months (Log rank Mantel-cox 0.018).
Conclusion: Based on a 228 gene panel, molecular subtype of head and neck cancer can be determined by nanostring analysis. For combined chemotherapeutic agents as applied in the CEFCID trial the retrospective analysis did not show a predictive value of molecular subtypes. Tumor prognosis was substantially different based on molecular subtype. Especially, in the light of evolving concepts of therapy stratification based on tumor biology in head and neck cancer, the easy to use approach of nanostring analysis on FFPE stored tissue proves the feasibility to determine molecular subtype of HNC.

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V260

Induction chemotherapy with Docetaxel, Cisplatin and Cetuximab results in improved response rates if compared to Docetaxel, Cisplatin and 5-FU for locally advanced or inoperable squamous cell carcinoma of the head and neck: promising results of the Austrian multicentric phase II trial (AGMT)

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Introduction: Induction chemotherapy (ICT) with Cisplatin (P), 5-FU (F) and Taxanes (T) is a therapeutical option in patients suffering from locally advanced or unresectable stage III or IV squamous cell carcinoma of the head and neck (SCCHN). The role of ICT is controversial and toxicity and/or delay of radiotherapy may reduce the potential benefit of this treatment regimen. Here we report promising results of a randomized phase II trial comparing TPF with TP and Cetuximab (C) replacing F.
Methods: In our trial, *N*=100 patients with locally advanced or unresectable stage III or IV SCCHN were randomly assigned to either Arm A (*N*= 49), receiving TPF, or Arm B (*N*= 51), receiving TPC, both followed by radiotherapy (RT) + C. The primary end-point of the study was overall response rate (ORR) three months after RT + C was finished.
Results: We observed a remarkable response rate (CR + PR) of 86.4% in the TPC-arm that compared favorably with 77.5% responding patients in the TPF-arm three months after RT + C was completed. OS and PFS were similar in both arms. After 400 days we observed an OS rate of 79% in the TPF and 86% in the TPC arm, and a PFS rate of 67% in the TPF and 70% in the TPC arm. TPC containing ICT led to less serious adverse events (SAEs), including blood and lymphatic disorders (40.8% in TPF arm, 27.5% in TPC arm) and metabolism and nutrition disorders (22.4% in TPF arm, 9.8% in TPC arm) during ICT. Interestingly, in HPVp16 positive patients, 88.24% in the TPF-arm and 93.33% in the TPC-arm showed CR or PR three months after RT + C, whereas only 69.57% in the TPF-arm and 82.76% in the TPC-arm showed CR or PR. We only lost one patient because of treatment-related mortality (TRM) and no delay from the end of ICT to local radiotherapy was observed in any patient. All patients received RT + C within three weeks after ICT was completed.

Conclusions: In conclusion, TPC is a feasible and tolerable therapy regimen and can be applied within one day with less hematological toxicities. In contrast, more local reactions were observed after TPC. TPC containing ICT leads to improved response rates, while OS and PFS were similar in both arms. TRM was extremely low with 1%. Therefore, we conclude, that TPC containing ICT could be a considerable therapeutical alternative for patients with locally advanced or unresectable stage III or IV SCCHN, who are eligible for ICT.

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Richard Greil: Advisory Role: BMS, Merck; Financing of Scientific Research: BMS, Merck; Expert Testimony: BMS, Merck

V261

HANNA - real-world evidence from a German, prospective, non-interventional study with nivolumab in patients with squamous cell carcinoma of the head and neck (SCCHN)

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Introduction: Nivolumab, a fully human IgG4 monoclonal antibody targeting the PD-1 receptor on activated T-cells, is approved in the EU for the treatment of patients with recurrent or metastatic SCCHN progressing on or after platinum-based therapy. The pivotal trial (CheckMate 141, NCT02105636) demonstrated significant superior overall survival (OS), higher response rates, and a favorable safety profile with stabilized quality of life (QoL) compared to investigator's choice therapy (methotrexate, docetaxel, or cetuximab). To evaluate the efficacy, tolerability and safety profile of nivolumab as well as QoL associated with the treatment in a broader patient population, further collection of data in a post-approval prospective non-interventional trial is useful.
Methods: HANNA, a prospective, observational, multicenter study, started in Germany in May 2017. Primary study objective is OS. Secondary objectives include progression free survival, response rates, baseline characteristics, safety profiles and patient reported outcomes. The study will enroll 385 adult patients diagnosed with SCCHN progressing on or after platinum-based therapy, who start a systemic therapy with nivolumab for the first time according to label.
Results: By March 2019, 200 patients were recruited in 54 study sites. Baseline characteristics are available for 191 patients: 83.9% male; median age 62.0 years ; 69.6% smokers; ECOG performance status 0 or 1 in 60.7%; ECOG PS 2 in 23.6% and ECOG PS 3 in 4.2%. 48.4% of the patients had a progression during or within 6 months after platinum-based therapy, whereas 29.8% of the patients had a progression more than 6 months after platinum-based therapy. 27.2% of the patients received nivolumab as first palliative therapy after platinum-based therapy, 59.2% as second therapy and 10.4% as later therapy. Drug related adverse events and serious adverse events are observed in 17.3% and 9.4% of patients, respectively. Interim quality of life data indicate a tendency towards stabilization or slight improvements reported by the patients for the FACT-H&N questionnaire. Survival probability at 6 months is 67% (CI 95% 0.59, 0.75).
Conclusions: While this SCCHN patient population was slightly older, with worse performance status, 6 month OS was improved compared with the pivotal CheckMate 141 trial. Treatment with nivolumab was well tolerated and QoL stabilized under therapy.

Disclosure: Eyck von der Heyde: Employment or Leadership Position: Gesellschafter der onkologischen Praxis Runde Straße Hannover; Advisory Role: Roche, Novartis, BMS, Boehringer Ingelheim; Financing of Scientific Research: Novartis, Roche, BMS, Boehringer Ingelheim; Expert Testimony: Novartis, Roche, BMS, Boehringer Ingelheim, Lilly, Ipsen
Andreas Dietz: Advisory Role: AstraZeneca, BMS, Merck Serono, MSD, Nordine, Roche, Sanofi; Financing of Scientific Research: AstraZeneca, BMS, Merck Serono, MSD, Nordine, Roche, Sanofi; Expert Testimony: Merck Serono, MSD, Roche

V262

Liquid biopsy in head and neck cancer: circulating cell-free DNA in plasma and saliva for minimally invasive cancer monitoring

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Introduction: In patients with head and neck cancer (HNC), disease monitoring and detection of tumor recurrence are currently based on clinical examination and imaging. Tumor-derived circulating nucleic acids are present in body fluids of patients with cancer. Liquid profiling of cell-free tumor DNA (ctDNA) in plasma and saliva could provide better tumor monitoring and improve the early recurrence detection. Here, we aim to determine to which extent circulating ctDNA and human papillomavirus (HPV) DNA can be detected in plasma and saliva, and which material is more suitable for liquid-based HNC profiling.
Methods: In 91 HNC patients, blood and saliva samples were prospectively collected after surgery. In 9 patients, mutations in the primary tumor tissue were analyzed with next-generation panel sequencing (45 genes) and ctDNA was quantified using individually designed mutation-specific digital droplet PCR (ddPCR) assays. Further, samples from all 91 patients were analyzed with ddPCR assays to detect two *TERT*promoter hotspot mutations, allowing ctDNA quantification without prior tumor sequencing. In 50 patients with HPV-associated tumor localizations, cell-free DNA (cfDNA) was tested for HPV16 (*E7*).
Results: In 25% (23/91), ctDNA was detected in plasma with mutation-specific ddPCR assays, of which 22% were early tumor stages (I/II). In the course of disease an increase in tumor load could be detected in blood or saliva on average 5.4 months (2 weeks to 13 months) earlier than by clinical imaging.
In p16-positive tumor patients (n=16), cfHPV16 DNA was identified in plasma in 39% (6/16), of which 50% were early tumor stages. In saliva, ctDNA was detected in 75% (3/4) of samples and cfHPV16 DNA in 25% (1/4) of samples to date.
Conclusions: CtDNA detection with ddPCR is a promising tool for cancer profiling even in early stages and could improve the early recurrence detection. Saliva seems to allow for higher ctDNA detection rates than blood plasma. In HPV-associated tumors, cfHPV DNA could be a complementary marker for disease monitoring.

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Christof Winter: Advisory Role: Beratungstätigkeit für Bristol-Myers Squibb

V263

Prospective molecular analysis and targeted treatment of salivary gland tumors

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Introduction: No standard therapy exists for advanced salivary gland tumors (SGT) and the prognosis is poor. We analyzed clinical information, genomic aberrations, therapy recommendations, and outcome of patients with advanced SGT discussed at the Charité molecular tumor board (MTB).

Methods: Patients with advanced SGT and no curative treatment option were presented at the Charité MTB. Fresh tissue sampling and whole exome (WES) and RNA sequencing (RNA-seq) was done within the DKTK-MASTER program. Immunohistochemical analyses (EGFR, HER2, AR as well as validation tests) and/or Panel Sequencing were either performed additionally, or in patients that did not qualify for the MASTER program. Results from molecular testing were annotated and discussed at the MTB. Patients were followed-up.

Results: Between 2016-2019, 25 patients (median age 56 years, 14 male, 11 female) with advanced SGT were presented at the MTB (10 adenoid-cystic carcinomas, 5 adenocarcinomas, 3 mucoepidermoid, 2 carcinosarcoma, 5 miscellaneous). Successful WES/RNA-seq was performed on tumor tissue from 18 patients. For another 3 patients, panel sequencing and/or IHC analyses was done. No results were available for 4 patients. After annotation and interdisciplinary discussion of results, a median of 2 recommendations were made for 21 patients, each. Most frequently proposed treatment options by the MTB were FGFR inhibitors in 8 patients, antiandrogen therapy in 6, mTOR inhibitors in 5 and EGFR and HDAC inhibitors in 4, each. Treatments following these recommendations were initiated in 8 patients, 1 of which received a second recommended therapy after progression (antiandrogen therapy in 4, EGFR inhibitor in 2, a PDGFR, mTOR and PARP inhibitor in 1, each). A clinical benefit (CR = 1; Mixed Response = 1, SD = 3) was achieved in 5 patients, including a complete response in a patient with an androgen receptor positive, metastatic adenocarcinoma of the parotid gland, treated with antiandrogen therapy.

Conclusions: Prospective molecular analyses are a feasible diagnostic tool in patients with advanced SGT. Early evidence of activity can be seen in a subset of patients treated with a precision oncology strategy. These results suggest further exploration of personalized therapy in these hard-to-treat tumors.

Disclosure: Damian Rieke: Advisory Role: Alacris Theranostics; Financing of Scientific Research: Bristol Myers-Squibb Ulrich Keilholz: Advisory Role: AstraZeneca; Bristol-Myers Squibb; Merck Serono; MSD Oncology; pfizer; Financing of Scientific Research: AstraZeneca; Bristol-Myers Squibb; Glycotope GmbH; Merck KGaA; MSD Oncology; Novartis; Pfizer; Roche/Genentech; Gylcotope; Novartis; Expert Testimony: Pfizer; Other Financial Relationships: AstraZeneca; Merck Serono; MSD Oncology

V264

Identification of an APOBEC-enriched subgroup of HPV-negative HNSCC with distinct immune activation and evasion

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Background: Immune checkpoint inhibition has become an important treatment option in head and neck squamous cell carcinoma (HNSCC). Robust biomarkers for immune checkpoint inhibition are lacking to date.

Methods: Viral status, gene expression signatures, mutational load and mutational signatures were assessed in whole exome and RNA-sequencing data of the HNSCC TCGA dataset (N = 496) and a validation set from the DKTK MASTER cohort (N = 10). APOBEC expression was validated in a public single-cell gene expression data from 17 HPV-negative HNSCC

Results: HPV-negative tumors showed lower levels of inflammation and APOBEC-activation than HPV-positive tumors. Among HPV-negative tumors, a subgroup of APOBEC3-enriched HNSCC showed higher T-cell inflammation and immune checkpoint expression compared to non-APOBEC-associated tumors. The APOBEC3-associated mutation signature (TCW motif), but not total mutational burden were significantly associated with inflammation in these patients. Distinct immune evasion was identified by significantly higher levels of immune checkpoint molecular expression and significantly more mutations in immune-evasion pathways. The expression of APOBEC3B and 3C genes was identified in tumor cells and correlated with inflammation. These results could be validated in a cohort from the DKTK MASTER program.

Conclusions: A subgroup of HPV-negative HNSCC shows features of APOBEC-activation and a distinct immunogenic phenotype. This subgroup should be further explored to better stratify patients for immune checkpoint inhibition.

Disclosure: Damian Rieke: Advisory Role: Alacris Theranostics; Financing of Scientific Research: Bristol-Myers Squibb
Ulrich Keilholz: Advisory Role: AstraZeneca; Bristol-Myers Squibb; Merck Serono; MSD Oncology; Pfizer; Financing of Scientific Research: AstraZeneca; Bristol-Myers Squibb; Glycotope GmbH; Merck KGaA; Merck Serono; MSD Oncology; Novartis; Pfizer; Roche/Genentech; Expert Testimony: Pfizer; Other Financial Relationships: AstraZeneca; Merck Serono; MSD Oncology

Freier Vortrag

Big Data

V265

A machine learning approach to acute graft-versus-host disease grading

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Introduction: Acute graft-versus-host disease (aGVHD) remains a major cause of morbidity and mortality after allogeneic hematopoietic cell transplantation (HCT). Since the first GVHD grading score by Glucksberg in 1974, several studies have tried to further improve aGVHD severity indexing (SI). Both Glucksberg grading- and the Center for International Blood and Marrow Transplant Research(CIBMTR) grading system have been prospectively validated and are equally performing. While aGVHD grading does correlate with overall survival (OS), poorly surviving patients are found across all GVHD categories. Recent concepts, such as epithelial damage, predictive biomarkers or Machine Learning (ML) may improve aGVHD grading.
Methods: We analyzed the modified Glucksberg scoring system in 1354 consecutive adult patients with aGVHD after HCT from a single center between 2008 and 2018 and compared it to a ML model, basedon the available aGVHD organ involvement staging, transplant- and OS data. We constructed a 3D discrete space (*V*), of which axes corresponded to the aGVHD stage of the corresponding organ (skin, liver, intestine). A principal component analysis was applied on the data and the first principal component adopted as the new space (*V**)of the SI. Then, by using the first principal component we formulated an algebraic relation to obtain aSI of each patient.The performance of the ML and Glucksberg grading systems were compared with Cox regression survival analysis.
Results: The ML model revealed insufficient correlations of Glucksberg aGVHD grading and OS with intergrade OS variability and overlap (Fig1). Cox regression analysis comparing ML grading system to Glucksberg's showed that the ML-based SI offered a finer grading (125 grades) allowing to use the SI as a continuous variable. The ML model was more stable with a small confidence interval and allowed to model patient's maximum survival expectation. Finally, the suggested ML algorithm offered a better predictive factor, creating cohorts with more distinct hazard rates.
Conclusions: ML based scoring system based on Glucksberg organ categories allowed refined aGVHD grading and improved OS prediction in all severity cohorts.

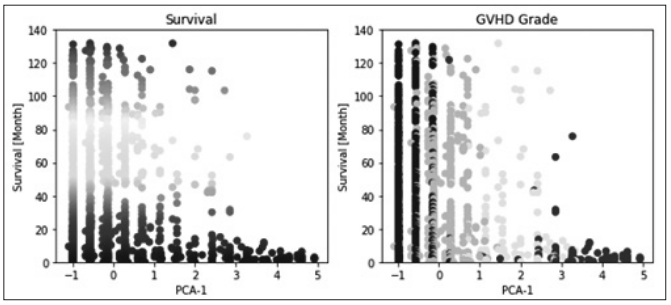

Fig. 1. ML analysis of GVHD grading and individual OS: Overlap across GVHD grades; intragrade OS variability

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Amin Turki: Employment or Leadership Position: Universitätsklinikum Essen; Advisory Role: Jazz, CSL Behring; Other Financial Relationships: Travel subsidies from Neovii Biotech.

V266

Automated whole exome sequencing analysis pipeline to support a molecular tumor board

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Introduction: Whole exome sequencing (WES) of patients with advanced tumors is becoming an established method in medical centers. However, somatic variant calling and interpretation as well as report creation and case presentation require both in-depth knowledge in bioinformatics and oncology. In addition to the analysis and interpretation of the data, the exchange of results and recommendations of a molecular tumor board (MTB) is also of vital importance. A prerequisite to achieve this is data harmonization and integration. MIRACUM (Medical Informatics for Research And Care in University Medicine, FKZ 01ZZ1801A/B) is rolling out three use cases in ten university hospitals throughout Germany. One is the support of interdisciplinary MTB, which combine extensive molecular diagnostics with state-of-the-art sequencing and bioinformatic analysis for personalized recommendation.
Methods and Results: In order to offer an adequate solution, we have developed a fully automated WES analysis pipeline (MIRACUM-Pipe), which only requires the sequencing files (fastq files) and the patient´s gender as input, in order to finally present the results in an automatically generated report. The pipeline consists of three major parts: (i)Alignment and quality control, (ii) analysis and annotation: subdivided in coverage, variant calling and copy number variations and (iii) final results reporting. The called somatic variants are annotated using ANNOVAR and are further classified into tumor suppressors or oncogenes according to OncoKB, cancer hotspot mutations are marked, while possible therapy options are identified from OncoKB and the drug-gene-interaction databases (DGIdb). For further biological interpretation of the identified variants a functional enrichment is performed based on Gene Ontology, Reactome and ConsensusPathDB. The results are finally summarized in a PDF report and are also made available in tabular form.
Conclusions: The MIRACUM-Pipe is currently used for the MTB at the University Medical Center Freiburg and has been further implemented at the MIRACUM partner sites Mainz and Gießen. We will further support existing and newly established MTBs at the MIRACUM partner sites with the aim to define a standardized procedure for analysis and annotation of WES or panel-sequencing for molecular tumor board's patients and to enhance the comparability of these data/results at several partner sites simultaneously in order to make any necessary adjustments.

Disclosure: No conflict of interest disclosed.

V267

Drowning in information: the Lack of integrating knowledge database

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Introduction: Searching in different knowledge databases (KD) for preparing molecular tumor board (MTB) cases is time-consuming. They have neither a common interface nor query language nor tooling in order to query multiple KDs at once. In molecular diagnostics, the preparation time per case differs considerably. Therefore, members of our MTB stated they need up to 20 minutes per KD and use an average of four KDs per case. Hence, this limits the number of patients being discussed in a tumor conference significantly. In order to reduce these time-consuming repeating tasks, the different KDs need to be queried automatically.
Methods: In a case study, the authors examined KDs which are commonly used in preparation for their MTB. Therefore, the focus lies on the ability of these KDs to expose their data via application programming interfaces (API), hence making it accessible to machine-to-machine (M2M) communication. We state four minimal requirements: 1) An API must be offered. 2) The API needs to expose syntactically and semantically interoperable data. 3) The API needs to support medical relevant search terms. 4) The exposed data needs to be semantically annotated.
Results: For the study, the five most relevant KDs for the MTB were identified: cBioPortal, ClinicalTrials.gov, OnkoKB, GeneCards and COSMIC. Three KBs offer an API and also expose syntactically interoperable data. Even though two offer no API, they offer a data download. However, no KD exposes semantic interoperable data nor annotations. Also, the search terms are highly heterogenous.
As the results show, even the minimal requirements for a successful M2M communication are not met. The reasons vary: as more and more data are published in KDs, the raised attention to this problem is novel. The same applies for heterogenous search terms. The consequences could be seen above: Every KD implements their proprietary API and data format. Hence, each of these needs to be implemented separately. Therefore, integrating KDs into existing systems is time-consuming and expensive. Also, as they vary in quality, the effects increase.
Conclusions: As more and more knowledge is generated and published in KDs, information retrieval gets harder, hence the information quality decreases. Therefore, integrating KDs becomes an important task. Even though the attention to the appealed problems raised over the last years, more work needs to be conducted in order to ensure a high-quality support for medical professionals.

Disclosure: Andreas Keil: Employment or Leadership Position: Mitarbeiter am MOLIT Institut
Christian Fegeler: Employment or Leadership Position: Gründer des MOLIT Instituts

V268

eBtM - a blockchain-based narcotic drugs prescription

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Introduction: Narcotic drugs are double-edged swords. On the one hand, they have the potential to improve quality of life, e.g. for cancer patients with severe pain. On the other hand, narcotics carry the potential to destroy lives, as they are highly addictive. The non-medical usage of these drugs is identified as a major threat to global public health. Therefore, their prescription is strongly regulated. The current paper-based prescription with the three-part form creates an enormous burden for all those involved and results in high personnel, print and administrative costs. Even more alarming is that these processes are still unsafe. Paper prescriptions can be easily stolen or manipulated. Already in 2003, the Federal Opium Agency has highlighted security loopholes and inefficiencies and demanded a digital process.
Methods: eBtM is a blockchain-based solution for the narcotic drugs circulation, where a prescription is handled digitally as a smart contract. It creates a decentralized network, which is administered by doctor's offices, pharmacies and regulatory authorities. The blockchain data model allows for the safe, immutable and comprehensive storage of all transactions in a decentralized register. eBtM protects patient data, employs decentralized storage, and creates a tamper-proof system.
Results: Mutual controllability in a decentralized system with no central intermediary is the key to more security when regulating addictive substances, as no central actor can be trusted blindly. The smart contract becomes effective automatically and irreversibly. This autonomous program provides the ideal basis to comply with the legislative requirements and the doctor's prescription. The redundant storage brings the three-part prescription to a digital level as data remains decentralized, while physical storage is omitted. Most importantly, blockchain is a safeguard against manipulation. Transactions are cryptographically secured, and sensitive patient data remains confidential.
Conclusions: As winners of the Federal Ministry of Health's blockchain challenge, the team has already established a dialogue with key political actors and pilot organizations.

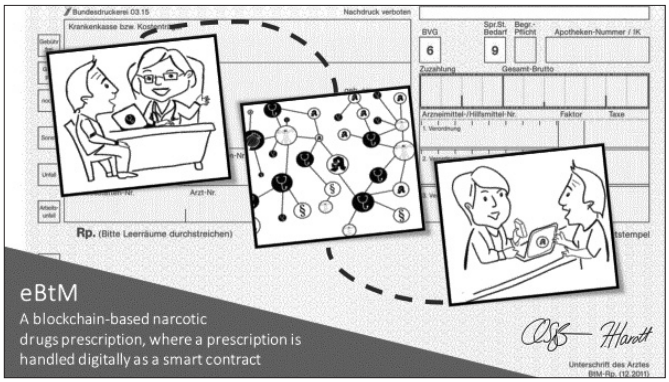

Fig. 1. Schematische Darstellung eBtM

Disclosure: No conflict of interest disclosed.

V269

Semantical interoperability: precondition for modern big-data approaches

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Introduction: Structured, interoperable and semantically annotated data is the prerequisite for the utilization of big-data methods in oncology. While oncological genomic reports today are mostly PDF based, some laboratories also offer structured data exports which are either exported as comma separated values (CSV) or XML. The lack of semantical interoperability and standardization of the reported variants exports hinders the utilization of modern big-data methods and clinical decision support systems.
Methods: Fast Healthcare Interoperability Resources (FHIR) is the newest and fast-growing standard published by HL7. As part of the clinical genomics (CG) workgroup of HL7 the authors contributed in the creation of an HL7 FHIR based Implementation Guide (IG) for genomics data reporting which heavily uses semantical coding of values utilizing code-systems, e.g. Catalogue of Somatic Mutations in Cancer (COSMIC), and computer interpretable grammars like the Human Genome Variation Society (HGVS) nomenclature.
Results: A converter from a proprietary, CSV-based variant export format to a FHIR CG IG format was developed in order to store the genomic reports in a structured and interoperable manner. A FHIR server was implemented at the SLK-Kliniken Heilbronn to store the variant data in the CG IG FHIR format.
This enables powerful searchability through all variants of all patients and therefore enables modern data science approaches like case-based reasoning and machine learning.
Conclusions: Genomic reports in the CG IG FHIR format are enabling physicians a structured and easier searchable access to the variants reported. Usage of this data in computer aided molecular tumor boards or clinical decision support systems is eased as it doesn't have to be entered or transformed manually before utilization and therefore reduce the time invested per patient.
Semantical interoperable data combined with modern data science methods and semantical interoperable knowledgebases will support the physicians even further leading to a more effective personalized approach in treating cancer.

Disclosure: No conflict of interest disclosed.

V270

Key factors for acceptance of an e-health solution

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Introduction: From online appointments for the doctor to electronical medical records: 'digitalization' and 'medicine 4.0' are keywords in medicine nowadays. Nevertheless, there are only a few solutions that please the user entirely.
This leads to the question, what key factors must be respected to develop an accepted solution and to profit from all benefits digitalization holds.
Methods: At first we did a literature research and created a concept for a questionnaire tool. After the development we tested our tool in a usability study at the SLK-Kliniken Heilbronn, Germany, including 92 patients over three weeks. Based on the feedback main key factors for a successful e-health solution were identified and compared with the literature research.
Results: In our usability study we gained a participation of 86% with an average age of 67 years. 86% of the patients can imagine to integrate questionnaires in their everyday life and 82% see additional benefits.
We identified three main factors for a good acceptance, which confirm our literature research. The first one is to use established and well-known technologies and frameworks. Since we are using web-technologies and responsive design, the content is accessible from a wide variety of end devices, such as personal computers, tablets and smartphones. It also allows dynamic rendering of questionnaires and forms based on a structured data model. That means users may individualize their view of data, which improves the user experience.
Semantic interoperability is the second key factor. We use the international standard HL7 FHIR for an exchange of data. Using this flexible concept, we can provide structured data for secondary use and include mobile devices for patients to connect with health professionals from any location.
The third main key factor is the separation of technical components, processes and content. This leads to a better adaption for various use-cases and reduces the maintenance time which improves sustainability.
Conclusions: The results of our usability study show, that patients can be motivated to be a part of digitalization, independent from their age and previous knowledge. It also confirms that questionnaires are an effective concept to collect and refine health data in a structured way.
Since our concept has been based on a literature research and accredited by our usability study, we will now evaluate the acceptance in long term usage. Depending on that feedback we will adapt our main key factors.

Disclosure: Chantal Nadine Luise Beutter: Employment or Leadership Position: Mitarbeiter des MOLIT Institut für Personalisierte Medizin
Christian Fegeler: Employment or Leadership Position: Gründer des MOLIT Institut für Personalisierte Medizin

Expertenseminar

E13: Studien verstehen

V271

Reading study publications

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Clinical trials generate potentially valuable knowledge. The commercial exploitation of the study results not only concerns manufacturers of new drugs with their patents, but also professional associations or journals securing the rights to publication. In addition, a high-ranking publication promises more visibility for the scientists and authors involved. All those involved in the publication of clinical trials have an interest in showing the results in a good light. A tension can arise between these interests and the results, occasionally interfering with a scientifically appropriate presentation. Based on publications of clinical trials, treatment decisions are being made by us physicians together with our patients. It is therefore helpful to recognize whether a publication involves a more or less correct presentation of clinical trial results.
We will take a closer look under scientific criteria at current publications from high-ranking journals claiming a "practice-changing" message. The aim is that, following this event, we will
1. Recognise with little effort whether the conclusions are consistent with the study question and the results,
2. Identify and avoid frequent pitfalls in the interpretation of study results, and
3. Recognise scientific semi-truth statements just by looking at the wording.
To achieve these goals, we will use current examples from haematological oncology with clinical relevance and strive for an interactive discussion. The event is aimed at physicians who have fun with reading trial publications, asking focused questions and looking for precise answers. Special prior knowledge is not required.

Disclosure: No conflict of interest disclosed.

Fortbildung

Hodgkin-Lymphom: Standards in der Therapie

V274

Therapy of relapsed and refractory Hodgkin Lymphoma

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The first-line cure rates in young patients with Hodgkin Lymphoma (HL) are excellent; however still 10%-20% of patients suffer from relapsed or refractory disease. Reinduction chemotherapy followed by high-dose chemotherapy (HDCT) and autologous stem cell transplant (ASCT) is standard of care for suitable patients with relapsed or refractory HL and allows for cure in approximately 50%. Due to the poor prognosis of high-risk patients even with HDCT and ASCT, consolidation strategies have been evaluated to improve the cure rates. Current consolidation strategies will be discussed. For patients with recurrence after HDCT and ASCT, treatment is palliative in most cases. The anti-CD30 antibody-drug conjugate brentuximab vedotin (BV) has been shown to induce high response rates in these patients but durable responses were reported in a small percentage of patients only. Anti-programmed death-1 (PD1) antibodies show even more impressive results in terms of response rates and progression-free survival; however, as extended follow-up data become available, most patients seem to relapse sooner or later. New combination studies with anti-PD1 antibodies aiming at more durable responses are currently ongoing. Additionally, clinical trials with PD1 antibodies in first relapsed HL assess the role of these new class of drugs in reinduction therapy and more recently even in the replacement of HDCT. For carefully selected patients with multiple relapses, dose-reduced allogeneic transplant (RICallo) is a potentially curative option. The role of RICallo in the era of anti-PD1 antibodies is currently being re-evaluated.

Disclosure: Bastian von Tresckow: Advisory Role: Amgen, Pfizer, Takeda, MSD; Financing of Scientific Research: Roche, Takeda, MSD; Expert Testimony: Novartis, MSD, Takeda; Other Financial Relationships: MSD, Takeda, Novartis (Kongressunterstützung)

V275

The role of PET/CT before, during and after treatment in Hodgkin´s lymphoma

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Introduction: FDG-PET has shown to be a reliable and meaningful diagnostic tool in the assessment of Hodgkin´s lymphoma (HL). Large international multicentric trials use PET-guided response-adapted treatment algorithms to maintain the excellent survival rates while avoiding side and late effects. The application of novel therapeutic agents like immune-checkpoint-inhibitors and the advent of quantitative PET parameters like metabolic tumor volume are promising developments and require adjustments of PET evaluation criteria.
Methods: This presentation is based on a review of literature, on current guidelines and on the long-time experience of our research group in the central reference evaluation of pediatric patients with HL (central review of all Euro-Net-PHL-C1 and PHL-C2 patients since 2007).
Results: The international standard for PET assessment in HL are the Lugano criteria, published in 2014. The Lugano criteria recommend the five-point Deauville score for PET response assessment. The qPET method, a semi-automatic quantification of lymphoma residuals in interim PET was developed by our group to address issues of a purely visual PET assessment like contrast illusions and inter-reader variability in borderline cases. New PET parameters such as the metabolic tumor volume or heterogeneity markers have the potential to further improve PET-guided personalized treatment. Novel immuno-modulatory therapeutic agents may be an alternative in second- and third-line therapy regimes. However, an immunomodulatory-related pseudoprogression is hardly distinguishable from a true progression by FDG-PET. Therefore, a refinement of the Lugano criteria, the Lyric criteria, were published in 2016. The German guidelines from 2018 reflect the current role of PET in early, intermediate and advanced stages of HL. However, the remuneration of the PET examination is still a major issue in Germany.
Conclusions: FDG-PET is the decisive method for staging and response assessment in HL. The international standard for PET assessment are the Lugano criteria. The current data on the role of PET is well defined in the German guidelines for HL in adults and children.

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Wissenschaftliches Symposium

AML: Perspektiven der Optimierung

V276

Leukemia stem cells as therapeutic target

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Relapse remains one of the major challenges in the treatment of Acute Myeloid Leukemia (AML) patients raising the question why current anti-leukemic therapies often fail to permanently eradicate the disease. While deep sequencing technologies enable us to predict overall or relapse-free survival based on genetic aberrations, they do not necessarily answer this question. Moreover, only a fraction of the mutated proteins found in AML patients represent suitable targets such as mutated IDH1/2 or FLT3-ITD. In the leukemia stem cell (LSC) concept, LSCs are considered the source of relapse due to certain functional characteristics shared with normal hematopoietic stem cells (HSCs) such as extensive self-renewal capacity and higher resistance to chemotherapeutic agents. LSC-identifying surface markers and pathways or genes essential for LSC propagation would therefore represent ideal alternative targets. Several strategies to eradicate LSCs are already being tested in clinical trials, while others are still at a pre-clinical stage. These efforts include monoclonal antibodies such as anti-CD47 or anti-CD123 antibodies and small molecule inhibitors. We recently identified the transcription factor Hepatic Leukemia Factor (HLF) as a key regulator of LSC function synergistically upregulated in AML triple-mutated for *NPM1*, *DNMT3A*, and *FLT3*-ITD. Triple-mutated AML is characterized by high leukemia stem cell (LSC) frequency and an aberrant leukemia specific GPR56highCD34low immunophenotype. Loss of HLF via CRISPR/Cas9 significantly reduced the CD34+GPR56+ LSC compartment of primary human AML cells in serial xenotransplantation assays. Interestingly, HLF knockout cells were more actively cycling when freshly harvested from mice, but rapidly exhausted when re-introduced in culture. RNA-sequencing of triple-mutated AML cells after shRNA mediated HLF knockdown revealed the NOTCH target HES1 and the cyclin-dependent kinase inhibitor CDKN1C/p57 as novel targets of HLF potentially mediating these effects. Future studies will reveal how these mechanistic insights might serve the development of more efficient LSC-eradicating therapies.

Disclosure: No conflict of interest disclosed.

Fortbildung

Aplastische Anämie

V283

Differential diagnosis of pancytopenia

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Pancytopenia is a reduction in the number of white blood cells, red blood cells, and platelets in the peripheral blood below the lower limits of the age-adjusted normal range for healthy people. The underlying causes may be quite variable, since many malignant and non malignant diseases may be associated with pancytopenia. Unless the cause of pancytopenia is already apparent by history, physical examination and laboratory tests, diagnostic mamagement requires bone marrow biopsy. Aplastic anemia is characterized by an empty bone marrow and can be distingushed by this feature from other diseases in many cases. Sometimes morphologic examination alone is insufficient and requires additional diagnostic tests such as immunologic and serologic tests and the characterization of hematopoietic cells by immunophenotyping, cytogenetics and molecular methods. In this presentation the most important differential diagnoses and their specific features will be discussed.

Disclosure: No conflict of interest disclosed.

Fortbildung

Reha nach allogener Stammzelltransplantation

V289

Rehabilitation after allogeneic stem cell transplantation - The needs of AYA

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Allogeneic hematopoietic stem cell transplantation is a potentially curative but intensive treatment for both benign and malignant hematogical conditions in adolescents and young adults (AYA). Among transplant recipients AYA represent a special patient group, displaying unmet health and supportive care needs. This age group often remains understudied as a separate entity because they are commonly lumped into either pediatric or adult subgroups.
Because of fundamental improvements in cure rates, a growing number of transplant survivors are facing a real chance of long-term survival and recovery. However, allogeneic hematopoietic stem cell transplantation can lead to serious effects on physical fitness, emotional and social well-being as well as to a disruption in education or difficulties in returning back to work. In addition, AYA have to deal with financial difficulties and may be faced with competing responsibilities, e.g. the care for their children.
Rehabilitation may mitigate loss of function and disability in AYA survivors after stem cell transplantation. Exercise has been shown to improve the functional capacity of survivors, reduce fatigue and has a positive impact on quality of life, mood and bone health. However, especially AYA suffering from chronic Graft-versus-Host disease may face difficulties to meet requirements of their work because of impaired physical and cognitive functioning. In addition, unemployed survivors were more likely to experience poorer quality of life. This emphasizes the need for specific rehabilitation programs for AYA after hematopoietic stem cell transplantation in order to support the transition back to education or work life even with cognitive, physical or psychological limitations.
Understanding the needs and satisfaction of AYA undergoing rehabilitation after hematopoietic stem cell transplantation is important for the development of effective programs in order to improve overall health and quality of life.

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V290

Results of pediatric-oncologic rehabilitation following allogeneic hematopoietic stem cell transplantation

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Introduction: every year about 2200 children and adolescents below the age of 18 years are diagnosed with cancer. A small but important fraction of of These patients undergo hematopoietic stem cell transplantations followed by a rehabilitation.
Methods: Increasing survival rates in pediatric oncology lead to an increasing importance of questions of quality of life, medical and psycho-social rehabilitation. In Germany, family oriented rehabilitation for children and their families and rehabilitation for adolescents and young adults (AYA) in their peer groups was established in 1985. Rehabilitation is performed in a very small number of highly specialized centers recommended by the Society of Pediatric Oncology and Hematology (GPOH).
Results: Children who are separated from their siblings, friends and their age specific peer group suffer in different ways. Their social and emotional development is impaired as well as the development of their sensory-motoric and psycho-motoric skills. Rehabilitation of these children together with their families not only helps the patient directly, but as well indirectly by stabilizing the whole family system. In our experience rehabilitation is most successful, when the patient has had the chance to spend some time at home with his or her family before rehabilitation. Depending on the main goals for the rehabilitation patients benefit especially, if they have little or no immunosuppressive therapy. If the therapy in a group context is most important, then children and their families or adolescents should come to rehabilitation at least two months after the end of the immunosuppressive therapy. This ensures that the patient can participate in most therapies including hippotherapy or physical therapiy in water.
Conclusion: family-oriented rehabilitation as well as rehabilitation for AYA in their age specific peer groups is a necessary, adequate and appropriate means to help children and their families as well as AYA after life-threatening oncologic disorders on their way back to a normal and self-determined life. In the last decade allogeneic hematopoietic stem cell transplantations for non-oncologic reasons, such as immune deficiencies like SCID or Wiskott-Aldrich-Syndrome, neurodegenerative disorders and hematologic disorders such as SAA or Thalassemia have become more important, which is reflected by the growing number of patients with these indications in pediatric rehabilitation.

Disclosure: No conflict of interest disclosed.

Wissenschaftliches Symposium

Ethik: Kollektivität und Teilhabe

V291

Opportunities and Challenges of Stakeholder and Public Patient Engagement - an Overview

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The rise of big-data driven research for more personalized medicine is accompanied by prospects for a new dimension of participation by patients or research subjects. Although reference to normatively loaded concepts, such as "patient engagement", "citizen science" or "participant-centric initiatives" is frequently made, the justification of this participatory terminology as well as the practical implementation of these concepts is far from clear.

Against this background, it is the aim of this presentation to reconstruct and analyse the specific use of participatory concepts in the context of biomedical research and related social-ethical debates. To this end, I will first distinguish ideal typical levels of stakeholder participation and public patient engagement. The spectrum ranges from approaches where patients/research subjects' participation is limited to the provision of data for research to more ambitious participatory practices where patients/subjects may even determine the direction of research. For this I will also provide an overview of different methodologies, from small scale involvement via larger forms and survey to public debates. I will provide some practical and theoretical advantages as well as concrete challenges raised by the different methodologies and aims of participation.

Disclosure: No conflict of interest disclosed.

V292

Stakeholder participation in clinical trials: recommendations from hiPS-cell research

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In the last decade, it has been possible to generate human induced pluripotent stem cells (hiPS cells) in the laboratory. Research in this field brings clinical applications within reach. In the public debate, this cell type, in contrast to human embryonic stem cells (hES cells), has often been presented as a morally unproblematic alternative. However, especially the clinical translation of research with hiPS cells and derived products raise its own problems. Amongst them are the selection of research participants, risk-benefit assessment, informed consent procedures and last but not least the appropriate involvement of the public. Especially, studies with such a high conflict potential require appropriate social participation procedures as well as scientific, ethical and legal recommendations for clinical translation.

To develop such recommendations, the specific problems associated with the clinical translation of hiPS cells and products derived from them were analyzed within BMBF-funded ClinhiPS project. A conference with stakeholders on hiPS cell research helped complement the subprojects. Plenary lectures and workshops aimed at a joint discussion on how to ensure fair and balanced risk assessment, transparency of decision-making processes and an informed public debate.

The presentation will address the following key questions: Given the pluralism of interests, how can researchers and clinicians conduct appropriate ethical discourses on such innovative and risky research projects? Which stakeholders should be involved and how do they facilitate a constructive discourse to solve challenges?

Research in this area that involves (potentially) high risk and high benefit is suitable to shed light on not only the task of stakeholder discourses and their practical implementation, but also on their limits. Stakeholder participation can grasp as many perspectives as possible. This applies in particular to the specific opportunities and problems of involving patients and other social groups in the design of clinical trials. The stakeholder procedure chosen in the project thus represents an important contribution to the ethical evaluation of research. However, it cannot replace the professional discussion and the resulting recommendations for practice.

Disclosure: No conflict of interest disclosed.

V293

Patient involvement: Tokenism or matter of course

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The German Healthcare Reform Act 2004 (Gesundheitsmodernisierungsgesetz) with §140f put into The Social Care Act (Sozialgesetzbuch V), and the Act of Patients' Rights 2013 (Patientenrechtegesetz) are defining the legal basis for patient involvement in reimbursement decisions within the German healthcare system, specifically in the German "Federal Joint Committee" ("Gemeinsamer Bundesausschuss") and certain subcommittees in the Federal States (Bundesländer). There patient representatives have the right to submit petitions and the right to participate in debates, but no right to vote. However, looking at it from a pan-European perspective, patient and public involvement is much wider than that. The terms 'patient advocacy' and 'patient involvement' stand for systematic approaches of informed patients and patient advocates acting as equal stakeholders among other actors in the health care system. On the EU level patient advocates are deeply involved in healthcare decision making. In comparison patient involvement in Germany is still in its infancy. By literature research and discussions, led with numerous experts, I will present where patient involvement in Germany is already successful and where it has to catch up compared to other countries with long-standing traditions of patient involvement. Success stories, perceived barriers and real challenges of implementing patient involvement on the German and European level will be described. Suggestions will be made how to overcome structural deficiencies and hierarchial structures to provide more meaningful and patient-need-based services to the German healthcare system. Still controversial is the recognition of patient advocates as a separate healthcare profession representing the best interests for the individual patient as well as for wider patient populations. In order to offer competent contributions and to collaborate on equal footing with other stakeholders in the healthcare system, -policy and research innovative approaches like independent, though certified patient education programs for German patient advocates are urgently needed. More and targeted patient involvement needs to be achieved on all organisational and system-relevant levels. This will be cost-effective and will make sure research, treatment, care and policy delivers on the real expectations of patients, increasing patient safety and regaining public trust in research and healthcare provisioning.

Disclosure: No conflict of interest disclosed.

Fortbildung

Neue Leitlinien zur Palliativversorgung onkologischer Patienten

V298

The criteria of clinical and ethical decision making in oncology as a part of an evidence-based (S3) guideline

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Background: The German Guideline Program in Oncology aims to provide evidence-based guidelines for all relevant cancer entities as well as for cross-sectional fields like psycho-oncology, supportive care, or palliative care. Especially in palliative oncology, balancing the indication for or against medical interventions also denotes a normative process, comprising medical, ethical and legal considerations. Therefore, the new S3 Guideline Palliative Care for Patients with Incurable Cancer, launched by the German Association for Palliative Medicine (DGP) and supported by 61 scientific associations, dedicates a whole chapter to this decision making process.
Methods: Standardized (S3, AWMF) development process of an evidence-based and consented guideline, scheduled for publishing in early 2019. Study evidence, legal framework and ethical positions were reviewed. Recommendations were made based on their clinical and normative relevance, and approved by the formal consensus process. Further legal explanations and ethical discourse was placed in the background text.
Results: The following topics were identified and processed with consented recommendations: scope and applicability of this guideline, the concept of medical indication and its underlying defining criteria, ways to determine therapeutic aims, models of informed consent and shared decision making, the role of a patient´s `wish` for anti-cancer treatment, the role of relatives, intercultural aspects and dissent, involvement of validated decision aids, early therapeutic planning / advance care planning, involvement of ethical counseling, special situations like prognostic uncertainty in hematology and oncology, and considerations on the term `incurability` as a precondition for a palliative care guideline.
Discussion: Illustrating the process of clinical decision making and the underlying medical, ethical and legal principles by means of an evidence-based guideline is feasible. Further research will have to demonstrate whether the confidence and certainty of oncologists and the reproducibility of normative decision processes may increase and ethical conflicts in clinical routine may be reduced by the implementation of this guideline in oncology and palliative care.

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V299

National Guideline: How to deal with desire to die

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Somatisch schwer erkrankte Menschen haben, so zeigen mehrere Arbeiten der letzten Jahre, relativ häufig einen bestehenden Todeswunsch. Während früher die Annahme herrschte, gute Palliativversorgung würde diesen „beseitigen", so ist heute klar, dass eine gute Versorgung dieser Menschen die Gedanken weg von schwerer körperlicher Symptomatik hin zu Lebenssinnfragen richtet. Wie sollen wir mit diesem Phänomen umgehen? Im Rahmen des onkologischen Leitlinienprogramms „S3-Leitlinie Palliativversorgung für Patienten mit nicht heilbarer Krebserkrankung" war dies ein Thema der Erweiterung. Beteiligt waren hier insbesondere neben der Deutschen Gesellschaft für Palliativmedizin auch die Deutsche Gesellschaft für Psychiatrie, die Deutsche Gesellschaft für Suizidprävention und das Nationale Suizidpräventionsprogramm. Im Rahmen der Konsentierung wurde erstmals eine Beschreibung des Phänomens „Todeswunsch" konsentiert, insbesondere in der Überlappung und zur Abgrenzung von Suizidalität. Eine weitere Schlüsselempfehlung auf Sollte-Ebene empfiehlt sogar das aktive Ansprechen dieser Phänomene. Hier hilft insbesondere die Erfahrung der Psychiatrie, wo es üblich ist, aktiv Suizidgedanken anzusprechen, ohne dass es zu Schaden beim Patienten kommt. Der nächste empfohlene Schritt ist das Hinterfragen der Todeswünsche bezogen auf die zugrundeliegenden Faktoren, die Bedeutung, warum gerade jetzt das Thema aktuell angesprochen wird und was es für die Betroffenen im Moment bedeutet. Und schließlich enthält die Leitlinie Empfehlungen zur Erarbeitung von Handlungsoptionen, welche insbesondere die Wünsche der Autonomie der Patienten aber auch weiterer palliativmedizinischer Maßnahmen wie palliativer Sedierung beinhaltet. Dieses Kapitel der S3-Leitlinie Palliativmedizin bedeutet für Deutschland erstmals eine breite Konsentierung konkreter Handlungsempfehlungen für diese ethisch herausfordernde klinische Situation.

Disclosure: No conflict of interest disclosed.

Freier Vortrag

B-Zell-Lymphom, aggressiv II

V304

Preliminary results of earlier steroid use with axicabtagene ciloleucel (Axi-Cel) in patients with relapsed/refractory large B cell lymphoma

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Introduction: Axicabtagene-ciloleucel (axi-cel) is an autologous anti-CD19 chimeric antigen receptor (CAR) T cell therapy approved in the European Union and United States for patients with relapsed/refractory large B cell lymphoma (R/R LBCL) with ≥ 2 prior systemic therapies. In the 2-year follow-up of ZUMA-1, the objective response rate (ORR) was 83%, with a complete response (CR) rate of 58%. Grade ≥ 3 cytokine release syndrome (CRS) and neurologic events (NE) occurred in 11% and 32% of patients, respectively; 26% of patients received steroids, and 43% received tocilizumab (Locke et al. *Lancet Oncol*. 2019). A safety expansion cohort was added to evaluate the effect of earlier steroid use on the rates of these adverse events (AEs).
Methods: Eligible patients with R/R LBCL were leukapheresed and received conditioning chemotherapy followed by a target dose of 2×10^6 anti-CD19 CAR T cells/kg. Patients in this cohort received early steroid intervention starting at Grade 1 NE and at Grade 1 CRS when no improvement was observed after 3 days of supportive care. The primary endpoint for this cohort was incidence and severity of CRS and NE.
Results: As of September 14, 2018, 21 of 40 planned patients received axicel with a minimum follow-up of 1 month (median, 2.6). The median age was 63 years (range, 36-73); 67% were male; 81% had disease stage III-IV; 76% were R/R to ≥ second-line therapy; and 10% had relapsed post autologous stem cell transplantation. Overall, 76% of patients received steroids, and 81% received tocilizumab. Most patients (81%) had Grade ≥ 3 AEs, most commonly neutrophil count decreased (33%), anemia (29%), and pyrexia (24%). Grade ≥ 3 NE occurred in 10% of patients; the most common symptoms were somnolence (10%) and confusional state (10%).

Grade 1 and 2 NE occurred in 38% and 5% of patients, respectively. No patient had Grade ≥ 3 CRS; 33% of patients had Grade 1 CRS, and 67% had Grade 2. There were no deaths due to AEs; 1 patient died due to disease progression. The ORR per investigator assessment was 76%, with 48% of patients achieving a CR. Pharmacokinetic data will be presented.
Conclusions: Early use of steroids may help to manage severe CRS and NE by potentially reducing their incidence in patients treated with CAR T cell therapy without affecting response rates. Optimizing AE management may help to further improve the benefit:risk profile of CAR T cell therapy.

Disclosure: Max S. Topp: Advisory Role: Kite, Amgen, Roche, Regeneron; Expert Testimony: Kite, Amgen, Roche, Regeneron; Other Financial Relationships: Kite, Amgen, Roche, Regeneron, Celgene
Marie José Kersten: Advisory Role: Kite/Gilead; Financing of Scientific Research: Kite/Gilead; Other Financial Relationships: Kite/Gilead

V305

BARs (B-cell receptor antigens) can substitute for the variable region of heavy and light chains of antibodies to target B-cell lymphomas

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Introduction: ARS2 was recently identified as the autoantigenic target of the B-cell receptor of approximately 25% of diffuse large B cell lymphomas (DLBCLs) of the ABC type. ARS2 can be used as immunotoxin or bispecific construct to target DLBCLs in an approach called BAR (*B*-cell receptor *a*ntigens for *r*everse targeting). The optimal therapeutic format BARs can be integrated in has yet to be found. Since antibodies are the most established approach to deliver therapeutic payloads to specific targets with well-defined pharmacokinetics, we constructed and tested a BAR-body incorporating ARS2 in substitution for the variable domains of an IgG1 antibody.
Methods: Heavy and light chain variable region sequences of an IgG1 antibody were replaced by a sequence of the ARS2 protein (aa 343-466) containing the DLBCL reactive epitope (aa 343-375). The BAR-body was assembled in a pSfi FLAG Tag vector and transfected into HEK293 cells for synthesis. Purification of the BAR-body was performed via anti-FLAG antibody affinity chromatography. We used flow cytometry to assess binding capacity of the BAR-body to ARS2-reactive DLBCL cell lines (U2932, OCI-Ly3) and a DLBCL cell line with a BCR of different specificity as control (TMD8). Cytotoxic effects of the ARS2 BAR-body on lymphoma cells with ARS2 reactive BCRs was measured by LDH release assays using human PBMCs as effector cells at an E:T ratio of 10:1.
Results: We generated an ARS2 containing BAR-body incorporating 4 molecules of the DLBCL-reactive epitope of ARS2 in exchange for the variable regions of an IgG1 antibody. The BAR-body bound specifically to the ARS2-reactive lymphoma cell lines U2932 and OCI-Ly3 and did not bind to the DLBCL cell line TMD8. In LDH release assays the Starting at concentrations of 0.1 µg/ml the ARS2 BAR-body induced PBMC mediated specific lysis of the ARS2 reactive lymphoma cell lines U2932 and OCI-Ly3 but did not affect the control DLBCL cell line TMD8. Cytotoxic effects reached a maximum of 50 % specific lysis at a concentration of 1 µg/ml and did not increase at concentrations of 10 µg/ml.
Conclusions: Here we show that BARs can substitute for the variable domains of an IgG1 antibody in a format called BAR-body to target B-cell lymphomas. By incorporating BARs into the well-known format of an antibody we hope to capitalize on years of experience with this therapeutic format from conducting and interpreting in vivo experiments to the translation of the BAR approach into the clinic.

Disclosure: No conflict of interest disclosed.

V306

Loss of TP53 modifies the quantity and protein load of extracellular vesicles in leukemic B-cells and influences functional crosstalk within the tumor microenvironment

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Background: Macrophages are key effector cells of the chemo-immunotherapy (CIT) response in B-cell malignancies. Loss of *TP53* in leukemic B-cells leads to CIT relapse/refractory disease, suggesting that this event might diminish the anti-tumor capacity of macrophages upon CIT.
Methods: The Double-Hit-Lymphoma model hMB and primary CLL and Multiple myeloma cells were utilized in macrophage co-culture systems for ADCP assays. The proteomic profile of control and *TP53*-deficient leukemic B-cells and their extracellular vesicles (EVs) isolated by differential ultracentrifugation were evaluated by mass spectrometry. The humanized hMB mouse model and TCL1 mouse model served as in vivo model.
Results: In order to analyze the influence of the DNA damage response pathway in lymphoma microenvironment generated from the hMB humanized Double-Hit-Lymphoma model by RNAi towards DDR genes such as ATM, DNA-PK or p53. Particularly p53 status displays a key regulatory role on macrophage mediated malignant cell depletion. Addressing the treatment in vivo using the hMB model for modeling of Double-Hit Lymphoma bearing mice we could demonstrate diminished and ADCP for p53-deficient lymphoma treated with cyclophosphamide in vivo.
As for the mechanism of p53-defined interaction within the tumor microenvironment we could identify up-regulation of PD-L1 in p53-deficient cells. Blocking this checkpoint in the ADCP assay could significantly restore phagocytic capacity of macrophages and overall therapeutic response.
Furthermore, we subjected p53-wild-type and p53-deficient lymphoma cells for proteomic analysis. Here we could identify a significantly deregulated protein expression profile for EV release in p53 deficient lymphoma cells. Verifying this finding by assessing size and frequency EVs released by respective cell populations we reveal profound changes induced by p53 loss. Using isolated EVs from respective lymphoma cells in co-cultures we could verify the functional impact on interaction with macrophages and reducing phagocytic function.
Conclusions: Here we observe that p53 functional status determines phagocytic function and therapeutic response to monoclonal antibodies. Especially, the loss of *TP53* regulates the EV-related protein expression and EV production in leukemic B-cells. Altered EV profiles and checkpoint inhibitor expression in lymphoma cells are novel mechanisms of macrophage modulation in the lymphoma microenvironment determining therapeutic response.

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Christian Pallasch: Advisory Role: Gilead; Financing of Scientific Research: Roche; Expert Testimony: Gilead, Genzyme

V307

Dynamic model for risk assessment in diffuse large B-cell lymphoma based on positron emission tomography scanning

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Introduction: To improve outcome prediction in diffuse large B-cell lymphoma (DLBCL) we analyzed total metabolic tumor volume (TMTV) and standardized uptake value (SUV-)based interim positron emission tomography (iPET) response in 510 patients participating in the Positron Emission Tomography-guided Therapy of Aggressive non-Hodgkin Lymphomas (PETAL) trial.
Methods: In the PETAL trial patients aged 18 to 80 years with a positive baseline PET received 2 cycles of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) followed by iPET and randomization. In total, patients received 6 or 8 cycles of standard R-CHOP or 2 cycles of R-CHOP followed by 6 cycles of an intensive protocol originally designed for the treatment of Burkitt's lymphoma. A good iPET response was defined as a reduction of the maximum SUV by >66% compared to baseline. TMTV was measured using the 41% maximum SUV thresholding (SUV_{41max}) and the fixed SUV_4 method. Welch's t-test was used to assess the association between TMTV and the International Prognostic Index (IPI) factors and a cox regression model including TMTV, iPET response, and all IPI factors was employed to investigate effects on time to progression (TTP), progression-free survival (PFS), and overall survival (OS). Discrimination performances were determined by receiver operating characteristic analysis using the Youden index to compute the optimal TMTV cut-off point with respect to TTP. Kaplan-Meier survival analysis was performed to estimate TTP, PFS, and OS.
Results: Median follow-up was 4.4 years. TMTV was associated with all IPI factors except age. In cox regression analysis including all IPI factors, TMTV and iPET response were the only independent outcome predictor with respect to TTP. By combining TMTV (cut-off: 328 cm^3 by SUV_{41max}) and iPET response we identified three groups at different risk of treatment failure (low [57.1% of patients]: low TMTV/good iPET response; intermediate [37.8%]: high TMTV/good iPET response or low TMTV/poor iPET response; high [5.1%]: high TMTV/poor iPET response), with corresponding 2-year probabilities of 93.8% vs. 67.3% vs. 38.5% for TTP, 90.9% vs. 62.5% vs. 29.9% for PFS, and 95.5% vs. 77.4% vs. 37.1% for OS.
Conclusions: TMTV was the only independent pretreatment outcome predictor with respect to TTP. Combining TMTV with iPET response into a dynamic PET-based risk model may help identify patients who may benefit from treatment modifications or novel approaches.

Disclosure: No conflict of interest disclosed.

V308

The deSUMOylase SENP6 controls chromatin dynamics to restrict B-cell lymphomagenesis

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Diffuse large B-cell lymphomas (DLBCL) are genetically heterogeneous malignancies with poor clinical outcome in about one third of patients. Here we describe a genome-wide transposon mutagenesis screen in a murine model of aggressive B-cell lymphoma and define a large set of lymphoma associated cancer genes. Surprisingly, we identified deregulated SUMOylation as one of the top altered pathways in this screen and show that the SUMO protease SENP6 is a tumor suppressor of B-cell lymphomagenesis which is recurrently deleted in DLBCL patients with frequencies exceeding 20%.
Mechanistically, SENP6 is the key regulator of poly-SUMO2/3 deconjugation in B-cell lymphomas and loss of SENP6 leads to strong hyperSUMOylation. Moreover, we describe a novel mechanism in which SENP6 promotes DNA damage checkpoint activation and show that lymphomas harboring SENP6 loss are genetically more instable.
To delineate SENP6-substrate interactions, we applied a multi-OMICs approach and show that SENP6 orchestrates the chromatin localization of the DNA repair protein CDC5L in a SUMO-dependent manner. Importantly, loss of SENP6 triggers removal of CDC5L from chromatin and CDC5L depletion phenocopies the effects which we observed after SENP6 depletion. Moreover, CDC5L has been identified as tumor suppressor in previous in vivo screens and we thus propose that loss of this substrate on chromatin is sufficient to promote B-cell lymphomagenesis.
Summarizing, we provide a catalogue of cancer genes which will serve as framework for the development of future mechanism-based therapies. Importantly, we show that SENP6 is a clinically relevant tumor suppressor in human aggressive B-cell lymphomas and define a functional relevant substrate. We extend the understanding of deregulated SUMOylation in cancer pathogenesis and identify a resistance mechanism to current standard lymphoma therapies.

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Ulrich Keller: Advisory Role: Roche, Janssen-Cilag, Takeda, BMS, Gilead, Hexal; Financing of Scientific Research: Gilead, Amgen, BMS, Roche, Takeda, MSD; Expert Testimony: Celgene, Takeda, BMS, Roche, Astra-Zeneka, Novartis, MSD; Other Financial Relationships: Roche, BMS, Gilead, Takeda, Janssen-Cilag, Celgene

V309

Favorable outcomes of young high-risk diffuse large B-cell lymphoma patients treated with dose-dense Rituximab-MTX/CHOP-14, a 7 years update

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Introduction: Treatment of diffuse large B-cell lymphoma (DLBCL) has improved with R-CHOP. Outcome in young high risk patients (age adjusted International prognostic index (aaIPI) of 2-3) remains poor with a treatment failure rate of 25%. We use an upfront treatment approach consisting of 6 cycles CHOP-14, dose-dense rituximab and high-dose MTX.
Methods: In this single-center retrospective analysis consecutive treated patients with high-grade B-cell lymphoma (aaIPI 2-3) were identified by database screening. Patients were treated according to local guidelines: From 2011- on all patients were intended to receive dose-dense R-MTX/CHOP-14 (6 cycles CHOP-14 and dose dense rituximab (375 mg/m^2) on days 0, 1, 4, 8, 15, 22, 29, 47, 61 and 75. HD MTX (3.0 g/m^2) was administered on days 16 and 47 before CHOP). Patients with double expressor (DEL) or double hit lymphoma (DHL) were treated with an abbreviated course of dose-dense R-MTX/CHOP-14 and were intensified after second MTX-CHOP with 2 cycles VIPE or VCPE followed by BEAM high-dose chemotherapy (HDCT) and autologous stem cell transplantation (ASCT).
Results: We identified 63 patients with aggressive B-cell lymphoma. Median age was 54 (19-65). 87.3% presented with stage III/IV disease and 95.2% had elevated LDH-levels. Most patients presented with high-intermediate (58.7%) or high risk (25.6%) aaIPI. Patients with aaIPI1 had molecular risk factors predicting a poor outcome (DE- or DH-Status). 79.4%

of patients had DLBCL, 9.5% had HGBL, NOS and 7.9% had HGBL, with MYC and BCL-2 or-6 translocation. 63.5% received dose-dense R-MTX/CHOP-14, 15.9% received the abbreviated course with primarily intensification. 20.6% received R-CHOP-based treatment due to co-morbidities or patient preference. With a median follow-up of 39.1m 3-y PFS and OS was 93% for the entire cohort. DHL (n=6) and DEL (n=11) patients had a better outcome than expected with a 18m- PFS and OS of 91%, however follow-up was shorter and data are still preliminary. aaIPI3 patients tend to have an inferior 3y-PFS of 82.4%. We observed no treatment related deaths. Compared to our historical control (n=33, 4x R-CHOP-21, intend for primary HDCT/ASCT) PFS and OS differ significantly in favor of the dose-dense R-MTX/CHOP-14 protocol (p< 0.0001, HR 5.893 with 95% CI (2.414 -14.39).

Conclusions: Dose-dense R-MTX/CHOP-14 is safe and feasible in young high-risk DLBCL patients. An abbreviated course with primary HDCT/ASCT revealed favorable outcomes in DEL/DHLs

Disclosure: No conflict of interest disclosed.

Freier Vortrag

Chronische myeloproliferative Neoplasien I

V310

Patient-reported outcomes (PRO) on the use of Ruxolitinib (RUX) in myelofibrosis (MF): data from the JAKoMo phase IV trial

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Introduction: The Janus tyrosine kinase 1/2 inhibitor (JAKI) RUX is approved for the treatment of MF in adult patients (pts) with disease-related splenomegaly or symptoms such as fatigue, night sweats, bone pain, weight loss, and fever. We present an updated analysis of a prospective, noninterventional study (JAKoMo, CINC424ADE05) of RUX in either JAKI-naïve (arm A) or JAKI-pretreated (arm B) MF pts.

Methods: The interim analysis included 855 pts (arm A: n=436; arm B: n=419) recruited in 100 and 92 German centers, respectively. Data cut-off was February 26th 2019. Here, we focus on the PROs from the MPN-SAF (Myeloproliferative Neoplasm Symptom Assessment Form) and SF-36 (Short Form Health Survey 36 items) questionnaires.

Results: The median age was 73 years in both arms. The mean MPN-SAF total symptom scores (TSS) at baseline were 29.0 in arm A and 21.2 in arm B. As expected, the mean scores of the SF-36 subscales at baseline were lower in arm A vs. arm B. The mean MPN-SAF TSS improved significantly at month (mo) 1, with mean changes of -7.7 and -1.8 in arms A and B, respectively. These changes remained constant up to mo 24 in arm A (-6.8), while the mean change at mo 24 was less pronounced in arm B (-0.7). In arm A, the analysis of the SF-36 questionnaire revealed clinically relevant improvements of 6 out of 8 subscores in the course of the trial, including role functioning/physical (p_{mo12}=0.0064), pain (p_{mo6}=0.0007), general health (p_{mo6}< 0.0001), vitality/fatigue (p_{mo6}< 0.0001), social functioning (p_{mo6}=0.0012), and emotional well-being (p_{mo6}< 0.0001). In addition, the physical (p_{mo12}=0.0028) and mental component summary (p_{mo6}< 0.0001) scores improved. In arm B, a worsening in the physical component summary score (p_{mo24}=0.0343) as well as the physical functioning (p_{mo6}=0.0023) and pain (p_{mo24}=0.0762) subscores was observed. The probability of having a quality of life (QoL) equal to that of the German general population increased in arm A at mo 24 (all SF-36 subscales). In arm B, this probability remained unchanged.

Conclusions: In this population of real-world MF pts, the administration of RUX resulted in significantly and clinically relevant improvements of symptoms as assessed by the MPN-SAF questionnaire. The QoL, as measured by the SF-36 questionnaire, improved in JAKI-naïve pts. Our results suggest that JAKI-pretreated pts maintained previous improvements in PROs, as their QoL had probably already improved prior to study enrolment.

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Michael Koehler: Financing of Scientific Research: Novartis

V311

Imatinib discontinuation in patients with FIP1L1-PDGFRA positive myeloid/lymphoid neoplasms

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Introduction: *FIP1L1-PDGFRA* is the most common tyrosine kinase fusion gene in myeloid/lymphoid neoplasms associated with eosinophilia (MLN-eo) and is exquisitely sensitive to treatment with imatinib. The rapidly achieved complete molecular remissions (CMR) as detected by nested RT-PCR can be maintained with low dose imatinib, e.g. 3x100 mg/week. Because imatinib can be safely stopped in a substantial proportion of patients with BCR-ABL positive CML, we sought to retrospectively analyze the clinical and molecular follow-up of patients who stopped imatinib in *FIP1L1-PDGFRA* MLN-eo.

Methods: In the "German Registry on Disorders of Eosinophils and Mast Cells", we identified 12 out of 76 *FIP1L1-PDGFRA* positive chronic phase patients (all male; median age 45 years; range, 27-70) who discontinued imatinib for various reasons.

Results: The median duration of treatment with imatinib and duration of CMR prior imatinib discontinuation was 80 months (range 43-175) and 66 months (range, 37-174), respectively. At stopping of imatinib, 4 patients were on 100mg/day and 8 patients on 3x100mg/week (median 33 months; range, 24-132), respectively. A molecular relapse was observed in 4 patients after 10, 22 (n=2) and 24 months, respectively. A second CMR was achieved in 3 patients after 3, 4 and 21 months after restart of imatinib, respectively. The other patient had not yet reached CMR after restart of imatinib for 7 months. Eight patients (62%) are in ongoing CMR [median 17 months; range, 3-71; 4/8 (50%) >12 months, 2/8 (25%) > 24 months]. The median relapse free survival was 24 months. There were no significant differences between patients in ongoing remission and relapse regarding dose and duration of treatment with imatinib or duration of CMR.

Conclusions: Our data demonstrate that 1) imatinib can be stopped in *FIP1L1-PDFRA* positive MLN-eo, 2) molecular relapses occur within the first 2 years, 3) a close monitoring is mandatory for the detection of a molecular relapse, 4) imatinib can induce a rapid second CMR and 5) imatinib discontinuation seems not to increase the risk for imatinib resistance.

Disclosure: No conflict of interest disclosed.

V312

Comparison of RNA-based versus DNA-based quantitative KIT D816V mutation analysis reveals significant disparity in patients with advanced systemic mastocytosis

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Introduction: Systemic mastocytosis (SM) is characterized by activating mutations in *KIT*, usually *KIT* D816V (>90% of patients). A reduction of the RNA-based *KIT* D816V expressed allele burden (EAB) of ≥25% at month 6 is a favorable predictor for improved survival in midostaurin-treated advanced SM (advSM) patients. However, only limited data exist upon the comparison of RNA-based versus DNA-based quantitative *KIT* D816V mutation analyses.
Methods: We used a real time reverse-transcriptase polymerase chain reaction (qRT-PCR) assay for assessment of the *KIT* D816V EAB and a chip-based digital PCR for the quantification of the DNA-based *KIT* D816V variant allele frequency (VAF). Overall, peripheral blood samples from 161 SM patients (indolent SM [ISM], n=40; advSM, n=121) were analyzed at time of diagnosis.
Results: In ISM patients, the comparison between EAB and VAF revealed a strong linear relationship with a correlation (r) of 0.91 and a coefficient of determination (R^2) of 0.84 (Figure 1A), which was significantly inferior (r=0.71; R^2=0.5) in advSM patients (Figure 1B). In 45/121 (37%) and 76/121 (53%) of advSM patients, the EAB/VAF ratio was ≤2 (cohort A) or >2 (cohort B). The comparison between both cohorts revealed significant differences in terms of a higher median hemoglobin level (p=0.006), a lower percentage of patients with hemoglobin < 10g/dL (p=0.02), a lower median monocyte level (p=0.01), a lower median alkaline phosphatase level (p=0.03), and a lower number of patients with a high risk molecular profile (at least one gene mutation in *SRSF2*, *ASXL1*, and/or *RUNX1*, S/A/R, p=0.02) in cohort A. Moreover, patients of cohort A had a significantly better overall survival (OS) (median OS 12.9 versus 3.3 years; hazard ratio 2.1; 95% confidence interval 1.2-3.5; p=0.005; Figure 1C).
Conclusions: We conclude that a) *KIT* D816V EAB and VAF are significantly different in advSM patients but not in ISM and b) advSM patients with an EAB/VAF ratio >2 present with an aggressive phenotype and adverse prognosis as compared to patients with EAB/VAF ratio ≤2. We therefore recommend to routinely determine *KIT* D816V EAB and VAF in advSM patients.

Disclosure: No conflict of interest disclosed.

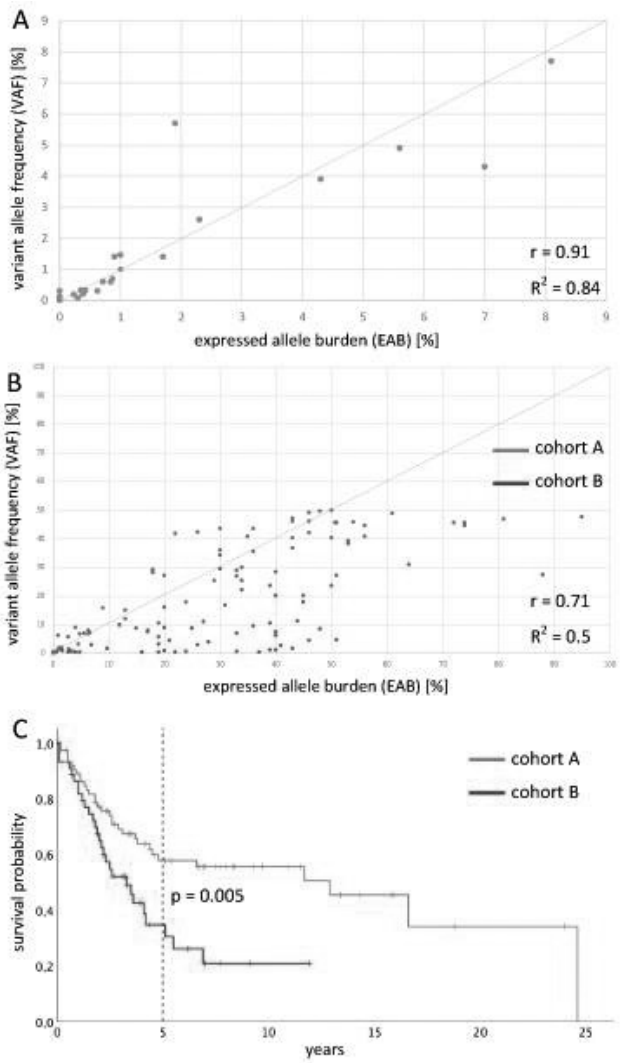

Figure 1: Comparison between EAB (cDNA) and VAF (gDNA) in indolent systemic mastocytosis (SM) and advanced SM (AdvSM). Correlation of EAB and VAF showed a strong linear relationship in ISM patients (A) but not in AdvSM patients (B). The overall survival of AdvSM patients with EAB/VAF ratio >2 (red) is significantly inferior in comparison to in patients with EAB/VAF ratio ≤2.

Fig. 1. Comparison between EAB (cDNA) and VAF (gDNA)

V313

Pharmacologic inhibitors of CDK4/CDK6 exert anti-neoplastic effects in CMML cells and synergize with ponatinib in producing growth arrest

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Introduction: In chronic myelomonocytic leukemia (CMML), no targeted therapy is established to date and therapeutic options are limited. Hydroxyurea (HU), which is used for cytoreduction in CMML, reduces CDK6 expression in various cell types. We have analyzed the impact of HU on CDK4/CDK6 expression and explored the effects of more specific CDK4/CDK6 inhibitors on proliferation of CMML cells. Furthermore, we evaluated potential cooperative effects of CDK4/CDK6-blockers and the multi-kinase inhibitor ponatinib.
Methods: Primary neoplastic cells obtained from patients (CMML I, n=1; CMML II, n=2; acute myelomonocytic leukemia, n=1; secondary acute

myeloid leukemia after CMML, n=2) as well as the monoblastic cell lines THP-1, Mono-Mac 6 (MM6) and U937 were used. Proliferation was determined by ^{3}H-thymidine uptake. Apoptosis and cell cycle distribution were quantified by flow cytometry. Expression of CDK4/CDK6 mRNA was assessed by qPCR and protein expression and phosphorylation by Western blot analysis.

Results: HU was found to inhibit proliferation in all primary samples (IC_{50}: 50-250 µM) and all cell lines (IC_{50}: THP-1: 25-50 µM; MM6: 100-150 µM; U937: 500-750 µM) tested. In THP-1 and MM6, growth inhibition was accompanied by cell cycle arrest, induction of apoptosis and substantial reduction of CDK4 and CDK6 expression. Next, the effects of 3 specific CDK4/CDK6-inhibitors were explored. In cell lines, palbociclib, ribociclib and abemaciclib suppressed the expression and phosphorylation of the retinoblastoma protein (Rb), the main target of CDK4/CDK6, and blocked cell proliferation (IC_{50} 0.5-10 µM). In all 6 primary samples tested, palbociclib also produced growth-arrest (IC_{50}: 0.01-0.5 µM). Finally, we investigated potential synergistic effects between CDK4/CDK6-inhibitors and ponatinib. When applied as single agent, ponatinib was found to inhibit proliferation in cell lines (IC_{50}: 0.01-2.5 µM) and in 6 primary samples at clinically meaningful concentrations (IC_{50}: 0.01-2.5 µM). Finally, we were able to demonstrate, that ponatinib synergizes with both HU and palbociclib in producing growth arrest in THP-1, MM6 and in primary CMML cells.

Conclusions: Together, our data suggest that inhibition of the CDK4/CDK6-pathway may be a new interesting therapeutic concept in CMML. Synergistic anti-proliferative effects were observed between HU/palbociclib and ponatinib. The clinical value of these drug combinations in CMML remain to be determined in forthcoming studies.

Disclosure: Max Vincent John: No conflict of interest disclosed.
Karoline Veronika Gleixner: Financing of Scientific Research: Novartis, Incyte, Sanofi, Pfizer

V314

Induced NETosis is increased in Myeloproliferative Neoplasms (MPN)

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Introduction: Thromboembolic events as well as bleeding episodes are the major causes of morbidity and mortality in myeloproliferative neoplasms (MPN). The underlying mechanisms of MPN-associated vascular events are still unclear. The formation of neutrophil extracellular traps (NETosis) is a regulated necroptotic cell death process implicated in venous and arterial thrombogensis in cardiovascular disease, autoimmunity, inflammation and recently also in MPN. Human data describing NETosis rates in MPN is limited in conflicting.

Methods: Peripheral blood samples from healthy donors (n=30) and MPN patients (n=62) were collected after written informed consent was obtained. Primary neutrophils were isolated following using a consecutive 2-step density gradient separation method. Neutrophil numbers were standardized using FACS- bead-based quantification. Neutrophils were incubated for 4h with 4µM ionomycin to induce NETosis. Extracellular DNA and citrullinated histones as NETosis surrogates were quantified using by ELISA.

Results: We analyzed the induced-NETosis rates in primary neutrophils isolated from 92 peripheral blood samples of 30 healthy donors 62 patients with MPN. Most patients were diagnosed with essential thrombocythemia (ET, n=30) while polycythemia vera (PV-) and primary myelofibrosis (PMF) patient groups were smaller (n=16) in each group. Comparing NETosis rates induced in-vitro we found a significant increase in both all MPN patients as well as subgroups of ET and PV patients compared to healthy donors. In 48 patients a JAK2-V617F mutation was present, while CalR-mutations and triple-negative mutational status were each detected in 7 patients. NETosis rates of JAK2-mutated but no CalR-mutated patients compared to healthy were significantly increased. (pVal= 0.0277). Correlations of clinical parameters such as blood counts, LDH or age did not reveal any significant associations.

Conclusions: Susceptibility to induced NETosis is significantly increased in patients with ET and PMF. Mutational status as the only significant correlation with NETosis rates hints to intracellular signaling as one relevant determinant of NETosis in MPN. Thus, NETosis could be a relevant cause of thrombosis in such patients. However, whether NETosis is the primary trigger of vascular events or is a facilitating factor adding to other thrombotic triggers is still to be elucidated.
ed.

Disclosure: Stefan Schmdt: Employment or Leadership Position: nicht zutreffend; Advisory Role: Incyte; Stock Ownership: nicht zutreffend; Honoraria: nicht zutreffend; Financing of Scientific Research: nicht zutreffend; Expert Testimony: Incyte, AOP Orphan; Other Financial Relationships: nicht zutreffend; Immaterial Conflict of Interests: nicht zutreffend
Clemens Feistritzer: Employment or Leadership Position: nicht zutreffend; Advisory Role: SOBI; Stock Ownership: nicht zutreffend; Honoraria: nicht zutreffend; Financing of Scientific Research: nicht zutreffend; Expert Testimony: SOBI; Other Financial Relationships: nicht zutreffend; Immaterial Conflict of Interests: nicht zutreffend

V315

BCL-2 family proteins as distinctive regulators of aberrant eosinophils

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Introduction: Eosinophilic granulocytes are multifunctional cells of the immune system and are key players in the regulation of inflammatory processes and tissue remodeling. Hypereosinophilic disorders can cause severe organ damage. Only in a limited number of patients disease-defining mutations can be detected. Due to a lack in understanding the underlying pathomechanisms targeted therapies are limited.

Methods: In this *in vitro* approach, we analyzed an enlarged number of primary samples (n=40) from patients diagnosed with hypereosinophilia (MPN-Eo, CEL-NOS, HES and EGPA) and healthy controls (n= 13). Peripheral blood was analyzed as well as bone marrow samples.
Eosinophils from peripheral blood were purified by density gradient centrifugation and magnetic cell separation.
Quantification of critical BCL-2 family proteins was performed by intracellular flow cytometry and qRT-PCR.
Cells were treated in growth-factor enriched media for up to 72h with ABT-199 (venetoclax), ABT-737, WEHI-539 and S63845 to target BCL-2, BCL-xL, BCL-w and MCL-1 alone or in combination. Viability was determined by flow cytometry.

Results: Pharmacological inhibition of BCL-xL alone (by WEHI-539) or in combination with BCL-2 and BCL-w (by ABT-737) showed a significant decrease in cell viability in eosinophils isolated from healthy controls. Inhibition of MCL-1 reduced cell viability dramatically while ABT-199 (venetoclax) showed no significant effect on healthy eosinophils.
RNA and protein levels of BCL-xL or MCL-1 did not correlate with the sensitivity to treatment.
In contrast, BIM RNA levels correlated strongly to treatment response - especially WEHI-539 (Pearson`s rho 0,896 with a p value of 0,003) and ABT-737 (Pearson`s rho 0,843 with a p value of 0,017). No correlation was found between levels of BIM and single BCL-2 family proteins.
Surprisingly, eosinophils isolated from patients with hypereosinophilia showed a different pattern. In comparison to the healthy controls, aberrant eosinophils were resistant to ABT-199, ABT-737 and WEHI-539.
Response to MCL-1 inhibition varied in dependence on the patient's diagnosis. Here, patients with EGPA responded the best.

Conclusions: In contrast to our previous understanding eosinophils extracted from patients with hypereosinophilic disorders show clear differences in their apoptotic threshold and their capability to undergo apoptosis compared to healthy controls. Here, BIM seems to be a critical regulator.

Disclosure: No conflict of interest disclosed.

V203

No evidence for Ruxolitinib treatment being a potential risk factor for secondary primary malignancies (SPM) in 201 BCR/ABL-negative myeloproliferative neoplasm patients

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A higher incidence of secondary primary malignancies (SPM) in patients (pts) with BCR/ABL-negative myeloproliferative neoplasms (MPN) has been reported. A recent retrospective study suspected an association between ruxolitinib (RUX) treatment and an increased risk for B-cell lymphomas. Here we report our experience concerning SPM in 201 MPN pts and RUX treatment compared with 448 MPN pts without ruxolitinib.
In this single center study, we retrospectively analyzed clinical data of 649 MPN pts regularly presenting in our institution during an enrollment period from May 2013 till March 2019. In 201 of 649 pts (31.0%) RUX was used for a median time of 2.0 years (range 0.1 - 7.1). Most RUX pts were female (56.7%) and younger than 60 years (69.1%) at time of MPN diagnosis, 87.1% were diagnosed with polycythemia vera or myelofibrosis (primary or secondary). In total, 17.4% (35/201 pts) discontinued ruxolitinib treatment after a median time of 0.6 years (range 0.1 - 6.7), mostly (48.6%) due to disease progression. There was only one SPM (melanoma) leading to discontinuation.
Out of 649 MPN pts, 61 pts (9.4%) developed 70 SPM in a median time of 4.5 years (range 0.1 - 22.9) after MPN diagnosis. In only 5.0% (10 of 201) of our MPN patients receiving ruxolitinib SPM occurred after a median time on treatment of 2.1 years (range 0.6 - 5.2). Comparing by log-rank test (Mantel-Haenszel test) "SPM free survival" in RUX treated pts versus no RUX treatment, there was a significant difference (p=0.01) in favor of RUX therapy.
Out of 10 SPM occurring during RUX treatment, there were eight solid cancers (three breast cancers, two basal cell carcinoma of the skin, one prostate cancer, one non-small cell lung carcinoma, and one melanoma) and two hematological malignancies (one T-cell non-Hodgkin-lymphoma of the skin and one aggressive B-cell non-Hodgkin-lymphoma (B-NHL)). The B-NHL was diagnosed after 1.3 years of RUX treatment and simultaneous application of hydroxyurea. After standard chemotherapy with R-CHOP there is still a complete remission at last follow-up.
According to this retrospective study, a clinical relevant SPM rate was seen in our MPN cohort. However, an association between RUX treatment and an increased risk for SPM could not be substantiated.

Disclosure: No conflict of interest disclosed.

Freier Vortrag

Immuntherapie I

V316

Characterization of naturally presented HLA ligands of $CD34^+CD38^-$ progenitor cells of acute myeloid leukemia (AML) - mutated and non-mutated peptides as novel targets for T cell-based immunotherapy

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Acute myeloid leukemia (AML) is characterized by high relapse rates and a poor overall survival, which has been attributed to the persistence of (chemo)therapy-resistant leukemic progenitor cells (LPCs). Thus, to achieve long-lasting remissions, novel strategies like T cell-based immunotherapy are required that hold promise to eliminate residual disease after standard treatment. The basis for clinically effective antigen-specific T cell-based immunotherapy is the availability of suitable target antigens. In a recent study, we characterized the antigenic landscape of AML blasts (n = 15) by mass spectrometry and identified HLA-presented AML-specific T-cell epitopes (Berlin *et al.* Leukemia 2015). Here, we now aimed to specifically analyze the HLA ligandome of primary AML progenitor cells to identify novel LPC-associated antigens that might allow specific targeting of putative AML stem cells. Furthermore, we focused on the identification of naturally presented neoepitopes derived from frequent mutations.
Enrichment of $CD34^+CD38^-$ LPCs (LPC_{enr}) of a total of 10 patients was conducted by magnetic-activated cell sorting resulting in an increase of the LPC-containing populations from 1-3% within the PBMC fractions to > 80%.
We identified more than 16,000 unique HLA class I ligands from 7,000 source proteins presented on LPCs and more than 72,000 unique HLA class I ligands from 12,000 source proteins in the total AML cohort (n = 47). Comparative profiling of LPCs (n = 10), AML blasts (n = 47), and a benign tissue database (n = 332) identified LPC-exclusive antigens as well as frequently presented AML-associated antigens expressed on both, LPCs and non-LPC_{enr} AML cells. Besides those non-mutated peptides, we were able to detect naturally presented neoepitopes derived from two frequent mutations (NPM1, IDH2).
Immunogenicity analyses of these mutated peptides using *in vitro* priming experiments revealed profound T-cell responses in terms of IFNγ and TNF release, CD107a expression as well as peptide-specific target cell killing. Experiments investigating the presence of preexisting memory T-cell responses against these antigens in AML patients are presently ongoing.
Taken together, we identified novel, naturally presented, AML-associated non-mutated and mutated antigens on AML blasts but notably also on LPCs, which are currently validated as targets for tailored T cell-based immunotherapeutic approaches for AML patients.

Disclosure: No conflict of interest disclosed.

V317

Standardised phage display panning protocols for the generation of AML-specific and internalising antibodies

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Introduction: Phage display technology (PD) is a powerful technique for the generation of disease-relevant antibodies (AB). However, for primary human cells as panning material no consensus strategy exists. We therefore describe standardised procedures of subtractive panning, which facilitate efficient isolation of AML blast-specific antibodies. The panning procedures were performed parallelly using intact primary blasts from AML patients. This enabled us to isolate specific, internalising antibodies against AML.

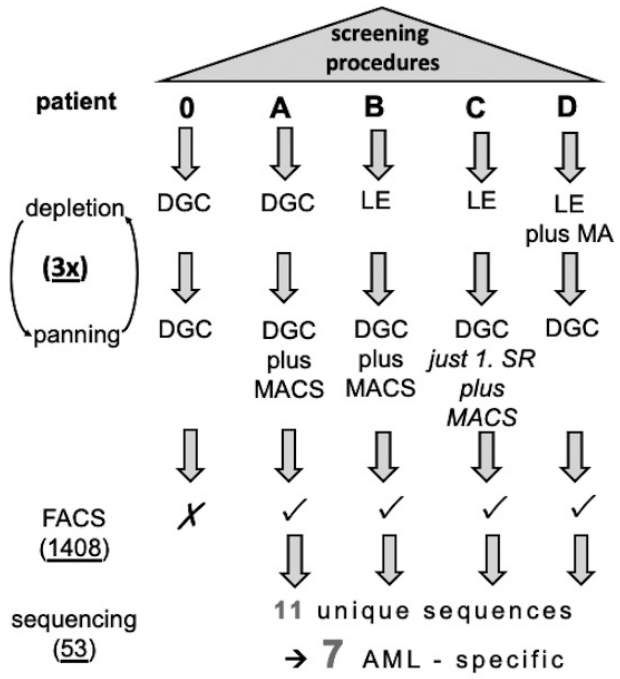

Fig. 1: PD strategies on AML blasts – After each depletion, panning followed directly. Both were performed 3 times (3x). *Abbreviations: DGC, density gradient centrifugation; LE, lysis of erythrocytes; MA, enrichment of monocytes via adherence; MACS, magnetic activated cell sorting;*

Methods: In total, we performed 3 PD selection rounds (SR) for each AML sample (n=5). 1 SR consisted of depletion on healthy blood cells and positive selection on AML blasts. Enrichment of blasts was conducted by CD34 MACS, if blast counts were below 90%. Cell-surface binding of phages was determined by flow cytometry. All phages which bound AML blasts, but no healthy cells were sequenced and converted into soluble AB fragments. Internalisation was confirmed by FACS and confocal imaging.
Results: 4 out of 5 PD screens showed AML-specific enrichment of phages. Overall, 1408 individual clones were screened for specific binding by FACS. While sequencing, 11 unique sequences were isolated. Among them 7 bound blasts exclusively and were converted into AB fragments. 4 of them showed efficient internalisation activity.

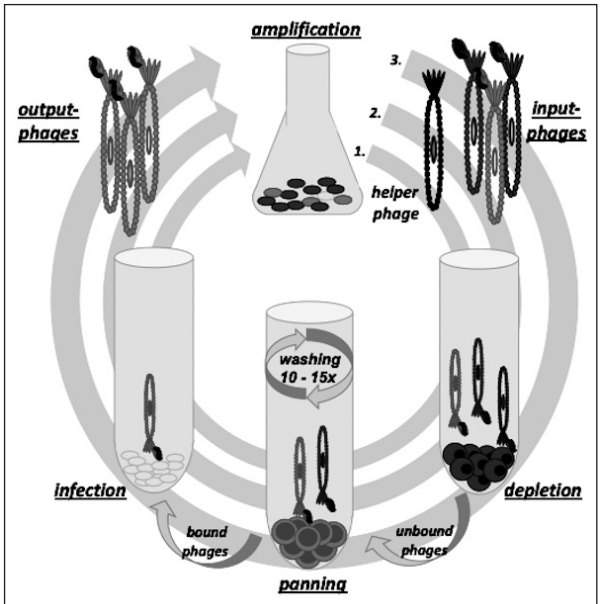

Fig. 2: Pattern of PD selection rounds – The red cells during panning depict AML blasts, the green cells among depletion show healthy cells, instead. The yellow flakes illustrate native bacteria, the coloured ones phage-harbouring bacteria. Washing during panning was performed 10 to 15 times (10 - 15x).

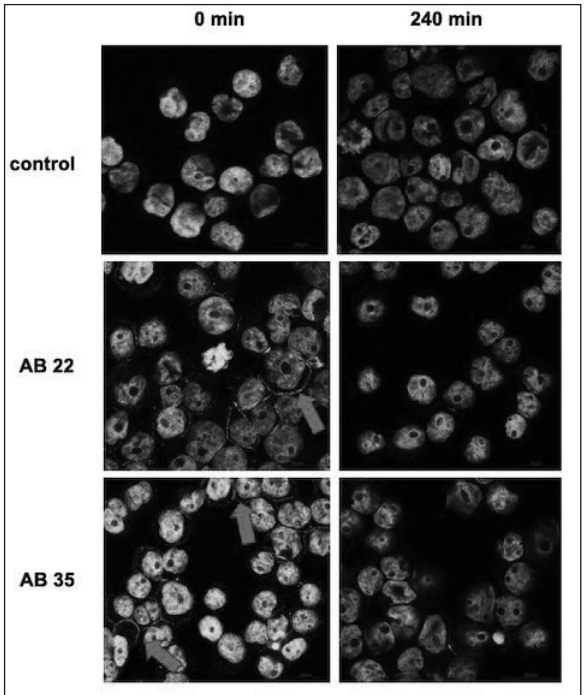

Fig. 3: Internalisation on Kasumi-1 (ACC-220, DSMZ) cells by confocal imaging – Exemplary, clone AB 22 and AB 35 are shown (scFv-Fc format). They were illustrated at 0 min and at 240 min after incubation under standard cell culture conditions to allow internalisation. As control the AB carrier medium without AB was used. Red arrows highlight AB staining of cell membranes. *Abbreviations: scFv-Fc, fusion protein containing the Fc region of murine IgG and an engineered human VH and VL antibody fragment.*

Conclusions: Here, we presented successful PD screening protocols for the generation of blast-specific, internalising AB. Thus, we showed PD as a feasible and encouraging method for the development of AML-specific and innovative immunotherapeutic agents.

Disclosure: Theresa Weber: Expert Testimony: JLU Trainee programme for young medical scientists of the Justus-Liebig-University Giessen, FB 11 Human Medicine, Germany
Mehmet Kemal Tur: No conflict of interest disclosed.

V318

Selective BET bromodomain inhibition by JQ1 suppresses dendritic cell maturation and antigen-specific T cell responses

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Introduction: Dendritic cells (DC) play an important role in the regulation of adaptive immune responses. DC maturation is required to effectively prime T cell responses, whilst immature DCs induce T cell-mediated immune tolerance. BET bromodomains have shown to be involved in the epigenetic regulation of immune responses by macrophages and dendritic cells. The aim of this study was to further characterize the effects of a selective BET bromodomain inhibition by JQ1 on DC maturation and DC-mediated antigen-specific T cell responses.
Methods: In vitro, bone marrow derived DCs (BMDCs) were characterized after selective inhibition of BET Bromodomains by JQ1. The expression of surface markers and cytokines was analyzed by RT-qPCR, ELISA and FACS. Antigen uptake by DCs was measured by a FITC-Dextran assay. The migratory capacity of DCs were examined in transwell migration assays. DC-mediated antigen-specific OT-II T cell proliferation was quantified by CFSE labeling. In vivo WT mice were challenged with sublethal LPS doses for the analysis of DC maturation and T cell activation.
Results: Selective BET Bromodomain inhibition by JQ1 impaires LPS-induced DC maturation, characterized by a lower expression of MHC-II, CD80, CD86, CD70, CD40 and CCR7 as well as reduced expression of pro-inflammatory cytokines, particularly of IL-1β, IL-6, IL-12 and TNFα. Furthermore JQ1 treatment inhibits the migrational activity of DCs while antigen uptake was not affected. JQ1-treated DCs have a reduced ability to induce an antigen-specific T cell proliferation. Moreover, antigen-specific T cells co-coltured with JQ1-treated DCs exhibit a less activated phenotype with a lower expression of CD25 and CD69, intracellular levels of INFγ in $CD8^+$ T cells were significantly reduced. In vivo, JQ1-treated mice show a limited immune response to sublethal doses of LPS, marked by a reduced white blood cell count, an immature phenotype of both splenic DCs and T cells as well as lower blood levels of IL-6.
Conclusion: Our study characterizes anti-inflammatory capacities of a selective BET bromodomain inhibition by JQ1 on dendritic-cell maturation and dendritic-cell mediated antigen-specific T cell responses, indicating a potential treatment option for T cell-mediated autoimmune diseases or GvHD.

Disclosure: Niklas Remke: No conflict of interest disclosed.
Peter Brossart: Advisory Role: MSD, Roche, BMS, Amgen; Financing of Scientific Research: MSD, Roche, BMS, Amgen; Expert Testimony: BMS

V319

Isolation of neoantigen-specific T cell receptors from different human and murine repertoires

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Introduction: Mutation-specific T cell receptor (TCR)-based adoptive T cell therapy presents a promising immunotherapeutic strategy for solid tumors with the potential for long-term remission. The isolation of mutation-specific TCRs, however, is time consuming and laborious. Here, we exploited different TCR repertoires to optimize isolation strategies for generating high-avidity TCRs for potential clinical applications.
Methods: Within the BIH-CRG study "Moving mutation-specific T cells into the clinic" nonsynonymous, somatic mutations of cancer patients were identified and potential neoepitopes, binding to the patient´s HLA molecules, were predicted. Peripheral blood lymphocytes (PBL) of patients or HLA-matched donors were stimulated *in vitro* with selected neoepitope candidates. For HLA-A*02:01 positive patients, HLA transgenic mice containing the human TCR repertoire were immunized with the same peptides. TCR sequences were identified from both, human and murine peptide-reactive T cells. Antigen recognition by identified TCRs was assessed in co-culture assays of transduced PBL with antigen-presenting cells by measuring T cell activation, degranulation and cytokine secretion.
Results: Four patients were selected for *in vitro* stimulation cultures and neoepitope-reactive TCRs could be isolated for two patients. However, it was possible to isolate TCRs only for a limited number of predicted neoepitopes. For colon carcinoma patient BIH-146, cultures of patient CD8 T cells did not generate neoepitope-reactive T cells. However, reactive T cells were isolated from one HLA-matched donor with reactivities against three out of 16 candidates and functional TCR rearrangements were identified. Interestingly, TCRs from immunized HLA-transgenic mice were specific for two different neoepitopes. Functional assays of donor PBL transduced with identified TCRs showed different avidities; whereby one TCR isolated from the healthy donor repertoire displayed higher peptide-specific activation compared to TCRs isolated from the murine repertoire.
Conclusions: As observed for patients, even from PBL of healthy donors and HLA transgenic mice, only a limited number of potential neoepitope-specific TCRs could be isolated. We assume that this is primarily a phenomenon of immunodominance, related to inherent characteristics of the epitope, the MHC class haplotypes of the donor and an inherent poor capacity of a given T cell repertoire to respond to a particular peptide-MHC complex.

Disclosure: No conflict of interest disclosed.

V320

MalheuR project: characterizing and establishment of a diagnostic and therapeutic management approach of rheumatic immune-related adverse events (irAEs)

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Introduction: The complex interrelations of malignancies and rheumatic and musculoskeletal diseases (RMDs) have attracted new attention due to the occurrence of rheumatic immune-related adverse events (irAEs) in patients receiving immune checkpoint inhibitors (ICPi). Since both disorders present two extremes of a dysregulated immune response, further research of these irAEs may contribute to scientific progress both in

oncology and rheumatology, particularly since better tumor response rates have been shown in affected patients. As these irAEs occur frequently in 5-20% patients treated with ICPi and are seldom life-threatening, they offer the opportunity for long-term observation of a larger cohort. So far, these irAEs have only been characterized in case reports and standardized evidence based guidelines for diagnostic and therapeutic management are still lacking.

Methods: The MalheuR project is a registry-based study that has been initiated at the university hospital Heidelberg, Germany in 08/2018 to close this gap. In one of three subregistries, we address the specific situation of patients suffering from rheumatic symptoms as a result of anti-cancer therapy with a special focus on irAEs.

Results: Herein, we present first data from TRheuMa registry: Until 04/2019, 41 of 44 patients in the TRheuMa registry were recruited due to a rheumatic irAE under ICPi (pembrolizumab n=16, nivolumab n=27, ipilimumab n=12, durvalumab n=1, atezolizumab n=1, history of >1 ICPi n=12). Of these, 19 (46.3%) suffered from lung cancer and 18 (43.9%) had a melanoma. Seven (17.1%) patients had a preexistent RMD that flaired under ICPi-treatment. Of the remaining 34 patients, irAEs resembling a rheumatoid arthritis were observed in 7 cases, a psoriatic arthritis in 19 patients and 4 suffered from symmetrical polymyalgia of proximal limbs similar to polymyalgia rheumatica. Based on the severity of symptoms and response monitoring, we developed a therapeutic management algorithm: The majority of patients were sufficiently treated by non-steroidal anti-inflammatory drugs and / or steroids, mostly below prednisone equivalent of 10 mg. Data on long-term remission status of the malignancies and rheumatic irAEs are being evaluated.

Conclusions: Overall, the so far obtained data in the MalheuR project show specific characteristics of rheumatic irAE and suggest a potentially suitable diagnostic and therapeutic management approach of rheumatic irAEs in patients receiving ICPi treatment.

Disclosure: Karolina Benesova: Advisory Role: Novartis; Financing of Scientific Research: Abbvie, Janssen, MSD, Novartis, Roche; Expert Testimony: Abbvie, Novartis; Other Financial Relationships: Reisekosten: Abbvie, BMS, Janssen, MSD, Mundipharma, Pfizer, UCB
Karin Jordan: Advisory Role: Hexal,Helsinn, Tesaro, Kreussler, Voluntis; Financing of Scientific Research: MSD, Merck, Amgen, Hexal, Riemser, Helsinn, Tesaro, Kreussler, Voluntis, Pfizer, Pomme-med

Freier Vortrag

Lungenkarzinom I

V322

Facing the urgent needs in Non-small cell lung cancer (NSCLC): Targeting "undruggable" genotypes

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Background: Recent developments in targeted therapy and immunotherapy have dramatically improved survival in a subset of non-small cell lung cancer (NSCLC) patients. Nevertheless, the majority of patients do not present with targetable genetic aberrations and a predictive link between genetics and benefit from either immunotherapy or chemotherapy has yet to be established. We set out our studies to fathom insights about genetics of patients without targetable mutations and possible therapeutic consequences.

Methods: We focused on patients with *KRAS*mutations and mutations affecting the redox-stress-system, namely *KEAP1*and *NFE2L2*,as well as on patients with squamous-cell carcinoma histology (SqCC). Additionally, we looked for mutations in *MAP2K1*and in*PIK3CA*. For communication with other interested colleagues, a ResearchGate project was created (http://bit.ly/2yq97lB).

Results: A comprehensive analysis (1200+ patients) of *KRAS*-mutated patients showed significantly distinct patterns of comutations depending on the*KRAS*-subtype. Specifically, G12C was exclusively co-occurring with *ERBB2*amplifications (p=0.002). Co-occurring mutations had a huge impact on overall survival, with *STK11*mutations being the worst in stage IV patients (3.2 months vs 10.0 months, p=0.002). Analysis 1410 SqCC patients revealed 22 patients (1.6%) with potentially targetable *EGFR*mutations. In 42 *PIK3CA*-mutated patients, we could not confirm the deleterious effect of these mutations when co-occurring with targetable aberrations. Patients with *KEAP1*(11.3% of all patients, n=157) and *NFE2L2*(3.5%, n=49) mutations showed no benefit from classical chemotherapy (no responses on monochemotherapy at all), but had unal-tered benefit from targeted therapy, whenever possible. Even though dif-ferently reported in the literature, patients with MAP2K1(n=66) mutations had a variety of activating co-mutations (86% with at least one additional mutation).

Conclusion: Comprehensive profiling of untargetable genotypes might lead to new insights and therapeutic options for these patients. Further analyses are needed and ongoing.

Disclosure: Matthias Scheffler: Advisory Role: Boehringer Ingelheim, Roche, Novartis, Mediolanum Biosciences, Takeda, BMS
Jürgen Wolf: Advisory Role: AbbVie, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Chugai Pharma, Ignyta, Eli Lilly, MSD Oncology, Novartis, Pfizer, Roche; Financing of Scientific Research: AbbVie, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, MSD, Novartis, Roche; Expert Testimony: Bristol-Myers Squibb, Novartis, Pfizer

V323

Sequential treatment of afatinib followed by osimertinib in T790M EGFR mutation positive non-small-cell lung cancer (NSCLC) pa tients: an observational study

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Introduction: The overarching aim of the treatment of lung cancer pa-tients is to find the right treatment sequence to prolong their overall sur-vival. For EGFR mutation positive (+) NSCLC patients the increasing knowledge about the underlying about the underlying mechanisms of resistance while treated with 1st or 2nd generation EGFR-TKIs like afatinib led to the registration of the 3rd generation EGFR-TKI osimertinib for the treatment of patients who acquire the most frequent T790M resistance mutation (60%). However, with the approval of osimertinib for 1st line treatment, individualized treatment approaches, based on specific patient characteristics, become more and more important. To date, there are only few data that have assessed the benefit of sequential EGFR TKIs in pa-tients with EGFR-M+ NSCLC. Therefore we aimed to assess outcomes in patients receiving afatinib followed by osimertinib in a real-world clinical setting. **Methods:** In this retrospective, observational, multicenter study, data from patients that had T790M+ disease following first-line afatinib and started osimertinib treatment, were collected from patient medical re-cords. Primary outcome was time on treatment. **Results:** A total of 204 patients were analyzed with a median age of 60 years (30-86). Two-thirds of the patients (n=138/68%) were of non-Asian ethnicity and 54% (n=110) were female. 73.5% (n=150) were initially tested positive for a deletion 19 (Del19) and 75% (n=31) were classified as ECOG0/1 patients. Median time on treatment was 27.6 months, 30.3 months and 31.3 months for the total set of patients, Del19+ patients and ECOG0/1 patients, respectively. The 2-year overall survival rate was 78.9% and the median overall survival was not calculated at the time of analysis, as maturity was only 31%. **Conclusions:** In this analysis of a broad real-world population, sequential afatinib and osimertinib facilitates prolonged, chemotherapy-free treat-ment in patients with T790M acquired resistance. This is especially true for patients with Del19+ disease with a median time on treatment of 30.3 months and for whom it is shown that they have a high probability for developing a T790M resistance mutation. In line with this, around 75% of the patients in this analysis (all T790M+) were positive for Del19. Fur-thermore, patients with ECOG ≥ 2 who are often underrepresented in clinical trials, also appeared to derive clinical benefit.

Trial registration number: NCT03370770

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Tanja Cufer: Advisory Role: AstraZeneca, Bristol Myers Squibb, Boehringer Ingel-heim, MSD, Pfizer, Roche; Financing of Scientific Research: AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, MSD, Pfizer, Roche

V324

Brigatinib vs Crizotinib in patients (pts) with ALK inhibitor-naive advanced ALK+ NSCLC from the phase 3 ALTA-1L trial

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Introduction: Brigatinib has demonstrated robust efficacy in crizotin-ib-resistantALK+ NSCLC, with median progression-free survival (mPFS) of 16.7 mo. We report results of the first interim analysis from ALTA-1L (NCT02737501), which evaluated efficacy and safety of brigatinib vs cri-zotinib in ALK TKI-naive ALK+ NSCLC. **Methods:** This open-label, multicenter study enrolled pts with ALK TKI-naive, advanced ALK+ NSCLC based on local ALK testing (FDA approved/other). Eligible pts had ECOG PS 0-2 and ≤1 prior systemic therapy for locally advanced/metastatic N SCLC. Asymptomatic CNS me-tastases were allowed. Pts were randomized 1:1 to brigatinib 180 mg QD (with 7-day lead-in at 90 mg) or crizotinib 250 mg BID. Blinded inde-pendent review committee (BIRC)-assessed PFS (RECIST v1.1) was the primary endpoint. Secondary efficacy endpoints included BIRC-assessed objective response rate (ORR), intracranial ORR (iORR), and intracranial PFS (iPFS). Interim analyses were planned at 50% and 75% of 198 expect-ed PFS events.
Results: 275 pts were randomized (brigatinib/crizotinib, n=137/138); me-dian age 58/60 yr. 26%/27% received prior chemotherapy for advanced disease and 29%/30% had baseline brain metastases. At data cutoff (19 Feb 2018), median follow-up for brigatinib/crizotinib was 11.0/9.25 mo; with 99 PFS events, brigatinib met the prespecified threshold for statistical su-periority vs crizotinib for the primary endpoint, BIRC-assessed PFS (HR 0.49, 95% CI 0.33-0.74, log-rank P=0.0007). Brigatinib median PFS was not reached (95% CI NR-NR) vs crizotinib 9.8 mo (95% CI 9.0-12.9). In-vestigator-assessed PFS HR: 0.45 (95% CI 0.30-0.68, log-rank P=0.0001). The table summarizes additional efficacy data. The most common treat-ment-emergent AEs grade ≥3: brigatinib: increased CPK (16.2%), in-creased lipase (13.2%), hypertension (9.6%); crizotinib: increased ALT (9.5%), AST (5.8%), and lipase (5.1%). Any grade ILD/pneumonitis: brigatinib, 3.7%; crizotinib, 2.2%. Discontinuations due to AE: brigatinib, 11.8%; crizotinib, 8.8%.

Conclusions: In pts with ALK inhibitor-naive ALK+ NSCLC, brigatinib showed statistically and clinically significant improvement in PFS vs cri-zotinib.

Tab. 1.

Endpoint,[a] %	Brigatinib (n=137)	Crizotinib (n=138)	*P* Value
All patients			
ORR[b]	76 (68–83[c])	73 (65–80[c])	
Confirmed ORR	71 (62–78[c])	60 (51–68[c])	0.0678
Patients with any intracranial CNS metastases			
	(n=43)	**(n=47)**	
iORR[b]	79 (64–90[c])	23 (12–38[c])	
Confirmed iORR	67 (51–81[c])	17 (8–31[c])	<0.0001
Median iPFS, mo	NR (11–NR[c])	6 (4–9[c])	
1-yr iPFS	67 (47–80[c])	21 (6–42[c])	
HR	0.27 (0.13–0.54)		<0.0001[d]
Patients with measurable intracranial CNS metastases			
	(n=18)	**(n=21)**	
iORR[b]	83 (59–96[c])	33 (15–57[c])	
Confirmed iORR	78 (52–94[c])	29 (11–52[c])	0.0028

[a]BIRC assessed; [b]Response, ≥1 assessment; [c]95% CI; [d]Log-rank.

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V325

Three-year overall survival update from the PACIFIC trial

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Background: In the PACIFIC study of patients with unresectable, St. III NSCLC without progression after chemoradiotherapy (CRT), durvalumab demonstrated significant improvements versus placebo in the primary endpoints of progression-free survival (HR, 0.52; 95% CI, 0.42-65; P< 0.0001) and overall survival (HR, 0.68; 95% CI, 0.53-0.87; P=0.00251). Safety was similar and durvalumab had no detrimental effect on patient-reported outcomes. Here, we report 3-year OS rates for all patients randomized in the PACIFIC study.

Methods: Patients with WHO PS 0/1 who received ≥2 cycles of platinum-based CRT were randomized (2:1), 1-42 days following CRT, to receive durvalumab 10 mg/kg i.v. every 2 weeks or placebo, up to 12 months, and stratified by age, sex, and smoking history. OS was analyzed using a stratified log-rank test in the ITT population. Medians and OS rates at 12, 24 and 36 months were estimated by Kaplan-Meier method.

Results: In total, 713 patients were randomized of whom 709 received treatment (durvalumab, n=473; placebo, n=236). The last patient had completed the protocol-defined 12 months of study treatment in May 2017. As of Jan 31, 2019 (data cutoff), 48.2% of patients had died (44.1% and 56.5% in the durvalumab and placebo groups, respectively). The median duration of follow-up was 33.3 months (range, 0.2-51.3). Updated OS remained consistent with that previously reported (stratified HR 0.69, 95% CI, 0.55-0.86), with the median not reached (NR; 95% CI, 38.4 months-NR) with durvalumab versus 29.1 months (95% CI, 22.1-35.1) with placebo. The 12-, 24- and 36-month OS rates with durvalumab and placebo were 83.1% versus 74.6%, 66.3% versus 55.3%, and 57.0% versus 43.5%, respectively. After discontinuation, 43.3% and 57.8% in the durvalumab and placebo groups, respectively, received subsequent anticancer therapy (9.7% and 26.6% subsequently received immunotherapy). OS subgroup results will be presented.

Conclusions: Updated OS data from PACIFIC, including 3-year survival rates (ITT & PD-L1 ≥1% subgroup), underscore the long-term clinical benefit with durvalumab following CRT and further establish the PACIFIC regimen as the standard of care in this population.

Disclosure: No conflict of interest disclosed.

V326

Evaluation of combined biomarkers for tumor response to immunotherapy (I/O) in patients with advanced non-small cell lung cancer (NSCLC)

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Background: Immune checkpoint inhibitors have revolutionized NSCLC treatment. At present, the only established predictive biomarker for I/O-therapy stratification are PD-L1 expression and MSI status. However, the expression of PD-L1 is limited by heterogeneous expression and even high expressors not always respond to I/O therapy. The aim of the study is to evaluate the value of combinations of positive (Tumor Mutational Burden, PD-L1) and negative (a.o. CD73 expression and inactivating STK11 mutations) predictive markers in patients (pts) with advanced NSCLC on I/O therapy.
Methods: A retrospective study was performed on a selected cohort of 54 pts with advanced NSCLC that have been treated with I/O between 2015 and 2018. Pts were selected by the availability of tumor tissue and based on tumor response evaluated by RECIST v1.1 criteria: only patients with durable tumor response (CR,PR $\geq$ 6 months) and patients with no tumor response (PD as best response) were analyzed for biomarkers: hybrid capture NGS assay for TMB (New Oncology) including STK11 mutations and IHC tests for PD-L1, CD73 and VISTA. Adjusted Cox regression and ROC analysis will be performed to evaluate the predictive value of the different biomarkers.
Results: A total 43/54 pts received nivolumab and 11/54 pembrolizumab in different therapy lines (from 1st to 5th line). Twenty four pts were defined as having a durable tumor response (median PFS 20 months, median OS not reached) 30 pts as primary progressors (median PFS 2 months, $p< 0.0001$; median OS 12 months, $p< 0.0001$). In 30/54 pts enough tumor tissu was available for TMB testing. The median TMB-value is 11.42 mutations/Mb. In 13 durable responders median TMB-value was 13.28 mutations/Mb versus 11.00 mutations/Mb in 17 primary non-responders. STK11 mutations were observed in 0/13 in durable responders (0%) vs. 3/17 primary non-responders (10%). Additional analyses of PD-L1, CD73, and VISTA will be presented at the meeting as well as their durable response and survival associations.
Conclusions: Our results suggest that integrating several biomarkers including positive and negative predictive markers may correlate better with responses to I/O than PD-L1 and TMB alone.

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V327

Osimertinib vs comparator EGFR-TKI as first-line treatment for EGFRm advanced NSCLC (FLAURA): final overall survival analysis

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Introduction: Osimertinib is a third-generation, irreversible, oral EGFR-TKI that potently and selectively inhibits both EGFRm and EGFR T790M, and has demonstrated efficacy in NSCLC CNS metastases. The Phase III FLAURA study (NCT02296125) compared first-line osimertinib vs comparator EGFR-TKI in EGFRm advanced NSCLC. Median progression-free survival (PFS; primary analysis, data cutoff June 12 2017) was significantly longer with osimertinib than comparator EGFR-TKI (18.9 months vs 10.2 months; $p< 0.001$). Overall survival (OS) data were immature (25% maturity) at the time of the primary publication.
Methods: Patients (pts; 556 globally) were randomised 1:1 to osimertinib 80 mg once daily (qd) orally (po) or comparator EGFR-TKI (gefitinib 250 mg qd or erlotinib 150 mg qd po) and stratified by race (Asian/non-Asian) and mutation status (Ex19del/L858R). Inclusion criteria: ≥18 years (Japan: ≥20); treatment-naïve with Ex19del/L858R EGFRm advanced NSCLC; WHO performance status 0-1; neurologically stable pts with CNS metastases were allowed, provided definitive treatment/steroids were completed for ≥2 weeks. Treatment beyond progression (by RECIST 1.1, per investigator) was allowed if clinical benefit continued; pts randomised to the comparator arm could crossover to osimertinib if T790M positive (tissue or plasma) on progression (confirmed by blinded independent central review). Primary endpoint: PFS by RECIST 1.1, per investigator. OS is a secondary endpoint. Safety and tolerability outcome measures include: adverse events (CTCAE v4); clinical and physical assessments.
Results: The protocol-defined maturity of data for final OS analysis (approximately 60% maturity across both arms) is anticipated by August 2019. Median OS and 2- and 3- year survival rates will be reported for each treatment arm. OS across predefined subgroups will be shown, including subgroups based on race and EGFR mutation type. Updated safety data will be reported.
Conclusions: We anticipate data from the comparator arm to be consistent with prior reports, and pts randomised to the osimertinib arm to show prolonged OS, reflected by the trend towards prolonged post-progression outcomes and the interim OS observed in the primary analysis.
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Suresh S Ramalingam: Advisory Role: Astra Zeneca, Amgen, BMS, Merck, Roche/Genentech, Loxo, Nektar, Tesaro; Financing of Scientific Research: Astra Zeneca, Amgen, BMS, Merck, Roche/Genentech, Loxo, Nektar, Tesaro; Expert Testimony: Astra Zeneca, Amgen, BMS, Merck, Tesaro, Advaxis, Takeda

Expertenseminar

E15: Supportive Therapien: Nebenwirkungsmanagement bei CAR-T-Zell-Therapie

V328

Management of side effects of CAR T cell therapy

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Treatment with genetically modified T cells expressing chimeric antigen receptors (CAR) has come into clinical practice. CAR T cells targeting CD19 were approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in October 2017 and August 2018, respectively. Axicabtagene ciloleucel (Yescarta ®) is available for treatment of patients with diffuse large B cell lymphoma (DLBCL) and primary mediastinal B cell lymphoma who have not responded to or who have relapsed after at least two treatment lines. Tisagenlecleucel (Kymriah®) is approved for patients up to 25 years of age with B cell acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse as well as for adult patients with DLBCL after two or more lines of systemic therapy. Additionally, numerous alternative CAR products for hematologic and solid malignancies are under clinical evaluation throughout the world. Besides of the benefit associated with CAR T cells particularly in heavily pretreated patients, CAR T cells display unique toxicities. These include cytokine release syndrome (CRS) and neurotoxicity, the latter termed CAR-related encephalopathy syndrome (CRES) and recently renamed into immune effector cell-associated neurotoxicity syndrome (ICANS). CRS and ICANS are commonly observed in treated patients and can be mild and self-limiting or potentially life-threatening. Along with differences in the CAR T cell trials, e.g. targeted disease entity, CAR construct, manufacturing process, used preconditioning therapy and/or dosage of infused CAR T cells, diagnosis and management of CRS and ICANS vary considerably across clinical trials and institutions. Nonetheless, it is of utmost importance to apply objective definitions and diagnostic criteria of CRS and ICANS.This will improve comparability of safety of the various CAR T cell products and allow standardized treatment of affected patients. Furthermore, other CAR T cell related side effects such as on-tumor-off-target toxicity, i.e. B cell aplasia in case of CD19-directed CAR T cells, require careful workup and supportive treatment.
This talk will give an overview on the definitions, diagnostics, grading and management of CAR T cell associated side effects and toxicities. Focusing on current management algorithms as well as supportive therapeutic approaches this talk aims to guide the way in daily practice of clinicians treating their patients with CAR T cells.

Disclosure: No conflict of interest disclosed.

Posterdiskussion

B-Zell-Lymphome, aggressiv

P330

The tumor-infiltrating T-cell receptor repertoire in Burkitt lymphoma is independently predictive of clinical outcome and differs from diffuse large B-cell lymphoma

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Introduction: Burkitt lymphoma is an aggressive B-cell malignancy derived from mature germinal centre B-cells. Treatment approaches of curative intent require intensive immunochemotherapy, which results in high degrees of treatment related morbidity and mortality, predominantly among elderly and frail patients. In recent years less toxic immunomodulatory treatment approaches, utilizing the patient's adaptive tumor-immune response have helped overcome this issue across a variety of malignancies.
The clonal architecture of the tumor-infiltrating T-cell receptor (TCR) repertoire in Burkitt lymphoma across its epidemiological subtypes, however, remains elusive to this date.
Methods: We performed a large-scale, next-generation sequencing (NGS) study of the CDR3 region of the T-cell receptor β-chain repertoire alongside an extensive immunophenotypic characterization of the tumor-infiltrating lymphocytes (TILs) in a large cohort of all epidemiological subtypes of Burkitt lymphoma (BL) and diffuse large B-cell lymphoma (DLBCL) samples. Molecular studies were subsequently assessed for correlation with clinical outcome.
Results: Our investigations revealed a homogenously diverse and independently reproducible immunoprofile with several public clonotypes suggestive of shared tumor-neoantigen selection throughout the epidemiological subtypes of Burkitt lymphoma at diagnosis clearly distinct from DLBCL (productive clonality; $p = 0.0181$) regardless of EBV and/or HIV status. Moreover, longitudinal analysis unveiled significant repertoire restrictions upon relapse (maximum productive frequency of the dominant TCR clonotype; $p = 0.0437$) while productive TCR clonality had a significant impact on both overall and progression-free survival (OS: $p = 0.0001$; HR: 6.220; CI: 2.263 - 11.78; PFS: $p = 0.0025$; HR: 3.086; CI: 1.555 - 7.030).
Conclusions: Out findings establish the clinical relevance of TIL TCR receptor repertoire clonality and suggest a potential role of CTLA4- and PD-1 directed therapies reinstating a diverse tumor infiltrating T-cell population and overcoming acquired immunoevasion in a relapsed or refractory setting.

Disclosure: No conflict of interest disclosed.

P331

Impact of treatment variability and clinicopathological characteristics on survival in patients with Epstein-Barr-Virus positive diffuse large B-cell lymphoma

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Introduction: Patients with EBV-positive diffuse large B-cell lymphoma (EBV-DLBCL) recurrently present with advanced age and reduced performance status. They are therefore insufficiently represented in clinical trials and treatment is likely to differ. Here we assess clinicopathological characteristics, therapeutic variability and clinical outcome in the largest EBV-DLBCL cohort published to date.
Methods: In total, 80 patients with EBV-DLBCL consecutively diagnosed between 2008 and 2018 (median age 70 years; range 19-90) were identified and assessed for clinicopathological and molecular baseline characteristics and outcome. Central hematopathological review was performed in all cases.
Results: 64 patients were treated with R-CHOP-type therapy and 16 patients received none or less intensive protocols. By immunohistochemistry 60/80 patients were CD30 positive. Further, we identified nine EBV-DLBCL patients with associated or composite peripheral T-cell lymphoma at diagnosis or relapse (preceded by clonal T-cell populations within the initial DLBCL biopsy in 4/5 cases). Upon univariate analysis both R-CHOP-type therapy (OS: p < 0.0001; HR: 2.708; CI: 1.281 - 5.724; PFS: p = 0.0617; HR: 3.043; CI: 1.415 - 6.548) and negativity for CD30 (OS: p = 0.0002; HR: 4.311; CI: 1.973 - 9.418; PFS: p = 0.0002; HR: 4.090; CI: 1.971 - 8.486) showed a protective effect, which was maintained upon multivariate analysis. In a propensity-score matched analysis with an extensive cohort of non-EBV DLBCL patients (n= 314), balanced for all R-IPI factors we found an EBV-association to hold no significant impact on progression-free and overall survival whilst displaying a trend favouring EBV-negativity (OS: p = 0.116; PFS: p = 0.269).
Conclusions: Our findings provide substantial insight into the clinical course of EBV-DLBCL, highlight the ramifications of CD30 expression and underline the superior therapeutic efficacy of R-CHOP immunochemotherapy. Alternative therapies, incorporating tumour biology (e.g. CD30 directed therapies) need to be explored in EBV-DLBCL patients. Moreover our data underscore the close relationship between EBV-DLBCL and peripheral T-cell lymphomas.

Disclosure: No conflict of interest disclosed.

P332

High-dose chemotherapy with autologous stem cell transplantation significantly increases overall survival of patients with primary CNS lymphoma: A retrospective single-center analysis

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Introduction: Optimal treatment for primary central nervous system lymphoma (PCNSL) is not fully defined. While the role of whole-brain radiotherapy (WBRT) as first-line treatment becomes more and more questionable, induction chemotherapy containing high-dose methotrexate (MTX) is nowadays considered the standard therapeutic approach for suitable patients. Ongoing studies address the role of subsequent consolidation therapy with autologous hematopoietic stem cell transplantation (autoHSCT). Here, we report our retrospective single-center experience in 73 PCNSL patients treated with or without autoHSCT.
Methods: After obtaining local ethical approval, we collected data from a total of 149 patients treated for their CNS lymphoma at our center between 2002 and 2017. After application of exclusion criteria 73 PCNSL patients were eligible for this evaluation. We assessed patients' characteristics, therapy protocols and outcome in a retrospective manner using their medical records. We compared patients regarding their treatment with or without high-dose chemotherapy followed by autoHSCT. Applying D'Agostino-Pearson omnibus K^2 test all assessed parameters showed non-Gaussian distribution. Continuous variables are presented as median values with ranges and were compared using Mann-Whitney *U* test. Categorical variables are presented as absolute numbers with percentage and were compared using Fisher's exact test. Survival analyses were performed applying Kaplan-Meier estimator.
Results: Median follow-up of all 73 patients was 20 (2-94) months. All patients received MTX- and rituximab-based immunochemotherapy. While 32 patients were treated with autoHSCT, 41 patients received no autoHSCT. No differences between these two groups were seen regarding patient and lymphoma characteristics except from age, which was as expected significantly lower in patients treated with autoHSCT (59 [20-74] vs. 72 [46-85] years; $p < 0.0001$). Significantly more autoHSCT patients reached complete remissions (75.0% [n=24] vs. 48.8% [n=20]; $p < 0.05$) after chemotherapy resulting in, albeit not significantly, lower employment of WBRT afterwards (18.8% [n=6] vs. 31.7% [n=13]; $p = 0.2847$). Finally, overall survival was significantly higher in patients treated with autoHSCT (median not reached vs. 20 months; $p < 0.01$).
Conclusions: These data support the use of autoHSCT as consolidation therapy in PCNSL patients. However, further prospective trials are required to verify these observations.

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P333

Autologous stem cell transplantation in patients with relapsed / refractory diffuse large B-cell lymphoma - a retrospective single-center analysis

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Introduction: Patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) are characterized by a dismal prognosis. Autologous stem cell transplantation (ASCT) following high-dose chemotherapy is the standard of care and a potentially curative treatment option in some patients. We performed a retrospective analysis to investigate the outcome and influencing factors of patients treated at our center.
Methods: We retrospectively reviewed the clinical records of 84 patients with relapsed or refractory DLBCL, treated with high-dose chemotherapy, followed by ASCT, between 2007 and 2017 at the University Hospital Muenster. The objective of this study was to analyze overall survival (OS), progression-free survival (PFS), toxicity and deaths not related to relapse/progression.
Results: Patients median age at diagnosis was 59 years (31-76), at time of ASCT 62 years (35-78). 30 (36%) of the patients were female, 54 (64%) male. At first diagnosis, DLBCL presented as advanced disease in 51/83 (61%) cases (stage III-IV), with an international prognostic index of high-intermediate/high-risk (IPI≥3) in 24/67 cases (36%). ECOG score was 0-1 in 87,9% and ≤2 in all cases. Firstline treatment consisted of a median of 6 cycles (1-8) of CHOP/CHOEP-like regimens in 79/84 patients (94%). 74/84 (88%) patients received rituximab. Salvage treatment prior to ASCT were ICE in 43 (52%), DHAP in 25 (31%), GDP in 5 (6%)

and other regimens in 9 patients (11%). High-dose BEAM conditioning was applied in 75/84 cases (89,3%). Relevant non-hematologic toxicities CTC grade ≥3 were infections in 67/84 cases (80%) and mucositis in 31/79 cases (37%) with a cumulative incidence of death not related to relapse or progression of 5% (4/84 patients, all related to ASCT) at day 100 and 24% (20/84) 3 years after ASCT. Overall response rate was 63/79 (80%) and median OS after ASCT was 29 months (95% CI: 15-43 mo.). Median PFS was 21 mo. (95% CI: 3-39 mo.). Patients with early relapse (< 12 mo.) after first line therapy had an inferior OS (p=.013) and PFS (p=.013) compared to patients with late relapse, with a median OS of 14 mo. (95% CI: 0-32 mo.) vs. median OS not reached and PFS of 7 mo. (95% CI: 3-11 mo.) vs. 71 mo. (95% CI: 3-149 mo.), respectively.
Conclusions: Our data confirms that "early relapse" (< 12 months) is a relevant prognostic factor for survival of patients with relapsed or refractory DLBCL. Moreover, long term follow-up revealed a relevant risk for late complication.

Disclosure: No conflict of interest disclosed.

P334

Renal toxicity of dose-intensified bendamustine-based high-dose chemotherapy in lymphoma and myeloma patients

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Background: Relapse after BEAM high-dose chemotherapy (HDCT) and autologous stem cell transplantation (ASCT) remains the major cause of death in patients with lymphomas and multiple myeloma (MM) after HDCT. Introducing dose-intensified bendamustine by replacing carmustine in the BEAM regimen (BeEAM) or by combining it with melphalan (BenMel) is a promising strategy to lower the relapse rates, but renal toxicity emerges as a major concern.
Methods: We investigated renal toxicity in a series of consecutive lymphoma patients treated with BeEAM and in consecutive MM patients treated with the same dose of 400 mg/m^2 bendamustine (split into 200 mg/m^2 on two consecutive days) together with full-dosed (200 mg/m^2) melphalan. Patients with a history of renal impairment before HDCT were included in the study population.
Results: 122 consecutive patients were analyzed. Acute kidney injury related to bendamustine (rAKI) occurred in 51 patients (41.8%) and was completely reversible in n=50/51 (98%). rAKI was mild to moderate in 90% of affected patients and did not increase treatment-related mortality after ASCT. 3 of 51 patients (6%) with rAKI required transient renal dialysis to enable recovery from renal damage. Occurrence of rAKI correlated (p< 0.05) with age >60 years, previous AKI, cardiovascular comorbidities and concomitant nephrotoxic drugs. In addition, rAKI correlated (p=0.004) with the development of cardiovascular complications during hospitalization. No differences in the incidence of rAKI were observed in both MM and lymphoma patients.
Conclusions: Our data suggest that treatment-related acute renal toxicity is a common event in lymphoma and MM patients receiving dose-intensified bendamustine HDCT before ASCT. However, renal impairment is reversible and manageable. Importantly, our data identify a subgroup of patients at increased risk for the development of renal damage following bendamustine-based HDCT. Accordingly, assessing the pre-transplant renal risk profile may help to identify those patients, which may not be candidates for bendamustine-based HDCT thereby avoiding prolonged hospitalization due to rAKI and eventually dialysis treatment.

Disclosure: No conflict of interest disclosed.

P335

Cooperative STAT/NF-kappaB signaling and metabolic reprogramming - comparative analysis of glutamine addiction in lymphoma

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Introduction: While the impact of deregulated MYC on tumor metabolism is well characterized, less is known about the role the tumor microenvironment plays. A better understanding of metabolic reprogramming could offer new opportunities to develop optimized therapies specifically targeting lymphoma cells.
Methods: We determined metabolic responses of the microenvironmental factors IL10 and CpG in a *MYC*-inducible human B cell line P493-6 and compared this with different cell lines from aggressive lymphoma. We used [13C]-glutamine, metabolite rescue experiments, and oxygen measurements.
Results: The IL10+CpG-mediated cell proliferation of MYC^{low}cells depends on glutaminolysis. we demonstrate that glutamine-utilizing transaminases are central to B cell proliferation and that GOT2 is a metabolic hub providing Asp and nucleotides to IL10+CpG-stimulated MYC^{low}rather than energy as for MYC^{high}cells. Corresponding metabolic differences were observed for Jak/STAT and NF-kB-dependent lymphoma cells (OCI-Ly3, L428) in contrast to MYC-dependent cells (CA-46). A model of GOT2 transcriptional regulation is proposed, in which the cooperative activation of STAT3 and p65/NF-kB and direct binding to the proximal *GOT2*promoter is important. Furthermore, the role of GPT2 and GOT1/2 is analysed. High aberrant *GOT2*expression is prognostic in diffuse large B-cell lymphoma.
Conclusions: The value of glutamine in our understanding of B cell lymphoma in the era of translational oncology will be discussed.

Disclosure: No conflict of interest disclosed.

P336

CD19 CAR T-cell therapy for relapsed/refractory diffuse large B-cell lymphoma (DLBCL) - the Munich Real Life Experience

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Introduction: The anti-CD19 CAR T-cell products Axicabtagene Ciloleucel (Axi-cel) and Tisagenlecleucel have recently been approved by the EMA for the treatment of patients with relapse/refractory (r/r) diffuse-large B-cell lymphoma (DLBCL). In clinical trials, both cell products induced complete responses in ≥ 40% of the patients and an overall survival rate ≥49% at 12 months. However, treatment was associated with significant toxicity.
Methods: Here, we evaluate the outcomes of DLBCL patients treated with Axi-cel and Tisagenlecleucel at the LMU Munich.

Results: As of April 2019, 14 out of 18 (78%) r/r DLBCL patients with confirmed CAR T cell treatment indication were leukapheresed. Three patients died before leukapheresis (two from lymphoma progression, one from sepsis). So far, eight patients have been treated with CAR T-cells. Two patients received out of specification products. Median age of the 8 treated patients was 63,3 years (range 55-74). Performance status was ECOG 0-1 (4 patients) and ECOG 2-3 (4 patients). Five patients had undergone prior stem cell transplant (4 autologous, 1 allogeneic SCT). Four patients received bridging chemotherapy between leukapheresis and CAR T cell transfusion.

CRS (according to ASBMT criteria) occurred in all patients (71% CRS °1 and 29% °2) with a median onset between day 3 and 4 (range days 1-11). Tocilizumab was administered at least once in all cases. Two patients experienced Immune Effector Cell associated Neurotoxicity Syndrome (ICANS) with onset on day 3 and 5, respectively, with ICANS °4 requiring mechanical ventilation in 1/2 patients. The number of patients with adequate follow-up is still low (1 patient with progression of disease, 1 patient with complete remission three months after CAR T-cell transfusion), currently limiting the outcome analysis.

Conclusions: Taken together, the CAR T cell program at LMU Munich was successfully implemented. The interdisciplinary ImmunoTaskForce^{LMU} has effectively been put in charge to manage safety and toxicity according to harmonized guidelines and local SOPs. We will present updated information on the clinical outcomes of our fast-recruiting CAR T cell program.

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P337

Clinical impact of low serum albumin and body mass index in elderly patients with diffuse large B-cell lymphoma

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Introduction: Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of aggressive lymphoma accounting for 30 % of all newly diagnosed non-Hodgkin lymphomas. With a median age of 72 years, DLBCL mainly occurs in elderly patients (pts). The aim of this study is to evaluate low Body Mass Index (BMI) and low pre-treatment serum albumin (SA) (< 3.5 g/dl) as a prognostic factor for overall (OS) and progression-free survival (PFS) in elderly pts (≥65 years) with initial diagnosis of DLBCL.

Patients and methods: In a single center retrospective study, 802 pts with aggressive lymphoma diagnosed between 2000 and 2017 at the University Medicine Göttingen were analyzed. In total, 135 pts met the inclusion criteria: age ≥65 years, initial therapy at University Medicine Göttingen, available SA level and BMI before therapy. The observation period was time of initial diagnosis and last contact or death, respectively. BMI and pre-treatment SA level were analyzed for PFS and OS.

Results: Main clinical features of the cohort analyzed were as follows: median age 73.8 years (65-89), 75% male pts, 56% of pts with advanced stage III/IV disease, 5% of pts with reduced performance status (ECOG >2), 69% of pts with elevated lactate dehydrogenase (LDH). Median SA level was 3.51 g/dl (1.8-5.1 g/dl), median BMI 27.0 Kg/m² (14.7-41.1). 89% of patients were treated with R-CHOP-like immunochemotherapy with a median observation time of 32 months (0,8-129). 90% of pts showed a good response to initial therapy: 58% complete remission (CR), 31% partial remission (PR). 1% achieved only stable disease, 10% failed to respond. 34% of pts with PR/CR relapsed later during follow-up.

In univariate analysis an SA level < 3.5 g/dL was shown to be a significant predictor of PFS (HR=0.39, 95% CI 0.21-0.72, P=0.003) and OS (HR 0.22, 95%CI 0.09-0.56, P=0,001). Elevated LDH, Ann-Arbor stage IV, Karnowsky-Index < 60, bone marrow involvement and age >80 years, Karnowsky-Index < 60, bone marrow involvement were also significantly prognostic for PFS and OS, respectively. BMI was not prognostic for OS or PFS in our population (P=0.327 and 0.52 for PFS and OS, respectively). In multivariate analysis SA continued to be an independent prognostic marker for PFS (HR=0.44, 95% CI 0.23-0.85, P= 0.01) and OS (HR 0.22, 95%CI 0.09-0.56, P=0,001).

Conclusions: Serum Albumin prior to therapy is a negative prognostic marker for PFS and OS in elderly patients with DLBCL.

Disclosure: No conflict of interest disclosed.

P338

Prognostic scores for patients with primary CNS lymphoma - bedside is good enough?

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Introduction: Patients with primary CNS lymphoma (PCNSL) have dismal prognosis. Various prognostic scores were developed to stratify patients into subcategories that are predictive for overall survival (OS). Currently, multiple scores are in use, however there is no generally accepted standard.

Methods: We retrieved data from our database on all consecutive patients with newly PCNSL treated in our institution between 11/2000 and 07/2017. Patients were grouped according to previously described prognostic scores: Memorial Sloan Kettering Cancer Center (MSKCC; 2006), International Extranodal Lymphoma Study Group (IELSG; 2003), Three-factor model (3-F; 2016) and Taipei (2017) score. All scores were calculated as indicated in the original references; only in IELSG score, missing data regarding cerebrospinal fluid protein level required adaptation in calculation; therefore the maximal score was 4 out of 5.

Results: Altogether, 89 patients with PCNSL with a median follow-up of 9.5 years were included in this analysis (median age 68 years [IQR, 57-74], median Karnofsky index 70%). High-dose methotrexate monotherapy was applied in the majority of the patients (85.4%). Patients were mainly classified into intermediate-risk group, (according to MSKCC, IELSG and Taipei score 48.3%, 61.8% and 43.8%, respectively), with the exception of 3-F model, that recognized most of them as low-risk patients (42.0%). The MSKCC score allocated a major proportion of patients 33 (37.1%) into high-risk group. Overall concordance among the 4 scoring systems was poor (15.7%), with the highest concordance in intermediate-risk group (13.0%). All 4 prognostic models discriminated well between subgroups with different OS probabilities (p< 0.05, for each). Interestingly, there were major differences in predicted OS for low risk patients: Median OS was 67.0 months, 49.4 months and 26.8 months for MSKCC, IELSG and 3-F/Taipei score, respectively. In multivariate analysis, carried out on all 4 prognostic scores, the MSKCC score was the only prognostic score independently predicting OS (for low-risk hazard ratio [HR] 0.38; p=0.011 and for high-risk HR 1.90; p=0.014).

Conclusions: In our study, all 4 scores are useful in predicting OS. Sufficiently accurate patient stratification can be done at bedside, based only on clinical prognostic factors (age and performance status) as incorporated in the MSKCC score. Thus, we support the use of MSKCC score for being easy applicable in clinical practice.

Disclosure: No conflict of interest disclosed.

P339

Treatment of high risk aggressive B cell lymphomas with DA EPOCH R - a retrospective analysis

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Introduction: Promising results in patients suffering from Burkitt`s lymphoma (BL) and primary mediastinal B cell lymphoma (PMBCL) treated with DA EPOCH R have been reported. Additionally DA EPOCH R seems to be an option in first line treatment in high risk aggressive B cell lymphoma (HR BCL) in phase II trials.
In our centres HR BCL - defined as DLBCL NOS with double protein expression (DEL) and/or high/ high-intermediate risk NCCN IPI, high grade B cell lymphoma with myc and bcl 2and/or bcl 6 rearrangements and high grade B cell lymphoma NOS - BL and PMBCL are treated with DA EPOCH R.
Methods: we performed a retrospective analysis of toxicity and efficacy in DA EPOCH R treated patients.
Results: So far 71 previously untreated patients with a median age of 52 years (range 18 - 89) have been treated with a total of 375 cycles of DA EPOCH R: 41 HR BCL, 18 PMBCL, and 12 BL. Dose escalation according to hematological toxicity was possible in 53 (77%) patients - but only in 7 (33%) of 21 patients ≥ 65 years . 29 (62%) of 48 patients aged < below 65 years received at least dose level 3 (144% dose intensity). Due to peripheral sensory neuropathy, vincristine had to be dose reduced in 37% of all cycles. Other CTCAE grade III/IV non-hematological toxicities were infrequent and manageable. After a median follow up of 21,5 months overall survival (OS) rate is 80% and PFS 60% for all 71 patients. OS and PFS rates are 90% and 92% in BL, 92% and 93% in PMBCL, respectively. In 41 HR BCL patients OS is 73% and PFS is 44% after a median follow up of 22 month, 2 years PFS is 58%. 2 years PFS for 22 patients in the subgroup of DEL is 51% (figure below), 2 years PFS in 10 patients with high risk NCCN IPI is 50%.
Conclusion: Despite limited data, DA EPOCH R is a feasible treatment with acceptable toxicity and a promising response rate. Dose escalation is age dependent. Excellent response rates to DA EPOCH R in BL and PMBCL are confirmed. As presented by Bartlett et al at ASH 2016 DA EPOCH R can not be recommended for standard risk DLBCL, but might be an valuable option for high risk aggressive BCL and can challenge more toxic regimens like R ACVBP or R Hyper CVAD.

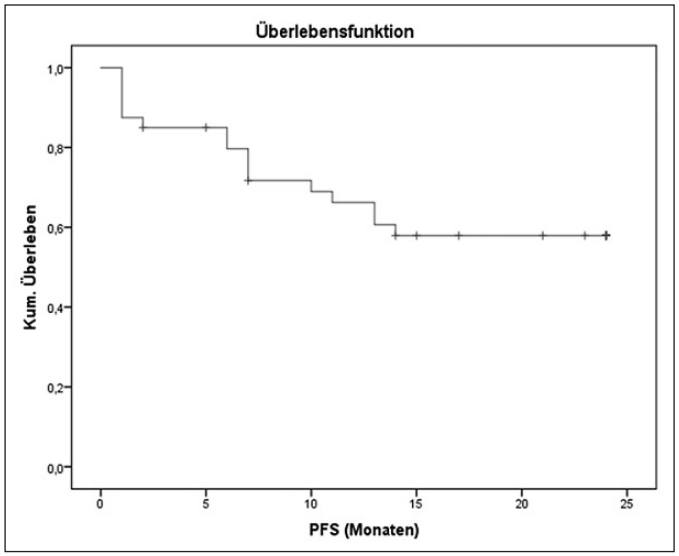

Fig. 1. PFS HR DLBCL

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P340

Dysregulated eukaryotic initiation factors may impact on the pathogenesis of primary central nervous system lymphomas

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Introduction: Primary central nervous system lymphoma (PCNSL) is a rare but aggressive extranodal Non-Hodgkin lymphoma which mainly affects eyes, spinal cord, brain and leptomeninges without systemic involvement. The current standard treatment for newly diagnosed PCNSL is high-dose methotrexate-based induction chemotherapy, which is less neurotoxic than previous treatments. However, relapses with poor prognosis are frequent within treated patients. Since our group demonstrated that eukaryotic initiation factors (eIFs) were significantly associated with clinical course of aggressive lymphomas, we aim to comprehensively study these factors in PCNSL.
Methods: By quantitative real-time PCR, we analyzed mRNA expression levels of 16 eIF in a patient cohort of 31 PCNSL patients. As controls, non-neoplastic germinal center (GC) B-cell specimens were included (n=5). We compared eIF expression to non-neoplastic controls and clinical data.
Results: Analysis of the mRNA expression revealed a higher expression of *EIF1A* (5.5-fold; p=0.027), *EIF2B3* (4 fold; p=0.013) and *EIF3D* (9.3 fold, p=0.028), and a lower expression of *EIF2A* (3.4-fold; p< 0.001), *EIF4BP1* (2-fold; p=0.002) and *EIF4G3* (5.4-fold; p=0.004) in PCNSL compared to GC B cells. Interestingly, by comparing the expression level to clinical data, we detected that 7 out of 16 eIF were associated with survival (p< 0.033): high expression of *EIF1*, *EIF2B4*, *EIF2B5*, *EIF2S1*, *EIF3L*, *EIF4A2,* and *EIF5* was associated with poor cancer-specific survival.
Conclusions: Our data indicate that eIFs play an important role in the pathogenesis of PCNSL. Thus, the expression pattern of the eIF subunits might serve as a useful clinical prognostic marker for risk stratification.

Disclosure: No conflict of interest disclosed.

P341

Liposomal non-pegylated Doxorubicin for treatment of aggressive lymphoma in elderly patients with heart disease

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Background: Aggressive lymphoma is a potentially curable disease. A mainstay of combined chemoimmunotherapy (e.g. (R-)CHOP) is a sufficient dose of anthracyclins. Due to cardiotoxicity the administration of doxorubicin is hampered in pts with heart disease, thus reducing the chance of cure. Liposomal non-pegylated doxorubicin (Myocet™) is licensed for the treatment of breast cancer because of its reduced cardiotoxicity.
Patients and methods: In two institutions pts suffering from aggressive lymphoma with concomitant heart disease were treated with Myocet instead of classical doxorubicine. Their charts were reviewed retrospectively, data concerning heart disease, treatment toxicity and outcome were collected. Median follow up is 69 months.

Results: 24 consecutive pts were treated from 2005 to 2014, 17 male, 7 female, age 56-90y, median 78y. The type of NHL was DLBCL in 17 pts, MCL in 3, FL grade 3B in 1, B-CLL (Richter transformation) in 1, and aggressive T-NHL in 1. Performance status was ECOG 0 in 11 pts, ECOG 1 in 10, and ECOG 2 in 3. Treatment was 1st line in 20 pts. Cardiac risk factors were heart failure in 19 pts (14 grade 1, 5 grade 2), atrial fibrillation in 1, and combinations of heart failure and atrial fibrillation in 4. Only 1 pt experienced deterioration of LVEF during therapy. 17/24 pts reached CR, 3 PR, 1 SD, 3 PD. 5 pts have died. The majority of pts was cured: overall survival was 79,2% after 5 and 10 years.
Conclusions: Liposomal non-pegylated doxorubicin is safe and effective in elderly pts with heart disease treated for aggressive lymphoma.

Disclosure: No conflict of interest disclosed.

P342

Differences of the chemokine receptor expression profile of aggressive lymphoma and GCB-cells and probable influence on clinical outcome

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Introduction: Chemokine receptors (CCR) and their ligands have been identified to play an important role in development of lymphoid neoplasms. Our aim was to investigate the different expression profiles in de novo diffuse large B-cell lymphoma (DLBCL), follicular lymphoma and Richter syndrome (RS) in comparison to germinal centre B-cells (GCB) and their probable influence on clinical outcome.
Material and methods: We analyzed mRNA expression levels of 19 chemokine receptors by using RQ-PCR in the aggressive component of RS (n=16), de novo DLBCL (n=31) and transformed follicular lymphoma (tFL, n=16). Germinal center B-cells (GC-B, n=4) served as non-neoplastic controls. After this analysis we investigated if there is an impact of expression levels on overall survival of patients with transformed FL and de novo DLBCL.
Results: The chemokine receptor expression profile of de novo DLBCL, tFLs and RS substantially differed from that of GC-B, with a at least five fold higher expression of 12 of our investigated CCR (*CCR1, CCR2, CCR4, CCR6, CCR7, CCR8, CCR9, CXCR5, CXCR6*and *XCR1,* $p < 0.05$) in de novo DLBCL, tFLs and RS. Interestingly, RS exhibited a different expression of 13 of the investigated chemokines (*CCR1, CCR4, CCR5, CCR6, CCR8, CCR9, CXCR3, CXCR4, CXCR5, CXCR6, CXCR7, CX3CR1 and XCR1, p< 0.05*) compared to FLIII and de novo DLBCL, with at least 5 fold higher expression of 9 of our investigated chemokines. Whereas no significant difference in CCR expression profile between de novo DLBCL and transformed FL was detected.
By comparing the CCR expression of de novo DLBCL and tFL to clinical data we observed that high CCR7 and CCR8 expression were associated with worse overall survival, whereas no association was detected for the other chemokines in the survival of de novo DLBCL and tFL.
Conclusion: Our data indicate that the CCR-expression profile of RS differs substantially from those of non-neoplastic GCB-cells, FL, and de novo DLBCL. CCR7 and CCR8 expression level were associated with overall survival. Therefore, these multiple deregulated CCRs might serve as useful prognostic tool and might be a valuable clinical marker.

Disclosure: No conflict of interest disclosed.

P343

New case of a Burkitt-like lymphoma with 11q aberration in an HIV patient

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Introduction: Burkitt-like lymphoma with 11q aberration (BLL-11q) has been listed as new provisional entity in the 2016 WHO-Classification. Morphologically and phenotypically BLL-11q resembles Burkitt lymphoma (BL), but a *MYC* rearrangement is missing. Typically, BLL-11q displays proximal 11q-gains and telomeric 11q-losses, however cases with only an 11q-terminal deletion have been reported. Although an accumulation of BLL-11q cases has been observed in posttransplant and immunocompromised patients, the incidence in HIV-positive patients is unknown.
Material and methods: A 34-year-old patient with pancytopenia, marked suppression of CD4+ T-cells, extensively elevated LDH, generalized lymphadenopathy, splenomegaly, thoracic wall tumor, and inflammatory markers was presented at our clinical department. Cerebrospinal fluid showed infiltration of lymphatic blasts with L3 cytomorphology. A previously undetected HIV1-infection was diagnosed. Routine cytogenetic analyses on R-banded metaphases and FISH with break-apart probes for *MYC*-, *IGH*-, *BCL2*-, and *BCL6*-genes as well as for *IGH-MYC* fusion was performed on bone marrow (BM) and a tumor-biopsy. Additionally, a FISH-assay for detection of specific BLL-11q-gains/losses in combined with centromere 11 probe as control was used (Wagener et al., Blood 2019).
Results: Histopathology of the thoracic tumor showed dense, sheet-like infiltrates of pleomorphic large lymphoid cells with plasmacytoid features with a starry-sky pattern and areas of necrosis. The infiltrates showed a mature germinal center B-cell immunophenotype ($CD20^+$, $CD79^+$, $CD10^+$, $BCL2^{+/-}$, Tdt^-) with high proliferation (Ki67: 70~95%). The lymphoma was EBV-negative. R-banding and FISH did not reveal any aberrations in BM. In the tumor, R-banding revealed a complex aberrant karyotype and 4 subclones with, in particular, a deletion in 11q. Accordingly, FISH excluded the presence of a *MYC*-, *IGH*-, *BCL2*-, *BCL6*-rearrangement or a cryptic *MYC-IGH* fusion. FISH confirmed the 11q-deletion and detected a solely 11q-terminal deletion without 11q-proximal gain.
Conclusions: We report here the case of the new provisional WHO entity BLL-11q in a HIV+ patient. The case did not show the BLL-11q characteristic 11q-gain/loss pattern but a solely 11q24.3-ter deletion. Accordingly, BLL-11q cases with a pattern of 11q-deletions in absence of a 11q-gain have been previously reported in four BLL-11q cases. This is, to the best of our knowledge, the first case of HIV-associated BLL-11q.

Disclosure: No conflict of interest disclosed.

P344

Model-based prediction of next-cycle haematotoxicity and its impact on clinical decision making

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We developed comprehensive biomathematical models of haematopioesis under chemotherapy in the past. These models are based on biological assumptions regarding cell differentiation, amplification, apoptosis rates, transition
times, and the interaction of cytotoxic chemotherapy with the bone marrow niche. We also included pharmacokinetic and -dynamic models of chemotherapy drugs and growth-factor applications.
By combining individual patient data with other biological and clinical data available for average patient populations, we could show that these

models can be used to make individual predictions of next cycle toxicity. This method was applied to data of patients with high-grade non-Hodgkin's lymphoma treated with CHOP-like therapies. Close meshed time series for 2-3 cycles are required to make sufficiently precise predictions of next cycle toxicity. To test whether our model predictions could impact clinical decision making, we conducted a so called virtual trial based on retrospective patient data. We asked clinicians about their decision on the basis of individual data or supported by the model predictions.
We present the design and scenarios of the trial and its results.

Disclosure: Markus Loeffler: No conflict of interest disclosed.
Markus Scholz: Expert Testimony: Pfizer Inc.

Posterdiskussion

AML I

P345

Cell stiffness, a novel biomarker of Midostaurin resistance in acute myeloid leukemia

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Introduction: Changes within the actin cytoskeleton have been associated with drug resistance development in various cancers, but it's role in response to Midostaurin, a novel Tyrosin kinase inhibitor used to treat Acute Myeloid Leukemia (AML) has not yet been assessed. Actin is found in two forms, depolymerized (Globular Actin) and polymerized, which forms Actin Filaments. Its polymerization increases rigidity of cells and is mainly regulated by GTPases of the RHO family (RHOA-GTP/CDC42-GTP/RAC-GTP), that have been previously reported by others to play a role in drug resistance development to cancer treatment. Therefore, we investigated the role of cell stiffness as a biomarker of drug resistance in AML cell line models using innovative single cell microscopy.
Methods: We developed two Midostaurin resistant AML cell lines (MID-RES, MV4-11 and MOLM-13). Single cell measurements of Cell Stiffness and Actin filaments were done by Atomic Force Microscopy and SIM microscopy, respectively. Cell viability assay was carried out by CellTiterGlo kit.
Results: The MID-RES cell lines MV4-11/MOLM-13 showed increased stiffness, compared to their MID sensitive parental cells, due to a higher load of actin filaments, that was visualized and quantified by immunofluorescence (Figure 1). MID-RES was overcome by the use of a RAC1 inhibitor (EHT1864) that, following our hypothesis, decreased cell stiffness and reduced the expression of positive regulators of actin polymerization (PFN1/N-WASP/ARP-2/3) and increased the negative regulator of actin polymerization (P-CFL1ser3). In addition, the specific knock down of PFN1, N-WASP and ARP2 with siRNAs equally reversed the resistance phenotype. Of note, RAC1 regulates the anti-apoptotic BCL2. Also in MID-RES, EHT1864 reduces anti-apoptotic family BCL2/MCL1 expression and increases the pro-apoptotic proteins BAX/PUMA.
In fact, our MID-RES cells showed higher sensitivity to BCL2 inhibitor Venetoclax, than their parental cells.
Conclusions: Changes within the actin cytoskeleton may induce Midostaurin drug resistance in AML that can be reversed by the use of specific inhibitors of actin polymerization or the use of BCL2 inhibition.

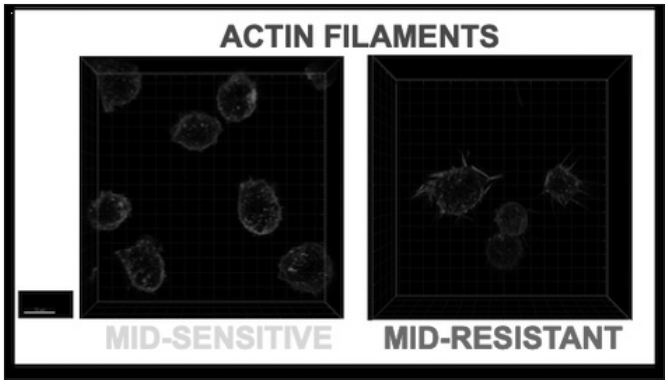

Fig. 1. Visualization of Actin filaments in MID-Sensitive and MID-Resistant AML cells

Disclosure: No conflict of interest disclosed.

P346

Evaluation of a novel dual BCL-2/XL inhibitor (AZD0466) in acute leukemia

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In recent years, it has become increasingly apparent that BCL-2 inhibition is a clinically highly effective approach - and the first BCL-2 inhibitor, venetoclax, has gained FDA approval for unfit patients with AML. However, responses in AML are infrequent and often short. Definition of resistance mechanisms or biological markers to predict response to BCL-2 inhibition are under active investigation. It becomes increasingly apparent that other BCL family members or regulators, such as BCL-XL or MCL-1 may play a more dominant role in acute leukemia or contribute to resistance towards BCL-2 inhibition.
We herein tested a novel inhibitor, dually targeting BCL-2 and BCL-XL (AZD0466) currently entering clinical trials.
BCL-2/XL expression was assessed flow cytometrically. Cell lines (MOLM14, Jurkat, Kasumi1, HL60 or K562) as well as freshly Ficoll-isolated mononuclear cells of consented bone marrow donors or patients suffering from de novo or refractory/relapsed (R/R) leukemia were used to determine proapoptotic efficacy of BCL-2/XL inhibition (using AZD0466) in annexin V-based dose-dilution assays. Venetoclax (BCL-2) or a selective BCL-XL inhibitor (A-1155463) were comparatively tested. Western immunoblotting validates induction of apoptosis pathways via cleavage of caspases. Epigenetic priming to increase proapoptotic regulators were determined using aza-nucleosides prior to BCL-2/XL inhibition.
Together, variable protein expression levels were detected - whereas BCL-XL frequently displayed the highest protein levels compared to BCL-2. Cells were typically either sensitive towards Venetoclax (e.g. MOLM14, IC50 250 nM) or A-1155463 (Kasumi1, IC50 not reached, Jurkat 500nM). Dual inhibition of BCL-2/XL using AZD0466 was highly sensitive in all tested cell lines with IC50s in the lower nanomolar range (5-50 nM). Superior proapoptotic activity of AZD0466 compared to venetoclax and A-1155463 was validated in native leukemia cells. Epigenetic priming using decitabine prior to AZD0466 resulted in synergistic proapoptotic efficacy, arguing for benefitial use of a combination strategy in acute leukemia.
Of note, BCL-XL expression levels were also frequently elevated in R/R patients (with only minor effects of venetoclax) - and BCL-2/XL inhibition resulted in potent proapoptotic efficacy in patient samples treated ex vivo.
We provide a rationale for dual BCL-2/XL inhibition in acute leukemia - which is even more effective with epigenetic priming strategies.

Disclosure: No conflict of interest disclosed.

P347

Anti-leukemic efficacy of Talazoparib and APE1 inhibitor III combined with decitabine in myelodysplastic syndromes and acute myeloid leukemias

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Introduction: Cells of myelodysplastic syndromes (MDS) and acute myeloid leukemias (AML) may be vulnerable to inhibition of poly(ADP ribose) polymerase 1/2 (PARP1/2) and apurinic/apyrimidinic endonuclease 1 (APE1). PARP1/2 and APE1 are critical enzymes involved in single-strand break repair and base excision repair, respectively. Here, we investigate the cytotoxic efficacy of talazoparib and APE1 inhibitor III, which are inhibitors of PARP1/2 and APE1, in distinct approaches in CD34+ MDS cells and in CD34+/- AML cells in comparison to healthy CD34+ donor cells.
Methods: The surviving fraction of healthy CD34+ donor cell samples (n = 7), CD34+ MDS cell samples (n = 6) (3 MDS and 3 chronic myelomonocytic leukemia samples) and CD34+/- AML cell samples (n = 15) was analyzed using the CellTiter-Glo luminescent cell viability assay (Promega, Southampton, UK). Cell proliferation was analyzed by the trypan blue exclusion assay (Merck, Darmstadt, Germany). PARP1/APE1 mRNA expression was evaluated using the QuantiTect primer assay (Qiagen, Venlo, Netherlands). Immunofluorescence microcopy of γH2AX foci was performed using a JBW301-derived mouse monoclonal anti-γH2AX antibody (Merck).
Results: Talazoparib demonstrated increased cytotoxic efficacy in selected MDS and AML cell samples as compared to healthy donors (Figure 1). Further, low doses of talazoparib increased the cytotoxic efficacy of decitabine in MDS and AML cells. In contrast, APE1 inhibitor III demonstrated no specific cytotoxic efficacy in primary MDS and AML cells; however, low subtoxic doses of APE1 inhibitor III increased the cytotoxic efficacy of talazoparib and decitabine in MDS and AML cells. The tested biomarkers are currently awaiting further evaluation.
Conclusions: Talazoparib demonstrated substantial anti-leukemic efficacy as a single-agent and in combination with decitabine. APE1 inhibitor III demonstrated no specific anti-leukemic efficacy as a single-agent; however, APE1 inhibitor III increased the anti-leukemic efficacy of decitabine. Hence, our data support further investigation of these agents in sophisticated clinical trials.

Disclosure: No conflict of interest disclosed.

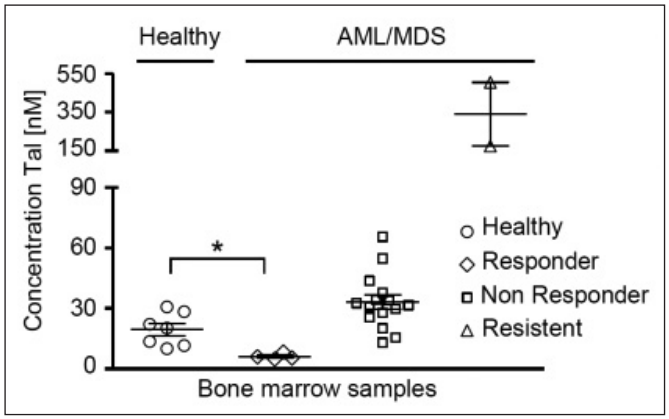

Fig. 1. Half-maximal inhibitory concentrations (IC50) of talazoparib in primary MDS and AML cells

P348

A simple acute phase protein score to predict long-term survival in patients with acute myeloid leukemia

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Introduction: High levels of acute phase reactants can be associated with adverse outcome in patients with various solid tumor types. For patients with acute myeloid leukemia (AML), this correlation is unknown.
Methods: We retrospectively investigated the prognostic value of pre-treatment acute phase protein levels in 282 consecutive newly diagnosed AML patients undergoing at least one cycle of intensive induction chemotherapy between 2000-2018. We developed a new score integrating pre-treatment C-reactive protein (CRP), fibrinogen, and albumin called the CFA ratio. Moreover, we assessed the modified Glasgow prognostic score (mGPS), which comprises elevated CRP and decreased albumin levels to predict outcome.
Results: Patients were stratified into two groups: Patients with a CFA ratio below 3.06 had decisively better progression free (26.2 vs. 7.7 months; $P < .001$), disease free (56.4 vs. 8.7 months, $P < .001$) and overall survival (61.2 vs. 13.8 months; $P < .001$; Figure 1). Results remained significant for PFS and OS when adjusting for confounders including ELN risk group. Early mortality also tended to be lower in the low CFA ratio group. Finally, patients with lower modified Glasgow prognostic score (mGPS) had better outcome.
Conclusions: In conclusion, our data suggest that an elevated CFA ratio as well as a high mGPS are associated with adverse outcome in patients with newly diagnosed AML undergoing intensive induction. These parameters should be prospectively evaluated for their contribution to risk profiling in AML patients as they may provide an additional, rapidly available assessment of prognosis at diagnosis.

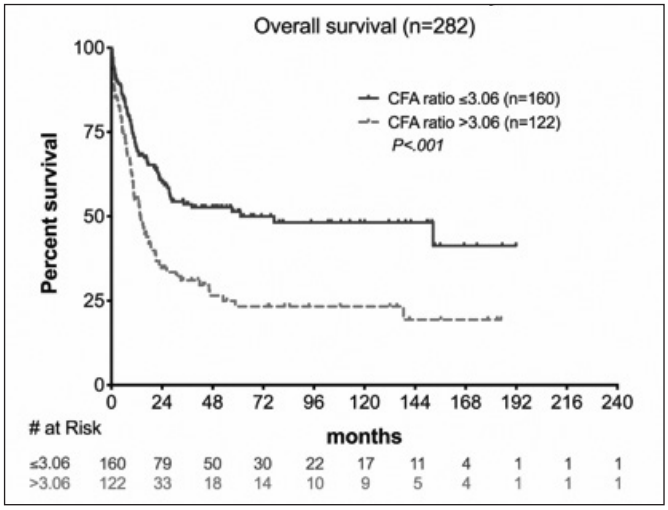

Fig. 1. Heini et al_Figure 1

Disclosure: No conflict of interest disclosed.

P349

Clinical value of molecular MRD monitoring by NGS in patients with IDH2 mutated AML

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Introduction: Mutations in the isocitrate dehydrogenase 2 (*IDH2*) gene occur in up to 20% of acute myeloid leukemia (AML) patients. However, the role of mutated *IDH2* for minimal residual disease (MRD) assessment remains poorly investigated. An emerging option for molecular follow-up of this marker is next-generation sequencing (NGS).
Methods: Using NGS and the myeloid Oncomine panel (Thermo Fisher, Reinach, Switzerland) on the Ion Torrent platform, we comprehensively investigated 13 patients with *IDH2*-mutated AML (12 pts) or myelodysplastic syndrome with excess blasts 2 (MDS EB-2) (1 pt) at the University Hospital Bern. Patients underwent various induction (intensive vs demethylating) and consolidation regimens including enasidenib in 8 of 13 pts. Molecular response by NGS was defined as follows: partial molecular response (PMR) with variant allele frequency (VAF) < 50% of all initial markers; complete molecular response (CMR) with negativity of initial markers; molecular relapse as re-emergence of at least one of the initial molecular markers by NGS following CMR, and molecular persistence with a VAF > 50% of the initial load.
Results: The predominant *IDH2* hotspot was R140 (n=10; 77%) followed by R172 (n=3; 23%). Ten patients (77%) had coincidental mutations, with a median number of two additional mutations per patient. *IDH2* follow-up analysis by NGS detected MRD in 5/8 (62%) among intensively treated patients with CR and CRi as best response. In the subgroup of the five patients receiving demethylating therapies, only two patients achieved hematologic CR demonstrating CMR and *IDH2* persistence, respectively. In 8/10 patients with coincidental mutations, *IDH2* and the additional mutations showed congruent dynamics. The two remaining patients demonstrated CHIP due to *IDH2* or persistence of second mutation. Tracking the *IDH2* mutation load by NGS enabled targeted treatment and monitoring of IDH2 inhibitor therapy with enasidenib in our cohort. All eight patients receiving enasidenib achieved at least PMR with three of them having CMR at last follow-up.
Conclusions: Our data suggest that mutated *IDH2* assessed by NGS is a reliable MRD marker. Given the high frequency of *IDH2* mutations in AML, multicenter studies should aim to further evaluate this marker for MRD monitoring and determine the most appropriate time points for monitoring.

Disclosure: No conflict of interest disclosed.

P350

In patients (pts) with acute myeloid leukemia (AML) a TET2 polymorphism is linked to TET2-mutation-associated clonal hematopoiesis (CH)

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Introduction: *TET2* mutations (mut) are associated with CH in AML pts. Several *TET2* single nucleotide polymorphisms (SNPs) present missense variants & link to altered gene expression. We analyzed the *TET2* coding region for SNPs associated with CH in AML.
Methods: Using a next-generation targeted amplicon sequencing (TAS) approach we analyzed *TET2* exons 3-11 in bone marrow at diagnosis (dx) in 111 AML pts (median age 64, range 33-75 years) on the MiSeq platform (Illumina). In a subset of 75 pts in morphologic complete remission (CR) or CR with incomplete blood count recovery (CRi) peripheral blood was tested for CH-associated mut applying TAS (*ASXL1, DNMT3A, IDH1, IDH2, IKZF1, JAK2, PPM1D, SF3B1, SRSF2 & TET2*). Mut with variant allele frequency (VAF) < 3% were excluded from analyses. European LeukemiaNet risk was 24% favorable, 28% intermediate & 48% adverse. Outcome analyses were performed in 102 pts receiving hematopoietic stem cell transplantation (HSCT) in CR/CRi. Median follow up after HSCT was 6.0 years.
Results: In *TET2* SNP rs34402524 (c.5162T>G; p.Leu1721Trp) minor allele (G) presence vs absence was associated with *TET2*-mut CH (26% vs 5%, P=.02), but not with the presence of CH mut in one of the other analyzed genes. *TET2* SNP rs34402524 allele distribution was 86% T & 14% G. The minor allele SNP frequency in AML was comparable to healthy Caucasians (12% GnomAD; P=.18). The incidence of *TET2* mut at dx did not differ between pts with minor allele (G) presence vs absence (18% vs 26%, P=.41). The mean VAF of *TET2*-CH mut did not vary for pts with minor allele (G) presence vs absence (21% vs 32%, P=.49).
Pts with minor allele (G) were by trend less likely to suffer relapse (32% vs 53%, P=.08) & tended to a lower cumulative incidence of relapse (P=.13, Fig. 1A), but had no different overall survival (P=.70, Fig. 1B).
Conclusions: We found the minor allele (G) in *TET2* SNP rs34402524 to be linked to *TET2*-mut-associated CH in AML pts, but not to the presence of *TET2* mut at dx. The polymorphism may be associated with reduced relapse incidence. Further analyses of a larger pts set & functional studies will improve our understanding of *TET2*-mut-associated CH in AML.

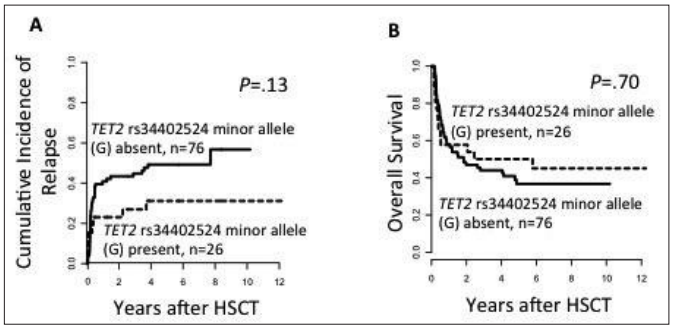

Fig. 1. Cumulative Incidence of Relapse and Overall Survival in AML pts with TET2 SNP rs34402524

Disclosure: No conflict of interest disclosed.

P351

AML-derived exosomes promote induction of myeloid-derived suppressor cells in an mTOR-signaling-dependent fashion

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Introduction: Acute myeloid leukemia (AML) is the acute leukemia with the highest incidence in adults. Despite recent advances in understanding the genomic landscape and the introduction of novel targeted therapies, long term survival remains unsatisfactory. The success of allogeneic stem cell transplantation in AML underscores its immune responsiveness. Consequently, different immune-based approaches such as T-cell-engaging antibodies or genetically engineered T-cells are currently under clinical investigation. The overall enthusiasm is however diminished given various immune escape mechanisms induced by the AML blast. We have recently described an accumulation of so-called myeloid derived suppressor cells (MDSC) in primary AML samples with T-cell inhibitory functions. In fact, AML blasts directly promote MDSC induction, which have been shown to negatively impact intrinsic anti-tumor immunity as well as immunotherapeutics. A better understanding of MDSC biology in AML could ameliorate treatment efficacy.
Methods: Primary AML blasts or cell lines (HL60, MOLM13, OCI-AML) were co-cultured with healthy donor-derived monocytes to investigate contact-dependency of MDSC induction. Critical signaling pathways (using kinase arrays) that are activated during MDSC formation and the MDSC's metabolic profile (using amongst other metabolic flux analyses) were evaluated to identify potential to interfere with AML-induced reprogramming.
Results: AML-derived exosomes promote reprogramming of regular monocytes into $IDO1^{+}$ $IL\text{-}10^{+}$ $HLA\text{-}DR^{low}$ MDSC with strong T-cell-suppressive capacity. This MDSC induction is controlled by the akt/mTOR signaling axis. Consequently, blocking mTOR efficiently abrogated IDO1 expression as well as the suppressive activity of MDSC. Furthermore, upon induction a metabolic skewing occurred towards aerobic glycolysis: expression of key glycolytic molecules such as *hk2* or *ldha*, surface density of glucose transporters, and the overall glycolytic activity were significantly elevated. Blocking glycolysis did not prevent MDSC induction but MDSC display an enhanced susceptibility towards glycolytic inhibitors.
Conclusions: AML exosomes trigger MDSC induction and we identified mTOR as the underlying signaling molecule. Interfering with mTOR signaling abrogates functional reprogramming of monocytes while blocking of glycolysis preferentially eliminated MDSC Harnessing cellular metabolism of tumor bystander cells could become a promising therapeutic tool.

Disclosure: No conflict of interest disclosed.

P352

Therapeutic disruption of the Menin-MLL1 complex synergizes with pharmacological BCL2 inhibition in acute myeloid leukemia

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Introduction: Acute myeloid leukemia (AML) is a neoplastic disease of hematopoietic progenitor cells characterized by blocked differentiation, increased self-renewal and evasion of apoptosis. Previous studies have shown that the Menin-MLL1 complex is a dependency in AML cells harboring a *NPM1* gene mutation ($NPM1^{mut}$) or *MLL1*-gene translocation (*MLL1*-r). Small molecule inhibition of the menin-MLL1 interaction (MI2-2) causes profound growth inhibition and differentiation. High level expression of the anti-apoptotic protein BCL2 is also frequently found and a promising drug target (Venetoclax) in AML. Here, we assessed the therapeutic potential of combined menin-MLL1 and BCL2 inhibition.
Methods: Drug sensitivity to MI2-2, Venetoclax or the combination was assessed in proliferation assays for 12 human AML cell lines and primary murine $Npm1^{mut}$ $Flt3^{mut}$ AML cells. An shRNA-based approach evaluated effects of a *MEN1* knockdown on proliferation. Changes on gene expression were evaluated by RNA sequencing and qPCR. Apoptosis was measured by Annexin V staining. Primary patient samples were cocultured with human stroma cells (HS27) and drug sensitivity assessed in proliferation assays.
Results: Strong growth inhibition and differentiation was observed in the majority of *MLL1*-r and all $NMP1^{mut}$ AML models upon pharmacological Menin-MLL1 inhibition. These results were validated using sh-RNA mediated *MEN1* knockdown in the *MLL1*-r MOLM13 cells. RNA sequencing and qPCR revealed profound transcriptional repression of *MEIS1*, *FLT3* and notably *BCL2* following MI2-2 treatment. These findings led us to assess potential drug synergism of combined MI2-2 and Venetoclax treatment in AML. While MI-2-2 alone caused predominantly cell differentiation and Venetoclax apoptosis, we found dramatically synergistic antiproliferative activity of the combination in all double-sensitive AML cells and a profound increase of apoptosis compared to single drug treatment or vehicle control. Similarly, we observed drug synergy on a primary $NPM1^{mut}$ AML patient sample. No sensitivity of the combination was observed in AML without $NPM1^{mut}$ or *MLL*-r cells lacking response to either of the drugs.
Conclusions: Transcriptional repression of BCL2 via the Menin-MLL1 interaction synergizes with pharmacological BCL2 inhibition. Combined pharmacological inhibition of menin-MLL1 and BCL2 therefore represents a novel therapeutic approach for $NPM1^{mut}$ and *MLL*-r AML that is already available for clinical testing.

Disclosure: Johanna Rausch: No conflict of interest disclosed.
Michael Kühn: Advisory Role: Abbvie

P353

Comparison of leukemia-associated immunophenotype (LAIP)-based and different-from-normal (DfN)-based analysis of measurable residual disease (MRD) in patients with AML

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Introduction: In acute myeloid leukemia (AML), detection of tumor cells below the limit of morphology is termed measurable residual disease (MRD). MRD positivity during the course of treatment has been shown to be of negative prognostic relevance. MRD can be assessed by different methods, but these usually lack harmonization, and results are not comparable between laboratories. The HARMONIZE consortium is a collaborative initiative with the aim to harmonize multicolor flow cytometry (MFC) MRD diagnostics in AML by using common wet and dry lab standards. Here, we aimed to compare two analytical strategies.
Methods: Strategy i) employs an individualized gating strategy based on Boolean gating and strategy ii) employs a uniform hierarchical gating strategy. Strategy i) aims at the detection of leukemia associated immunophenotypes (LAIP) and therefore is dependent on LAIP definition at initial diagnosis. Strategy ii) allows the simultaneous detection of LAIP and additional aberrant populations (DfN=different from normal). MFC

data of patients with AML (n=48) from initial diagnosis and after intensive induction therapy were independently analyzed using both strategies.
Results: All patients were treated with intensive induction therapy. 29 of 48 patients (60%) were classified by morphology as responders (CR n=22, CRi n=6, MLFS n=1). Both analytical strategies were capable to detect at least one aberrant immunophenotype in >95% of AML cases at initial diagnosis. The most common aberrancies were cross-lineage expression of CD56 and CD13 deficiency. In both analytical strategies, MRD positivity was defined as an excess of the reference value by 0.1%. Comparing both strategies, the rate of MRD positivity (48%) was identical in responders, while in non-responders strategy ii) revealed a significantly higher rate of MRD positivity (58 vs. 89%). MRD positivity in strategy ii) was never exclusively based on DfN. The consistency rate between both strategies was 59% and 68% in responders and non-responders, respectively. Quantitative MRD results were significantly correlated between both strategies but only showed a moderate contingency (r^2=0.59).
Conclusions: The HARMONIZE panel is suitable to detect LAIP in the vast majority of AML cases, irrespective of the analysis approach. However, the concordance rate in the detection of MRD was only moderate. The prognostic relevance of strategy ii) remains to be elucidated as clinical outcome data is still immature.

Disclosure: Malte von Bonin: Other Financial Relationships: Reisekostenerstattung durch Kite, Daiichi Sankyo
Marion Subklewe: No conflict of interest disclosed.

P354

IL-3 receptor beta chain promotes the oncogenic potential of FLT3-ITD

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Introduction: FLT3-ITD is the most predominant mutation in AML being expressed in about one third of the patients and is associated with a poor prognosis. Efforts to inhibit FLT3-ITD are ongoing and FLT3 tyrosine kinase inhibitors (TKIs) are providing new tools to treat patients with this mutation. However, responses to TKI monotherapy are still short lived. Efforts to better understand downstream signalling of FLT3-ITD and possibly enhance treatment response are needed. We examine the significance of the IL-3 receptor beta chain (IL3RB) for FLT3-ITD's oncogenic signalling and its' potential as a treatment target.
Methods: Interaction of FLT3 and IL3RB was analyzed using *in situ*proximity ligation assay (PLA), immunofluorescent stainings as well as pull-down assay. Altered signaling and transformation capacity of FLT3-ITD was shown in human cell-lines with IL3RB knockdown *in vitro*by western blot and MTT assays. Bone marrow transplantation as well as xenograft experiments with bioluminescence imaging (BLI) in mice were performed to investigate the significance of IL3RB in the presence of oncogenic FLT3-ITD mutations to survival and tumour growth *in vivo*.
Results: Knock down IL3RB in human FLT3-ITD positive cell-lines MV4-11 and MOLM13 impaired downstream STAT5 activation and cell growth. Injection of IL3RB knock-down MOLM13 cell-line together with a BLI marker into RAG2 knockout mice showed significantly slower tumour growth compared to wild-type controls. IL3RB wild-type and knock-down bone marrow was transfected with FLT3-ITD. Bone marrow was transplanted it into lethally irradiated C57BL/6 mice. Compared to control FLT3-ITD bone marrow, IL3RB knock-down bone marrow resulted in significantly later disease onset in vivo.
Conclusions: Our results demonstrate that the oncogenic potential of FLT3-ITD is dependent on IL3RB in vitro and in vivo. Thus, IL3RB might constitute a rational treatment target in FLT3-ITD positive AML. More detailed analyses of the interaction of FLT3-ITD and IL3RB via PLA, immunofluorescence and pull-down assays might allow to delineate the mechanism of interaction and thus to design therapeutic strategies to block the interaction of FLT3-ITD and IL3RB.

Disclosure: Anne Charlet: No conflict of interest disclosed.
Nikolas von Bubnoff: Advisory Role: Fa. Novartis; Expert Testimony: Fa. Novartis

P355

Bone marrow stroma cells promote a S100A8/A9high subset of chemoresistant AML blasts with distinct metabolic features in a Jak/STAT-dependent manner

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The bone marrow stromal niche can serve as a protective environment in hematological malignancies such as AML. Intensive research of the bidirectional interactions between leukemic blasts and stromal cells already highlighted numerous mechanisms how malignant cells are capable of shaping their local milieu in an opportunistic fashion. However, the complex mechanisms remain to be fully elucidated.
We found two small intracellular calcium-sensing molecules, S100A8 and S100A9, among the top upregulated genes in primary AML blasts upon stromal contact. They are members of the S100 protein family that can modulate cellular responses such as proliferation, migration, inflammation, and differentiation. Dysregulation of S100 protein expression is described as a common feature in several human cancers. Particularly, expression of S100A8 in leukemic blasts predicts poor survival in *de novo* AML patients. Thus, we aimed to decipher the underlying pathways of the stroma-mediated S100A8/A9 upregulation as well as its functional consequences.
Stromal induction of S100A8/A9 as measured in our microarray analyses of primary AML samples was confirmed on mRNA and protein level in AML cell lines (OCI-AML3, Molm-13). We could demonstrate formation of a S100A8/A9^{high} subpopulation by HS-5 stroma cells both in a contact-dependent and independent setup. We found this to be at least partly mediated by HS-5-derived IL-6 that triggered Jak/STAT downstream signaling, which was abolished when using IL-6/IL-6R blocking antibodies. The S100A8/A9^{high} population was characterized by altered metabolic features including increased fatty acid uptake, CD36 expression, mitochondrial biomass, and ROS production. Uptake of external free fatty acids was further determined as a prerequisite for S100A8/A9 induction as blocking of CD36 with SSO diminished the S100A8/A9^{high} frequency. Simultaneously, S100A8/A9^{high} cells revealed an increased expression of maturation markers such as CD14 and CD11b. Finally, we could demonstrate an enhanced chemoresistance (Doxorubicin, Mitoxantrone) of the S100A8/A9^{high} cells.
Taken together, we demonstrate a stroma-induced S100A8/A9 upregulation in AML blasts (patient samples and cell lines), which is mediated by soluble factors activating the Jak/STAT pathway. S100A8/A9 overexpression is linked to metabolic alterations and increased differentiation of AML cells conferring enhanced chemoresistance and thus represents a potential therapeutic target against AML.

Disclosure: No conflict of interest disclosed.

P356

Expression of CD105 (Endoglin) shows correlation with clinical outcome in AML patients

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Risk stratification of AML patients mainly relies on genetic and morphological markers. However, the establishment of further prognostic markers is urgently needed to guide rational treatment decisions. CD105 (Endoglin) is an auxiliary receptor within the TGF-beta complex and is expressed on various solid and hematological malignancies including ALL and AML. While CD105 expression correlates with adverse outcomes in a variety of solid tumors, the impact of CD105 on survival in AML patients has never been assessed. Here, we aimed to establish CD105 as a prognostic marker for immunophenotyping of AML blasts to allow for a better risk stratification.

We here generated and characterized a novel hybridoma-derived CD105 antibody and employed it for flow cytometric analysis of peripheral blasts from 62 AML patients. We correlated CD105 expression with different clinical parameters such as overall survival, progression-free survival, response to induction therapy, duration of remission, blast count, FAB classification and NCCN risk score. Using receiver-operating characteristics, we established a cut-off SFI level to distinguish between low and high CD105 expression.

In this study, we analyzed 62 patients with AML for the expression of CD105 using a newly generated monoclonal antibody. Flow cytometric analysis showed relevant expression of CD105 in all FAB types, with higher levels seen in M0 and M6 and lower expression in FAB M3 type. By grouping patients into CD105hi and CD105lo groups and employing receiver-operating characteristics, we were able to establish a cut-off SFI value of 5.22. High CD105 expression correlated significantly with poor overall and progression free survival. Most notable the lowest quartile of CD105 expression significantly correlated with a good prognosis as evaluated using the National Comprehensive Cancer Network (NCCN) risk score.

In conclusion, our study described high CD105 expression as a relevant prognostic marker in AML with the ability to identify possible adverse disease courses.

Disclosure: No conflict of interest disclosed.

P357

Effects of decitabine, combined with all-trans retinoic acid or valproate, on fetal hemoglobin (HbF) induction in elderly AML patients

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Introduction: We recently reported fetal hemoglobin (HbF) induction as a predictor of outcome in elderly AML/MDS patients treated with the DNA-hypomethylating agent decitabine (DAC). HbF induction following 2 courses of DAC treatment was associated with a higher response rate (AML, MDS patients) and longer survival (MDS patients; Stomper et al., Haematologica 2019). HbF induction was associated with cytogenetic remissions and reversed at relapse, suggesting that HbF is preferentially induced in non-clonal erythroid cells.

The DECIDER randomized phase II trial (NCT00867672) addresses, by 2x2 factorial design, the effects of DAC in combination with all-*trans* retinoic acid (ATRA) or the histone-deacetylase inhibitor valproate (VPA) in elderly non-M3 AML patients unfit for induction therapy. A higher response rate and longer overall survival is observed when DAC is combined with ATRA; add-on of valproate to DAC does not affect patients´ outcome (Lübbert et al., ms. in 1st revision).

Methods: We serially studied HbF levels in 16 AML patients (median age 73, range 66-82 years) from a single center who received >2 cycles of treatment within the DECIDER trial. Regarding allocation to each of the 4 treatment arms, 4 patients received DAC-only, 5 received DAC+VPA, 5 received DAC+ATRA, 2 received DAC+VPA+ATRA. HbF levels were measured in peripheral blood erythrocytes by HPLC before treatment and after each treatment course. HbF levels 0.0-1.0% were considered normal, HbF levels >1.0% were considered induced.

Results: Median pretreatment HbF was 0.4% (range 0.0-10.2%) whereas maximum HbF attained with continued treatment was 1.6% (range 0.2-17.8%). When interrogating HbF induction by type of add-on drug to DAC, median peak HbF levels in the no-ATRA treatment arms (9 patients) were 1.0% (range 0.2-17.8%), compared to 2.1% (range 0.3-5.0%) in 7 patients having received ATRA as add-on to DAC. The median peak HbF level in the no-valproate treatment arms (9 patients) was 2.1% (range 0.4-17.8%), compared to 1.0% (range 0.2-4.8%) in 7 patients having received valproate as add-on to DAC.

Conclusions: These results, albeit derived from a limited patient cohort, suggest higher HbF induction when DAC is combined with ATRA compared to treatment without ATRA. They warrant additional analyses on response rate and survival in these patients, and prospective serial measurements of HbF (which are easy to determine and inexpensive) in a multicenter validation trial.

Disclosure: Julia Stomper: No conflict of interest disclosed.
Michael Lübbert: Advisory Role: Janssen-Cilag; Other Financial Relationships: Ratiopharm, Janssen-Cilag, Celgene

P358

Analysis of the cellular immune response to acute meyloid leukemia (AML)

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The role of T and NK cells in the development and progression of AML is relatively poorly understood. Immunotherapy targeting the PD1/PD-L1 axis proved to be successful in other malignancies. Besides, the composition and functional state of T and NK cells significantly change in case of a Cytomegalovirus (CMV) infection, as best reflected by an expansion of NK cells expressing the activating receptor NKG2C. Interestingly, several studies reported a reduced relapse risk for patients suffering from CMV reactivations following allogeneic blood stem cell transplantation (SCT). Reactivations in turn are associated with increased IFNγ levels that can induce the expression of the NKG2C ligand HLA-E.

We examined T cell populations of AML bone marrow samples regarding their PD1 expression using FACS analysis. Secondly, we looked whether NK cells would contribute to the beneficial effects of CMV reactivations as observed in recipients of allogeneic SCT. Therefore, we performed *in vitro* killing assays in which the AML cell line MM6 was incubated with PBMCs of CMV^{pos} donors.

AML patients (n = 7) showed increased proportions of $PD1^+$ CD8 T cells compared to allo-SCT recipients in remission (n = 9). *In vitro*, we found that $CD34^+$ cells from leukemic patients as well as MM6 cells induce HLA-E upon IFNγ stimulation. Interestingly, these IFNγ pre-incubated MM6 cells showed significantly more apoptosis when they were exposed to PBMCs from CMV^{pos} donors compared to MM6 cells without IFNγ preincubation. In addition, we could show that $NKG2C^+$ NK cells showed higher levels of Granzyme B compared to their $NKG2A^+$ counterparts that is further increased following stimulation with MM6 cells.

Our data indicate that PD-1 could be a target for the treatment of patients with AML. As far as the setting of allogeneic SCT is concerned, our *in vitro* studies imply that NK cell mediated induction of apoptosis could

contribute to the reduced risk of relapse in patients with CMV reactivations following allo-SCT. Next, we will assess the IFNγ level in serum of patients following allo-SCT with regard to phenotypical and functional status of their PBMCs, in particular during acute CMV infection.

Disclosure: No conflict of interest disclosed.

Posterdiskussion

Chronische myeloproliferative Neoplasien

P359

Impact of various blood parameters on diagnosis, subclassification and prognosis of systemic mastocytosis

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Systemic mastocytosis (SM) is subclassified into indolent SM (ISM) and advanced SM (advSM), which is further distinguished into aggressive SM (ASM), SM with associated hematologic neoplasm (SM-AHN) and mast cell leukemia (MCL). Laboratory parameters obtained from peripheral blood including blood counts and serum parameters like tryptase are most relevant for diagnosis, subclassification and prognosis of SM. We therefore sought to investigate established (e.g. tryptase, hemoglobin, albumin) but also more recently appreciated parameters, e.g. monocytes (monos), eosinophils (eos) and alkaline phosphatase (AP), in 380 patients (ISM n=178; SSM, n=13; SM-AHN, n=143; ASM n=18; MCL±AHN, n=28) registered within the "German Registry on Disorders of Eosinophils and Mast cells". At least one measurable laboratory C-finding (hemoglobin< 10g/dL, platelets < $100x10^9$/µL or albumin < 35g/dL) was present in 13/18 (73%), 90/143 (63%) and 27/28 (96%) patients with ASM, MCL+/-AHN and SM-AHN, respectively. Elevated serum tryptase (>20ug/l) was identified in 149/191 (78%) of ISM and 169/180(94%) of advSM patients. All 11 advSM patients with a normal serum tryptase had SM-AHN. In ISM, 16/191 (8%) patients had a tryptase level of >200ug/L, while 35/145 (19%) patients with advSM showed a tryptase of < 50mg/L. In contrast, elevated monos and eos were almost exclusively identified in advSM. Within advSM, monos >$1x10^9$/L (3.1 vs 3.8 years, p=0.025), eos >$2x10^9$/L (1.6 vs 3.9 years, p< 0.0001) and combination of monos >$1x10^9$/L and eos >2 $x10^9$/L (1.8 vs 4.7 years, p>0.0001) were associated with inferior survival (OS). Moreover, elevated AP (normal value< 126U/L) is rare in ISM (9/180, 5%) but frequent in advSM (118/184,64%). Consequently, AP>200U/L was associated with inferior OS (3.3 vs 6.2 years,p=0.012). Massive elevation of vitamin B12 (>900ng/mL) was frequent in advSM (68/140, 61%) but rare in ISM (6/123, 5%). In conclusion, i) a normal serum tryptase does not exclude diagnosis of SM and the absolute serum tryptase level is of limited value for subclassification and prognosis, ii) diagnosis of SM-AHN is challenging in case of normal/low serum tryptase and/or AP, iii) elevated vitamin B12, possibly reflecting granulocytic transcobalamine production, is frequent in advSM, iv) monos and eos are strongly associated with advSM and absolute numbers are prognostically relevant, and v) beside classical C-findings, elevated AP is of outstanding importance for diagnosis and prognosis of advSM.

Disclosure: No conflict of interest disclosed.

P360

CAG promoter driven c-myc overexpression causes rapidly lethal cardiomyopathy

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Introduction: We have previously reported that mice expressing elevated levels of NFE2 display a myeloproliferative phenotype which spontaneously transforms to acute leukemia. Upon leukemic transformation, a high percentage of mice acquire amplification of the murine c-myc locus. The CMV early enhancer/chicken-beta-actin (CAG) promoter has been reported to direct high level heterologous gene expression specifically to hematopoietic stem cells and myeloid progenitors. We hypothesized that elevated expression of both NFE2 and c-myc synergize to induce leukemic transformation. Therefore, we compared the hematological phenotype of mice carrying either augmented NFE2 or c-myc levels alone to mice overexpressing both genes.
Methods: We crossed mice expressing a CAG-driven tetracycline activator (CAG-rtTA3) with the tet-O-myc mouse strain, in order to achieve high levels of doxycycline-inducible c-myc expression in the hematopoietic compartment. Double transgenic CAG-myc mice were subsequently bred to heterozygous knock-in mice expressing the NFE2-D297-300 mutation of the endogenous promoter, generating both CAG-myc-NFE2-wt and CAG-myc-NFE2mut mice. C-myc expression was induced by doxycycline treatment administered through drinking water, oral gavage or food pellets.
Results: Unexpectedly both CAG-myc and CAG-myc-NFE2 mice died rapidly, between 6 and 7 days following c-myc induction, independent of the route of doxycycline administration. Autopsy and histological analysis revealed marked cardiomyocyte hypertrophy, with heart volume more than double the wt control. In addition to hematopoietic stem and progenitor cells, the CAG promoter has been reported to direct expression to cardiomyocytes. C-myc overexpression in adult cardiomyocytes by tet-mediated c-myc induction has previously been shown to cause cell cycle re-entry that leads to cardiomyopathy. However, it was not expected that the CAG promoter, seen as a "highly effective tool for probing hematopoietic development and disease", would have a similarly cardiotoxic effect.
Conclusions: While our murine model did not allow us to investigate our hypothesized synergistic effect between c-myc and NFE2 in leukemic transformation, the CAG-myc mouse strain generated constitutes an excellent model for studying rapidly lethal cardiomyopathy. Our data serve to alert researchers in the hematopoietic field to possible side effects of using the CAG promoter to drive gene expression in hematopoietic stem and progenitor cells.

Disclosure: No conflict of interest disclosed.

P361

Concordance of a decreased von Willebrand factor (VWF) activity-to-antigen ratio with loss of larger VWF plasma multimers in patients with essential thrombocythemia or polycythemia vera

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Introduction: Acquired von Willebrand syndrome (AVWS) associated with myeloproliferative neoplasia (MPN) has been mainly reported in

essential thrombocythemia (ET) and polycythemia vera (PV). The prevalence of AVWS in ET and PV varies markedly, mostly due to different diagnostic algorithms. In daily practice, the diagnosis of AVWS is challenging, because no single test is usually sufficient to prove or exclude AVWS. A decreased VWF activity-to-antigen ratio of < 0.6 is considered as useful parameter implicating the loss of biologically active larger plasma multimers. In this study, we aimed to compare different diagnostic tools in order to develop the optimal algorithm to diagnose AVWS in MPN patients.
Materials and methods: This study included 40 patients (20 with ET and 20 with PV) treated at the University Medical Center Hamburg-Eppendorf, Germany, during the year 2018. ET and PV were diagnosed on the basis of the WHO criteria published in 2016. VWF antigen (VWF:Ag) and VWF activity (VWF:Ac) were measured by turbidimetry using the VWF Ag® and the INNOVANCE® VWF Ac assay, respectively. VWF plasma multimers were analyzed by SDS-agarose gel electrophoresis with luminescent visualization. Complete blood counts were measured using standard laboratory techniques.
Results: Patient characteristics including type of MPN, platelet and leukocyte counts, hematocrit levels, cytoreductive treatment, and type of driver mutation are presented in Table 1, and the correlation between VWF:Ac/VWF:Ag ratio and multimer analysis is presented in Table 2.
Conclusions: The VWF:Ac/VWF:Ag ratio was not sufficient to diagnose AVWS in our patient cohort. VWF multimer analysis is thus required as an additional diagnostic tool. Interestingly, hematocrit levels, but not peripheral platelet counts, were increased in PV patients exhibiting loss of larger VWF plasma multimers, pointing to distinct pathophysiological mechanisms of AVWS evolution in PV and ET patients. Furthermore, cytoreductive therapy appeared to be associated with a decreased prevalence of AVWS.

Tab. 1. Patient characteristics

Table 1

		Unit	PV (n=20)		ET (n=20)	
Loss of larger VWF plasma multimers			yes (n=9)	no (n=11)	yes (n=6)	no (n=14)
Medium hematocrit level		%	47.5	43.9	42	40
Medium platelet count		x 10^9/L	454	507	871	423
Medium withe blood cell count		x 10^9/L	10.7	12	8.0	6.5
Cytoreductive therapy		n	5	11	2	11
Driver mutations	JAK2V617F	n	9	11	3	11
	CALR		-	-	2	2
	MPL		-	-	1	-
	triple negative		-	-	-	1

Table 2

		PV (n=20)		ET (n=20)	
VWF:Ac/VWF:Ag ratio		< 0.6	> 0.6	< 0.6	> 0.6
Loss of larger VWF plasma multimers	yes	2	7	1	5
	no	1	10	2	12

Disclosure: No conflict of interest disclosed.

P362

Fedratinib (FEDR) in patients with myeloproliferative neoplasm (MPN)-associated myelofibrosis (MF) previously treated with Ruxolitinib (RUX): a reanalysis of the phase 2 Jakarta-2 study

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Background: MF is a life-threatening MPN for which RUX is the only approved treatment (Tx). The JAKARTA2 study evaluated FEDR, an oral selective JAK2 inhibitor, in patients (pts) who were resistant/intolerant to RUX per investigator assessment. To confirm FEDR efficacy, JAKARTA2 data were reanalyzed using ITT principles without last-observation-carried-forward imputation and a more stringent definition of RUX failure (Fig A).
Methods: Pts with Int- or High-risk MF previously treated with RUX, palpable splenomegaly and ≥50 × 10^9/L platelets received FEDR 400 mg QD in 28-day cycles. The primary endpoint was spleen volume response rate (SVRR): ≥35% spleen volume reduction from baseline (BL) to end of cycle 6 (EOC6). A key secondary endpoint was symptom response rate (SRR): ≥50% decrease in MFSAF total symptom score (TSS) from BL to EOC6. Efficacy endpoints were reanalyzed for the ITT population, the subgroup of ITT pts who met the more stringent criteria for RUX relapsed/refractory (R/R) or intolerant (RUX Failure cohort; Fig A), and RUX Failure pts who received 6 FEDR cycles or discontinued before cycle 6 for reasons other than study termination (Sensitivity cohort).
Results: Of all 97 pts (ITT), the RUX Failure cohort included 79 pts (81%): RUX R/R (n=65), RUX intolerant (14). 66 pts comprised the Sensitivity cohort. Median prior RUX Tx duration was 10.7 mo for the ITT population and 11.5 mo in the RUX Failure and Sensitivity cohorts. Other BL characteristics were similar among the 3 cohorts.
SVRR was 31% (95%CI 22, 41), 30% (21, 42), and 36% (25, 49) in the ITT, RUX Failure, and Sensitivity cohorts, respectively. SRR was 27% (95%CI 18, 37) in the ITT population, 27% (17, 39) in the RUX Failure cohort, and 32% (21, 45) in the Sensitivity cohort. Individual spleen volume and TSS changes for pts in the RUX Failure cohort with EOC6 data are shown in Figs B-C.
Median FEDR cycles was 6 (1-20) in the ITT population and 7 (1-20) in the RUX Failure and Sensitivity cohorts. FEDR safety was consistent with prior reports.
Conclusions: FEDR provided clinically meaningful improvements in splenomegaly and symptom burden in MF pts who met stringent criteria for prior RUX failure.

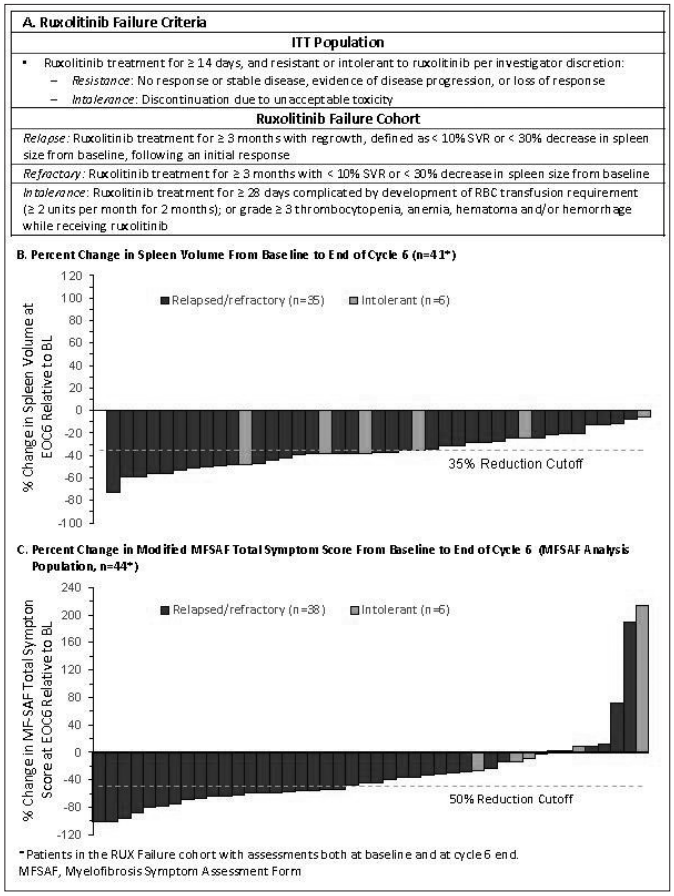

Fig. 1. Fedratinib-JAKARTA-2

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P363

Aggressive systemic mastocytosis: a diagnostic challenge

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Systemic mastocytosis (SM) is a clonal neoplastic disease of mast cells (MCs) with heterogeneous clinical symptoms and is often overlooked.
A 55-year-old caucasian woman with known familial myotonic dystrophy type 2 (DM2) proven by CCTG-repeat expansion in the *ZNF9* gene was referred with a diagnosis of unclassified myeloproliferative neoplasm with 10% bone marrow (BM) blasts and mutations in *KRAS*, *ASXL1* and *RUNX1*. In the last two months, she complained of weight loss, muscle weakness, progressive dysphagia, and fever. Clinically, a body mass index of 13.6 kg/m², normal skin, and hepatosplenomegaly were seen. Laboratory analysis showed a WBC count of 39.80x10⁹/L with left shift, Hb of 4.4g/dl, platelets of 78x10⁹/L, hypoalbuminemia, and an elevated lactate dehydrogenase.
Rapid neurological deterioration is typical in myotonic dystrophy type 1, which is associated with a worse prognosis and is unusual for DM2.
Assessment of serum tryptase is part of our routine diagnostic work-up for hematologic diseases and was 46.9 µg/L (reference range < 11 µg/l). A repeat BM biopsy revealed a hypercellular marrow with delayed myelopoietic maturation and normal blast count. There were nodular areas with clustering MCs (at least 15/cluster) co-expressing CD2, CD25, CD117, and mast cell tryptase were detected. Cytogenetics were normal but *KIT*-D816V mutation was present.
Diagnosis of SM was made based on the major criterion (≥ 15 MC in clusters) and three minor criteria (the *KIT* mutation, CD25/CD2 co-expression, serum tryptase > 20µg/l). Due to the presence of C-findings (transfusion dependent anemia, splenomegaly with thrombocytopenia, malabsorption with weight loss), the criteria for aggressive SM (ASM) were fulfilled.
Together with the neurologist, we hypothesized that ASM and not the natural course of DM2 was causative for the rapid neurological deterioration. We treated with the KIT-tyrosine kinase inhibitor midostaurin. Within three months, the patient gained weight, regained muscle power, dysphagia disappeared, and the blood count normalized. Currently, allogeneic hematopoietic cell transplantation is planned because of the poor prognosis of ASM, particularly if KIT-independent oncogenic driver mutations such as *KRAS*, *ASXL1* and *RUNX1* were found.
In summary, awareness of physicians to SM in case of unclear clinical scenarios is the first step to make the diagnosis and offer adequate therapy. Serum tryptase is a simple tool and can be a hint for SM.

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P364

Fast and precise diagnosis of chronic myeloproliferative and myelodysplastic neoplasia by next generation sequencing (NGS) independent of cytogenetic diagnostics

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Introduction: Chronic myelomonocytic leukemia (CMML) and atypical chronic myeloid leukemia (aCML) are rare clonal hematopoetic disorders sharing features of chronic myeloproliferative disorders and myelodysplastic syndromes. These entities are typically diagnosed by exclusion since no specific driver mutations are known. Next generation sequencing in combination with histomorphology and immunophenotyping enables diagnostic confirmation by proof of clonality after only 2 weeks in comparison to oftentimes 2-4 years without molecular diagnostics.
Methods: 160 CMML and 30 aCML cases routinely diagnosed in our hematopathology were genetically analysed by next generation sequencing using an amplicon-based NGS panel for clonal hematopoetic disorders. The assay was designed and validated in our institution and covers 22 diagnostically, prognostically and therapeutically relevant genes. Prior to NGS, all cases were evaluated by Pappenheim staining and eight-coloured immunophenotyping for detection of atypical morphology or antigens.
Results: All CMML and aCML cases harboured at least one mutation within the 22 genes analysed. The most frequently mutated gene in CMML was TET2 (64%; 102/160), followed by SRSF2 (43%; 68/160), ASXL1 (37%; 59/160) and NRAS (16%; 26/160). Of 160 CMML cases analysed for mutations, 53 patients were routinely screened for cytogenetic abnormalities and 14 of them (26 %) were positive. In aCML patients the most frequently mutated gene was ASXL1 (77%; 23/30), followed by SRSF2 (53%; 16/30), TET2 (37%; 11/30) and SETBP1 (23%; 7/30). 14 of these 30 patients had been analysed cytogenetically and only 4 (29%) of them had chromosomal aberrations.
Conclusions: Next generation sequencing analysis revealed one to seven mutations per patient in all genes tested. These are not specific for the particular entity but proof clonality and thus malignancy. Since all patients were symptomatic i.a. suffered from leukocytosis or monocytosis respectively for months or even years, clonal hematopoiesis of indeterminate potential (CHIP) could be ruled out. Next generation sequencing allows confirming diagnosis of CMML or aCML much faster and more precise than histomorphology and immunophenotyping alone so that convenient therapeutic strategies can be quickly initiated.

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P365

Treatment of myeloproliferative neoplasia (MPN) in Germany. Update of the real world data from the office based MPN-registry (NIHO-MPN-registry)

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For historical reasons MPN are subclassified in essential thrombocytosis (ET), polycythemia vera (PV), myelofibrosis (MF) and undefined MPN (u-MPN). In 2016 we started a registry to learn about the diagnostic procedures and therapies of MPN in regular care in Germany. It was the aim of the current analysis (April, 10th 2019) to describe the vascular events and treatment given in the different MPN-subtypes.

Methods: Patients (pts) with MPN were included in the online database (Oncalizer®, GermanOncology, Hamburg Germany) if the MPN diagnosis suited the needs of the WHO-criteria and if pts had given their written informed consent to the pseudonymized documentation. Baseline parameters at the time of diagnosis and the clinical course were documented quarterly.

Results: 1,204 patients (pts) with MPN were included in the NIHO-MPN-registry by 35 office based hematologic centers between June 2016 and December 2017 (18 month). In April 2019, 1,143 of 1,204 pts (94.9%) were evaluable since all relevant diagnostic basic parameters were documented. Median age was 73 years (range 23-99), 54.4% were women and mean duration of observation was 5.69 years (SD 15.58). 46 pts (4%) died, from whom 24 pts (52.2%) were rated as MPN-related death. The rate of vascular events and the first-line therapies of 1143 pts (94.9%), evaluable for the course of the disease, are given in table 1+2.

Tab. 1. + 2.

Table 1: Frequency of vascular events during the observation period after diagnosis of MPN

	ET	PV	MF	u-MPN	All
Arterial event	40 (9.4%)	28 (8.2%)	15 (7.9%)	6 (3.8%)	89 (8.0%)
Venous event	2 (0.5%)	3 (0.9%)	7 (3.7%)	2 (1.3%)	14 (1.3%)
Lung embolism	5 (1.2%)	6 (1.8%)	2 (1.1%)	3 (1.9%)	16 (1.4%)
Bleeding (subarachnoidal)	1 (0.2%)	0 (0%)	0 (0%)	0 (0%)	1 (0.1%)
Cardiovascular event	23 (5.4%)	21 (6.1%)	11 (5.8%)	7 (4.4%)	62 (5.5%)
No event	**356 (83.4%)**	**285 (83.1%)**	**155 (81.6%)**	**140 (88.6%)**	**936 (83.7%)**
	427 (100%)	343 (100%)	190 (100%)	158 (100%)	1118 (100%)

Arterial event: Stroke, TIA, pAOD
Venous event: Deep vein-, ophthalmic vein-, portal vein - thrombosis, Budd-Chiari-Syndrome
Cardiovascular event: Myocardial infarction, AP, atrial fibrillation, aortic aneurysm

Table 2: 1st-line treatment that started within 90 days after diagnosis of the hematologist

	ET	PV	MF	u-MPN	Other MPN	All
Pts N	427 (37.4%)	343 (30.0%)	190 (16.6%)	158 (13.8%)	25 (2.2%)	1143 (100%)
w+w*	178 (41.7%)	78 (22.7%)	101 (53.2%)	65 (41.1%)	15 (60.0%)	437 (38.2%)
Hydroxyurea	278 (65.1%)	193 (56.3%)	80 (42.1%)	71 (44.9%)	11 (44.0%)	633 (55.4%)
Anagrelide	45 (10.5%)	2 (0.6%)	3 (1.6%)	2 (1.3%)	-	52 (4.5%)
Ruxolitinib	1 (0.2%)	7 (2.0%)	40 (21.1%)	10 (6.3%)	3 (12.0%)	61 (5.3%)
Interferon	3 (0.7%)	8 (2.3%)	1 (0.5%)	1 (0.6%)	-	13 (1.1%)
Phlebotomy**	5 (1.2%)	139 (40.5%)	5 (2.6%)	18 (11.4%)	-	167 (14.6%)
TEP* of it ASS*	202 (47.3%) 195 (96.5%)	136 (39.7%) 129 (94.9%)	56 (29.5%) 51 (91.1%)	57 (36.1%) 53 (93.0%)	3 (12.0%) 3 (100%)	454 (39.7%) 431 (94.9%)

*Abbreviations: w+w: watch and wait only, TEP: Thrombo-embolic-prophylaxis could be combined with w+w or specific therapy, ASS: Acetylsalicylate
** Phlebotomy could be combined with other specific therapy

Conclusions: The frequency of vascular events and MPN-related fatal outcome is low. There don´t seem to be mayor differences between the MPN-subgroups. The intention for the different therapies will be analyzed.

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P366

Few mutational changes in myelofibrosis at relapse after allogeneic stem cell transplantation

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Myelofibrosis (MF), either primary (PMF), as post-essential thrombocythemia (post-ET MF) or post-polycythemia vera (post-PV MF), is a myeloproliferative neoplasm (MPN) characterized by molecular mutations in three driver genes and further somatic candidate genes. Whilst vivid clonal evolution has been described in other myeloid malignancies, existing data on this phenomenon suggest it be of small extent in MPN, especially MF.

Paired sequencing from peripheral blood of 30 patients with MF who relapsed after allogeneic hematopoietic stem cell transplantation (alloSCT) was performed using amplicon-based deep sequencing. A median of 3 (range 0-13) nonsynonymous mutations was found in a median of 2 (0-8) genes before alloSCT. At relapse, also 3 (median, range 0-13) nonsynonymous mutations were found in 2 (median, range 0-6) genes. Taking gains and losses of nonsynonymous mutations at relapse into account, between 0 and 10 changes (median 1) were observed.

In six of these patients, whole genome sequencing was performed, but no additional molecular changes were observed. Thus, molecular changes were moderate at best and rather included losses than gains of mutation. Taken together, clonal evolution at relapse of MF after alloSCT seems to be limited, and alloSCT seems to select specific clones of MF.

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P367

Antiphospholipid syndrome in patients with Philadelphia-chromosome negative myeloproliferative neoplasm: an association or coincidence?

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Introduction: Classical Philadelphia-chromosome negative (Ph-neg) myeloproliferative neoplasms (MPNs) are associated with an increased risk for thromboembolic events. Elevated levels of circulating microvesicles and the occurrence of an acquired activated protein C resistance are the most prominent features of hypercoagulability in these patients, whereas a pathophysiological role of antiphospholipid antibodies (aPL) has not yet been established. It might be speculated that MPN patients exhibiting aPL, or having antiphospholipid syndrome (APS), have an even further

increased risk for thromboembolic complications or recurrences. However, it is not clear, which MPN patients are at highest risk for developing APS, thus warranting routine testing for aPL.

Materials and methods: Our study included seven patients suffering a thromboembolic event who were simultaneously diagnosed with classical Ph-neg MPN and APS. Serum IgG and IgM antibodies to cardiolipin (aCL) and β_2-glycoprotein-I (β_2-GP-I) were measured by enzyme-linked immunosorbent assays. Lupusanticoagulant (LA) was detected in plasma by an activated partial thromboplastin time (APTT) and a dilute Russel's viper venom time (dRVVT) based assay. The V617F mutation in the Janus kinase-2 gene (*JAK2*) and *JAK2*^{V617F} allele burden were analyzed by polymerase chain reaction.

Results: Patient characteristics including age at diagnosis, type of thromboembolic events, platelet and leukocyte counts, hematocrit levels, aPL and LA test results, and *JAK2*^{V617F} allele burden are presented in Table 1.

Discussion: All patients in our case series tested positive of the *JAK2*^{V617F} mutation and tended to suffer from rather atypical thromboembolic events. Our findings have important clinical implications, since diagnosis of APS might prompt oral anticoagulation instead of (or even additionally to) antiplatelet therapy. Furthermore, thromboembolic recurrence rates appear to be higher in MPN patients with additional APS. In our opinion, it is important to distinguish the group of MPN patients who have coincident APS, since this group might be at much higher risk for recurrent thromboembolism.

Tab. 1. Patient characteristics

	Normal	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Age (years)		65	75	55	47	42	45	44
Gender		female	female	male	female	male	female	female
Type of MPN		PV	MPN not specified	ET	ET	MPN not specified	prefibrotic early stage of PMF	PV
Platelet count	150–400 x 10^9/L	469	670	748	569	515	550	266
WBC count	3.8–11 x 10^9/L	22.8	19.0	12.2	7.5	4.8	10.1	8.3
Hematocrit level	35–45 %	48.6	49.0	52.8	41.1	38.8	46.5	45.5
JAK2^{V617F} allele burden	negative	7.07	9.5	2.27	1.6	2.6	20.4	18.2
IgM aCL	< 10 U/mL	55.5	-	-	28.0	76.0	77.0	70
IgG aCL	< 10 U/mL	-	29	21	-	-	-	-
IgM anti-β_2GP-I	< 7 U/mL	29	-	-	384	-	-	-
IgG anti-β_2GP-I	< 7 U/mL	-	65	52	-	-	-	-
LA dRVVT	negative	-	-	n. d.	-	-	-	-
LA APTT	negative	-	+	n. d.	+	-	-	-
Clinical presentation		TE occlusion of A. radialis, lower-extremity DVT, PE, MI	portal vein thrombosis, lower-extremity DVT splenic infarction	recurrent PE	recurrent stroke	MI	skin necrosis	splenic vein thrombosis
latest antithrombotic and antiplatelet regimen		phenprocoumon + ASA	apixaban+ ASA	rivaroxaban + ASA	phenprocoumon + ASA	enoxaparin + ASA + clopidogrel	phenprocoumon+ ASA	phenprocoumon + ASA

Abbreviations: aCL antibody to cardiolipin; **APTT** activated partial thromboplastin time; **ASA**: acetylsalicylic acid; **dRVVT** dilute Russell's viper venom time; **DVT** deep vein thrombosis; **ET** essential thrombocythemia; **GP** glycoprotein; **JAK2** Janus kinase-2; **MI** myocardial infarction; **MPN** myeloproliferative neoplasm; **n. d.** not determined; **PE** pulmonary embolism; **PMF** primary myelofibrosis; **PV** polycythemia vera; **TE** thromboembolic; **WBC** white blood cells;

Disclosure: No conflict of interest disclosed.

P368

Cooperation of BCR-ABL1_p210 and CBFB-MYH11_A in chronic myeloid leukemia is not sufficient to induce myeloid blast expansion in the absence of other class I mutations

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We report here a patient with BCR-ABL_p210 positive CML and co-occurrence of CBFB-MYH11_A at primary diagnosis, who simultaneously acquired three different indel mutations in exon 8 of *KIT*, all affecting codon 419, while undergoing treatment with a TKI.

At time of progression to blast crisis extensive mutational analyses identified three different in-frame deletion plus insertion mutations in *KIT* exon 8 with consistent loss of the codon for Asp419 *(KIT* exon 8 c.1248_1257delGACTTACGACinsTTAC, p.Thr417_Asp419delinsTyr, *KIT* exon 8 c.1249_1256delACTTACGAinsGT, p.Thr417_Asp419delinsVal, *KIT* exon 8 c.1253_1258delACGACAinsGGT, p.Tyr418_Arg420delinsTrp) by targeted next generation sequencing.

Using a mutation-specific hydrolysis-probe based digital droplet PCR assay we were able to identify all three indel mutations in the samples acquired at treatment failure and thereafter, but not in any previous samples, including the one at primary diagnosis.

In order to verify that the various *KIT* mutations occurred in different clones, we performed genetic analyses at the single-cell level on the bone marrow sample collected at progression to blast crisis. We identified c.1248_1257delGACTTACGACinsTTAC in 6 cells, c.1249_1256delACTTACGAinsGT in 4 cells and c.1253_1258delACGACAinsGGT in 3 cells. In each cell, only one mutation was present. In addition, occurrence of allele dropouts could be excluded in 6 *KIT* mutated cells based on the concurrent presence of a wild-type allele or heterozygosity in the additionally analyzed SNP. In summary, our single cell data indicate that the *KIT* mutations indeed occurred in different clones.

During the course of the disease in our patient the main driver BCR-ABL1 appears to have been downgraded to a passenger mutation during TKI-treatment, after the competing Ph$^+$ subclone harboring the fusion protein CBFB-MYH11_A acquired a mutation in *KIT* exon 8, which then cooperated with CBFB-MYH11_A to induce a myeloid blast crisis.

This is the first description of co-occurrence of BCR-ABL1, CBFB-MYH11 and a *KIT* mutation in the same clone of a myeloid leukemia.

In conclusion, the observations made here suggest that t(9;22) does not cooperate with t(16;16) in the pathogenesis of myeloid blast expansion and that an additional class I mutation in one of the CBF-AML related kinases is needed for the transformation of the Ph$^+$ subclone harboring the t(16;16) translocation.

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Nikolas von Bubnoff: Other Financial Relationships: institutional financial support from Novartis

P369

Clinical and genetic features in patients with a BCR-ABL negative myeloproliferative neoplasm and concurrent monoclonal gammopathy

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BCR-ABL negative myeloproliferative neoplasm (MPN) and monoclonal gammopathy (MGUS) co-occur in 5-15% of MPN patients. MGUS associates with worse outcomes in essential thrombocythemia (ET) and polycythemia vera (PV) patients. Moreover, JAK1/2 inhibitor treatment of myelofibrosis (MF) has been linked with B-cell lymphoma development. However, literature on the co-occurrence of MPN and MGUS is limited, the molecular underpinnings are unknown and it remains elusive whether affected patients require specific management. Here, we assessed the presence of MGUS in MPN patients and studied the clinical and genetic features.

MPN patients seen at our center were prospectively studied for an M-protein by serum immunofixation, and the Freiburg MPN registry was inquired for patients with pertinent data. Clinical and genetic features were studied, and available samples were additionally analyzed via gene panel sequencing. MPN diagnosis was based on the WHO classification, MGUS on IMWG criteria.

We studied 112 MPN patients (age at MPN diagnosis: median 57 years, range 9-86) for an M-protein. In 8 (7%) of these patients, an M-protein was detected. In the Freiburg MPN registry, 9 further MPN/MGUS patients were identified. Among the total of 17 MPN/MGUS patients, 5 had PV, 8 ET and 4 MF. Five of the ET/PV patients developed secondary MF.

One patient developed a multiple myeloma and acute myeloid leukemia. Aberrant cytogenetics were identified in 4 of 10 patients with data available. *JAK2*, *CALR* or *MPL* mutations were present in 13, 3 and none of the patients, respectively. Additional mutations (e.g. in *ASXL1* or *TET2*) were identified in 8 of 13 patients analyzed. M-protein was mainly IgG (12/17), followed by IgM (4/17); one patient had urine λ-light chain excretion only. Six patients received JAK1/2 inhibitor treatment. Two patients underwent allogeneic hematopoietic stem cell transplantation (HSCT). In one of these patients, the *JAK2* mutation and the M-protein were no longer detectable at day 30 after HSCT, but an IgG-(λ/k) protein recurred one year after HSCT.
In conclusion, the prevalence of MGUS in our unselected cohort of MPN patients was 7%, thus in the range of previous reports and slightly higher than in an average age-adjusted population. MGUS occurred across all MPN entities, and no correlation with specific genetics was identified. Studies are ongoing to better understand the MGUS origin in MPN patients and the differences in comparison with MPN patients and no MGUS.

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P370

Comparison of proteome composition of serum enriched in extracellular vesicles isolated from polycythemia vera patients and healthy controls

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Introduction: Extracellular vesicles (EVs), e.g., exosomes and microvesicles, are one of the main networks of intercellular communication. In myeloproliferative neoplasms, such as polycythemia vera (PV), excess of EVs originating from overabundant blood cells can directly contribute to thrombosis through their procoagulant activity. However, proteomic composition of these vesicles in PV patients has not yet been investigated.
Methods: We examined proteomic composition of serum EVs of PV patients in comparison to healthy controls. We processed EV-enriched serum samples using Multiple Enzyme Filter Aided Sample Preparation approach (MED-FASP), conducted LC-MS/MS measurements on a Q-Exactive HF-X mass spectrometer, and quantitatively analyzed the absolute concentrations of identified proteins by Total Protein Approach (TPA).
Results: 38 proteins were present at statistically significant different concentrations between PV patients' study group and healthy controls' group. The main protein components deregulated in PV were primarily relate excessive amounts of cells (TFRC, SELL, GP5), increased platelet activation (SERPINE1, MMRN1), elevated immune and inflammatory response (HPSE, CAMP, LYZ, SELL, LTF), high concentrations of procoagulant and angiogenic agents (ANG, HPSE), as well as oncogenic proteins (NOTCH3).
Conclusions: Our study provides the first quantitative analysis of the serum EVs' proteome in PV patients. This new knowledge may contribute to a better understanding of the secondary systemic effects of PV disease and further development of diagnostic or therapeutic procedures.

Disclosure: No conflict of interest disclosed.

P371

RUNX1 mutation in a patient with myeloproliferative neoplasm - case report

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Introduction: Abdominal vein thrombosis is associated with JAK2 positive myeloproliferative neoplasm (MPN) in some patients. With development of next generation sequencing (NGS), there is an increase of patients diagnosed with MPN even with no abnormalities in peripheral blood count. NGS allows broad screening of further hematologic neoplasm associated mutations besides the commonly in MPN detected JAK2, MPL, and CALR mutations.. Detection of such mutations can be of considerable interest.
Method: The diagnostic and therapeutic procedure of a 49-year-old female patient with abdominal vein thrombosis and prefibrotic MPN is presented. Targeted NGS was employed to screen hematopoietic cancer associated mutations with a minimum coverage of 500 reads.
Results: The patient presented in the outpatient department after diagnosis of portal and splenic vein thrombosis. Targeted NGS of PBMC DNA revealed the JAK2 V617F mutation (allele frequency 17,3%). Bone marrow biopsy was performed to further characterize the disease. Morphology showed abnormal megakaryopoiesis, suggesting essential thrombocythemia, histology classified the bone marrow as prefibrotic myelofibrosis. Comprehensive targeted NGS analyses of bone marrow DNA confirmed the JAK2 V617F mutation (allele frequency 17,8%) and detected additionally a p.L56S RUNX1 mutation (allele frequency 48,04%). The observed mutation is described as germline SNP mutation associated with familial platelet disorder with propensity to myeloid malignancies. However, the patient shows until now no abnormalities in platelet, leukocyte or erythrocyte count and is in close follow up.
Conclusion: This report describes the parallel detection of a germline RUNX1 mutation, associated with familial platelet disorder, and somatic JAK2 V617F mutation, characteristic of MPN, in a patient presenting with extensive thromboses of portal and splenic veins. Interestingly conventional blood counts are normal until now. Follow up will further elucidate the clinical course and possibly evaluate the effect of this rare combination of mutations.

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P372

One colibri meets another - a result of clonal hematopoietic evolution?

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Chronic neutrophilic leukemia (CNL) is an extremely rare disease that belongs to the group of BCR-ABL- negative myeloproliferative neoplasms. To date approximately 200 patients have been reported diagnosed with CNL. The disease-defining activating CSF3R mutations are one of the five key diagnostic components of CNL. In November 2018, an 83-year old man presented in our clinic in reduced physical condition. We detected a third degree AV block, that was treated with a pacemaker. The first laboratory analyses showed an elevated number of leucocytes (39/nl) with > 80 % neutrophils, a mild anemia (Hb 12 g/dl), an elevated platelet count (404/nl), and an elevated LDH (311 U/l). About 20 years ago the patient was treated for multiple myeloma including high dose melphalan and autologous stem cell support resulting in an stringent CR. Current bone marrow analysis showed a left-shifted granulopoiesis representing > 90 % nucleated with myeloblasts < 5 %. No clonal plasma cells were seen indicating an ongoing CR of myeloma. However, molecular analysis revealed a CSF3RT618I mutation and additional gene mutations for ASXL1, SETBP1, and U2AF1 could be found, but no BCR-ABL transcripts. Altogether

the WHO diagnostic criteria for CNL were met. At time of diagnosis no therapy was started considering the low dynamics of the blood cell parameters during hospitalization and the asymptomatic course. The patient was discharged from our hospital in December 2018 and referred to an outpatient oncology center. In summary, this patient showed two very rare and interesting hematological findings: a very long CR (curation?) of multiple myeloma following ASCT and chronic neutrophilic leukemia. Regarding the above mentioned CHIP-like lesions, one may speculate about clonal hematopoietic evolution following myeloma therapy resulting in CNL.

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P723

Cutaneous adverse events (CAE) in MPN patients with cytoreductive therapy are strongly associated with hydroxyurea (HU): results from a prospective non-interventional study

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Hydroxyurea (HU) is the most common used cytoreductive drug in patients (pts) with myeloproliferative neoplasms (MPN). Although HU is well tolerated in many cases cutaneous adverse events (CAE) are frequent side effects and may limit its long-term use. As most data concerning HU associated CAE are retrospective, we conducted a prospective non-interventional study including 172 MPN pts with 211 therapy intervals and a median follow-up time of 4.0 years (0.1-7.2). Our aim was to investigate the incidence, type, and dose dependence of CAE associated with frequently used cytoreductive drugs: HU (96 of 211 therapy intervals (TI), 45.5%), ruxolitinib (64 TI, 30.3%), anagrelide (27 TI, 12.8%), and (peg-) interferon (24 TI, 11.4%). The median corresponding times on treatment (range) were: HU: 5.4 years (0.1-21.0), ruxolitinib: 1.8 years (0.2-5.3), anagrelide: 2.6 years (0.1-18.0) and (peg-) interferon: 6.1 years (0.3-22.3). In 53 of 96 (55.2%) HU therapy intervals we observed 60 CAE occurring after a median treatment time of 4.3 years (range 0.2 to 15.3 years). The most common HU-associated CAE were ulcers (15 of 60, 24.6%, 12 leg ulcers and three oral ulcers). Remarkably, we found four local skin cancers (three basalioma and one squamous cell cancer, 4 of 96 = 4.2%) and ten precancerous lesions (one vulva dysplasia and nine actinic keratoses, 10 of 96 = 10.4%) Median cumulative HU dosage until CAE was 1533 g (90-7520). In contrast, only five CAE occurred with non-HU treatments (three CAE were IFN and two CAE ruxolitinib associated).
Taken together, drug associated CAE occurred significantly more frequently during HU therapy intervals compared to non-HU treatments (53/96 [55.2%] vs 5/115 [4.3%]; p< 0.0001). Moreover, due to CAE HU therapy was significantly more discontinued compared with non-HU treatments (19/96 [19.8%] vs 1/115 [0.9%]; p< 0.0001). Based on our study HU associated CAE are frequent and clinically relevant.

Disclosure: No conflict of interest disclosed.

Posterdiskussion

Nicht maligne Hämatologie (exkl. Anämien)

P373

Iron chelation therapy in German MDS patients with chronic iron overload under routine clinical practice (an interim analysis of EXCALIBUR study)

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Introduction: Iron overload (IOL) due to chronic blood transfusions can lead to significant end organ damage and is negatively associated with survival. EXCALIBUR is an ongoing prospective non-interventional study aimed to assess the utility, efficacy, safety, and frequency of switch of all approved iron chelators in routine clinical practice in Germany. Here, we present results of a subgroup interim analysis in patients (pts) with myelodysplastic syndrome (MDS).
Methods: Adult pts with transfusional IOL, meeting the criteria as per summary of product characteristics of respective approved iron chelators, were included. Observation time for each pt is up to 24 months (mos), extended by up to 24 mos in case of switch of iron chelator.
Results: From 90 centers, 187 pts (median age [range], 76 [33-90] years (ys); 73% were ≥70 ys) with MDS (International prognostic scoring system, %: low=24; int-1=20; int-2=12; high=4; unknown=40) were analyzed; 61.5% were males and all were Caucasians. Of the 187 pts, 69 and 108 were on deferasirox dispersible tablets (DT) and film-coated tablets (FCT) respectively, and 10 on deferoxamine (DFO). Median time from start of blood transfusions to start of current iron chelation therapy (ICT) was 13.4 (0.7-124.9) mos. Median number of transfusions remained stable during course of the study (6 within last 8 weeks). Overall, 28 pts (2 pts with 2 treatment changes) switched from DT to FCT. Median (range) last dose of DT and first dose of FCT were 11.8 (1.6-30) and 16.1 (2.1-38.3) mg/kg (conversion factor=1.43), respectively. There was a greater reduction in serum ferritin (SF) levels in pts on FCT vs DT (median [range] change from baseline [BL] to mo 12, ng/mL: -182 [-3102-3428] vs -65 [-2120-2051]); an additional reduction was seen in pts who switched from DT to FCT (n=26; median [range] change from BL of switch to mo 12, ng/mL: -420 [-816-893]). In pts who switched from DT to FCT (n=28), median (range) serum creatinine levels during last visit on DT and FCT were 1.0 (0.6-1.9) and 1.1 (0.8-2.2) mg/dL, respectively. Overall, FCT group experienced less serious adverse drug reactions at a higher median dose (13.5% [FCT]; 20.5% [DT]; 23.1 % [DFO]). Most commonly reported adverse events were diarrhea (19%), nausea (11%), and fatigue (10%).
Conclusions: Overall, SF levels declined more predominately in FCT group. An additional reduction in SF levels was seen in pts who switched from DT to FCT. ICT was well tolerated in German pts with MDS.

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P374

Transfusion requirements in adult patients with paroxysmal nocturnal hemoglobinuria naive to complement inhibitors receiving Ravulizumab or Eculizumab: results from a phase 3 non-inferiority study

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Introduction: Paroxysmal nocturnal hemoglobinuria (PNH) is characterized by hemolytic anemia and can be further complicated by aplastic anemia (AA). Accordingly, PNH patients (pts) may require red blood cell (RBC) transfusion. Ravulizumab is a novel long-acting C5 inhibitor administered every 8 weeks, shown to be non-inferior to eculizumab administered every 2 weeks for treating adult PNH pts. A phase 3 study in complement-inhibitor-naive PNH pts showed that 74% of pts on ravulizumab avoided transfusion vs 66% on eculizumab over 26 weeks. About 1/3 of pts enrolled had a history of AA, allowing to evaluate the efficacy of ravulizumab in pts with and without bone marrow failure.
Methods: Transfusion data from ALXN1210-PNH-301, a phase 3, randomized, active-controlled, open-label study conducted in 123 centers in 25 countries from the 6-month primary evaluation period were analyzed. Complement-inhibitor naive pts were randomized to ravulizumab or eculizumab. Protocol-specified transfusion guidelines were used. The number of pts receiving RBC transfusion, number of transfusions and total number of units [U] received during treatment were analyzed. Treatment group results were shown by presence or absence of AA.
Results: In total, 246 pts were randomized (ravulizumab, n=125; eculizumab, n=121). In each group, ~75% of pts had received a transfusion within 6 months prior to 1st dose (ravulizumab, 400 transfusions [533 U]; eculizumab, 337 transfusions [492 U]). A history of AA was seen in 33% of pts in the ravulizumab arm and 31% in the eculizumab arm, rates representative of those expected in the general PNH population. In both arms, reticulocyte counts were higher at baseline for pts with no history of AA vs. those with an AA history, remaining stable throughout treatment. After 6 months, 26% of pts on ravulizumab received 107 transfusions (155 U) vs 33% of pts on eculizumab (144 transfusions, 222 U). In pts with a history of AA, 24% received transfusion while on treatment in the ravulizumab arm and 40% in the eculizumab arm.
Conclusions: Transfusion requirements of pts treated with ravulizumab or eculizumab were similar. Fewer pts with a history of AA received transfusions on ravulizumab compared to those on eculizumab, suggesting that AA pts may benefit more of a consistent C5 blockade by ravulizumab. Additional studies are needed to confirm these differences. These findings support the use of ravulizumab in treatment-naive PNH pts, with or without history of AA.

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P375

The epidemiology of β-thalassemia in Germany: Results from a claims database analysis

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Introduction: β-thalassemia is a rare genetic disease characterized by reduced or absent production of functional β-globin, resulting in chronic anemia and other serious complications. Worldwide, it is one of the most common autosomal recessive disorders with endemic populations primarily in South Asia, the Middle East, North Africa, and Southern Europe. Due to migration it gains in importance in Europe. The aim of the study was to evaluate the current prevalence and incidence of β-thalassemia and transfusion dependent β-thalassemia (TDT) patients in Germany.
Methods: Retrospective claims data from the InGef research database were used. The sample represents about 4.8% of the German population. Prevalent, incident, and TDT patients were identified by ICD-10 German Modification code D56.1 in 2017. Incident patients were additionally required to have a diagnosis-free pre-observation period of five years. TDT was classified by having at least 8 red blood cell (RBC) transfusions defined by Operation and Procedure (OPS) Codes for transfusions and Pharmaceutical Registration Numbers (PZN) for blood products. To validate the TDT classification, the number of patients receiving iron chelation therapy (ICT) was assessed by using Anatomical Therapeutic Chemical (ATC) Codes. Patient counts were extrapolated to the German population in 2017.
Results: A total number of 786 prevalent β-thalassemia patients was identified in the database in 2017 with a mean age of 42.2 years and 54.1% were females. 107 patients were newly diagnosed, of which 9 patients were born between 2012 and 2016. At least one RBC product was transfused in 4.8% (n=38) of patients and 1.7% (n=13) had at least 8 RBC transfusions in 2017. Out of these, 9 patients were aged ≥12 years and received ICT due to iron overload. Extrapolated to the German population, this indicates that about 15,018 patients (95% CI 13,986-16,105) suffered from β-thalassemia, 2,699 patients (95% CI 2,212-3,261) were newly diagnosed, and 248 (95% CI 132-425) patients received at least 8 RBC transfusions of which 172 (95% CI 79-326) were aged ≥12 years and received ICT.
Conclusions: This claims data analysis provides valuable insights in the epidemiology of β-thalassemia and patient demographic. With extrapolated 15,018 prevalent β-thalassemia patients, a notable burden of disease in Germany is present. Only about 248 patients in Germany need regular RBC transfusions and probably require more intensive healthcare.

Disclosure: No conflict of interest disclosed.

P376

Transient thrombocytopenia in an adult patient with TAR-syndrome efficiently treated with prednisone

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Introduction: The „*thrombocytopenia absent radius (TAR)-Syndro*me"is a rare inherited disorder characterized by bilateral radius aplasia and (transient) thrombocytopenia especially in the first years of life. Until now, only a few hundred cases are described. Transient, often self-limiting phases of severe thrombocytopenia, especially in the childhood, are described in literature and frequently treated with platelets (PLT) transfusions until spontaneous recovery. On a genetic level, a microdeletion of chromosome 1q21.1 combined with a mutation in the RNA Binding Motif Protein 8A (RBM8A) gene were found in TAR-Syndrome. However, the exact pathophysiology especially of thrombocytopenia remains unclear.
Patient history: We report a 27-year-old female patient (pt) with TAR-Syndrome developing for the first time a transfusion dependent thrombocy-

topenia in adulthood. In January 2019 the pt presented with petechiae and PLT counts of 2/nl. Hemoglobin and leukocyte values were within the normal range. The pt reported a single self-limiting phase of thrombocytopenia as a baby. Assuming a transient, disease-related, self-limiting episode of thrombocytopenia, the pt received platelet (PLT) regular transfusions. The initial increment after PLT transfusions showed good PLT counts with a corrected count uptake of 14,70 arguing against the diagnosis of immune thrombocytopenic purpura (ITP). Showing persistent thrombocytopenia for 18 days, a bone marrow puncture revealed normal bone marrow morphology except for an increased number of megakaryocytes with small dysplastic changes. The morphology of thrombocytes was normal. In view of persistent thrombocytopenia with signs of bleeding e.g. increased petechiae and enhanced menstruation, a treatment attempt with Eltrombopag (EPAG) was initiated. EPAG was escalated to 150 mg daily showing no improvement of PLT counts. After 3 months, EPAG was stopped and the patient received 80 mg prednisone (PRD) daily with an increase of PLT counts above 100/nl within 10 days. During follow-up PRD was gradually reduced with stable PLT count between 50 to 150/nl.
Conclusions: We describe a clinically relevant thrombocytopenia in an adult TAR-syndrome pt responding to therapy with PRD, but not to EPAG. Based on the clinical course, ITP cannot be completely ruled out. The question whether steroids might play a role in the pathophysiology of TAR syndromes similar to diamond-blackfan anemia remains unclear requiring further studies.

Disclosure: No conflict of interest disclosed.

P377

Successful treatment of long-lasting neutropenia refractory to granulocyte-colony stimulating factor (G-CSF) with immunosuppressive drugs

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Introduction: Acquired isolated neutropenia is a serious finding, potentially leading to life-threatening infetions. Management of neutropenia is based on the etiology, severity and chronicity of the disorder.
Case presentation: A 66-year-old male patient came into our hematology department with a long-lasting grade IV neutropenia (absolute neutrophil count ANC below 100/µl) since December 1999, resistant to G-CSF and complicated by recurrent opportunistic and fungal Infections (pneumonia, otitis, sinusitis and herpes Zoster). We performed a thorough differential diagnosis to exclude drug-induced, nutritional and immune causes of neutropenia. In addition, splenic sequestration, cyclic neutropenia, other forms of chronic neutropenia and a developing myelodysplastic syndrome could also be excluded, by laboratory evaluation and bone marrow examination. The patient developed severe progressive atypical pneumonia that did not respond to broad-spectrum antibiotics and antifungal medication. Despite application of G-CSF at high dosages (48 µg twice a day subcutaneously), the ANC did not increase above levels of 0.1-0.2/µl. Repeat bone marrow examination confirmed profound reduction of the granulocytic lineage without maturation arrest whereas the erythropoiesis and megakaryopoiesis were quantitatively and qualitatively normal. Our hypothesis included an autoimmune cause of the neutropenia. We therefore decided to pursue the concept of an anti-thymocyte globulin therapy (ATG), parallel to ciclosporin and prednisone, similar to the treatment of child autoimmune neutropenia. Horse ATG was applied at the usual dosages (40mg/kg daily over 5 days intravenously). The normal count of platelets and reticulocytes did not suffice for the diagnosis of an aplastic anemia. Beginning 7 days after administration of ATG, the neutropenia gradually resolved and subsequently the patient recovered from atypical pneumonia. After 3 months of immunosuppressive treatment, ciclosporin was stopped. Up to now, the patient remains now in complete remission more than 2 years after institution of immunosuppressive therapy.
Conclusions: The resolution of neutropenia after administration of ATG supports our hypothesis that there was an autoimmune mechanism for the patient's disorder.

Disclosure: No conflict of interest disclosed.

P378

Treosulfan- versus melphalan-based reduced intensity conditioning in HLA—haploidentical transplantation using PTCY as GvHD prophylaxis in high-risk MDS /AML of the elderly: a matched-pair analysis

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Standard conditioning regimens prior to allo-HSCT are often associated with a considerable risk of severe adverse events in elderly patients (pts) suffering from high-risk (HR) MDS/AML. Previous studies have demonstrated feasibility of treosulfan-based RIC by stable engraftment, low non-relapse mortality (NRM) in elderly pts undergoing HLA-matched related or unrelated allo-HSCT. However, data for treosulfan-based conditioning in the TCR HLA-haploidentical (haplo-HSCT) setting in HR AML/MDS pts are rare. Here we report on a matched pair analysis of 22 patients treated with either a treosulfan- or melphalan-based conditioning for haplo-HSCT using PTCY as GvHD prophylaxis in HR MDS/AML.
11 pts with HR AML/MDS who underwent haplo-HSCT using treosulfan ($3x10g/m^2$) for RIC were considered for potential matching with recipients (n=24) of a melphalan-based RIC regimen for haplo-HSCT. All pts were ≥ 54 years old and were transplanted between Jan 2009 and Feb 2018 at our institution. Matching criteria comprised (1) disease activity (blast yes or no), (2) disease status (relapse, refractory, high-risk cytogenetics) and (3) HCT-CI. 11 pts undergoing treosulfan-haplo-HSCT were successfully pair-matched with 11 recipients of melphalan-based haplo-HSCT, respectively ((1) p=1.0; (2) p=1.0; (3) p=1.0). All but 4 pts presented with active disease at time of haplo-HSCT.
Median age of the entire cohort was 63 years (54-71). Each group consisted of 2 MDS pts and 9 AML pts. All pts treated with treosulfan showed neutrophil engraftment with a median of 20 days. In the melphalan group 9/11 pts achieved neutrophil engraftment while one graft rejection occurred. Acute GvHD °II-IV occurred in 18% (no severe aGvHD) and 38% (one severe aGvHD) of the pts treated with treosulfan or melphalan, respectively. Severe (°III-IV) non-hematologic regimen-related toxicities were seen in 2/11 (treosulfan) and 6/11 (melphalan) pts, predominately affecting the GI-tract. NRM at day +100 was 0% and 36% for the treosulfan and melphalan group, respectively. Four treosulfan-treated pts relapsed within the first year after haplo-HSCT, whereas no melphalan treated pt relapsed.
TCR haplo-HSCT using treosulfan and PTCY in elderly HR MDS/AML pts is safe, resulting in lower NRM but higher relapse rate if compared to a melphalan-based approach. We suggest that treosulfan-based RIC in haplo-HSCT might be an alternative in elderly pts with low leukemic burden, however, its intensity should be reconsidered.

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P379

Impact of T cells transduced with an HLA-independent T-cell receptor (TCR) against the alpha chain of the GM-CSF receptor (CSF2RA) on hematopoietic progenitor cells

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Introduction: The alpha chain of the GM-CSF receptor (CSF2RA) is expressed by a variety of solid and hematopoietic cancer types and has been reported to support per se malignancy by improving glucose utilization and by anti-apoptotic effects. We have isolated tumor-reactive CD8+ alpha/beta T cells from the blood of melanoma patient Ma-Mel-86 recognizing CSF2RA in an HLA-independent fashion. Their CSF2RA-specific T-cell receptor (TCR) has been cloned and is currently studied in preclinical experiments. Herein we investigated the effect of the anti-CSF2RA TCR in vitro on hematopoietic progenitor cells using a methylcellulose colony-forming cell assay.
Materials and methods: Colony-forming unit (CFU) assays were performed in semi-solid, methylcellulose-based medium according to the manufacturer´s instructions (STEMCELL Technologies, Cologne). CD34+ target cells were isolated from leukaphereses of two healthy stem cell donors and of a lymphoma patient. Control targets were HLA I/II-deficient K562 cells untransfected or stably transfected with CSF2RA cDNA as well as the CSF2RA+ AML cell line NOMO-1. In preliminary tests all targets formed colonies in the assay medium, whereas T cells failed to grow. Autologous T cells were retrovirally transduced with the anti-CSF2RA TCR or with an irrelevant TCR [HLA-independent, anti-TRP2 (tyrosinase-related protein 2)]. Both TCR had been cloned as chimerized bicistronic constructs into a retroviral expression vector.
Results: Target cells were seeded on CFU assay plates without pretreatment or after 6h co-incubation at a 1:1 effector-to-target ratio with TCR-transduced T cells generated from the same donors as CD34+ cells. The functionality and specificity of each effector population was verified by IFNγ-ELISpot and CD107a degranulation assays. After 7-14 days the colonies were counted. TCR-transgenic (TCRtg) anti-CSF2RA T cells specifically inhibited the growth of NOMO-1 and CSF2RA+ K562 cells while TCRtg anti-TRP2 T cells did not. In contrast, none of the TCRtg T cell populations measurably impeded colony formation of CD34+ target cells in any case, even when the TCRtg T cells were 100% CD8+.
Conclusions: We have demonstrated that leukemia-reactive TCRtg anti-CSF2RA T cells did not impact on the proliferation and differentiation of hematopoietic progenitor cells in vitro. These findings support further preclinical and ultimately clinical testing.

Disclosure: No conflict of interest disclosed.

P380

GvL without GvHD ? Role of different NK-cell subpopulations after allogeneic stem cell transplantation

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Introduction: Allogeneic hematopoietic stem cell transplantation (HSCT) is the only curative treatment option for many hematological malignancies. The transplanted immune system exerts a graft versus leucemia effect but can also act against healthy tissue and cause GvHD.
In this context NK-cells are of particular interest as they can mediate GVL-enhancing and GvHD-limiting effects.
Here we analyze reconstitution of different NK-cell populations and their impact on GvHD or relapse.
Methods: We analyzed blood samples from 28 AML patients after allogeneic HSCT with 2 different conditioning regimen (18 refractory patients after FLAMSA-RIC, 10 patients in CR after RIC), collected on d+50, +100, +150, +200, +365 post HSCT prospectively. All patients received ATG / Cyclosporin A as GVHD prophylaxis.
NK-cells were divided into different groups using flow cytometry (FACS): CD56bright/CD16neg, CD56bright/CD16pos, CD56dim/CD16pos, CD-56dim/CD16neg. Additionally we examined expression of Nkp44, Nkp46, NKG2A, NKG2C, NKG2D, CD69, CD62L, Tigit and Nkp30 and correlated our findings with GVHD and relapse.
Results: 17 patients developed acute GvHD (aGVHD), 4 chronic GvHD (cGVHD), 2 relapse and 5 patients had no complications.
In patients who developed GvHD we observed an impaired reconstitution of NK-cells with a smaller proportion of immature CD56bright/CD16neg NK-cells early after HSCT. From day 150 on these patients had less mature and fully cytotoxic CD56dim/CD16pos NK-cells compared to patients with no complications.
HSCT itself causes an upregulation of almost all receptors, especially NKp46 and NKG2D compared to healthy adults. In patients, developing GVHD, the early increase in CD62L in immature NK cells was smaller than in patients without GVHD.
The inhibitory NKG2A-expression remains increased in patients suffering from GVHD, without GVHD, the expression normalized later on.
Activating NKG2C showed the opposite as in patients without complication expression would increase over time whereas in patients with GvHD it remained low throughout.
Tigit was highest in patients with cGvHD.
Conclusions: Patients developing GvHD have an impaired reconstitution of NK-cells with an altered receptor expression profile. This may impair the functionality of these cells and contribute to the pathophysiology of these complications.
A better understanding of how these changes affect functionality of NK-cells could lead to future individualized NK-cell-based donor lymphocyte infusions.

Disclosure: Jonas Wißkirchen: No conflict of interest disclosed.
Eva M. Wagner-Drouet: Advisory Role: Novartis / Pfizer / MSD

P381

Severe adverse events including epileptic seizures and cardiac arrest during infusion of autologous peripheral blood stem cells

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Introduction: The transplantation of autologous stem cells (auto-SCT) is a safe and effective standard procedure for many hematologic malignancies. Our recent experience with one patient who experienced a cardiac arrest and seizures during infusion of DMSO (Dimethyl sulfoxide) cryopreserved stem cells prompted us to review our clinical database for adverse events (AEs) and to survey the literature for auto-SCT associated AEs.
Methods: We analyzed transfusion-related reactions during auto-SCT between 2017 and 2019 at the University Hospital of Wuerzburg and identified five patients. Patient characteristics were taken from the clinical database and supplemented with data from the Institute of Transfusion Medicine. We compared our findings to the published experience from other centers performing a Pubmed search.
Results: 416 patients received autografts at the University Hospital of Wuerzburg between January 2017 and April 2019. In five cases (0,72%) unexpected AEs were reported. These patients suffered from multiple myeloma, AL amyloidosis, mantle cell lymphoma and diffuse large B-cell-lymphoma. As conditioning regimen, we used high dose melphalan and BEAM. Symptoms included neurotoxicity (confusion, impairment of

consciousness, nystagmus, tonic-clonic seizure) and cardiotoxicity (bradycardia, hypotension, cardiac arrest) and were reversible after short time. Four patients left the hospital in a good shape without sequels. The patient who suffered from cardiac arrest showed a return of spontaneous circulation after 10 minutes of cardiopulmonary resuscitation but died from sepsis with multi organ failure 10 days after auto-SCT. Similar cases of neurotoxicity have been reported, previously (epileptic seizures, transient global amnesia, cerebral infarction) and were reversible in most of the cases. Cardiac arrest with fatal outcome due to pneumonia and sepsis was reported in another case.
Conclusions: Neurotoxicity and cardiotoxicity during transplantation of DMSO cryopreserved autologous stem cells is rare and seen in < 1 % of our patients. We could not identify specific disease- or patients characteristics. However, four of five patients received relatively large volumes of cryopreserved products and, consequently, large amounts of DMSO, which had been described previously to increase the risk for AEs. Therefore, patients at risk for adverse events (e.g. low body surface area, large volumes of cryopreserved product) should be monitored closely.

Disclosure: No conflict of interest disclosed.

P382
DOAC vs. LMWH for the treatment of cancer-associated VTE - What physicians think

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Recently direct acting oral anticoagulants (DOACs) have become a new therapeutic option besides parenteral anticoagulants to treat cancer-associated venous thromboembolism (CAT). With this survey we wanted to identify factors influencing the choice between LMWH and DOAC among physicians treating cancer patients.
A questionnaire was presented at several medical educational activites on cancer care and CAT-management between August 2018 and January 2019. Besides physicians' characteristics, treatment setting, and anticoagulation preferences it contained 22 scenarios that potentially influence treatment choice. A 5-point Likert scale was applied to rank physicians' preferences.
One hundred fifteen physicians returned their surveys. The two most compelling arguments pro DOAC were when the patient had no chemotherapy and when he expressed unwillingness to apply injections. The two most important arguments against DOACs were if the patient had problems with taking oral medications or when he had a history of severe bleeding (Table).
New treatments usually need many years until they become firmly established in clinical practice. In- and exclusion criteria of pivotal studies are difficult to transfer into daily practice and prescribing physicians are afraid of medicolegal consequences if a patient suffers any harm. This survey shows, that future studies need to consider many more factors, particularly patient preferences and physician concerns on bleeding risk, to improve their applicability in daily practice.
Table: scenario-ranking from strongly pro DOAC to strongly pro-LMWH
Pro-DOAC
1 Patient receives no chemotherapy
2 Patient unwilling to take injections, prefers oral therapy
3 Localized cancer, no metastases
4 „Mild"Chemo
5 Patient cannot apply injections, nursing service required
6 Patient has VTE, no PE
7 Solid tumor, not hematologic malignancy
8 Patient lives alone or is old
9 Patient also takes aspirin
10 Patient needs no home nursing service
11 Physician has experience with DOACs for other indications
12 Patient has numerous concomitant diseases
13 Tumor has metastasized
14 Hematologic neoplasia
15 „What the guideline says"
16 Renal insufficiency
17 „Strong"chemo
18 Thrombocytopenia
19 CNS metastases or primary brain cancer
20 High bleeding risk
21 Patient has bled before
22 Nausea, vomitus, mucositis
Pro-LMWH

Disclosure: Axel Matzdorff: Advisory Role: Berater- und/oder Vortragstätigkeit für Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Daiichi Sankyo, LEO Pharma, Pfizer
Florian Langer: Advisory Role: Berater- und/oder Vortragstätigkeit für Aspen, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, LEO Pharma, Pfizer und Sanofi

P383
Analytical criteria for sCD40L detection

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Introduction: CD40 Ligand is a multifunctional ligand of the tumour necrosis superfamily with activated platelets as major source. The sCD40L basal level could be used as a biomarker. Because of difficulties with preanalytical detection of sCD40L levels it is necessary to standardize the determination of sCD40L under clinical as well as experimental conditions.
Material and methods: Serum and plasma samples of healthy blood donors (n = 17) were used to determine sCD40L concentrations under different conditions, sCD40L basal levels and the maximum release of sCD40L. Those conditions were different anticoagulants, different storing temperatures and different timepoints of centrifugation. For detection of sCD40L levels an Enzyme-linked immunosorbent Assay Kit for sCD40L was used.
Results: The determined mean value of the basal sCD40L (obtained at t = 0 min) was 450.37 pg/mL. The basal levels reached from 113.19 ± 58.73 pg/mL (inhibitor treated citrate samples) to 621.89 ± 162.77 pg/mL (L-Heparin samples). The serum samples stored at room temperature or 37 °C showed a steady increase of sCD40L concentration over time. While the concentration of the samples stored at 37 °C showed a maximum range of 10000 to 14000 pg/mL after 120 min, there is no maximum seen by the samples stored at room temperature.
Conclusion: sCD40L levels could be used as a clinical parameter but it depends on analytical conditions. Thus, a standardization of storing conditions and detection in general is necessary to prevent the blood samples from blood clotting and activation of platelets which are the major source of sCD40L in peripheral blood. Following studies should examine the interaction between platelets more precisely, sCD40L and matrix-metalloproteinases (MMP) to generate diagnostical options for sCD40L.

Disclosure: No conflict of interest disclosed.

P384
The implementation of a ROTEM® sigma-based algorithm for the management of coagulopathic bleeding in a tertiary center

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Introduction: Viscoelastic assays are used for the management of perioperative or traumatic bleeding. Recently, the manufacturer of ROTEM® has

introduced the automated sigma model. The change in technology results in new normal ranges and therefore new cutoff values triggering intervention compared to previous published ROTEM®delta cutoff values. Here, we describe the analysis performed to identify new cutoff values and the specific algorithm for the ROTEM®sigma.
Methods: 78 samples were obtained from 39 patients with various hemostatic defects and 12 healthy volunteers. Chosen standard laboratory test (SLT) cut-offs were fibrinogen (Fi) < 1.5 g/l, platelet count (Pltc) < 50 G/l or < 100 G/l, prothrombin ratio (PR) < 80 % and activated partial thromboplastin time (aPTT) >37 sec or 1.5x the normal value. PLTEM was calculated as EXTEMA5 - FIBTEMA5. The clinically critical range (CCR) of SLT was defined as the range around the threshold that leads to treatment. Correlation was sought between SLT and ROTEM parameters. The best cut-off for the different ROTEM parameters to identify the chosen SLT thresholds (ROC analysis) were integrated in a step-by-step algorithm (Figure 1).
Results: Correlation between Fi and FIBTEMA5 was very strong (r=0.94) but was lower in the CCR (0-2.5 g/l) (r=0.65). The correlation between Fi and EXTEMA5 was weakly moderate (r=0.42). PLTEMA5 showed very strong correlation (r=0.96) with Pltc in the CCR (< 150 G/L). INTEMCT showed very strong correlation with aPTT (r=0.84). EXTEMCT correlated moderately with PR (r=-0.58). Cut-off based on ROC curve analysis for different parameters are showed in Table 1.
Conclusions: In-house cut-off values of key ROTEM®sigma parameters differ from the published ones for ROTEM®delta. We report the first preliminary ROTEM®sigma-based algorithm for hemorrhage. Diagnostic and therapeutic performances shall be prospectively validated.

Disclosure: No conflict of interest disclosed.

P385

Extracellular vesicles in cancer diagnostics and as surrogate marker for cancer associated VTE

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Elevated levels of extracellular vesicles (EVs) have been correlated with inflammatory diseases as well as progressive and metastatic cancer. By presenting tissue factor (TF) on their membrane surface, cellular microvesicles (MVs), which are a subset of EVs, activate both the coagulation system and cell-signaling pathways such as the PAR/G-protein/ERK axis. We have shown before that TF^+MVs isolated from malignant effusions can activate the PAR/G-protein/ERK pathway and induce migration of human pancreatic carcinoma cells. This effect can be inhibited by pre-incubation of the malignant cells with Tinzaparin, a low molecular weight heparin, which has a high potency to induce the release of TF pathway inhibitor (TFPI). However, the clinical relevance of this *ex vivo* / *in vitro* observation is still unclear.
In the project presented here, we collected plasma and urine from patients with bladder carcinoma. MVs were purified by sequential centrifugation and quantified by high-resolution flow cytometry. Furthermore, MVs were characterized by electron microscopy, and the exposition of phosphatidylserine (PS) and active TF on their surface was assed. Results were correlated with clinical data such as the occurrence of VTE and bladder carcinoma staging.
In this ongoing project, 8 out of 75 collected samples have been analyzed so far. We found a high inter-individual variability of MV numbers as well as the exposition of PS and active TF on their surface. Notably, for an accurate MV quantification by flow cytometry, fluorescence triggering as well as an appropriate instrument adjustment are essential. The analysis of MVs from clinical material was adapted accordingly. To our surprise, urine-MV levels were much lower compared to plasma-MV levels suggesting the intact renal filter apparatus to be a barrier for MVs.
The analysis of patient-derived EVs has to be adapted for translational research projects. Among EVs, MVs are potentially useful as liquid biopsy for diagnosis, tumor staging and monitoring of patients with malignancies such as bladder carcinoma.

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Frank Gieseler: Expert Testimony: Unterstützung der Forschungsarbeit durch LEO Pharma; Other Financial Relationships: Reisekostenerstattung durch LEO Pharma

P386

Congenital protein C deficiency: life threatening complications due to inadequate treatment in a 14 year old girl

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Severe protein C deficiency is a strong risk factor for thromboembolic events. Absent knowledge of this condition caused major complications and lifelong sequalae for the patient.
Presentation: 14 year old girl with spontaneous deep vein thrombosis (DVT) of the right leg. Known protein C deficiency with residual activity of 7% - 23%.
Treatment with unfractionated iv heparin was initiated. Clinical deterioration occurred over 10 days (compartment syndrome; bilateral pulmonary embolism (PE)). Hemodynamically unstable patient was transferred to thoracic ICU. Systemic infection originating from the affected leg rather than PE was deemed to be the source of hemodynamic problems. The leg was amputated including the hip joint. Additional complications; extensive DVT of the contralateral leg & arterial thrombosis in the left am. Intensive care was followed by diagnosis of aggression, anxiety and depression.
Ten days after amputation pediatric hemostaseology was consulted. Family history revealed strong positivity for DVT and post thrombotic syndrome, known protein C deficiency and FV Leiden mutation in several family members.
Treatment regimen was changed to low molecular weight heparin (LMWH) and iv substitution of protein C. Since then, no consequential thromboembolic problems occurred. Subsequently iv Protein C was given as a continuous subcutaneous infusion for 5 months and LMWH was exchanged for off label use of Apixaban. We opted for Apixaban instead of vitamin K antagonists in order to avoid thromboembolic complications. Due to their short half-life Protein C & S are the first to disappear from circulation, which causes a relative overload of procoagulant factors during vitamin K introduction and every time the drugs are restarted after treatment breaks or drug intake incompliance.
After 5 months, MRI of the arm showed residual arterial vessel disease, MRI of the leg revealed complete resolution of DVT.
Treatment continues with Apixaban and acetylsalicylic acid as well as intensive physiotherapy.
Protein C substitution stopped recurrence of thromboembolic events in our patient with congenital protein C deficiency. Thrombosis in children is not common, positive family history is indicative of severe inherited thrombophilia. Underlying cause for DVT needs to be identified and treated!

Disclosure: Madlen Reschke: Other Financial Relationships: Veröffentlichung dieses Falles in einem Kasuistikbuch für die Firma Shire
Hans Jörg Hertfelder: No conflict of interest disclosed.

Posterdiskussion

Solide Tumore

P387

NTHL1 associated head-neck carcinoma mimicking fanconi anaemia

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Mutational signature analysis reveals NTHL1 deficiency to cause a multi-tumor phenotype. Biallelic germline mutations affecting *NTHL1* predispose to multiple tumors, including a predisposition to colon and breast cancer (1). The first families described with *NTHL1* mutations were of Dutch origin, all having the same truncating germline mutation (p.Gln90*) in a homozygous state (2). Eight different pathogenic germline *NTHL1* mutations have now been described, all resulting in truncation of the gene. Next to polyposis and colon cancer, breast cancer, endometrial (pre)malignancies, UCCs, brain tumors, hematologic malignancies, basal cell carcinoma, HNSCC, and cervical cancer in multiple individuals, and at least five other cancers in single individuals, including duodenal cancer have been reported. Head and neck squamous cell carcinomas (HNSCC) were described in four individuals.

We report in detail a consanguineous Turkish family, who was living in Western Austria and Southern Germany, with a novel truncating mutation (p.Trp182*), described also by Grolleman et al. (2). Four members of the family were affected. The mother was affected with endometrial carcinoma, the daughter with an unclassified brain tumor, both sons with biallelic germline mutation were diagnosed with HNSCC under thirty years with fatal outcome.

Reference:

1) Grolleman et al., 2019, Cancer Cell 35, 256-266. 2) Weren et al., Nat Genet. 2015 Jun;47(6):668-71.

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P388

Effects of a 12-week low to moderate intensity exercise intervention on physical function and quality of life in head and neck cancer survivors

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Introduction: Head and neck squamous-cell carcinoma (HNSCC) patients suffer physical and psychosocial impairments due to long-time toxicity of surgery, chemotherapy and/or radiation. During rehabilitation, exercise therapy may be a key factor as physical activity improves physical function, well-being, fatigue, and general quality of life (QoL). Common exercise interventions with HNSCC patients in aftercare used large exercise machines, that are scarcely available at patients´ home and requiring specialized training facilities. Especially patients with visible stigmata prefer training privately. This study analyzed the feasibility and effects of a home executable training program without large exercise devices considering physical and psychological impairments of HNSCC patients.

Methods: The training program consisted of mobilization, coordination, strengthening, stretching, and relaxation exercises. The group interventions lasted 50 min twice a week for 12 weeks. Primary outcome was set as completion of the 12-week intervention phase (>70%). Secondary outcomes were QoL (EORTC-QLQ-30, EORTC-HN35) and physical function (range of motion (ROM) of the shoulder joints and cervical spine, stand and reach test, short physical performance battery (SPPB), 6-minute walk test (6MWT). HNSCC patients were enrolled by their attending physician during follow-up care. Interested physically capable patients meeting the inclusion criteria (>18 years, walking without help, german-speaking) were enrolled. Statistics were done using t-tests.

Results: 12 patients were included (6m, 6f, 68 ± 9 years). 10 participants completed the training (83%). An average of 20 ± 3 training sessions were performed (attendance rate 83%, max. 24). Improvements were observed in physical function ($p = 0.009$), cognitive function ($p = 0.021$) sexual function ($p = 0.034$), and global QoL ($p = 0.077$). Shoulder and cervical spine ROM improved partially. Further, SPPB ($p = 0.022$) and 6MWT ($p = 0.012$) improved significantly.

Conclusions: Compliance of participants maintained high, once the training was started. Low to moderate intensity exercise led to significant physical, psychological, and general QoL improvements. The objective improvement in physical function is also reflected in the subjective physical perception. Further evaluation of this home based program will focus patients exercise adherence in a home setting.

Disclosure: No conflict of interest disclosed.

P389

Cyclin-dependent kinases as target structures for cancer therapy - an in vitro analysis on head and neck cancer cell lines

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Introduction: Cyclin-dependent kinases are compelling targets for pharmacological inhibition. In preclinical and early clinical studies, Cyclin-dependent kinase inhibitors (CDKI) have shown promising cytotoxic activity against different malignancies, including head and neck squamous cell carcinomas (HNSCC). By coordinating DNA damage response, these substances may be combined with cytostatic drugs to enhance cytotoxicity.

Methods: A panel of HNSCC cell lines (n=4) was treated with CDKI (Palbociclib, Abemaciclib, Dinaciclib) alone or in combination with standard chemotherapy (5-FU, Cisplatin) and radiation (5 Gy). Read out was performed using crystal violet staining as well as flow cytometric apoptosis/necrosis discrimination. The impact on immunogenic cell death (ICD) was studied using surface-exposed Calreticulin. Finally, an allogeneic co-culture system with peripheral blood leukocytes (PBL) was used to assess the impact on tumor immunogenicity by CDKI pre-treatment.

Results: Dinaciclib, a potent multi-CDKI, displayed promising anti-neoplastic activity as single agent and enhanced radiosensitivity. Antitumoral mechanisms could be traced back to inhibition of CDK 4, 6, 7, and 9, being detectable after low-dose treatment for 24 hours (50 nM). While numbers of early and late apoptotic cells increased initially (24h treatment), necrosis dominated after 72h treatment. Surface bound Calreticulin increased during CDKI treatment and was even higher compared to standard 5-FU and Cisplatin therapy, both known to be potent ICD inducers. Antitumoral effects of selective CDK4/6 inhibitors Palbociclib and Abemaciclib were weaker and only detectable at higher concentrations (5 µM). Dinaciclib or Palbociclib synergistically potentiated 5-FU toxicity, however, in a cell-line specific manner. Antitumoral effects of CDKI were boosted after tumor and immune cell co-culture. Here, pre-treatment with CDKI Palbociclib significantly enhanced cytotoxic activity of PBL to effectively kill tumor targets. Simultaneous treatment of tumor cells with selected CDKI had minor impact on PBL activity in the co-culture.

Conclusion: Dinaciclib should be further investigated as a potential targeted therapeutic agent for HNSCC, individually or in combination with selected drugs. The ability of Palbociclib to increase immunogenicity of tumor cells renders this substance a particularly interesting candidate for subsequent immune-based oncological treatment regimens.

Disclosure: No conflict of interest disclosed.

P390

Immunoncology is a successful treatment option in third line therapy of head and neck tumours

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Introduction: We report on a 66- year- old male suffering from a right tonsil carcinoma, which was first diagnosed in July 2015 (pT3, pN2, M0, R0, HPV- negative, PDL- 1 positive: 44%).
Radical surgery with ND on both sides was initially conducted followed by CRTX in the following combination: Four cycles of DDP/ 5 FU were apllied simultaenously to radiotherapy ad 66 Gy until November 2015. Tumourfree observation was done until November 2017. Extended local recurrence and skin infiltration was observed in December 2017. A second line chemotherapy with Taxol/ Carboplat was planned followed by radical surgery after expected tumour- regression by CTX. After four cycles stable disease was detected and the patient refused the planned surgery.
Treatment: Immunoncology was proven to be effective also in head and neck tumours, therefore a third line therapy was initiated in February 2018 and the patient recieved weight adapted Nivolumab every two weeks on an out patient basis at the time of this report. Clinical, imaged and endoscopoly evaluation was done every two months.
Results: a PR after four cycles and a CR after eight cycles were observed. Immunoncology therapy has continued until now (May 2019) without any side effects and CR was sustained. Therefore the therapy will continue.
Conclusions: Immunoncology is a well - proven therapy in many tumours entities. It is becoming a leading method of treatment and also in head and neck tumours could be a more successful option on ist own or in combination with other treatment in the future. Further studies are necessary.

Disclosure: No conflict of interest disclosed.

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Patients with metastatic colorectal cancer receiving third-line treatment - real-life data from the clinical tumor registry colorectal cancer (TKK)

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Introduction: There is no established standard of care for 3rd-line therapy of metastatic colorectal cancer (mCRC) and few data are available on higher-line treatments used outside of clinical trials. We have previously shown that about 40% of patients (pts) with mCRC receive at least three lines of treatment. Thus, here we investigated characteristics, treatment and outcome of mCRC pts receiving current 3rd-line therapy in daily routine in Germany.
Methods: Since 2006, the Tumor Registry Colorectal Cancer (TKK) prospectively documents routine treatment of pts with CRC by medical oncologists. Pts are treated according to physician's choice. Data on all systemic treatments, pts and tumor characteristics, outcome and quality of life are collected. By March 2018, 170 sites had recruited 6525 pts with CRC, of whom 4409 had mCRC. Here, we focus on pts, who started their 3rd-line therapy between 08/16 - 03/18 (n=202).
Results: Median age at start of 1st-line was 66 years, 68 years at start of 3rd-line. Potentially prognostic factors at start of 1st-line were more favorable in pts receiving 3rd-line treatment compared to the overall 1st-line cohort: Charlson Comorbidity Index (CCI) of ≥1 17%/ 22%, ECOG = 0 54%/ 46%, right-sided primary 22%/ 26%. Overall, 41% of 3rd-line pts had a RAS wild-type tumor, 48% a RAS mutation. Most frequently applied 1st - 2nd-line sequences were chemotherapy with VEGF or EGFR-antibody in both lines (68%), 25% of pts had received combined chemo-antibody-therapy in one of the two lines and 7% of pts chemotherapy only. In 3rd-line Lonsurf (LON) was the most frequently applied regimen (16%), more often used in pts with RAS mutation (23%) than with wild-type tumor (11%). Other frequently applied 3rd-line regimes were FOLFOX+BEV (10%), FOLFIRI+BEV (9%), FOLFIRI+AFL (8%), and FOLFIRI+CET or FOLFOX (each 5%). Median Progression-free- and overall survival from 3rd-line were 4.4 and 9.4 months, respectively (confidence interval 3.3 - 5.2/ 7.0 - 11.1).
Conclusions: At least a third of pts with mCRC reach 3rd-line therapy receiving a broad variety of individualized treatment regimes. Pts with good performance status and without comorbidities at diagnosis of mCRC seem more likely to reach 3rd-line therapy. While evidence on optimal sequential treatment from clinical trials is still missing, data from the TKK could provide valuable information on decision making and outcome.

Disclosure: Steffen Dörfel: Stock Ownership: Inhaber von iOMEDICO Aktien
Norbert Marschner: Employment or Leadership Position: iOMEDICO; Advisory Role: Roche GmbH; Stock Ownership: iOMEDICO; Expert Testimony: Roche GmbH

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CRP and weight loss are independent prognostic variables in patients with newly diagnosed advanced colorectal cancer - a retrospective analysis

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Introduction: Weight loss (WL) in cancer patients is associated with poor prognosis, often accompanied by systemic inflammation, represented by increased C-reactive-protein (iCRP) levels. Aim was to investigate, whether patients with newly diagnosed colorectal cancer (CRC) lose weight and to detect risk factors (RF) for WL and overall survival (OS).
Methods: Retrospective data analysis. Weight was documented in the chemotherapy-subscription-program. A WL of ≥5% compared to the first entry was considered as clinically significant WL. Multivariate Cox regression analysis was performed to identify statistically significant RF for WL and OS.
Results: 232 patients with advanced CRC (median age 71.0 years [interquartile range (IQR) 61.3-77.0 years]), 57.8% male, 42.2% female, treated between Nov 08 and Sep 16 at 2 different departments were analyzed. Within 12 months, the cumulative probability of WL ≥5% was 41.6% (95% confidence interval [CI] 34.1-49.1), within 48 months 62.3% (95%CI 51.5-73.1). RF for WL were iCRP (hazard ratio (HR] 3.45, 95% CI 2.24-5.29, p=0.000), but not age, sex, BMI, right-sided-tumor, use of cetuximab. Median OS was 24.2 months (IQR 9.8-37.1 months), 101 patients (43.5%) died, 53 (22.8%) within the first year. RF for OS were iCRP (HR 1.69, 95%CI 1.07-2.66, p=0.025) and use of cetuximab (HR 1.72, 95%CI 1.07-2.79, p=0.026), but not WL, age, sex, BMI and right-sided-tumor. A combination of WL and iCRP seem to represent a high risk population with regard to survival, however, this difference was not statistically significant.
Conclusions: WL is common in advanced CRC patients but had no impact on survival in our patient population. iCRP, probably descriptive for systemic inflammation, is a RF for WL. iCRP and use of cetuximab were RF for reduced OS.

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Felix Keil: Financing of Scientific Research: Merck, AbbVie, Takeda, Novartis, Daiichi Sankyo, Bionorica, Celgene, Jannsen, Pfizer, Roche; Expert Testimony: AbbVie, Bionorica, Jannsen, Takeda, Merck

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S. pyogenes ADI for arginine-auxotrophic patient-derived glioblastoma cell lines

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Introduction: Arginine auxotrophy constitutes a metabolic defect that renders tumor cells vulnerable towards arginine-depleting substances, such as bacterial arginine deiminase (ADI). In our previous studies, ADI-susceptibility was confirmed on patient-derived glioblastoma multiforme (GBM) models in vitro and in vivo. Functionally, effects were attributable to induction of autophagy, senescence and necrosis. To refine this approach, we here examined the expression profiles upon ADI treatment on a transcriptome level and addressed the question of whether sensitivity is preserved in 3D-culture models.
Methods: A panel of low passaged patient-derived GBM cell lines (n=5) with different molecular characteristics were cultured in 2D and 3D (=neurospheres and Glioma stem cell populations; GSC). Impact of S. pyogenes ADI on proliferation and viability was examined (35 mU/ml) after sphere formation in 3D. Read out was performed using 3D-Glo-viability assays. Underlying molecular alterations were identified by taking advantage of the Clariom™ S Assay on one selected cell line. Gene expression changes were quantified upon 24 and 72 hours ADI exposure, respectively.
Results: Arg-depletion altered gene expression profiles. Generally, genes mediating cellular plasticity and neuronal differentiation, such as GPM6A, EPHA4, and TCF4 were highly upregulated. Plasminogen activator inhibitor SERPINB2; TRIB3, known to activate AKT signaling as well as the oxidoreductase Sestrin 2 were down-regulated. Other differentially expressed genes primarily function in stress response and chemotaxis. By transferring the therapeutic approach to the 3D-culture system, cytotoxic effects were partially preserved. Of note, morphology of GSC was considerably impaired upon Arginine-depletion, finally contributing to significantly reduced viability in all tested cell lines. However, viability of GBM neurospheres was not affected by ADI, suggesting activation of mechanisms that abrogate ADI-susceptibility only in the neurospheres.
Conclusion: Our results provide additional evidence for evaluating this approach clinically in treatment of Arginine-auxotrophic GBM. ADI alters gene expression profiles to generate potential novel targets for combined approaches. The successful eradication of cells with stem-like characteristics may even allow incorporation of this concept in combination therapies.

Disclosure: No conflict of interest disclosed.

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Metastatic brain colonization, a major determinant of survival, is supported by LEF1-regulated glutathione metabolism in breast cancer

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Introduction: Brain metastases are a major determinant of outcome in patients with breast cancer. However, how disseminated cancer cells colonize the brain parenchyma is still unknown. Recently it was discovered that metastases infiltrate the adjacent brain, causing neurosurgeons to change clinical practice. We hypothesized that invasion mechanisms activated in primary tumors are re-activated during infiltration of the brain parenchyma.
Results: LEF1, an epithelial-mesenchymal transition (EMT) transcription factor, is overexpressed in brain-seeking breast cancer cells. Therefore, we investigated whether LEF1 improves colonization of breast cancer cells by inducing EMT at the infiltration front. In an in vivo breast cancer brain colonization model LEF1 shortened survival, however without engaging EMT. We rather observed up-regulation of E-cadherin at the metastatic infiltration front. By differential proteome analysis of moderately and highly metastatic, LEF1 overexpressing cancer cells, we identified LEF1 as a regulator of the glutathione (GSH) system, the principal cellular redox buffer. LEF1 also conferred resistance against therapeutic GSH-depletion.
Conclusions: We conclude that LEF1-upregulation facilitates brain colonization by improving the anti-oxidative capacity of breast cancer cells during colonization of the brain.

Disclosure: No conflict of interest disclosed.

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Primary results from SAUL, a prospective multinational single-arm study of Atezolizumab (atezo) for locally advanced or metastatic urothelial carcinoma (UC) or non-UC of the urinary tract

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Background: Atezo, a monoclonal antibody that targets PD-L1, is an approved therapy for locally advanced/metastatic UC based on results of phase II and III clinical trials. SAUL (NCT02928406) evaluated safety and efficacy of atezo in a broader patient (pt) population, including pts ineligible for the IMvigor211 phase III trial.
Methods: Pts with locally advanced ($T4bN_{any}$ or $T_{any}N2$-3) or metastatic (M1) UC or non-UC of the urinary tract received atezo 1200 mg every 3 weeks until disease progression or unacceptable toxicity. IMvigor211-like pts and pts with renal impairment, ECOG PS 2, treated asymptomatic CNS metastases or stable controlled autoimmune disease were eligible. The protocol was approved by Institutional Review Boards/Ethics Committees. The primary endpoint was safety; efficacy endpoints included overall survival (OS), progression-free survival (PFS), overall response rate (ORR) and duration of response (DoR).
Results: Between Nov 2016 and Mar 2018, 1004 pts were enrolled; 997 received atezo. Median age was 68 years, 10% had ECOG PS 2, 5% had

non-UC histology, 77% were male and 98% were platinum pretreated ([neo]adjuvant or advanced setting). Immune cell PD-L1 status (VENTANA SP142) was low (IC0/1) in 66% and high (IC2/3) in 27% (unknown in 7%). By 16 Sep 2018, median duration of follow-up was 12.7 mo. Median number of atezo cycles was 5 (range 1-28); 220 pts (22%) remained on atezo and 555 (55%) had died. Treatment-related grade (G) ≥3 adverse events (AEs) occurred in 13%, most commonly fatigue, asthenia, colitis and hypertension (each in 1%). Median OS was 8.7 (95% CI 7.8-9.9) mo, 6-mo OS rate 60% (95% CI 57-63%), median PFS 2.2 (95% CI 2.1-2.4) mo and ORR 13% (95% CI 11-16%), including complete responses in 3%. Median DoR is immature (95% CI 13.2 mo-not estimable). In the IMvigor211-like subgroup (ie excluding pts with ECOG PS 2 and other IMvigor211 exclusion criteria), median OS was 10.0 (95% CI 8.8-11.9) mo, 6-mo OS rate 65% (61-69%), median PFS 2.3 (2.2-2.6) mo and ORR 14% (11-17%).

Conclusions: SAUL confirms the tolerability of atezo in a 'real-world' UC and non-UC population. Efficacy in both the IMvigor211-like subgroup and the broader unselected population is consistent with previous anti-PD-L1/PD-1 pivotal UC trials. These results support use of atezo in UC or non-UC, including pts with limited available treatment options.

References: Merseburger et al. EAU 2019

Disclosure: Margitta Retz: Advisory Role: Astellas, Bayer, Bristol Myers Squibb, GSK, Ipsen, Janssen Cilag, Merck, MSD, Pfizer, Pierre Fabre, Roche, Sanofi Aventis, Takeda, Teva; Financing of Scientific Research: Astellas, Bayer, Bristol Myers Squibb, GSK, Ipsen, Janssen Cilag, Merck, MSD, Pfizer, Pierre Fabre, Roche, Sanofi Aventis, Takeda, Teva
Cora N. Sternberg: Advisory Role: AstraZeneca; Bayer; Bristol-Myers Squibb; Clovis Oncology; Eisai; Incyte; Ipsen; MSD; Novartis; Pfizer; Roche; Sanofi; Financing of Scientific Research: Astellas Pharma; AstraZeneca; Ipsen; Janssen; Pfizer; Sanofi; Expert Testimony: Aragon Pharmaceuticals; Array BioPharma; AstraZeneca; Aveo; Bayer; Boehringer Ingelheim; Bristol-Myers Squibb; Clovis Atlas; Clovis Oncology; Eisai; Exelixis; Genentech; Genzyme; GlaxoSmithKline; Incyte; Janssen; Lilly; Medivation; Merck; Millennium; Myovant Sciences; Nektar; Pfizer; Roche/Genentech; Sanofi

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A phase 3, randomized, open-label, multicenter, global study of Durvalumab and bacillus calmette-Guérin (BCG) vs BCG alone in high-risk, BCG-naïve non-muscle-invasive bladder cancer (NMIBC) patients (POTOMAC)

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Background: Standard of care (SoC) for high-risk NMIBC patients is transurethral resection of the bladder tumor followed by BCG. Although several randomized clinical studies have demonstrated the efficacy of BCG in NMIBC, recurrence rates are as high as 50% in the first 3 yrs of follow up and can be even higher for aggressive histologic subtypes. Immunotherapy agents active in the programmed cell death (PD) pathway responsible for suppressing anti-tumor immunity present an emerging treatment opportunity. In trials treating patients with metastatic urothelial cancer who progressed after platinum-based chemotherapy, response rates doubling those with traditional chemotherapy have been reported for immunotherapies targeting programmed cell death-1 (PD-1) and programmed cell death ligand-1 (PD-L1). Durvalumab is a selective, high affinity, engineered human IgG1 mAb that blocks PD-L1 binding to PD-1 and CD80 with a manageable safety and tolerability profile. PD-L1 inhibition with durvalumab in combination with other immunotherapies, including SoC BCG, may improve response rate and duration of tumor response.

Methods: POTOMAC (NCT03528694) is an open-label, multicenter, global Phase 3 trial enrolling approximately 1300 patients ≥18 yrs with histologically confirmed high-risk NMIBC who have undergone complete resection of papillary tumors (patients with residual carcinoma in situ [CIS] are eligible) and are BCG-naïve. Of those, approximately 975 patients will be randomized (1:1:1) to durvalumab (1500 mg every 4 wks for 13 cycles) + BCG induction (6x every 1 wk instillation) and 2 yrs of maintenance (3 doses x every 1 wk at 3, 6, 12, 18, and 24 months), durvalumab + BCG (induction only) or BCG (induction and 2 yrs of maintenance). Randomization will be stratified by high-risk papillary disease (Y/N) and CIS (Y/N). The primary endpoint is disease-free survival. Secondary endpoints include proportion of patients alive and disease free at 24 months, overall survival at 5 yrs, pharmacokinetics, immunogenicity, safety and tolerability, and HRQoL.

Disclosure: No conflict of interest disclosed.

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The derivatives of marine alkaloid Ascididemine exhibit anticancer effect in Urothelial carcinoma cells alone and in combination with the established drugs

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Introduction: The natural marine compound Ascididemine was isolated from the ascidiae Didemnum sp. Several derivates of the marine compound were synthesized in order to improve efficacy and selectivity of the mother substance. Throughout our testing we found two derivates to be most effective in cancer cells in vitro. The purpose of the current study is to investigate the anticancer effects and the mechanism of action of the marine substances in p53-wild type and p53-deficient human urothelial carcinoma cell lines.

Methods: The inhibition of cell viability was measured by MTT, effects of combinational assays by Chou-Talay method. Induction of apoptosis was examined by FACS analysis, the cell cycle distribution was analyzed by flow cytometry using PI staining. Protein regulation was determined by Western-Blot.

Results: The two investigated Ascididemine derivatives (UKE-1 and UKE-2) were found to be highly active in RT112 and T24 urothelial carcinoma cell lines *in vitro,* independent of their p53-status in low micromolar and nanomolar concentrations, while the standard chemotherapy cisplatin had an IC_{50} of ~20μM. Both compounds revealed anti-proliferative effects and induced G1 arrest in urothelial carcinoma cells. Synergistic effects were observed in combination with Cisplatin. Most interestingly, strong synergism was observed using the combination of UKE-1/2 with PARP-inhibitor olaparib in BRCA1-deficient and non-deficient cells. UKE-1 induced apoptosis, executed via consecutive caspase-9 and caspase-3 activation, PARP cleavage and phosphatidylserine externalization, ultimately resulting in DNA fragmentation and cancer cell death. In contrast, cells treated with UKE-2 exhibited signs of caspase-independent apoptosis.
Additionally, the PI3K/AKT-pathway, which is involved in bladder cancer cell growth, migration and invasion, was inhibited by UKE-1. Both compounds induced activation of pro-apoptotic JNK1/2 kinase.

Conclusions: Two novel derivatives of the marine alkaloid ascididemine exhibited potent and promising in vitro anticancer activity alone and in combination with cisplatin or olaparib in urothelial carcinoma. Currently, experiments further elucidating the mechanism of action with a focus on DNA repair are ongoing.

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Long-term outcomes in elderly patients (pts) from IMvigor210: Atezolizumab (atezo) in metastatic urothelial cancer (mUC)

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Background: Cisplatin-based chemotherapy is currently the standard 1L treatment for mUC, but many pts are ineligible and progression is common. Atezo (anti-PD-L1) is approved for certain types of mUC, and long-term efficacy and safety have been shown (Balar, ASCO 2018). Elderly pts in particular tend to have poor outcomes and may be chemotherapy intolerant, so this analysis sought to evaluate clinical outcomes in pts aged ≥ 65 and ≥ 75 y from the Phase II IMvigor210 study.

Methods: This 2-cohort, single-arm study enrolled pts ineligible for 1L cisplatin (Cohort 1; Balar Lancet 2017; NCT02951767) and previously platinum-treated pts (Cohort 2; Rosenberg Lancet 2016; NCT02108652). Atezo 1200 mg IV q3w was given until PD (Cohort 1) or loss of clinical benefit (Cohort 2). RECIST v1.1 ORR (independent review; primary endpoint) and DOR and OS (secondary) were evaluated in pts subgroups based on PD-L1 status and age.

Results: Evaluable pts as of July 12, 2018, are shown in the Table. In Cohort 1 pts ≥ 75 y, ORR was 29% overall, CR rate was 8%, DOR was NE and median OS was 21.4 mo. In Cohort 2 pts ≥ 75 y, ORR was 23%, CR rate was 7%, mDOR was 20.9 mo and mOS was 9.2 mo. Updated safety analyses in elderly pts will be presented.

Conclusions: Efficacy outcomes in IMvigor210 elderly pts with mUC, and PD-L1 subgroup analysis appear generally consistent with those in the overall population in this long-term analysis.

References: Balar AV et al. ASCO-GU 2019

Disclosure: Gunhild v. Amsberg: Advisory Role: Roche, BMS, Astellas, Sanofi, MSD; Financing of Scientific Research: Roche, BMS, Sanofi, Astellas, Ipsen, EISAI, Pierre Fabre, MSD und Astra Zeneca; Expert Testimony: Roche, BMS, MSD, Astra Zeneca, Sanofi, Bayer (Durchführung klinischer Studien)
Jonathan E. Rosenberg: Advisory Role: Lilly, Merck, Agensys, Roche/Genentech, Sanofi, AstraZeneca/MedImmune, Bristol-Myers Squibb, EMD Serono, Seattle Genetics, Bayer, Inovio Pharmaceuticals, BioClin Therapeutics, QED Therapeutics, Adicet Bio, Sensei Biotherapeutics, Fortress Biotech, Pharmacyclics, western oncolytics; Stock Ownership: Merck, Illumina; Honoraria: Predictor of platinum sensitivity; Financing of Scientific Research: UpToDate, Bristol-Myers Squibb, AstraZeneca, Medscape, Vindico, Peerview, Chugai Pharma; Expert Testimony: Genentech, Oncogenex, Agensys, Mirati Therapeutics, Novartis, Viralytics, Genentech/Roche, Incyte, Seattle Genetics, Bayer, AstraZeneca; Other Financial Relationships: Genentech/Roche, Bristol-Myers Squibb (Travel, Accommodations, Expenses)

Tab. 1. ORR and median OS in elderly patients

		Cohort 1[a]				Cohort 2[b]			
Age, y (n[c])		< 65 (20)	≥ 65 (90)	< 75 (70)	< 65 (127)	< 65 (127)	≥ 65 (183)	< 75 (253)	≥ 75 (57)
ORR (95% CI), %	ITT	25 (9, 49)	23 (15, 33)	20 (11, 31)	29 (17, 43)	14 (9, 21)	18 (13, 24)	15 (11, 20)	23 (13, 36)
	IC2/3	17 (0, 64)	31 (14, 52)	18 (5, 40)	50 (19, 81)	24 (12, 40)	29 (18, 42)	27 (17, 37)	29 (10, 56)
	IC0/1	29 (8, 58)	21 (12, 32)	21 (10, 35)	23 (11, 39)	9 (4, 18)	13 (8, 20)	9 (5, 15)	20 (9, 36)
Median OS (95% CI), mo	ITT	18.7 (6.1, NE)	15.9 (9.8, 25.2)	16.3 (8.1, 24.5)	21.4 (9.2, NE)	8.8 (6.5, 10.9)	7.6 (6.0, 9.5)	7.6 (6.4, 9.3)	9.2 (5.7, 13.3)
	IC2/3	9.1 (5.4, 16.7)	13.4 (6.3, NE)	12.3 (5.4, 24.9)	NE (3.1, NE)	17.1 (9.4, NE)	11.4 (5.8, 17.9)	12.8 (9.0, 17.9)	11.9 (2.1, NE)
	IC0/1	22.4 (13.3, NE)	16.2 (9.2, 25.8)	19.1 (7.7, 33.6)	21.4 (9.2, NE)	6.1 (3.9, 9.0)	7.1 (5.7, 8.3)	6.4 (4.6, 8.0)	8.3 (5.4, 12.8)

PD-L1 status on immune cells per VENTANA SP142 IHC assay. [a] ITT, N = 119; IC2/3, n = 32; IC0/1, n = 87; mFU, 29.3 mo. [b] ITT, N = 310; IC2/3, n = 100; IC0/1, n = 210; mFU, 32.9 mo. [c] Based on ITT populations.

Posterdiskussion

Lunge (inkl. Pleura)

P399

Patients with metastatic non-small cell lung carcinoma and targetable oncogenic molecular alterations in Germany. Treatment and first outcome data from the prospective German registry CRISP (AIO-TRK-0315)

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Background: Guidelines for metastatic non-small cell lung cancer recommend stratified treatment by biomarker test results. We used CRISP to evaluate treatment and outcome of patients (pts) with targetable molecular alterations.
Methods: Currently 163 sites in Germany have recruited >3700 pts at start of 1st-line who will be followed until death or end of project. Data from 2204 pts recruited by 133 sites from 12/2015 to 06/2018 was analyzed for molecular testing, treatment and outcome. Progression-free survival (PFS) was determined in pts observed ≥1 year (recruited < 06/2017 (n=906), outcome sample (ous)).
Results: 94%/65% of 1732/472 pts with non-squamous/squamous tumors were tested for any type of biomarker. In 2018 test rate was 96%/75% and 49%/33% were tested for all four biomarkers (EGFR, ALK, ROS1, BRAF) with approved targeted therapies (aTT). An alteration in EGFR, ALK, ROS1 or BRAF was detected in 9%, 3%, 2%, and 2% of pts, respectively. Details on the type of alteration will be presented.
Of pts with druggable EGFR mutation (EGFR+ pts, n=149) 78% received EGFR-aTT in 1st-line. In 2nd-line, 20% received EGFR-aTT, 15% a different treatment, 11% died prior to 2nd-line, remaining pts were still in 1st-line. Median PFS of EGFR+ pts was 7.1 months (n = 67, 61% events, 95%-CI 5.2-10.1 months), in total 46% (n=31) of pts had died (ous).
Of pts with druggable ALK alteration (n=55), 47% received ALK-aTT in 1st-line. In 2nd-line, 22% received ALK-aTT, 11% a different treatment, 13% died prior to 2nd-line, remaining pts were still in 1st-line. In the ous (n=29), 55% (n=16) of tumors had already progressed after 1st-line, in total 24% (n=7) of pts had died.
All 6 pts with druggable ROS1 alteration received chemotherapy as 1st-line, while 6 of the 9 pts with druggable BRAF mutation and start of treatment in 2017/18 received a BRAF-ATT in 1st-line.
Conclusions: CRISP presents current real life data from Germany. Pts are frequently tested for molecular alterations. While EGFR-aTT is well established as 1st-line treatment and first data are promising for BRAF-aTT, pts with ALK/ROS alteration do not seem to be routinely treated with 1st-line aTT, reasons are as of yet unclear and will be further evaluated. Outcome of pts will be further analyzed after longer follow-up.

Disclosure: Frank Griesinger: Advisory Role: Ariad, Astra-Zeneca, Boehringer-Ingelheim, Bristol-Myer-Squibb, Celgene, Clovis, Lilly, Merck-Sharp-Dome, Novartis, Pfizer, Roche; Financing of Scientific Research: Ariad, Astra-Zeneca, Boehringer-Ingelheim, Bristol-Myer-Squibb, Celgene, Clovis, Lilly, Merck-Sharp-Dome, Novartis, Pfizer, Roche; Expert Testimony: Astra-Zeneca, Boehringer-Ingelheim, Bristol-Myer-Squibb, Celgene, Lilly, Merck-Sharp-Dome, Novartis, Pfizer, Roche
Michael Thomas: Advisory Role: MSB, BMS, Lilly, Astrazeneca, Roche, Pfizer, Celgene, Novartis; Financing of Scientific Research: MSB, BMS, Lilly, Astrazeneca, Roche, Pfizer, Celgene, Novartis

P400

PD-L1 expression and immune infiltration throughout different tumor stages in adenocarcinomas of the lung.

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Introduction: Immune oncological therapies are offering an alternative treatment approach for driver mutation negative lung cancer. High tumor PD-L1 expression has been verified as a predictive marker for PD1/PD-L1 checkpoint inhibition in Stage IV NSCLC. Recently Pembrolizumab received an expanded FDA approval for stage III disease. As earlier stages increasingly gain attention, it will become important to verify PD-L1 expression status of stages earlier than IV.
Methods: We collected tumor resections from 157 patients with lung adenocarcinomas that were primarily diagnosed between 2013 and 2015 at our institution. We retrospectively analyzed PD-L1 tumor cell (TC) and immune cell (IC) scores (0%, ≥ 1-25%, ≥ 25-50%, ≥ 50%) with two different antibodies (SP142 and SP263, Ventana, Roche Diagnostics) and correlated these data with the UICC tumor stage and comprehensive next-generation sequencing (NGS) data.
Results: Of the 157 cases 148 samples gave rise to sufficient material for PD-L1 evaluation on tumor cells and tumor-infiltrating lymphocytes (TIL). Of those, 93 samples were staged UICC I, 12 patients were stage II, 26 patients stage III and 17 patients stage IV. We observed significantly lower staining intensity with the SP142 AB clone compared to SP263, for both tumor PD-L1 and TIL PD-L1. Importantly, we did not detect any significant association of PD-L1 TC/IC scores with UICC tumor stage. PD-L1 expression was distributed evenly throughout tumor stages. We will show correlation of TC/IC scores and NGS data.
Conclusions: Evaluating TC and IC scores, the used antibody clone needs to be considered, as staining intensity may differ significantly. PD-L1 tumor expression appears independent of tumor stage, arguing for a biological basis for immune oncological treatment of earlier stage disease.

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P401

Tumor mutation burden in non-small cell lung cancer: real world data from the routine lab

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Introduction: Recently immune oncologic (IO) checkpoint inhibition has become standard of care for NSCLC patients either in first line or beyond for driver negative tumors. Until now, PD-L1 tumor expression confers the only approved predictive biomarker for PD-L1/PD-1 checkpoint inhibition. However PD-L1 negative tumors might also respond to IO, limiting the diagnostic value of PD-L1. Additive IO-predictive biomarkers are needed and tumor mutational burden (TMB) has emerged as a potential candidate. TMB is the most complex biomarker so far and

imposes significant challenges to diagnostic institutions. We provide real world data on 115 routinely tested NSCLC samples.
Methods: We retrospectively collected mutational data of 115 lung cancer tissue biopsies that were routinely diagnosed between May 2018 and January 2019 at our institution. TMB estimation within a genomic territory of 1.14 MB and driver mutation analysis was performed using NEOplus v2 RUO (New Oncology GmbH, Cologne). Turnaround time (TAT) for different sections of the workflow was documented for each patient. PD-L1 status was assessed using AB clone 22C3 on the automated BenchMark Ultra platform (Roche Diagnostics).
Results: The study cohort (n=115) comprised 43% (49/115) female and 57% (66/115) male patients, with a mean age of 65 years at time of diagnosis. Histological classification revealed 74% (85/115) adeno-ca, 9% (11/115) squamous cell-ca, 1% (1/115) SCLC, 14% (16/115) large cell and 14% (16/115) NSCLC NOS. In 82% (94/115) of cases, TAT of 10 working days or less was achieved. Underlying causes for longer TAT were delays in reporting (33%, 7/22), workflow delay (38%, 8/22), other technical issues (19%, 4/22) or delays in data transfer (10%, 2/22). The presence of targetable driver alterations or KRAS mutation was not significantly associated with lower TMB (10.22 w/driver vs. 13.32 for wt, p=1; KRAS-mut p=0.1497). Presence of TP53 mutations however were significantly associated with TMB >10Mut/MB (p=0.00001). PD-L1 tumor expression appeared independent of TMB.
Conclusions: TMB value was independent of PD-L1 tumor cell expression, reiterating the concept of two independent, additive biomarkers. TP53 mutation status strongly correlates with high TMB and might serve as a surrogate marker in the future.

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Markus Tiemann: Employment or Leadership Position: CEO Institut für Hämatopathologie Hamburg; Advisory Role: Novartis, Boehringer Ingelheim, Roche, Astra Zeneca, MSD, BMS; Financing of Scientific Research: Novartis, Boehringer Ingelheim, Roche, Astra Zeneca, MSD, BMS

P402

Real-world management after failure of first and second generation EGFR inhibitors for NSCLC

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Background: Osimertinib is the preferable therapeutic option for many epidermal growth factor receptor (EGFR)-positive non-small cell lung cancer (NSCLC) patients failing other tyrosine kinase inhibitors (TKI), but implementation of EGFR TKI sequencing is often problematic.
Methods: We retrospectively studied the clinical course of EGFR$^+$ NSCLC patients that received first-/second-generation TKI at our institutions and had their last follow-up after osimertinib approval (02/2016).
Results: A total of n=283 EGFR$^+$ NSCLC patients received erlotinib (45%), gefitinib (19%) and/or afatinib (36%) in the 1st-4th treatment lines with a median age of 66 years, a median ECOG performance status of 0 (137/266 patients with available data) and a predominance of female (183/283=65%) never-/light-smokers (177/283=63%). Median overall survival (OS) from treatment start was 32.7 months (95% confidence interval [CI] 28.1 - 37.3) with 2.2 treatment lines on average (standard deviation 1.4). EGFR T790M testing was performed for 139/203 (68%) patients after TKI failure, with a positive result in 77/139 (55%) and subsequent treatment with osimertinib in 50/77 (65%). Overall, 50/203 (25%) of patients received osimertinib, with a median OS of 44.9 (27.9 - 62.1) months, significantly longer than the 30.4 (20.6 - 40.3) months for patients with alternative or no subsequent therapies (logrank p=0.053, Breslow p=0.002). Among the 134 deceased patients with complete follow-up, 84 (63%) received additional systemic treatment (37% chemotherapy, 16% osimertinib, 8% only alternative EGFR inhibitors, 2% only immunotherapy), while 50/134 (37%) died without next-line therapy. For patients that subsequently received chemotherapy, median time to start of chemotherapy was 11.6 (8.9 - 14.3) months.
Conclusions: Sequential treatment with osimertinib after first- or second-generation EGFR inhibitors significantly prolongs OS, but in the real-world setting a considerable fraction of patients will not be able to benefit from that. Main obstacles in our cohort were lack of EGFR T790M testing (32% of total cases), T790M-negative progression (45% of tested cases), and rapid clinical deterioration without the chance of next-line therapy (about one-third of patients).

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Michael Thomas: Advisory Role: AbbVie, BMS, Boehringer, Celgene, Lilly, MSD, Novartis Roche, Takeda; Financing of Scientific Research: Lilly, MSD, Takeda, BMS, Boehringer, MSD, Novartis; Expert Testimony: AstraZeneca, BMS, Celgene, Roche

P403

External validation and longitudinal extension of the LIPI (lung immune prognostic index) for immunotherapy outcomes in advanced non-small cell lung cancer

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Introduction: The Lung Immune Prognostic Index (LIPI), consisting of an elevated derived neutrophil-lymphocyte ratio (dNLR, 1 point for dNLR > 3 units) and an elevated lactate dehydrogenase level (LDH, 1 point for LDH > upper limit of normal) has recently been proposed as a biomarker for predicting immune checkpoint inhibitor (ICI) therapy outcomes in advanced non-small cell lung cancer (NSCLC). We sought to validate the LIPI in an external cohort, and quantify the evolution of the LIPI over time during ICI therapy.
Methods: dNLR levels, LDH levels and ICI treatment outcomes including disease control rate (DCR), 1-year progression-free survival (PFS), and 1-year overall survival (OS) were ascertained from 87 patients with advanced NSCLC who were treated with ICIs at a single academic center in Austria (Table 1).
Results: DCR estimates were 59%, 43%, and 32% in patients with good (0 points, n=22), intermediate (1 point, n=40), and poor (2 points, n=25) LIPI risk (p=0.171). One-year PFS estimates were 36%, 27%, and 10% (log-rank p=0.015), and corresponding 1-year OS estimates were 53%, 52%, and 20% (log-rank p=0.003), respectively. During ICI treatment, 1,227 LIPI measurements were available. In linear mixed modeling, the LIPI remained stable over time in the 29 patients without disease progression (average change/month=0.0 points, 95%CI: -0.1-0.0, p=0.161), but increased over time in the 56 patients who developed disease progression (average change/month=0.02 points, 95%CI: 0.0-0.03, p=0.004).
Conclusions: This study externally validated an elevated LIPI as a biomarker for poor ICI treatment outcomes in patients with advanced NSCLC. The LIPI increases before disease progression.

Disclosure: No conflict of interest disclosed.

P404

An uncommon EGFR exon 25 mutation in a patient with lung adenocarcinoma successfully treated with Afatinib

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Introduction: *EGFR* mutations are found in approximately 15% of non-small cell lung cancers (NSCLC), most frequently in exons 19, 20 and 21. Treatment with tyrosine kinase inhibitors (TKI) is associated with improved response rates, prolonged overall survival and much better treatment tolerability compared with conventional chemotherapy. Exon 19 indels are associated with better responses to therapy than exon 21 mutations, while alterations in exon 18 or exon 20 are generally less sensitive to EGFR inhibitors. Afatinib is approved for first-line treatment of EGFR+ NSCLC since july 2013.

Case report: A 75-year-old male patient was admitted to our hospital in February 2018 with suspicion of pleural mesothelioma due to several pleural lesions in external CT along with calcified plaques typical for asbestosis for further workup, including biopsy. A pleural carcinomatosis was confirmed by video-assisted thoracoscopy. Histological examination, however, confirmed the presence of a lung adenocarcinoma, while staging with brain MRI and technetium bone scintigraphy did not reveal any distant metastases. Molecular workup with combined RNA- and DNA-NGS revealed a point mutation in exon 25 of *EGFR* (c.2963A>G, p.His988Arg) which had not been described in the literature before. This mutation is located beyond the tyrosine kinase domain, so that an activation of the EGFR due to its presence appeared to be unlikely. Nevertheless, since the patient presented with reduced general condition, a therapy with the second-generation EGFR inhibitor Afatinib was initiated under close clinical and radiological monitoring. The first control CT after four weeks of treatment showed considerable improvement of the pleural carcinomatosis. The therapy was therefore continued, resulting in further improvement of the patient's general condition. Further CT's were performed every 3 months with the last examination in February 2019 showing complete resolution of the pleural nodes and paratracheal lymph node metastases.

Conclusions: Besides the common activating *EGFR* mutations with confirmed TKI-sensitivity, several less frequent, atypical *EGFR* alterations can be encountered in clinical practice, for which previous experience might be lacking. For these patients, an initial trial of TKI-treatment is generally warranted, especially in the setting a reduced general condition that would render treatment with chemotherapy problematic.

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P405

Patients with metastatic non-small cell lung cancer without molecular alterations or PD-L1 expression in Germany. Treatment and first outcome from the prospective German registry platform CRISP (AIO-TRK-0315)

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Background: Guidelines for metastatic non-small cell lung cancer recommend stratified treatment by biomarker test results. We used CRISP to evaluate treatment and outcome of patients (pts) in whom neither targetable molecular alterations nor any PD-L1 expression were detected.

Methods: Currently 163 sites in Germany have recruited >3700 pts at start of 1st-line who will be followed until death or end of project. Data from 2204 pts recruited by 133 sites from 12/2015 to 06/2018 was analyzed for treatment and outcome. These pts started treatment prior approval of immune checkpoint inhibitors (ICI) for this group of pts. Progression-free survival (PFS) was determined in pts ≥1 year under observation (recruited until 06/2017 (n=906), outcome sample (ous)).

Results: 6% of pts with non-squamous (nsq) and 35% with squamous (sq) tumors received no type of biomarker testing prior to start of 1st-line, and in 49% and 36% no targetable alterations or any PD-L1 expression were detected. Thus, 55% and 71% of pts (nsq/sq) were eligible for chemotherapy (ctx) but no type of targeted therapy at start of 1st-line. Median age at start of 1st-line was 66 and 68 years (nsq/sq). 29%/23% had an ECOG=0 and 82%/90% had at least one comorbidity. 10%/6% were never-smokers. Most frequently used ctx regimens were carboplatin-based (55%) or cisplatin-based (24%), 13% received targeted therapy (e.g. ICI as clinical trial, switch to TKI but test result not yet documented).

At database cut, 33% of all pts had started 2nd-line, 24% had died prior to a 2nd-line and remaining pts were still in 1st-line. In the ous, median PFS was 5.0 months (66% events, 95%-CI 4.5-5.5 months, n=457) for nsq tumors and 4.5 months (66% events, 95%-CI 3.4-5.3 months, n=154) for sq tumors. In total 55% of pts with nsq and 53% of pts with sq tumors had died.

Conclusions: CRISP presents current real life data from Germany. Despite recent break-throughs with targeted therapies and high test rates in routine care, the majority of pts do not qualify for targeted therapy because no targetable alterations are found. First outcome results indicate that prognosis is poor in pts without targetable alterations. These data hopefully will improve in the cohort from now on treated with ctx-ICI combination.

Disclosure: Frank Griesinger: Advisory Role: Ariad, Astra-Zeneca, Boehringer-Ingelheim, Bristol-Myer-Squibb, Celgene, Clovis, Lilly, Merck-Sharp-Dome, Novartis, Pfizer, Roche; Financing of Scientific Research: Ariad, Astra-Zeneca, Boehringer-Ingelheim, Bristol-Myer-Squibb, Celgene, Clovis, Lilly, Merck-Sharp-Dome, Novartis, Pfizer, Roche; Expert Testimony: Astra-Zeneca, Boehringer-Ingelheim, Bristol-Myer-Squibb, Celgene, Lilly, Merck-Sharp-Dome, Novartis, Pfizer, Roche
Michael Thomas: Advisory Role: MSB, BMS, Lilly, Astrazeneca, Roche, Pfizer, Celgene, Novartis; Financing of Scientific Research: MSB, BMS, Lilly, Astrazeneca, Roche, Pfizer, Celgene, Novartis

P406

Long-term survival outcomes with Nivolumab (Nivo) in patients with previously treated advanced non-small cell lung cancer (NSCLC): Impact of early disease control and response

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Introduction: Historically, 5-year (y) overall survival (OS) with chemotherapy for patients with metastatic lung cancer was ~5%; with the advent of immunotherapy, this has increased to ~15%. CheckMate 017, 057, 063, and 003 are Nivo studies with extensive follow-up in patients with previously treated advanced NSCLC. Using pooled data from these studies, we evaluated the long-term benefit (up to 4 y) of Nivo and impact of early response or disease control on subsequent long-term OS.
Methods: Progression-free survival (PFS) and OS were estimated for patients with NSCLC across histologies treated with Nivo in pooled analyses of CheckMate 017, 057, 063, and 003 (n=664), and for patients randomized to Nivo (n=427) or docetaxel (Doc; n=427) in pooled analyses of CheckMate 017/057. Other analyses for CheckMate 017/057 included estimation of OS in patients alive at 6 months (mo) by response status at 6 mo, and OS in all responders (complete or partial response [CR/PR]) from time of response.
Results: In pooled analyses of the 4 studies, 4-y OS rates for Nivo in all patients and those with PD-L1 ≥1% and < 1% were 14%, 19%, and 11%, respectively. In CheckMate 017/057, the 4-y OS rate in all patients was higher with Nivo vs Doc (14% vs 5%). Patients with either CR/PR or stable disease (SD) at 6 mo had longer subsequent OS with Nivo vs Doc; for patients with progressive disease at 6 mo, 1-y OS rates were higher with Nivo vs Doc, while 2-4 y OS rates were similar (Table). For responders (CR/PR) in CheckMate 017/057, 4-y OS rate from time of response with Nivo vs Doc was 54% vs 12%; median duration of response was 24 mo vs 6 mo, respectively. Overall, the Nivo discontinuation rate due to treatment-related adverse events (AEs) was 8.7%; most common treatment-related select AEs were skin reactions (incidence rate, 38.6 per 100 person-y).
Conclusions: These large pooled analyses show patients with CR/PR or SD with Nivo at 6 mo derived marked OS benefit; this long-term benefit was improved vs patients with Doc with the same response status at 6 mo. The Nivo safety profile was consistent with prior reports.

Tab. 1.

Table. 6-Month Landmark Analysis of OS by Response Status at 6 Months in Pooled CheckMate 017/057[a]

Patients alive at month 6	Response status at 6 months, %[b]	Post-landmark 1-year OS rate, %	Post-landmark 2-year OS rate, %	Post-landmark 3-year OS rate, %	Post-landmark 4-year OS rate, %
Nivo 3 mg/kg Q2W n = 280	CR/PR, 25 SD, 24 PD, 51	81 58 40	63 35 13	61 24 8	58 19 4
Doc 75 mg/m² Q3W n = 264	CR/PR, 13 SD, 39 PD, 48	62 35 22	38 18 12	26 7 8	12 2 5

[a]The 6-month landmark timepoint was used to allow sufficient time for the majority of responses with Nivo to occur, while allowing meaningful time to assess OS post landmark: median time to response, 2.1 months; 75th quartile, 3.5 months.
[b]% of patients alive at 6 months.

Disclosure: Markus Wohlleber: Other Financial Relationships: Investigator for BMS
Scott J Antonia: Other Financial Relationships: Investigator for BMS

P407

Identifying immune infiltration pattern of PD-L1 positive and negative lung adenocarcinoma

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Introduction: Immune check-point inhibition has shown promising results in the treatment of several tumors but there is an urge to closely characterize mechanisms of tumor immune infiltration based on tumor PD-L1 expression. In this study we aim to identify specific transcriptomic patterns that correspond to the immune cell infiltration in lung adenocarcinoma taking into account tumor PD-L1 positivity as well as the total tumor immune cell infiltration, defined either by "hot" or "cold". In this manner, we aim to investigate whether tumor immune cell infiltration specificity depends on the tumor PD-L1 expression.
Methods: 142 lung adenocarcinomas were assessed for the PD-L1 expression by the means of IHC and divided into "PD-L1 positive" and "PD-L1 negative" groups. When assessing tumor PD-L1 positivity, we set a high threshold (>50%) in order to minimize the effect of PD-L1 expression heterogeneity. Lung adenocarcinoma cases were further classified according to the total immune cell infiltration into the two groups assessed by pathological microscopy. Tumors with high total tumor immune cell infiltration were characterized as the "hot tumors" while the tumors with low or absent total tumor immune cell infiltration as the "cold tumors". In this way, we assembled four groups of cases, namely PD-L1 pos. and "hot", PD-L1 pos. and "cold", PD-L1 neg. and "hot" and PD-L1 neg. and "cold" which were analyzed for differential expression of 770 genes covering 24 different immune cells by the NanoString nCounter PanCancer Immune Profiling Panel analysis.
Results: We first assessed the distribution of "hot" and "cold" lung adenocarcinoma in PD-L1 positive and PD-L1 negative cases. As shown in Figure 1, PD-L1 positive tumors were significantly more infiltrated than PD-L1 negative counterparts. Furthermore, PD-L1 positive tumors attract more cytotoxic CD8+ immune cells than their PD-L1 negative

counterparts but only when heavily infiltrated ("hot" tumors) (Figure 2). Next steps include transcriptomic profiling of defined groups for genes identifying a panel of infiltrated immune cells.
Conclusions: The distribution of total immunological "hotness" depends on the PD-L1 status in lung adenocarcinoma. Tumors expressing PD-L1 also attract more cytotoxic CD8+ lymphocytes than their PD-L1 negative but also heavily infiltrated counterparts. Upcoming experiments will reveal whether PD-L1 expression selects for the specific tumor infiltration pattern in lung adenocarcinoma.

Disclosure: No conflict of interest disclosed.

P408

EATON: An open-label, multicenter, phase I dose-escalation trial of nazartinib (EGF816) and trametinib in patients with EGFR-mutant non-small cell lung cancer - preliminary data on safety and tolerability

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Introduction: Multiple mechanisms of resistance to EGFR tyrosine kinase inhibitor (TKI) therapy have been described in EGFR-mutant non-small cell lung cancer (NSCLC). Besides secondary mutation in EGFR, preclinical models and clinical findings showed that co-occurring activation of the RAS/MEK pathway may result in reduced EGFR dependency and that co-inhibition of MEK resensitized cells to EGFR-targeted treatment. We thus hypothesize that the combined inhibition of EGFR and MEK may restore sensitivity to EGFR inhibition in patients with acquired resistance to EGFR TKIs and may as well prolong the acquisition of resistance in treatment-naïve patients.
Methods: EATON is an international, multicenter, phase I, dose escalation investigator-initiated trial investigating the recommended phase 2 dose (RP2D), safety and preliminary efficacy of the combination of the third-generation EGFR inhibitor EGF816 with the MEK inhibitor trametinib (NCT03516214). Eligibility criteria: Advanced NSCLC harboring EGFR del19 or p.L858R, first-line or after failure of any EGFR TKI including osimertinib, independently of p.T790M status. Patients with high-level MET amplification are excluded. Dose level escalation will be based on a modified traditional cumulative 3+3 design, i.e. "up and down" (dose level 1: 100 mg nazartinib (EGF816) QD + 1 mg trametinib QD). A total number of 24 patients is planned to be enrolled in 8 trial sites in Germany and Spain. At a first stage, 18 (6´3) patients will be treated and evaluated. Exploratory endpoints aim at the identification of potential mechanisms of resistance to the trial treatment by massively parallel sequencing (MPS), FISH, phospho-protein analyses and whole exome/genome sequencing of baseline and PD biopsy tumour tissue. Additionally blood samples for MPS of cell free DNA will be collected throughout the trial treatment.
Results: At the time of data-cut off for this abstract, one patient received treatment at dose-level 1. Treatment was withdrawn due to a serious, bacterial soft tissue infection of the hand outside the DLT period.
Conclusions: Data on safety and tolerability of the combination of nazartinib and trametinib is premature. Updated results will be presented at the conference.

Disclosure: Sebastian Michels: Financing of Scientific Research: Novartis, Roche, Boehringer Ingelheim, Pfizer; Expert Testimony: Novartis, Pfizer, Bristol-Myers Squibb
Jürgen Wolf: Financing of Scientific Research: Abbvie, AstraZeneca, BMS, Boehringer-Ingelheim, Chugai, Ignyta, Lilly, MSD, Novartis, Pfizer, Roche; Expert Testimony: Novartis, Pfizer, Bristol-Myers Squibb

P409

Pioglitazone and Clarithromycin combined with metronomic low-dose chemotherapy versus Nivolumab in patients with advanced non-small-cell lung cancer treated in 2nd-line and beyond: outcomes from a randomized phase II trial (ModuLung)

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Background: The ModuLung trial addresses the medical need for low-toxic therapies in frequently comorbid patients with relapsed or refractory non-small cell lung cancer (NSCLC). We evaluated safety and efficacy of a biomodulatory approach in >=2nd-line, aiming for induction of anakoinosis i.e. communicative reprogramming of dysregulated cellular and intercellular homeostasis.
Methods: Patients with stage IIIB/IV squamous or non-squamous NSCLC and disease progression during or after at least one platinum-based chemotherapy were stratified according to histology and randomly assigned 1:1 to treosulfan 250 mg twice daily, pioglitazone 45 mg once daily and clarithromycin 250 mg twice daily (experimental arm) or nivolumab 3 mg/kg every 2 weeks (control arm). The primary endpoint was progression-free survival (PFS).
Results: Due to the approval of checkpoint inhibitors in first-line, the study was prematurely closed after randomization of 40 of the 86 initially planned patients. The main efficacy and safety results are presented in the table and show no statistically significant difference between groups. The two-year survival rate achieved in the biomodulatory arm was 10% (95% CI, 1.2 to 31.7) and 5.9% (95% CI, 0.1 to 28.7) in the nivolumab arm. 75% and 53% of the patients proceeded to a further line of therapy, respectively.
Conclusions: Combination of clarithromycin, pioglitazone and metronomic chemotherapy is active in the >=2nd line treatment of NSCLC and warrants further investigations. Nivolumab did not induce any tumor response and was relatively toxic in this population. Novel treatment approaches are urgently needed for patients who previously received platinum-based chemotherapy for advanced squamous and non-squamous NSCLC (Funded by Anticancer Fund, EudraCT number 2014-004095-31).

Disclosure: No conflict of interest disclosed.

Tab. 1. Results

	Biomodulatory Arm (n=20) 35% > 2nd-line	Nivolumab Arm (n=17) 41.2% > 2nd-line	HR & 95% CI or p-value
PFS, median in months	1.6	2.1	HR=1.17; 95% CI, 0.59-2.34
OS, median in months	8.2	6.9	HR=0.86; 95% CI, 0.38-1.96
ORR, n (%)	2 (10%)	0 (0%)	P=0.49
Grade 3-5 AE, n (%)	2 (10%)	6 (35%)	P=0.06

P410

Genome-wide DNA methylation profiling in early stage I lung adenocarcinoma reveals predictive methylation markers for early recurrence

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Introduction: Currently, in early stage lung cancer little is known about molecular mechanism driving proneness for relapse nor are suitable prognostic biomarkers available that identify patients at high risk for recurrence. This study aimed to identify aberrant methylation markers for early recurrence with predictive value that may become important tools for the development of new treatment modalities.
Methods: Genome-wide DNA methylation profiling was performed on 30 stage I lung adenocarcinomas comparing 14 patients with early metastatic recurrence to 16 patients with a long-term relapse-free survival period using methylated-CpG-immunoprecipitation (MCIp) followed by high-throughput next generation sequencing. Differentially methylated regions (DMRs) between the two subgroups were validated in two independent cohorts using the MassCleave Assay, a high resolution quantitative methylation analysis.
Results: Unsupervised clustering of patients in the discovery cohort based on DMRs separated tumor from normal tissue and showed enrichment of the sub-cohorts in separate clusters. In two validation cohorts hypermethylation of the intergenic genomic region chr13:28393229-28491428 was significantly associated with shorter relapse free survival (RFS; $p < 0.01$) and could be shown to be an independent prognostic factor in the multivariate analysis by applying multivariate cox regression model.
Conclusion: Hypermethylation of the intergenic genomic region chr13:28393229-28491428 can identify patients with early stage I adenocarcinoma at high risk for early recurrence. DNA methylation analysis of this genomic region may be easily implemented in clinical algorithms for early identification of those patients in need of more aggressive treatment.

Disclosure: No conflict of interest disclosed.

P411

Non-small cell lung cancer (NSCLC) patients harboring mutations in FGFR2 and FGFR3: clinical and genomic features

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Background: Amplifications in *FGFR1* have been shown to be a potential target for FGFR inhibition in squamous cell carcinoma NSCLC (SqCC). Recent insights in entities such as bladder cancer demonstrate that efficacy of FGFR inhibitors is not limited to FGFR1 but affects the whole receptor family. especially aberrations in *FGFR2* and *FGFR3*. We set out this analysis to identify NSCLC patients with mutations in *FGFR2* and/or *FGFR3* and to describe clinical and genomic features.
Methods: Stage IV patients of the Network Genomic Medicine (NGM) Lung Cancer diagnosed between 2015 and 2018 underwent genomic testing using next-generation sequencing (NGS) in order to detect point mutations or deletions.
Results: Of 6000 patients analyzed, we identified 26 (0.4%) with *FGFR2* mutation and 21 (0.4%) with *FGFR3* mutation. 95% of the detected mutations have not been reported so far. Clinically, both subgroups differed from each other, most strikingly in the clinical presentation: The vast majority of *FGFR2* mutations were detected in non-SqCC (76.9%), whereas *FGFR3* mutations occurred more commonly in SqCC (57.1%). In the *FGFR2* group, more female patients were affected (57.7%), contrasting 71.4% male patients in the *FGFR3* group. *KRAS* mutations co-occurred more frequently in the *FGFR2* group (23.1% vs 9.5%) and *PIK3CA* mutations more frequently in the *FGFR3* group (19.0% vs 7.7%). For both groups, most mutations did not affect the kinase domain. Patients with *FGFR2* mutation seem to have a favorable outcome as compared to *FGFR3* patients (median overall survival not reached vs 8.0 months), but follow-up is still immature (p=0.201).
Conclusion: Patients with *FGFR2* and *FGFR3* mutations represent two vastly different subgroup of NSCLC patients. Both mutations are not limited to SqCC and seem to have different prognoses for the outcome of the patients. Further work on characterization of the different mutations is ongoing.

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Jürgen Wolf: Advisory Role: AbbVie, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Chugai Pharma, Ignyta, Eli Lilly, MSD Oncology, Novartis, Pfizer, Roche ; Financing of Scientific Research: AbbVie, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, MSD, Novartis, Roche ; Expert Testimony: Bristol-Myers Squibb, Novartis, Pfizer

P412

Comparative mutation analysis of conventional molecular testing and amplicon-based next-generation sequencing (NGS) of lung adenocarcinomas in a northern German patient collective

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Introduction: Lung cancer is the leading cause of cancer related death in the world. The success of molecularly stratified therapies in driver mutation positive patients has urged the medical need for molecular testing at primary diagnosis. NGS based assays are increasingly replacing conventional test methods in the routine diagnostic setting. Since conventional testing principally allows for detection of all companion diagnostic biomarkers in lung cancer, we pursued the question what additional therapeutically relevant information can be derived from an NGS based method.
Methods: 75 patient biopsies were routinely evaluated for genetic alterations in EGFR, ALK, ROS1 and BRAF V600E in our institution. DNA was additionally analyzed with a lab developed 17 gene amplicon based NGS panel. Data were comparatively evaluated.
Results: Using conventional diagnostics, KRAS mutations were found in 24% (18/75) of cases, EGFR mutations in 16% (12/75) and ALK translocations in 3% (2/75). The following mutations were detected with NGS: 43% (32/75) TP53, 28% (21/75) KRAS, 15% (11/75) EGFR, 12% (9/75) MET, 5% (4/75) PTEN, (3/75) 4% (3/75) BRAF non-V600E. 3% (2/75) PIK3CA, 3% (2/75) MAP2K1, 1% (1/75) FGFR2 and 1% (1/75) NRAS mutations. As part of our diagnostic panel, we also examined the genes AKT1, CTNNB1, DDR2, ERBB2, HRAS and PTPN11. Within these genes no mutations were detected. Overall, more mutations could be detected with NGS (95 NGS vs. 34 conventional). In addition, treatment relevant mutations could be detected only by NGS.
Conclusions: Regarding driver mutations KRAS and EGFR, the two methodological approaches were comparable. Generally more mutations could be detected by NGS, including 12 additional treatment-relevant genetic alterations. It is therefore justified and reasonable to use NGS in routine diagnostics to ensure optimal patient care.

Disclosure: No conflict of interest disclosed.

P413

Patients with metastatic non-small cell lung cancer and PD-L1 expression in Germany. treatment and first outcome from the prospective German registry platform CRISP (AIO-TRK-0315)

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Background: Treatment guidelines for metastatic non-small cell lung cancer recommend stratified treatment according to biomarker testing results. Here we used the prospective, national clinical research platform CRISP to evaluate treatment and outcome of patients (pts) with PD-L1-expressing tumors.
Methods: Currently 163 centers in Germany have recruited over 3700 pts at start of 1st-line who will be followed until death or end of project. Data from 2204 pts recruited by 133 centers between December 2015 and June 30th 2018 was analyzed regarding PD-L1 testing, treatment and outcome. Progression-free survival (PFS) was determined in patients being ≥1 year under observation (recruited until June 30th 2017 (n=906), outcome sample)) .
Results: Test rates for PD-L1 increased from 25% (2016) to 75% (2018) in pts with non-squamous tumors (n=1732), and from 20% (2016) to 62% (2018) in pts with squamous tumors(n=472). Of pts with test results (n=1221) PD-L1 antibodies mostly used were Ventana SP263 (19%), DAKO 28-8 or 22-C (8% each) or not known to the documenting site (56%)..PD-L1 TPS was ≥50% in 16% of pts, 1-49% in 18% of pts, and < 1% in 7% of pts, while 3%/12% of pts were classified by pathologists as PD-L1 positive/negative with TPS not specified. In 9% and 4% an EGFR or ALK alteration had also been detected, respectively.
Of all pts with PD-L1 TPS≥50% 70% received pembrolizumab-based 1st-line treatment, 21% chemotherapy and 9% another/targeted therapy. At database cut, 20% had started 2nd-line, 19% had died prior to receiving a 2nd-line and the remainder were still in 1st-line. In the outcome sample, median PFS of all pts with PD-L1 positive tumors was 4.4 months (62% events, 95%-CI 3.5-5.5 months, n=185), in pts with PD-L1 TPS≥50% (n=83) so far 53% had a progression after 1st-line. In total 49% of pts with PD-L1 positive tumors and 41% of pts with PD-L1 TPS≥50% had died (outcome sample).
Conclusions: CRISP presents current real life data from all treatment sectors in Germany. Testing for PD-L1 has been quickly integrated into routine care diagnostics. The majority of pts with PD-L1 positive tumors and a TPS≥50% receive an immune-oncology therapy. The impact of these novel targeted treatment approaches on the outcome of pts will be subject of future analyses.

Disclosure: Martin Sebastian: Advisory Role: BMS, MSD, Roche, Novartis, AstraZeneca, Boehringer, Celgene, Lilly, Pfizer; Financing of Scientific Research: BMS, MSD, Roche, Novartis, AstraZeneca, Boehringer, Celgene, Lilly, Pfizer
Michael Thomas: Advisory Role: MSB, BMS, Lilly, Astrazeneca, Roche, Pfizer, Celgene, Novartis; Financing of Scientific Research: MSB, BMS, Lilly, Astrazeneca, Roche, Pfizer, Celgene, Novartis

Posterdiskussion

Immuntherapie

P414

Leukemic progenitor and stem cells could be targeted by anti-programmed-death 1 stimulated specific T cells

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Targeted immunotherapy in cancer treatment has become more and more omportant in the past few years. The potency of immunotherapeutic approaches such as immune-checkpoint inhibitors, bi-specific T cell activating antibodies or chimeric antigen receptor T cells is becoming increasingly obvious. Leukemia-associated-antigens (LAA), such as PRAME (P300), RHAMM (R3), Wilms' Tumor 1 (WT1) and Proteinase 3, represent immunogenic structures to target malignant cells, thus LAA might be relevant for the elimination of malignant cells by cytotoxic T cells (CTL). At the same time, mechanisms of immune responses involved and responsible antigen structures have to be further elucidated.

Here, we investigated the influence of the anti-programmed-death 1 antibody (anti-PD-1) Nivolumab and anti-cytotoxic T-lymphocyte-associated protein 4 antibody (anti-CTLA-4) Ipilimumab on the antigen-specific immune responses by CTL against leukemic myeloid progenitor and stem cells (LPC/LSC) in functional T cell assays using ELISpot, Tetramer-analysis and Colony Forming Immunoassays (CFI). Expression of different LAA was correlated to functional T cell assays.

CFI showed a significant inhibition of colony forming units in 50 AML patient samples when adding LAA-specific CTL. In all patient samples, T cells activated against at least one LAA were successful to decrease the colony number significantly. The intensity of immunogenic reactions using the LAA P300 as target ranged from 14-86% (mean: 44 %), for WT1 from 0-85% (mean: 40%), and for R3 from 0-90% (mean: 48%). Specific immune responses were detected by ELISpot assays and correlated to results detected in CFI. Immune effects increased considerably when Nivolumab was added to CTL for several days before starting CFI. Notably, no effect was measured when CTL were incubated with Ipilimumab only. The combination of Nivolumab and Ipilimumab showed no additional effect of immune responses compared to Nivolumab alone.

Taken together, the immune checkpoint inhibitor Nivolumab increases specific T cell responses of LAA-stimulated cytotoxic T cells and the cytotoxic effect of T cells against LPC/LSC. No additional effect was detected with Ipilimumab. These data suggest that anti-PD-1 antibodies could be an immunotherapeutic approach in AML and combination with LAA-directed vaccination strategies might open interesting application possibilities.

Disclosure: Jochen Greiner: Expert Testimony: Bristol-Myers Squibb
Marlies Götz: No conflict of interest disclosed.

P415

Generation of functional human NK cells from of umbilical cord CD34+ hematopoietic stem cells by artificial thymic organoids

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Introduction: Natural Killer (NK) cells are promising tools for the development of anticancer therapies due to their high cytotoxic activity. The limited clinical application results from low numbers and difficult expansion in vitro. Multiple protocols developed to circumvent these obstacles showed the possibility to generate NK cells from hematopoietic progenitors but either in insufficient numbers or of poor functionality. We here show an alternative method of generating high numbers of cytotoxic NK cells from of umbilical cord hematopoietic stem cells (HSC) by artificial thymic organoids (ATO).

Methods: The MS5 murine stromal cell line was transduced with human Delta-like protein 1 (DLL1) and clones with highest hDLL1 expression were chosen for the experiment. Human $CD34^+$ HSC were isolated from umbilical cord blood via magnetic beads. $1{,}5*10^5$ MS5-hDLL1 cells were aggregated with 7500 HSCs per ATO by centrifugation and cultured on a cell culture insert to form organoids. Serum-free media was changed every 3 to 4 days and supplemented with Interleukin 7 (IL7), Interleukin 15 (IL15) and Fms-related tyrosine kinase 3 ligand (Flt3L). The functionality of generated NK cells was determined by spontaneous and Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC) assay using an anti-GD2 Antibody and GD2-positive neuroblastoma cell line.

Results: $CD56^+CD3^-$ NK cells were observed after 2 weeks including a mature $CD16^+$ population. At 4 weeks the majority of cells consist of immature and mature $CD16^+$ NK cells. The procedure generated $1*10^6$ NK cells out of 7500 HSC. ADCC assay showed up to 70% killed target cells using the anti-GD2 Antibody and up to 30% in an antibody-independent assay.

Conclusions: The previously established in vitro T cell differentiation system (ATO) modified by supplementing IL15 to the culture media showed the potential for the generation of functional NK cells. Beside their characteristic, spontaneous and antibody-directed cytotoxicity against tumor cells we achieved over 100-fold expansion.

Disclosure: No conflict of interest disclosed.

P416

CART cells with 4-1BB as co-stimulatory domain are not hampered by apoptosis inhibitor blockade agents

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Chimeric antigen receptor (CAR)-engineered T cell therapy is currently revolutionizing the field of cancer immunotherapy. Moreover to enhance the treatment response combination therapies are under investigation. In hematological malignancies apoptosis resistance is common with overexpression of anti-apoptotic proteins of the B-cell lymphoma 2 (Bcl-2) family. Apoptosis inhibitor blockade agents (AIBAs) like Bcl-2, Mcl-1 and COX inhibitors resensitize malignant cells to apoptosis. Combining CART cell therapy with AIBAs might be a promising approach to increase the treatment response. However, CART cells with a 4-1BB co-stimulatory domain triggering a signaling cascade with upregulation of anti-apoptotic molecules might be hampered by AIBAs. Therefore we analyzed the influence of AIBAs on CART cells with CD28 and 4-1BB co-stimulatory domains.

Materials and methods: CD19 CART cells were manufactured using a 3rd generation CAR vector containing both CD28 and 4-1BB co-stimulatory domains. The expression of Bcl-2 family members in leukemia/lymphoma cell lines and in CD19 CART cells have been assessed by qRT-PCR and western blot. The optimal concentrations of inhibitors and the number of cells have been determined by CellTite Glo™ assay. The effect of inhibitors on the killing function of CART cells has been evaluated by ^{51}Cr release assay and Calcein AM™ assay. Intracellular cytokine staining and apoptosis assays were performed.

Results: Western blot (WB) and qRT-PCR showed that leukemia/lymphoma cell lines 380 and U698M had the highest BCL-2 (WB: 2.03 ± 0.54, $p = 0.016$; qRT-PCR: 1.73 ± 0.04, $p = 0.000$) and Mcl-1 (WB: 1.92 ± 1.08,

p = 0.142; qRT-PCR: 12.39 ± 1.37, p =0.000) expression. The killing efficiency of CD19 CART cells was enhanced after pretreatment of 380 cells by ABT199 (% of lysis without / after pretreatment: 25.48% ± 5.31 / 80.65% ± 0.54; p = 0.000). A slightly enhanced killing effect of CART cells was observed when 380 cells were co-cultured with CART cells in the presence of ABT199. This result has been explained by a higher sensitivity of 380 cells to ABT199 than CART cells and by an increase of CD107a secreting CART cells. Neither the pretreatment nor the concomitant strategy showed a negative influence of COX inhibitors on CART cells.
Conclusions: CART cells with a 4-1BB co-stimulatory domain are not hampered by AIBAs like Bcl-2, Mcl-1 and COX inhibitors. The Bcl-2 inhibitors combined with CART cells might even enhance the cytotoxic effect.

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P417

Immune evasion and systemic immune response profiling of patients with metastasized MSI colorectal cancer

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Background: Microsatellite instability (MSI) arises through deficiency of the DNA Mismatch Repair (MMR) system. It represents one of the major mechanisms of genomic instability in cancer, characterized by accumulation of frameshift mutations at short repetitive sequences, called microsatellites. Mutations affecting coding microsatellites can lead to the inactivation of critical tumor suppressor genes and in parallel the synthesis of frameshift peptide neoantigens. The high number of neoantigens renders MSI tumors highly immunogenic. This is demonstrated by the dense tumor immune infiltration, systemic immune responses against frameshift peptides, frequent development of immune evasion mechanisms, such as *Beta-2-Microglobulin* (*B2M*) mutations, and high response rates to immune checkpoint blockade (ICB) in MSI tumor patients. In the present study, we evaluated (1) molecular features related to tumor cell immune evasion and (2) systemic immune responses in patients with metastasized MSI colorectal cancer undergoing ICB.
Methods: We analyzed 21 MSI tumor specimens for *B2M* mutation status by Sanger sequencing. Expression of HLA class I and HLA class II-related proteins including B2M was monitored by immunohistochemistry (IHC). Systemic immune responses against a set of shared frameshift peptide neoantigens (n=10) was evaluated by IFN-y ELISpot assay. Whenever available, patient response to ICB was recorded.
Results: All patients with hepatic metastasis displayed retained expression of *B2M*. However, *B2M* mutations were detected in individual patients clinically presenting with peritoneal metastasis. Interestingly, a significant increase of systemic frameshift peptide neoantigen-specific immune responses was measured upon ICB therapy in responders. No significant relation between systemic immune responses and tumor cell-mediated immune evasion phenomena could be observed, potentially due to the limited sample size.
Conclusions: Our study demonstrates that patients with metastasized MSI colorectal cancer are a heterogeneous group, potentially explaining differing responses to ICB. We demonstrate a clear influence of *B2M* mutation status on the metastatic behavior of MSI colorectal cancer. Our study highlights the need to implement systemic immune responses and tumor features into clinical studies when assessing tumor response to ICB therapy.

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P418

Longitudinal C-reactive protein (CRP) trajectories predict immune checkpoint inhibitor response and progression in advanced non-small cell lung cancer

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Introduction: Elevated C-reactive protein (CRP) levels have been implicated in poor prognosis in patients with advanced non-small cell lung cancer (NSCLC). However, the prognostic and predictive potential of CRP for immune checkpoint inhibitor (ICI) treatment outcomes in this setting are unknown. Here, we study the longitudinal dynamics of CRP during ICI therapy, and quantify its relationship with ICI response and progression.
Methods: We studied 89 patients with advanced NSCLC who received ICI monotherapy at a single academic center (Table 1). Linear mixed models were implemented for quantifying the relationship between CRP, objective response rate (ORR), and progression-free survival (PFS).
Results: ORR was 20.2% (95%CI: 12.4-30.1) and median PFS was 7.2 months (95%CI: 6.9-7.6). During a median follow-up of 1.3 years from ICI treatment initiation until disease progression, death, or censoring, these patients contributed n=1,399 CRP values (average: 16 values/patient). Elevated CRP at treatment initiation was associated with worse ORR (Odds Ratio per doubling of CRP=0.67. 95%CI: 0.51-0.89, p=0.006) and worse PFS (Hazard ratio per doubling of CRP=1.49, 1.24-1.78, p< 0.0001). In longitudinal analysis of CRP levels, CRP significantly decreased by 2.2%/month (95%CI: 0.8-3.5, p=0.002) in patients who developed an objective response, but increased by 2.0%/month (95%CI: 0.1-3.7, p=0.030) in patients who developed disease progression.
Conclusions: Elevated pre-treatment CRP levels predict for poor response and shorter PFS during ICI therapy of advanced NSCLC. CRP levels change during ICI therapy in these patients, with increasing CRP preceding disease progression and decreasing CRP preceding treatment response.

Disclosure: No conflict of interest disclosed.

P419

Extracorporal photophoresis therapy could maintain the antiviral and anti-leukemia effects in patients with graft-versus-host disease

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Introduction: Systemic steroids are the current gold standard for graft-versus-host disease (GvHD) treatment. However, 30-40% of patients develop a steroid-refractory GvHD. Extracorporal photophoresis (ECP) with established clinical benefits can restore the destroyed balance between effector and regulatory cells in the case of GvHD. Of note, there is no clinical data showing that ECP is associated with an increased risk of

infection. However, the exact mechanism of action how ECP preserves the anti-viral/-leukemia effects on the cellular level has yet to be discovered.
Materials and methods: Thirty-four patients with steroid-refractory aGvHD ≥ II and moderate to severe cGvHD received ECP treatments at the University Hospitals Heidelberg, Greifswald in Germany and Chaim Sheba Medical Center in Israel. A comprehensive analysis of cell subsets was performed using multi-parametric flow cytometry. The quantity and quality of CMV-specific T cells were determined by tetramer staining and interferon-γ enzyme-linked immunospot assay, respectively. The NK activity in terms of killing functionality and cytokine release was analyzed by intracellular cytokine staining and chromium-51 release assay, respectively. The proliferative capacity of effector cells was determined by carboxyfluorescein succinimidyl ester (CFSE) staining.
Results: ECP proved to be favorable in treating GvHD, with an overall response of 75% for aGvHD and 78% for cGvHD patients. Additionally, all patients showed neither increased susceptibility to infections nor reactivation of CMV nor tumor relapse. On the cellular level, the frequency of cytotoxic $CD8^+$ T cells, the most important mediators of GvL activity, remained constant under treatment. Besides this, no significant influence of ECP therapy on $CD4^+CD8^+$ T, γδ T and NKT cells as other well-established protective cell subsets could be observed. ECP therapy could maintain not only the frequency of CMV specific T cells with T_{EM} subsets but also the capacity of IFN-γ release. Moreover, the intact NK activity could be kept via maintaining specialized anti-viral/leukemic $CD57^+NKG2C^+CD56^{dim}$ NK cells as well as the quality and quantity of cytokine release by NK cells. The proliferation of NK cells and T cells providing an expanded pool of effector cells against the pathogens was not hampered by ECP therapy either.
Conclusions: ECP therapy proves to be an attractive strategy to treat GvHD without losing the anti-viral and anti-leukemia function.

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P420

Network topology of the immune infiltrate of lung cancers reveals distinct patterns of tumor-immune interactions

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Introduction: Cancer immunotherapy has established itself as one of the most effective treatment options for many solid tumors, including lung cancer. However, the mechanisms underlying successful tumor immunotherapy are incompletely understood. In order to gain insight into the immune landscape of lung cancer we employed an integrative network-based analytic strategy to explore the complex architecture tumor-immune system interactions.
Methods: Using data on lung cancer patients obtained from The Cancer Genome Atlas we generated a data set that characterized different features of adenocarcinoma and squamous cell carcinoma of the lung and the associated immune infiltrates. Using cell type deconvolution, mutation prediction, and gene expression analysis we computationally characterized the immune cell subset composition, neoantigen frequency, and mutation load of the tumors. From this data we constructed a scale-free undirected network representation of the interaction between tumor and immune system.
Results: Analysis of the topological properties of the network revealed functional immune modules that correlated with tumor traits such as tumor mutational load, driver-mutations, and expression of immune checkpoints. We found that although the immune infiltrates of human lung cancers are highly heterogeneous our network model could identify distinct immunotypes.
Conclusion: Our work demonstrates that integrative analysis using network theory can provide a system-wide understanding of the molecular and cellular regulatory mechanisms that underlie the dynamic interactions between the host immune system and lung cancer. The network-based computational modeling of the immunologic features of the lung cancer microenvironment generated testable hypotheses with regard to novel therapeutic targets for cancer immunotherapy.

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P421

Modulation of antibody-dependent phagocytosis by macrophages under metabolic regulation in the tumor microenvironment

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Introduction: Treatment of B-cell lymphoma by chemoimmunotherapy largely depends on the tumor microenvironment and the functional status of macrophages as important effector cells. Metabolic status and alterations have pronounced effects on macrophage polarity and function. Since the tumor microenvironment has an altered supply of nutrients and oxygen availability metabolic changes might have a deep and specific impact on polarity, functional status and particularly phagocytosis capacity of macrophages.
Methods: As macrophage polarization and function is sensitive to metabolic alterations, we addressed macrophage lymphoma cell co-cultures to assess the impact of metabolic pathway alteration using selected metabolism pathway inhibitors. THP1 and J774A.1 macrophage cell lines, murine peritoneal macrophages and human monocyte derived macrophages were used as effector cell models while hMB Double-Hit Lymphoma cells and primary CLL cells served as target cells for Antibody-Dependent Cellular Phagocytosis Assays (ADCP). Metabolic activity of macrophages was assessed by SeaHorse analysis.
Results: Screening various aspects of cellular metabolism the inhibition of AMP kinase, glycolysis or the mitochondrial ATP-production had no positive effect on the phagocytosis rate. However, inhibiting the pentose phosphate pathway (PPP) by Oxythiamine, p-Hydroxyphenylpyruvate, Physcion and 6-Aminonicotinamide led to an increased target cell phagocytosis and Fc-receptor expression. These effects could be seen in independent effector cell types (J774A1 and THP1). Adding educts and products of the PPP further affected the activity of macrophage-mediated target cell depletion. Under PPP-inhibition, the oxygen consumption and the glycolysis in macrophages was increased. Moreover, the sedoheptulose-kinase was downregulated which lead to a more proinflammatory and active macrophage-phenotype.
The activated phenotype and increased phagocytosis rate could also be seen in PPP-enzyme knockdown using Transketolase and 6-Phosphogluconatdehydrogenase (6-PGD) specific shRNA in J774A.1 macrophages and by inhibiting the PPP in primary murine and human macrophages.
Conclusions: We hypothesize the pentose phosphate pathway as a regulator of macrophage activity determining therapy outcome specifically in the context of monoclonal antibodies depending on ADCP and aim to identify specific modulators of macrophage polarization and function in tumor immunotherapies.

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Christian Pallasch: Advisory Role: Gilead; Financing of Scientific Research: Roche; Expert Testimony: Gilead, Genzyme

P422

Radip response to chekpoint inhibition therapy in a patient with malignant peritoneal mesothelioma

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Introduction: Malignant peritoneal mesothelioma (MPM) is a rare disease of the peritoneal cavity with dismal prognosis. Due to its rarity there

are no large randomized trials which would establish a standard of care. Based on extrapolated data from malignant pleural mesothelioma, the majority of MPM patients receive platinum-based first-line chemotherapy (+/- surgery) and upon progression single-agent chemotherapy (mostly vinorelbine or gemcitabine). There is emerging interest for the role of immunotherapy (IO) in mesothelioma and there are several ongoing trials for the pleural variant. Still, there is considerable lack of information about efficacy and toxicity of IO in MPM. Here we describe a case of MPM patient treated with the anti-PD-1 antibody pembrolizumab.

Methods: A 54-year old male patient diagnosed with MPM in June 2016 and underwent cyto-reductive surgery with additional hyperthermal intraperitoneal chemotherapy (HIPEC) therapy. Pathology showed MPM, PD-L1 10%, no presence of microsatellite instability. Additive platinum-pemetrexed chemotherapy was applied and patient obtained complete remission. In November 2017 he deteriorated clinically (ascites, B-symptoms) and radiology showed local progression. Gemcitabine-monotherapy was initiated but tumor further progressed after cycle 5 and chemotherapy was changed to pemetrexed re-challenge. This led to disease stabilization as best response, as seen clinically and radiologically, but ultimately (January 2019) the patient presented with cough, dyspnea and weight loss. CT scans confirmed progression in retroperitoneal and mesenterial lymph nodes as well as new pleural effusion and ascites.

Results: At that time labor showed markedly elevated CRP and leucocytosis with monocytosis as well as thrombocytosis. There was no presence of infection, thus labor pointed to disease activity. Given the lack of adequate further treatment options and the emerging data of IO in pleural mesothelioma, patient started on pembrolizumab in february 2019 which led to a rapid clinical as well as laboratory improvement. CT-staging confirmed response. Toxicity was manageable with grade 1 fatigue.

Conclusions: Pembrolizumab-IO given as 4th line treatment in this MPM case showed rapid response with to date no toxicity and ongoing efficacy. IO should be further investigated in MPM patients in a clinical trial.

Disclosure: No conflict of interest disclosed.

P423

Evaluation of psychosocial factors concerning the management of side effects of oncological patients undergoing checkpoint-inhibitor immunotherapy

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Introduction: Immune checkpoint inhibitors (ICI) have led to substantial improvement of cancer therapy but are associated with adverse events (irAEs) which need regular assessment and prompt treatment. The implementation into standard cancer therapy is associated with new psycho-social challenges for patients.The aim of this study was to identify specific needs and psycho-social burden of patients and to define specific interventions in order to increase patient's health related quality of life (HRQL) and adherence related to side-effects management.

Methods: Semi-structured qualitative interviews were conducted in 14 patients with different cancers undergoing ICI therapy. Results were analyzed via evaluative, type-building content analysis.

Results: Data shows that the subjectively perceived psycho-social burden results from long patient journeys, fear of death, loss of quality of life, missing social support, lack of information regarding the treatment, and a missing self-conception of co-determination rights. However, patients report satisfaction with fewer therapy-associated side-effects. The patients have strong belief in oncological care and the decisions of the physicians. Yet the feeling of not being sufficiently informed and seeing themselves as medical laymen was perceived a distinct burden. Patients often admitted that information had been offered but wasn't acknowledged. Both the result of fewer side-effects and patient reluctance to retain information should be considered, given that patients think their therapy will be terminated once they report any kind of side-effect and that they may expect to die soon. Overall, they trust in the decisions of the doctors.

Conclusions: To ensure that both adherence to side-effects management and high quality of life is maintained, therapy-specific training should be offered to patients. Information sharing should focus on a comprehensive, patient-oriented language and method of presentation. To increase self-efficacy in patients, non-physician professionals may also present the information. Training by nurses, psychologists, or moderated patient groups may be more successful. Introducing patients to specific apps or scientifically validated websites might be a useful addition. Since these would be continuously available, patients could decide for themselves when to access the information. Since physicians play a crucial role for patients, physicians should introduce such additional information sources.

Disclosure: No conflict of interest disclosed.

P424

Facilitated immunoglobulin administration registry and outcomes study (FIGARO): first results

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Introduction: fSCIG (HyQvia) is a dual-vial unit consisting of recombinant human hyaluronidase (rHuPH20) and 10% normal immunoglobulin (IgG) solution. In the registration study, fSCIG was effective, safe, and bioequivalent to intravenous IgG at the same administration intervals, with fewer systemic reactions. FIGARO is expected to provide real-world data about fSCIG usage in patients in daily routine.

Methods: Multicenter, prospective observational study in European countries under the auspices of ESID. Patients are eligible for documentation if treated for PID or SID and if they provided informed consent. An interim analysis with a cut-off date of 6 April 2018 was prepared. ClinicalTrials.gov: NCT0305418.

Results: Patient characteristics are shown in the Table. For the majority of patients, average time between infusions was every 4 weeks (59.6%) or every 3 weeks (25.0%). Median dose of the last fSCIG infusion was 30 g (IQR 20.0-32.5g). It was given at patient's home in 73.1%, at doctor's office in 17.3%, or at the hospital in 9.6%. Infusions were self-administered by 81.6%, otherwise given by the nurse. One application site (abdomen) was used in all cases. An infusion pump was used in 95.7%. Technical problems occurred only in 1 case. In all cases, the full planned dose of fSCIG was administered.

Conclusions: fSCIG infusions offer the flexibility to be performed by the patient at home or in the hospital setting. Dosing schedule allows variability, but the majority of infusions are administered every 4 weeks into one infusion site. The cohort is recruiting and patient observation continues.

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David Pittrow: Other Financial Relationships: D Pittrow: reports personal fees from Actelion, Bayer, Aspen, Boehringer Ingelheim, Sanofi, Biogen, and MSD, outside the submitted work. D.Pittrow has acted as consultant for Baxalta.

Tab. 1. Patient characteristics

Characteristics	n	Value
Age, years, mean (SD)	54	47.0 (16.2)
years, range		8-88
Sex, Male, %	34	54
Female, %	29	46
Race, Caucasian/white	60	98.4
Body mass index, kg/m^2, mean (SD)	63	24.1 (4.2)
PID, all, %	48	76.2
CVID, %	40	83.3
x-chrom, agammaglobulinemia, %	5	10.4
SID, all, %	15	23.8
chronic lymphatic leukemia, %	8	53.3
indolent lymphoma, %	2	13.3

P425

SENEQA: Study on the utilization of fSCIG (10% normal immunglobulin and recombinant human hyaluronidase) in elderly patients

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Introduction: HyQvia (facilitated subcutaneous immunoglobulin; fSCIG) consists of immunoglobulin 10% and recombinant human hyaluronidase, which facilitates the dispersion and absorption of the subcutaneously administered immunoglobulin. SENEQA provides real-life data about fSCIG usage in elderly patients in The Netherlands and Germany.
Methods: Interim analysis of a retrospective chart review. Patients were eligible if they provided written informed consent, were at least 65 years old, had PID or SID, and had received at least 1 HyQvia infusion in the past. No explicit exclusion criteria were specified to avoid selection bias. This study is registered at Paul-Ehrlich Institut (supervising authority) under NIS367.
Results: Sixteen patients (6 SID, 10 PID) between 66 and 77 years were documented in 4 centers. At the most recent fSCIG infusion (20-35 g IgG), the treatment interval was 3 weekly in 11 patients and 4 weekly in 5 patients. fSCIG was given at the patient's home in 15 patients and at the doctor's office in 1 patient. fSCIG was administered by the patient in 11 cases and the nurse in 5 cases. One infusion site was used in 14 patients and 2 sites in 2 patients. Most infusions were administered into the abdomen. All patients used infusion pumps without any technical problems. Local adverse reactions were noted in 6 patients and systemic reactions in 2 patients. In 15 patients, the full planned dose of fSCIG could be administered. All patients were rated to be adherent to therapy by their physicians. Serum IgG levels were measured in 12 patients (mean value 10.2 ± 2.2 g/L).
Conclusions: The majority of elderly patients were capable to self-administer fSCIG at home without encountering technical problems.

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P426

Soluble serum markers predicting response to PD-1 blockade

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Introduction: Cancer immunotherapies targeting PD-1 and its ligand PD-L1 have shown durable responses in patients with various malignancies. However, a considerable number of patients seems to be refractory to the treatment showing tumor progress shortly after initiation of immunotherapy.
Several studies aiming to identify predictive biomarkers for response have been performed, mostly focusing on tumor associated factors such as mutational burden, surface PD-L1 expression and immune infiltration. Although superior in clinical applicability, soluble serum markers predicting response to PD-1 blockade have been rarely delineated.
Methods: In the present study enrolling 30 patients with diverse tumor entities, we scanned soluble factors significantly differing in the blood of responders compared to non-responders.
Results: Our explorative analysis yielded three promising serum biomarkers. While the free androgen index and serum low density lipoprotein showed elevated values in responders, the soluble form of the embryonic protein cripto-1 (CR-1, EGF-CFC family) was associated with a poor response.
Conclusions: Although validation in a higher number of patients is required, these findings might provide a feasible opportunity to identify patients who show a response to immune checkpoint inhibition. Furthermore, in-vitro and in-vivo studies are indispensable to further characterize the functional impact of these biomarkers.

Disclosure: No conflict of interest disclosed.

Posterdiskussion

Sonstige Onkologie I

P427

Extraordinary eosinophilia of >100 G/l with Löfflers endocarditis and multiple embolisms due to pulmonary adenocarcinoma with associated Langerhans' cell histiocytosis

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A 57 y/o male Caucasian never smoker presented to a Middle East hospital with fever, cough and extraordinarily high eosinophils (eos) of >100 G/l. CT revealed a pulmonary infiltrate in the right upper lobe and slightly enlarged mediastinal lymph nodes. Video-assisted thoracoscopy with biopsy led to diagnosis of an "eosinophilic tumor". Diagnosis of a hypereosinophilic syndrome was made and treatment with systemic corticosteroids (CS) and antibiotics was initiated. After return to Germany

and referral, clonal eosinophilia was best possibly ruled out by extensive genetics (cytogenetics, fusion genes, mutations) and bone marrow histology. Shortly after, the patient presented with wide spread splinter hemorrhages covering the nails of all fingers indicating endocarditis. Cardiac MRI revealed a late myocardial gadolinium enhancement at multiple sites and multiple left ventricular thrombi in terms of Loeffler endocarditis. Cerebral MRI showed multiple embolisms in both hemispheres. In due course, the patient did not respond to high-dose CS, cyclophosphamide, hydroxyurea or imatinib. Because of this inadequate response, a second pulmonary biopsy was performed at another hospital leading to diagnosis of Langerhans' cell histiocytosis (LCH; positivity for CD1a, S100, CD 207, negative for BRAF V600E). However, there was no response to cladribine. New pulmonary infiltrates led to respiratory failure and the patient died despite maximal intensive care and without any response of eos. Autopsy unexpectedly showed an undifferentiated pulmonary adenocarcinoma [aT4, L1, aN2 (19/19), G3] with peritumoral inflammatory histiocytic infiltrates, typical for LCH. Retrospective analysis of the second biopsy revealed that the pulmonary adenocarcinoma was overlooked. Although an independent occurrence of lung cancer and LCH with eosinophilia cannot be excluded, a literature search revealed several case reports upon the potential association of lung cancer with LCH which is otherwise well known to be associated with eosinophilia. This is the first report upon a histologically proven pulmonary adenocarcinoma with peritumoral infiltrates by LCH in association with extraordinary and therapy-resistant eos of >100G/l in peripheral blood causing life-threatening organ damage. We conclude that the diagnostic work up of eosinophilia should also take into account non-clonal, paraneoplastic eosinophilia as consequence of clonal neoplasms such solid tumors or lymphomas.

Disclosure: No conflict of interest disclosed.

P428

Combined inhibition of BTK and PI3K acts synergistically in a canine B-cell lymphoma in vitro model

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Introduction: B-cell receptor (BCR) signaling plays a critical role in the progress of most B-cell malignancies. Accordingly, the pathway is targeted for the evaluation novel compound combinations. The Bruton's tyrosine kinase (BTK) as well as the phosphoinositide 3-kinase (PI3K) are two kinases targeted in different tumor entities. Canine (dog) lymphoma represents a spontaneously occurring in vivo model for human defuse large B-cell lymphoma as biology and presentation are highly comparable. Herein we investigated the effect of Ibrutinib (BTK inhibitor) as well as AS605240 (PI3K inhibitor) mono- and combined applications in a canine lymphoma in vitro model system.
Methods: Whole transcriptome sequencing was used to identify basic expression of both targets in several cell lines and >20 de novo samples characterizing the representative value of the cell lines. Following, the canine B-cell lymphoma cell line CLBL-1 was exposed to increasing concentrations (0.001 µM - 10 µM) of mono- or combined Ibrutinib and AS605240 for 24, 48 or 72h. Proliferation (trypan blue), metabolic activity (WST-1), early/late apoptosis (flow cytometry), cell morphology (pappenheim staining) as well as protein expression of several target proteins (Western Blot) were comparatively evaluated.
Results: BTK targeting showed dose and time dependent anti-proliferative effects on CLBL-1 starting at concentrations of 0.5 µM in the 24, 48 and 72 h groups. Concentrations of > 2.5 µM led significant increase ($p < 0.01$) of early/late apoptotic cells. PI3K targeting resulted in inhibition beginning at 5 µM. Combined application of Ibrutinib (1 µM) and AS605240 (2.5, 5, 10 µM) acted synergistically. The combined application reduced cell proliferation and metabolic activity to 11.4% and 12.5%, while apoptosis rates increased up to 50.7%. Morphology of the exposed CLBL-1 cell showed formation of membrane blebs and ruptured cell integrities. Further, the condensation of chromatin, breakdown of nucleus and cellular fragmentation were observed. Combined compound application induced reduction of pGSK3ß and pERK1/2 in CLBL-1 at 24h.
Conclusion: The observed pronounced synergistic in vitro effect of Ibrutinib and AS605240 indicates that the combination represents a promising approach for further in vivo evaluation. As canine lymphoma represents a highly comparative model for the human counterpart, an experimental trail in dogs could bear significant value for both species.

Disclosure: No conflict of interest disclosed.

P429

Spinal drop metastases of glioblastoma multiforme before and after introduction of the"Stupp" scheme

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Objective: Glioblastoma multiforme(GBM) is the most common and most malignant primary brain tumor in adults.Metastatic lesions are rare. We investigated the occurrence of spinal drop metastases in patients with GBM before and after introduction of combined radio-/chem otherapy with temozolomideaccording to the EORTC ("Stupp") scheme.
Methods: We performed a retrospective analysis includingall patients who have been operated onGBM (WHO IV)in our department between1990 and 2014.
Results: We encountered a total of 740 patients with histologically proven GBM who were treated within these25 years in our department. Four patients were found to develop spinal drop metastases (0,54 %).The median age of patients with spinaldrop metastases was 57 years (range 20-64 years). The time interval between first surgery and the occurrence of spinal drop metastases was 5, 9, and 11 months, and 13 years months.All of these patients were initially diagnosed and treated before introduction of the "Stupp" schema. One patient, however, has received temozolomide for local GBM recurrence. In this case, the time interval between initial surgery for GBM and the occurrence of spinal drop metastases was as long as 13 years.
In two patients, the spinal metastases were treated surgically with proven histological diagnosis. Spinal drop metastases were associated with a rapid deterioration of the clinical condition in all patients.Among the GBM patients who received radio-/chemotherapy according to "Stupp scheme", no one developed spinal drop metastases.
Conclusions: Spinal GBM drop metastases are rare. In our series we discovered four of 740 patients (0.54%) suffering from spinal drop metastases. All of these patients were initially treated before combined chemo/radiotherapy with temozolomide was available. One patient, however, received temozolomide for local GBM recurrence.There were no spinal drop metastases detected in patients who were treated according to the "Stupp" scheme

Disclosure: No conflict of interest disclosed.

P430

Adenocarcinoma of unknown primary - metastatic pattern and prognosis in 214 patients

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Introduction: Adenocarcinoma of unknown primary (Adeno-CUP) is defined as a histologically proven metastatic stage of an adenocarcinoma with unknown origin. Early and aggressive dissemination of metastases may explain the poorer prognosis of Adeno-CUP in comparison to patients with adenocarcinomas of known primary p.e. colorectal cancer. Data about the metastatic pattern of Adeno-CUPs may give insight into the metastatic process and its influence on prognosis. Therefore, we retrospectively analysed the impact of metastatic site and pattern on the survival of 214 patients with Adeno-CUP.
Methods: From January 2005 to July 2017 data from 239 consecutive patients with carcinoma of unknown primary (CUP) not belonging to a specific subgroup (including CUP with single metastatic site) have been collected by the Augsburg Cancer Registry. From this group of patients with unspecific CUP, cases with squamous cell carcinoma (n=25) were excluded because of their potential better prognosis. This results in a group of 214 patients with adenocarcinoma including undifferentiated carcinoma.
Results: In 15% of patients with Adeno-CUP one organ was affected by metastases, in 31% two organs, in 19% three organs and in 35% more than 3 organs. The overall survival of patients with metastases in one organ was significantly better than the overall survival of patients with spread of metastases to two or more organs (34 vs. 7 months, log-rank-test, p=0.015). All patients with one organ involved had more than one metastasis, patients with single metastasis were excluded from the investigated group. There was no difference in overall survival between patients with 2, 3 or more than 3 afflicted organs. Lymph nodes, liver and lung were the most frequently affected organs. Patients with liver metastases had a poorer prognosis than patients without liver involvement (7 vs. 15 months, log-rank-test, p=0.15) irrespective of the number or sites of simultanously involved organs. The presence of metastases in lymph nodes, bone, lung, pleura, peritoneum, adrenal gland and brain did not influence the prognosis independently from simultanously involved organs.
Conclusion: The reported case series demonstrate the poor prognosis of patients with metastases in more than one organ and of patients with liver metastases. A better understanding of the molecular mechanisms underlying these characteristics of the metastatic process in Adeno-CUP may enable the development of more effective therapies.

Disclosure: No conflict of interest disclosed.

P431

Chemotherapy markedly reduces B cells but not T cells and NK cells in patients with cancer

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Introduction: Chemotherapy is still the backbone of systemic treatment in the majority of most cancers. However, immunotherapies, especially those based on checkpoint inhibition, are additional therapy options for many. For this, functional T cells are a mandatory requirement. The aim of this prospective study was to investigate the influence of chemotherapy on the cellular immune status of individual patients.
Methods: Peripheral blood samples of 26 patients with solid malignancies undergoing chemotherapy were analyzed regarding lymphocyte populations and their subsets in a longitudinal approach.
Results: Chemotherapy decreased total B lymphocyte counts (median value [25-75 percentile]: before chemotherapy 76/µl [39-160] vs. after chemotherapy 49/µl [24-106]; p=0.001). Among B cells, specific subsets decreased in particular (naive B cells (49/µl [21-111] vs. 25/µl [13-56]; p=0.001), memory B cells (3/µl [2-8] vs. 2/µl [1-4]; p=0.001), and class-switched B cells (11/µl [6-20] vs. 6/µl [3-12]; p=0.011)). In contrast, chemotherapy had no influence on the total numbers of CD4+ and CD8+ T lymphoycytes or on their subsets (T helper cells 1, 2, and 17 as well as cytotoxic T cells in early, intermediate, late, terminal effector, exhausted status as well as both T cell types with naive, center memory, effector memory, activated, or regulatory phenotype). Further, the count of natural killer (NK) lymphocytes showed no significant change before and after chemotherapy.
Conclusions: In summery, this study shows a decrease of B lymphocytes during systemic chemotherapy but no relevant effect on T lymphocytes, NK lymphocytes and their subsets. This supports the idea of an effective additive T cell dependent immunotherapy to chemotherapy.

Disclosure: No conflict of interest disclosed.

P432

Metabolic tumour volume as prognostic factor for early response to treatment in advanced stage Hodgkin lymphoma

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Rationale: 18F-FDG PET/CT for staging Hodgkin lymphoma may allow for accurate and reliable assessment of the metabolic tumour volume (MTV) as baseline risk factor. Our aim was to analyse the prognostic impact of MTV measurements, obtained by different means in advanced-stage Hodgkin lymphoma patients treated within the German Hodgkin Study Group (GHSG) HD18 trial.
Methods: Within the GHSG trial HD18, 310 patients underwent 18F-FDG PET/CT scanning for staging which was available to the central review panel for quantitative analysis. We calculated the MTV by four different thresholding methods and performed ROC analysis to evaluate the potential for prediction of early response determined by PET-2, i.e. after two cycles dose-escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (eBEACOPP). Logistic regression was used to evaluate its potential prognostic value concerning progression-free survival (PFS).
Results: All different MTV calculations used predicted PET-2 response to a moderate and comparable degree (area under the curve = 0.62-0.63, p = 0.01-0.06). With none of the measuring methods did the ROC curves point to any unique cut-off values, but indicated a wide range of possible cut-offs. However, none of the MTV measurements was prognostic for PFS (Hazard Ratio 1.2-1.5, p = 0.15-0.52).
Conclusions: Tumour burden as determined by baseline MTV is a prognostic factor for early response to eBEACOPP. We observed this prognostic impact of baseline MTV with different evaluation methods. Baseline MTV assessment should be evaluated in future clinical trials on its potential to adapt treatment intensity to the patient´s individual need.

Disclosure: No conflict of interest disclosed.

P433

Demand, desire and assessment of mood: Investigation during radiooncological treatment by an advanced valid standard screening

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Introduction: It should be verified whether cancer patients with acute stress were recognized by their close environment (relatives and the medical staff in clinical routine) in accordance with the personal information of the patient himself.
Methods: Evaluation of the demand with a standardized procedure: HSI-F (Hornheide screening inventory, questionnaire) for the self-assessment of current conditions (threshold ≥ 4). Extension of the instrument for relatives and the medical staff for patient assessment and for selfassessment. An additional question was about need or the recommendation on psychooncological support.
Results: The need assessment by doctors (N=192) is 38%, by nurses (N=50) 48%, by radiological assistants (N=188) by 49%. Their recommendation is between 50% and 72%. Radiooncologists agree surprisingly well with the assessment of acute sensitivities with their patients. The most reliable are the current physical status (r=.52), p< .001) and the mental state (r=.33, p< .001). They also detect additional fatigue outside the tumor (r=.31, p< .001). These significant results are also apparent to relatives (N=90). They recognize the situation of information about disease and treatment (r=.65, p< .001), as well as the patient´s wish for professional support (r=.60, p< .001).
Conclusions: Our results extend published data with knowledge of relevant details regarding the consistency of condition assessment and announcement of the need between cancer patients and their close environment. Physicians can take on "medical advice", but due to limited content resources, specialized trainees should be included in the overall treatment plan, especially in the psychooncological area.

Disclosure: No conflict of interest disclosed.

P434

Suicidality and mental disorders among patients with cancer

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Introduction: To explore patterns of suicidality and their association with mental disorders and disease-related variables among patients with cancer.
Methods: We assessed 2,141 cancer patients in an epidemiological multi-center study by the standardized Composite International Diagnostic Interview-Oncology (CIDI-O). Assessment for mental disorders included mood, anxiety, adjustment, somatoform, and disorders due to general medical condition (4-week-prevalence). Assessment of suicidality included 1) thoughts about death, 2) wish to die, 3) suicidal ideation, 4) suicide plans, and 5) suicide attempts. We conducted latent class analyses (LCA).
Results: Of the sample, 9.9% reported thoughts about death, 4.7% the wish to die, 4.0% suicidal ideation, 1.5% suicide plans and 0.6% suicide attempts. The prevalence of any mental disorder was 31.8%. The LCA indicated three groups with distinct patterns of suicidal symptoms, but similar patterns of mental disorders. Class A (79% of the sample) showed no suicidality and low probability for mental disorders. Class B (16%) showed low probability for thoughts about death and wish to die, and moderate probability for mental disorders. Class C (5%) showed high probability for symptoms 1 to 3, moderate probability for suicide plans, and moderate probability for mental disorders. Incurable disease was significantly less likely in class C, the longest illness duration occurred in class B. Classes were not associated with recurrent vs. primary disease. Classes B and C were both characterized by younger age, female gender, a higher physical symptom burden, and breast cancer. Gynecologic cancer was more likely in class C.
Conclusions: Thoughts about death are frequent, but they co-occur with suicidal ideation and suicide plans only in a minority. The similar occurrence of mental disorders (including depression) and distinct patterns of disease-related variables across classes strengthen the observation of a) suicidality subtypes in cancer, that b) are more closely associated with the disease and resulting distress than with an underlying mental disorder.

Disclosure: No conflict of interest disclosed.

P435

Need for psychooncological support for cancer patients and their relatives. Screening at a radiation therapy ambulance in Feldkirch/Austria

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Introduction: In the situation of stress (diagnosis, critical point of the disease eg tumor progression or change of therapy intention), patients and their relatives need acute support adapted to their situation. The goal of the presented study was to evaluate the demand and desire for acute support.
Methods: Evaluation of the demand with a standardized procedure: HSI-F (Hornheide screening inventory, questionnaire) for self-assessment of current conditions (threshold ≥ 4). Extension of the instrument for relatives and the medical staff for patient assessment. An additional question was about need or recommendation on psychooncological support.
Results: The result of all evaluated patients (N=148, 52% female), age 20 to 89 years (M=62.40, SD=13.31) showed a demand of 35% for support. 37% of the patients express the desire for psychooncological support, regardless of need. Overall, the urgency of a psychooncological consens increases to 49%. Relatives (N=90) consider the need for 51% of their affected family members, and 44% (N=52) need to consider themselves as in need. 28% of those involved expressly wish to support themselves. There are no significant differences in gender (female: M=2.91, SD=3.19; male: M=2.89, SD=2.54; d=-.01, p=.481) and age (r=-.10, p=.114). Women tend to have a higher need and men show a higher subjective need. The need is all the more intense the younger the patients are (r=-.21, p=.006).
Conclusions: In line with published data our surveys clearly show that the need for acute psychooncological support for cancer patients and their relatives is evident.

Disclosure: No conflict of interest disclosed.

P436

Cabazitaxel for the treatment of refractory germ-cell cancer - a retrospective registry study of the German testicular cancer study group

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Introduction: Cisplatin-refractory germ cell cancer (GCC) patients failing two or more lines of platinum-based chemotherapy have a dismal prognosis. Median survival times are limited to a few months only. Objective response rates to single agents, i.e. oral etoposide or temozolomide achieve 10-15%. New treatment options are urgently needed. Cabazitaxel (CABA) was shown to be active in GCC in a pre-clinical model.
Methods: Refractory GCC patients treated with CABA were retrospectively analysed. Patients had been treated off label with CABA 25mg/m^2, day 1, every three weeks for cisplatin-refractory disease between Nov 2014 and March 2019. Data on disease characteristics at primary diagnosis and before onset of CABA and outcomes after CABA were centrally collected and analysed. 12-week progression-free survival (PFS) was the primary end-point. 24-week overall survival (OS), median PFS and OS, objective response rate (ORR), and serum tumor marker responses were secondary outcome measures to assess efficacy.
Results: A total of 11 cases were collected from 7 centres. Median age was 33 years (IQR 9). All patients had non-seminomatous histology. Pts had received a median of four (range, 2 - 6) prior lines of treatment before CABA, where 91% had undergone high-dose and 100% conventional paclitaxel-based salvage chemotherapy. The 12-week PFS-rate was 18% (2/11), median PFS was 5 weeks (95%-CI, 3.1 - 6.9). 24-week OS-rate was 27%, median OS was 12 weeks (95%-CI, 0 - 28.8). One patient achieved a marker-positive partial remission (ORR 9%), 3 patients (27%) had transient disease stabilisation, and transient tumour marker declines were achieved in 6/10 (60%) of patients. A median of two cycles (range, 1 - 6) of 6 planned CABA cycles were applied, all but two patients discontinued early due to unequivocal disease progression. After a median follow-up of 11 weeks (IQR, 19), 8/11 (72%) of patients were deceased due to disease progression.
Conclusions: This is the first reported series of CABA treatment in refractory GCCs. Among 11 heavily pre-treated, refractory non-seminoma patients, single-agent CABA showed only limited activity. Despite transient tumour marker declines in 60% of patients, the 12-week PFS-rate was 18%, only. Median PFS and OS achieved was dissatisfactory. An updated analysis including further 2 patients will be presented. Two single-arm phase II trials prospectively evaluate CABA in refractory GCC patients, but results are pending.

Disclosure: No conflict of interest disclosed.

P437

Phase 3 (COSMIC-312) study of cabozantinib in combination with atezolizumab vs sorafenib in patients with advanced hepatocellular carcinoma (aHCC) who have not received previous systemic anticancer therapy

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Introduction: Cabozantinib inhibits tyrosine kinases involved in tumor growth, angiogenesis, and immune regulation, including MET, VEGFR, and TAM kinases (Tyro3, AXL, MER). Cabozantinib is approved in the United States and Europe for treatment of aHCC after prior sorafenib based on improved overall survival (OS) vs placebo in the phase 3 CELESTIAL trial (Abou-Alfa NEJM 2018). Cabozantinib may promote an immune-permissive tumor environment, which could enhance response to immune checkpoint inhibitors. Cabozantinib is being evaluated in combination with the anti-PD-L1 antibody atezolizumab in multiple tumor types including HCC in a phase 1 study; recommended dose, preliminary clinical activity, and safety of the combination have been established in aRCC (Agarwal Ann Oncol 2018). Atezolizumab in combination with bevacizumab, an anti-VEGF antibody, has shown preliminary clinical activity in first-line aHCC (Pishvaian Ann Oncol 2018). Here, we present the study design of a phase 3 trial of cabozantinib + atezolizumab vs sorafenib in patients with aHCC who have not received prior systemic therapy.
Methods: This global, randomized, open-label phase 3 trial (NCT03755791) is evaluating the efficacy and safety of cabozantinib + atezolizumab vs sorafenib as first-line treatment for aHCC. Eligibility criteria include age ≥18 years, BCLC stage B or C, Child-Pugh A, ECOG PS ≤1, and measurable disease per RECIST 1.1. Patients are randomized 2:1:1 to an experimental arm of cabozantinib (40 mg qd) + atezolizumab (1200 mg infusion q3w), a control arm of sorafenib (400 mg bid), and a cabozantinib monotherapy arm (60 mg qd). 740 patients are planned to be enrolled at ~250 sites globally. Randomization is stratified by disease etiology (HBV [with or without HCV], HCV [without HBV], or other), region (Asia, other), and the presence of extrahepatic disease and/or macrovascular invasion (yes, no). Progression-free survival (PFS) and OS for cabozantinib + atezolizumab vs sorafenib are primary endpoints, and PFS for cabozantinib vs sorafenib is a secondary endpoint. Additional endpoints include safety, pharmacokinetics, and correlation of biomarker analyses with clinical outcomes. The first patient was enrolled in December 2018, and enrollment is ongoing.

Disclosure: Arndt Vogel: Advisory Role: Lilly, Ipsen, Bayer, Roche, MSD, BMS, AstraZeneca; Financing of Scientific Research: Lilly, Ipsen, Bayer, Roche, MSD, BMS, AstraZeneca
Lorenza Rimassa: Advisory Role: Lilly, Bayer, Sirtex Medical, Italfarmaco, Sanofi, ArQule, Baxter, Ipsen, Exelixis, Amgen, Incyte, Celgene, Eisai; Financing of Scientific Research: Lecture fees: AstraZeneca, AbbVie, Gilead, Roche; Immaterial Conflict of Interests: Travel expenses: ArQule, Ipsen

Posterdiskussion

Multiples Myelom I

P438

The SUV of PET-CT of patients with multiple myeloma with progressive disease following high-dose therapy and autologous or allogeneic stem cell transplantation is an independent prognostic parameter for survival

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Introduction: ^{18}F-FDG Positron-emission tomography (PET-CT) in patients with multiple myeloma (MM) is not only of prognostic value but also permits to evaluate the response to therapy. While the prognostic role of PET-CT for pre- and post-therapy evaluation is relatively well established, data on its relevance for patients with relapse or progressive disease is limited. We addressed this question in a retrospective, single centre study including 37 patients.
Methods: Between 2012 and 2018, 37 patients with MM who had received a high dose therapy and autologous or allogeneic SCT (31 and 6 [5 with previous autologous], respectively) and suffered from relapse or progressive disease underwent ^{18}F-FGD-PET-CT. The patients (17 females/20 males) had a median age of 60 years (range: 39 - 74). The intensity of tracer uptake - as defined by a standardised uptake value (SUV) with a cut-off >4 - , the presence of PET-positive extramedullary lesions and the number of focal bone lesions (cut-off >3) were considered as prognostic parameters in the context of PET-CT and used for our evaluation of overall survival (OS) based on Kaplan-Meyer log-rank tests and multiparametric Cox-regression analysis. For the multiparametric analysis we additionally included the concentration of β-2-microglobulin, albumin and LDH in serum as well as the relative increase of the concentration of the patient's paraprotein and/or FLC observed between the time point of "best response" and that of PET-CT.
Results: The median time of OS of the 37 patients is 15 months (range: 2 - 63). Of the entire group, 17 are alive with a median follow-up time of 27 months (range: 6 to 63). Both, SUV >4 and presence of more than 3 focal lesions, are statistically significant negative prognostic parameters of OS, while presence of extramedullary lesions did not reach statistical significance. For instance, the median survival of the 14 patients with an SUV below the cut-off of 4 was not reached, while in the 23 patients with an SUV of greater than 4 the median survival was 13 months (p=0.002). In the multivariative analysis we found that an SUV of greater than 4 was an independent significant negative prognostic factor for OS, while the presence of 3 focal lesions was not any longer statistically significant.
Conclusions: A PET-CT with SUV>4 provides an independent prognostic parameter in patients with clinical or serological findings suggesting progressive disease following autologous or allogeneic SCT.

Disclosure: No conflict of interest disclosed.

P439

Role of N6-methyladenosine (m6A) RNA modification in Multiple Myeloma

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Multiple myeloma (MM) is considered a chronic and incurable disease due to its highly complex and heterogeneous molecular abnormalities. In recent years, integrating proteasome inhibitors and immunomodulatory drugs into MM frontline therapy has significantly improved treatment efficacy with a median overall survival (OS) being prolonged from 3-4 to 7 years. Despite this progress, patients refractory to the aforementioned agent classes display a median OS of only 9 months. Thus, the clinical necessity for developing novel therapeutic alternative approaches is self-evident.
Methylation of N6-adenosine (m6A) is known to be important for diverse biological processes including gene expression control, translation of protein, and messenger RNA (mRNA) splicing. m6A regulatory enzymes consist of "writers" METTL3 and METTL14, "readers" YTHDF1 and YTHDF2, and "erasers" FTO and ALKBH5. However, the functions of m6A mRNA modification and the specific role of these enzymes in MM remain unknown.
Here we report that METTL3, a key component of the m6A methyltransferase complex, is highly expressed in MM cell lines and in isolated patient´s MM cells. In contrast, we found no significant differences in the expression of the m6A demethylases FTO and ALKBH5. Accordingly, compared to plasma cells from healthy donors, global PolyA$^+$ RNA showed a significant increase in m6A content in patient´s MM plasma cells. Depletion of METTL3 by shRNA had little effect on global mRNA levels, but specifically reduced protein levels of c-Maf and Cyclin D1. Moreover, downregulation of METTL3 in several MM cell lines results in cell cycle arrest and apoptosis. Cross-linking immunoprecipitation showed that METTL3 bound to the m6A peak within MAF and CCND1 mRNA. Together, these results describe a role for METTL3 in promoting translation of a subset of oncogenes in MM and identify this enzyme as a potential therapeutic target for multiple myeloma.

Disclosure: Christian Bach: No conflict of interest disclosed.
Heiko Bruns: Expert Testimony: Celgene und Morphosys

P440

Characterization of HUWE1 functions in multiple myeloma

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Currently Multiple Myeloma (MM) therapies include different classes of agents such as alkylating agents, immunomodulatory agents, and proteasome inhibitors. However, many patients still relapse or become refractory to treatment therefore it is necessary to develop new therapeutic strategies. Targeting of specific ubiquitin pathways can overcome resistance to currently used therapeutics.
Recent studies have shown the essential role of several E3 ubiquitin ligases like HDM2 and APC/C in MM pathogenesis. Their inactivation correlates with growth and survival of MM cells. HUWE1 (HECT-family ubiquitin E3 ligase) has be shown to target a broad range of substrates for degradation in several types of human malignancies including breast and colorectal cancer, but its function in MM pathogenesis remains unclear.
To clarify HUWE1 role in MM we generated stable MM cell lines with doxycyline-inducible HUWE1 shRNA expression system. The success of HUWE1 knockdown was analyzed by real time PCR and western blot. We examined their growth and proliferation by growth curves and bromodeoxyuridine incorporation assay in absence or presence of HUWE1 protein. Furthermore we investigated sensitivity of MM cells to DNA damage after depletion of HUWE1 by alkaline single-cell electrophoresis "Comet Assay". Cell sensitivity to Melphalan, an alkylating agent, with and without HUWE1 expression was quantified using a MTT based assay. We also analyzed the behavior of MM cell line MM1.s *in vivo in* NOD/SCID/gamma mouse with bioluminescence imaging (BLI) in absence or presence of HUWE1 protein.
The knockdown of HUWE1 led to decreased growth and to accumulation of DNA strand breaks in JJN-3, U266, U266Myc and MM1.s cell lines. The depletion of HUWE1 in MM1.s cells resulted in apoptosis and increased sensitivity to Melphalan. The results in *in vivo* experiments showed decreased growth of MM cells after HUWE knockdown. Melphalan

treatment in combination with HUWE knockdown led to almost completely tumor cell repression *in vivo*.
Our results establish that ubiquitin E3 ligase, HUWE1 plays an essential role in MM cell proliferation and DNA repair. Moreover, the enhancement of melphalan cytotoxity can be increased by inhibition of HUWE1 protein.

Disclosure: No conflict of interest disclosed.

P441

The IMiD target Cereblon determines transmembrane protein quality control via the HSP90-AHA1 axis

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Introduction: Cereblon (CRBN) is the target for immunomodulatory drugs (IMiDs) such as thalidomide and its derivatives lenalidomide and pomalidomide, which are key therapeutics for hematologic malignancies such as multiple myeloma (MM) and del(5q) myelodysplastic syndrome (MDS). We have previously described a chaperone-like function of CRBN, which stabilizes the transmembrane proteins CD147 and MCT1. IMiDs interfere with this chaperone-like function of CRBN in a competitive manner to mediate both their anti-tumor and their teratotoxic effects. So far, the underlying mechanisms of transmembrane protein maturation and the global impact of CRBN on the cell surface proteome remain unclear.
Methods: Novel CRBN-clients were identified by cross-validation of the CRBN-interactome with a cell surface proteomic screen. Binding and function of proteins was ascertained via immunoprecipitations and GST-pulldowns. *In vitro* and *in vivo* xenograft experiments were performed using MM cell lines and patient-derived CD138+ MM cells. Imaging was performed with ^{18}FDG- and ^{18}FET-PET.
Results: We found CRBN to function as a new selective co-chaperone of HSP90, which antagonizes the negative effect of the HSP90 co-chaperone AHA1 on transmembrane protein stability. CRBNs activity and interaction with the HSP90 dimer are interrupted by IMiDs. Our unbiased screening approaches imply a global role of CRBN in transmembrane protein maturation. In addition, we further characterize the amino acid transporter LAT1 and its functional subunit CD98hc as new client proteins of the CRBN-HSP90 machinery, which become destabilized and inactivated upon IMiD treatment, thereby further linking IMiD-activity to tumor-metabolism.
Conclusions: We establish CRBN as a transmembrane protein-specific co-chaperone for HSP90 and identify modulation of the CRBN-HSP90 axis as crucial means by which IMiDs mediate their anti-tumor activity.

Disclosure: Michael Heider: No conflict of interest disclosed.
Florian Bassermann: Expert Testimony: Celgene

P442

Low-dose grafts in multiple myeloma after autologous stem cell transplantation

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Introduction: High-dose (HD) chemotherapy followed by autologous blood stem-cell transplantation (ABSCT) is the standard of care for multiple myeloma (MM) patients. The indication for up to three HD/ABSCTs might occur over the course of MM treatment. As a prerequisite hematopoietic stem cells must be available. However, many factors might be associated with poor PBSC mobilization, which results in borderline sufficient (< 2.0-2.5 x10^6 CD34+ cells/kg bw) grafts. The aim of this study was to evaluate the safety and feasibility as well as the hematopoietic reconstitution after reinfusion of low (2.0-2.5 x10^6/kg bw) or a very low (< 2.0 x10^6/kg bw) number of PBSCs after ABSCT.
Methods: A retrospective single-center analysis of MM patients (n=148) who underwent HD melphalan chemotherapy and ABSCT was performed. The patients were grouped according to the number of reinfused CD34+ cells at ABSCT: 4-3 x10^6 (n=86, group 1), 2.5-2 x10^6 (n=53, group 2), and < 2 x10^6 (n=9, group 3) CD34+ cells/kg. The groups were homogeneous with regard to induction treatment and remission status prior to ABSCT.
Results: All patients reached hematopoietic reconstitution after HD/ABSCT treatment, even those who received < 2 x10^6 CD34+ cells/kg. The median duration to leukocyte recovery ≥1.0 x10^9/L was 12 days in every group. The median duration to platelet recovery ≥20 x10^9/L was 11, 13 and 13 days for groups 1, 2 and 3, respectively. Overall, the univariate analysis revealed an association between a high number of reinfused CD34+ cells and fast platelet recovery (p< 0.001) but with no change in leukocyte reconstitution (group 1 versus 2). In the multivariate analysis, a low number of reinfused CD34+ cells (group 1 versus 2) was associated with statistically prolonged, but clinically irrelevant, time until leukocyte reconstitution ≥1.0 x10^9/L (p=0.010, HR 0.607, $CI_{95\%}$ 0.416-0.885) and platelet recovery ≥20 x10^9/L (p< 0.001, HR 0.438, $CI_{95\%}$ 0.299-0.642). G-CSF support significantly accelerated leukocyte reconstitution (p< 0.001, HR 16.742, $CI_{95\%}$ 8.514-32.923) but not platelet reconstitution.
Conclusions: Hematopoietic reconstitution is sufficient, even if a low (2.0-2.5 x10^6/kg bw) or a very low (< 2.0 x10^6/kg bw) number of PBSCs is reinfused during ABSCT. While the impact of the CD34+ cell dose is significant but clinically marginal, G-CSF support substantially accelerates the time until leukocyte recovery.

Disclosure: No conflict of interest disclosed.

P444

Ixazomib plus Lenalidomide-Dexamethasone (IRd) in Relapsed/Refractory Multiple Myeloma (RRMM) patients in real-world experience: a pooled analysis from the INSIGHT MM observational study and the Czech Registry of Monoclonal Gammopathies (RMG)

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Introduction: IRd is approved in >60 countries for treatment of RRMM patients (pts) who have received ≥1 prior therapy. Data comparing clinical trial efficacy with real-world effectiveness of MM therapies are limited. We performed a pooled analysis of patient-level data for IRdtreated RRMM pts from the ongoing, global, prospective, observational INSIGHT MM study (NCT02761187), which is enrolling ~4200 MM pts, and the Czech RMG, comprising clinical data for >6000 MM pts (19 Czech; 4 Slovak centers).

Methods: IRd-treated RRMM pts with 1-3 (INSIGHT MM) or ≥1 (RMG, Czech centers) prior therapies were identified. Pts required prospectively collected data on IRd therapy; pts who received additional treatment within the same line as IRd were excluded. Demographics, disease characteristics, prior therapies, effectiveness, and safety data were pooled and analyzed.

Results: Overall, 163 IRd-treated RRMM pts (50 INSIGHT MM, 113 RMG) from 9 countries were analyzed. Median age was 67 years. At diagnosis, 26% of pts had ISS Stage III disease. Median time from diagnosis to starting IRd was 42.6 mos; 71% of pts had ECOG PS ≥1; 50%/30%/20% of pts received 2nd/3rd/≥4th-line IRd; the most common reasons for starting IRd were relapse/progression (90%) and bone lesions (53%). Prior therapies included bortezomib (89%), transplant (61%), thalidomide (42%), lenalidomide (21%), carfilzomib (11%), daratumumab (3%), and pomalidomide (2%). Median duration of therapy was 14.0 mos (95% CI 11.2-23.0); 62% of pts were on treatment at data cut-off. Of 105 evaluable pts, overall response rate (ORR) was 74%, with 31% very good partial response or better. Median time to first (RMG)/best (INSIGHT MM) response was 1.1/3.7 mos. Median follow-up was 9.3 mos (64 pts on study at 12 mos); outcomes should be interpreted with caution due to limited maturity of data. Median progression-free survival (PFS) was 20.9 (95% CI 13.0-28.7) mos (12mo PFS rate: 65%). Median time to next therapy (TTNT) was 26.2 (95% CI 9.6-42.8) mos (12-mo TTNT rate: 73%); 23% of pts received subsequent therapies (bortezomib 24%, pomalidomide 24%, thalidomide 16%, daratumumab 16%, carfilzomib 14%, or lenalidomide 8%). Median overall survival (OS) was not reached (12-mo OS rate: 81%). Ixazomib/lenalidomide dose reductions were needed in 18%/37% of pts.

Conclusions: This pooled analysis shows that IRd effectiveness in routine clinical practice is comparable to the efficacy reported in TOURMALINEMM1 (ORR: 78%; median PFS: 20.6 mos)

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P445

The prognostic significance of comorbidity scores and performance status for efficacy and therapy-associated-toxicity in patients with multiple myeloma treated in the LenaMain-trial following high-dose therapy and autologous blood stem cell transplantation

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Introduction: When first diagnosed with multiple myeloma, most patients already suffer from various comorbidities affecting their daily living. We compared 4 comorbidity/frailty scores of patients treated in the LenaMain trial a prospective, randomized, open label, multicenter phase III trial on lenalidomide consolidation and maintenance, which included patients up to the age of 75 years 3 months after first-line high-dose therapy (HDT) and autologous stem cell transplantation. The study randomized low versus high-dose lenalidomide maintenance until progression after a uniform 6 months 25 mg consolidation (NCT00891384).

Methods: 162 patients were assessed at diagnosis, before HDT and at enrollment. They were classified as fit, intermediate and frail using Frailty-Score, Revised Myeloma Comorbidity Index (RMCI), Hematopoietic Cell Transplantation-Comorbidity Index (HCTCI) and HCTCI/age. We correlated the scores' impact on response, outcome, lenalidomid dose reductions and adverse effects after consolidation therapy and after one, two and three years of maintenance.

Results: The distribution of patients: Frailty-Score at diagnosis Arm A: 46 fit, 18 intermediate, 9 frail, Arm B: 61, 11 and 5 respectively. RMCI at diagnosis Arm A: 45 fit, 27 intermediate, Arm B: 43 and 31 respectively. Before HDT in HCTCI Arm A: 44 fit, 20 intermediate, 14 frail, Arm B: 45, 25, 10 respectively. HCTCI/age Arm A: 57 fit, 15 intermediate, 6 frail, Arm B: 65, 12, 5 respectively. Frailty-Score at enrollment Arm A: 67 fit, 12 intermediate, 1 frail, Arm B: 69 fit, 13 intermediate. RMCI at enrollment Arm A: 61 fit, 17 intermediate, Arm B 69 fit and 13 intermediate. In all scores unfit patients showed the same EFS and OS in within each study arm ($p>0.05$). Similarly, within each arm unfit patients achieved similar remission rates ($p>0.05$). There were no significant differences in lenalidomide dose reductions in different risk stratification groups during therapy ($p>0.05$). In the high-dose as well as in the low dose group similar rates of adverse reactions like neutropenia or infections were seen in all fitness groups ($p>0.05$).

Conclusions: As a result of trial design, only patients tolerating high-dose therapy were included in the LenaMain. Among these patients fitness

according to the scoring systems did not influence PFS, OS or drug tolerance, which corroborates lenalidomide as a well tolerated consolidation and maintenance treatment after HDT even for intermediate and unfit patients.

Disclosure: No conflict of interest disclosed.

P446

Targeting protein homeostasis regulation in multiple myeloma (MM): role of ER stress-induced unfolded protein response (UPR)

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Introduction: In multiple myeloma (MM), immunoglobulin production and malignant transformation lead to an increase in protein synthesis which in turn induces chaperon activity and protein degradation to cope with fatal proteotoxic stress as caused by accumulation of unfolded proteins. Therefore, it has been hypothesized that targeting proteostasis regulation might represent a reasonable therapeutic strategy in MM. In accordance with this assumption, therapeutic strategies to inhibit adaptation mechanisms to proteotoxic stress, such as increased proteasome or aggresome activity, have been successfully introduced into MM therapy. Recently, it has been shown that proteasome, HDAC or p97 inhibitors also affect stress regulation within the endoplasmic reticulum (ER). We therefore hypothesized that the ER stress-induced UPR might represent another critical adaption mechanism, and therefore analyzed its role and regulation under conditions of therapy-induced proteotoxic stress.
Methods: Expression of the ER stress sensor proteins GRP94 or GRP78 in MM cells was analyzed by Western blot. Upon inhibition of GRP94 or GRP78 activity, either by RNAi-mediated knockdown or pharmacological inhibition, MM cells were kept either in the absence or presence of different ER stress inducers prior to cell viability assessment by annexin V/PI staining, and analysis of ER stress-induced UPR signaling including PERK, ATF4, LC3AB, phosphorylation of eIF2α, IRE1α, SAPK and XBP1 splicing by Western.
Results: The ER stress sensor proteins GRP94 and GRP78 were overexpressed in MM cell lines and in primary MM cells. Inhibition of GRP94 and/or GRP78 activity in therapeutically unstressed cells increased the ER stress-induced UPR signaling, but had only modest apoptotic effects. In contrast, concomitant treatment with proteasome, HDAC or p97 inhibitors strongly increased the effects of GRP94/GRP78 inhibition on ER-stress UPR signaling and apoptosis.
Conclusions: Our data show a GRP94/GRP78-dependent, protective role of UPR under therapy-induced ER stress suggesting further attempts to develop suitable combination approaches.

Disclosure: No conflict of interest disclosed.

Fortbildung

MPN: Neues zur Diagnostik und Therapie

V451

Stem cell transplantation in myelofibrosis

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Patients with primary or post-essential thrombocythemia/polycythemia vera myelofibrosis have a median survival of approximately 6 years but survival varies between from less than 2 to more than 15 years. Risk scores such as IPSS, dynamic IPSS (DIPSS), or DIPSS plus are currently used in clinical practice to determine the prognosis of patients with PMF. Recently molecular markers have been introduced into the PMF risk score and a specific score for post ET/PV myelofibrosis has been proposed. In the absence of data from prospective randomized studies, allogeneic stem cell transplantation is currently recommended for patients less than 70 years with an estimated median survival of less than 5 years. This would include patients with IPSS or DIPSS intermediate-2 and high risk and is based on a comparison between transplanted and non-transplanted patients in the pre-ruxolitinib era. In a recent expert consensus paper there was a recommendation to consider allogeneic SCT in intermediate-1 patients if other high risk features such as ASXL1 mutation, more than 2% peripheral blasts, refractory transfusion-dependent anemia, or adverse cytogenetics according to DIPSS plus, are present. More recently to predict also outcome after allogeneic stem cell transplantation a transplant risk score for myelofibrosis has been introduced which include beside disease specific also patient- and transplant specific risk factor, because alternative donors and poor performance status are associated with a worse outcome
To reduce spleen size prior to transplantation some centers recommend splenectomy but morbidity can be high and mortality has been reported. Several investigators have used ruxolitinib prior to transplantation to improve constitutional symptoms and to reduce spleen size.
Bone marrow fibrosis as hallmark of the disease, regresses rapidly after allogeneic SCT and about 60% of the patients have a complete or nearly complete remission of bone marrow fibrosis on day+100 and the percentage of patients increased to 90% at day+180.

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Wissenschaftliches Symposium

Leber: Hepatische Tumore und Metastasen

V453

Primary and secondary liver malignancies: the role of radiotherapy

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Introduction: In the past, the role of radiotherapy in the treatment of liver malignancies has been controversial. However, recent technological advances in imaging , radiotherapy planning and delivery allow the safe delivery of ablative irradiation to a defined cancer volume with simultaneously effective sparing of the remaining functional liver tissue. Stereotactic body radiotherapy (SBRT) shows promising results through combining all technological advances into one concept, where the treatment is delivered non-invasively in an outpatient setting and usually in only 1-10 treatment sessions.
Methods: We performed a comprehensive literature research focusing on the keywords "stereotactic body radiotherapy", "ablative radiotherapy", "liver metastases", "hepatocellular carcinoma" and "cholangiocellular carcinoma", critically evaluated the results of prospective trials and comprehensive reviews and compared them to existing national and international guidelines.
Results: SBRT for hepatocellular carcinoma (HCC) provides 1-year-local control rates (LCR) of ca. 90% and for cholangiocellular carcinoma >80%, even for challenging central tumor localizations. Furthermore, superior survival has been demonstrated for SBRT alone or in combination with TACE, compared to systemic treatment with sorafenib alone. Toxicity rates are relatively low, especially for patients with normal liver function or CHILD A cirrhosis. Today, SBRT is implemented in guidelines as an additional option for local treatment and bridging for transplantation. There exist no phase-III prospective data for treatment of liver metastases,

yet after application of a sufficiently high biologically effective dose (>100 Gy) 2-year local control and overall survival both amount over 50% in large series and systematic reviews. SBRT for liver metastases provides high control rates and is feasible without relevant toxicity even for tumors located adjacent to central vessels or biliary structures, despite the mostly negative selection of the patients.
Conclusions: As life expectancy of patients with liver malignancies increases, local tumor control is becoming crucial in order to avoid complications and improve quality of life. Novel advances in image-guidance and application-techniques and mainly the advent of stereotactic ablative radiotherapy produce favorable tumor control rates, so that radiotherapy has become an integral part of treatment decisions for both primary and secondary liver tumors.

Disclosure: No conflict of interest disclosed.

V454

Radiological interventional treatment: which procedures might "come"?

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Introduction: Over the last 20-30 years, many minimal-invasive radiological procedures - e.g. thermal ablation or chemoembolization - got accepted as primary or secondary treatment options in various oncological scenarios. This treatments could parallel or even surpass the results of "classical" treatments as surgery and medical oncology under specific conditions.
Methods: Radiological interventional modalities encompass radio-, electromechanical-, thermal-, and chemo-ablative techniques. In recent years, many of this techniques underwent some refinements, improving the therapeutical outcome in terms of technical and clinical success as well as safety. Nevertheless, with the rapid evolving field of immune-oncology the application of minimal-invasive, radiological interventional techniques might change. For almost all this techniques some immune-system related effects have been detected whereas both immune-stimulating and -supressing effects have been observed.
Results: There are already very promising results mostly in advanced HCC where the combination of radiological interventional therapies with „biological" therapies is improving the patients survival significantly, whereas in other tumor types as hepatic colorectal cancer metastases it is not yet clear which combination therapies will be meaningful. Nevertheless, there is also a growing understanding of specific conditions and prognostic factors, e.g. neutrophil-leucocyte-ratio, which may allow a more individualised selection of patients who might benefit from such combined therapies.
Conclusion: Beyond the already established potential, Minimal-invasive, radiological interventional techniques have the capability to play an important role in the currently developing more personalised treatment concepts - mainly by utilising, supporting, and enhancing medical immune-therapies. Therefore, it seems worthwhile to put more study efforts in this field of multimodality treatment concepts.

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V457

Work-related medical rehabilitation in oncology: Current state and research evidence

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Introduction: In recent years, medical rehabilitation on behalf of the German pension insurance has shifted its focus towards a stronger emphasis on occupational/work-related issues. This is due to legal regulations as well as evidence that return to work and the ability to work are a central part of participation in social and professional life and also an indicator of recovery.
Methods: This presentation gives an overview of the current research evidence regarding work-related medical rehabilitation. It also highlights relevant concepts and standards defined by health and care insurance providers.
Results: Work-related medical rehabilitation concepts were first developed in orthopedics. Only recently, oncological rehabilitation has addressed return to work and occupational issues in cancer patients. This transfer was aided by existing work-related rehabilitation standards developed by the German pension insurance, which proved to be adaptable to oncology and were instrumental in designing work-related rehabilitation concepts for cancer patients. Available studies show promising results with regard to work-related outcomes (Böttcher et al. 2013). For instance, one study with prostate cancer patients showed a return to work rate of 72% three years after medical rehabilitation (N=519 patients; prospective multicenter study; Bergelt et al. 2017).
Conclusions: Encouraging approaches to promote return to work in oncological rehabilitation exist and should be further disseminated and extended. Work-related issues should also be included in aftercare and follow-up.

Disclosure: No conflict of interest disclosed.

V459

Reasons for the non-utilisation of oncological rehabilitation treatment results of paper-and-pencil survey with patients of oncological Healthcare Centers

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Introduction: Incidence and survival rates of oncological diseases are increasing. The complex therapy in cancer patients may lead to considerable physical and psychological problems. These can be reduced through medical rehabilitation. Medical rehabilitation is an integral part of oncology care and is defined in the S3 oncology guidelines. In contrast to the inceasing incidence of oncological diseases medical rehabilitation treatment is decreasing. The reasons for this decline are not yet fully understood.
Methods: Retrospective paper-and-pencil survey of cancer patients with breast, colon or prostate cancer after acute treatment. Patients from seven health care centers participated in the study; the questionnaire asked for utilization of oncological rehabilitation, the reasons for non-use of rehabilitation treatment and health-related outcomes (e.g. limitations of participation, health-related quality of life, self-efficacy).
Results: Of the 520 patients who were asked for participation in the study, 376 (74%) completed the questionnaire. Fourty-three percent were breast cancer patients, 28% had colon or prostate cancer. Half of the patients stated, that they had utilized of rehabilitation measure (50.3%). Among these there were no differences between the cancer diagnosis. When used, the cancer indications do not differ. Younger patients and patients who are still in employment have significantly more often utilized oncological

rehabilitation, as well as patients with a higher severity of the disease. In all dimensions of subjective health, patients who have used rehabilitation had significantly worse health status. Patients who were more seriously ill were more likely to opt for rehabilitation. Major reasons for the non-use of a rehabilitation treatment were family, personal and private as well as organizational reasons.
Conclusions: Basically, patients with cancer are open to medical rehabilitation. Non-use of the rehabilitation results mainly for personal and private, but also for organizational reasons. From this, suggestions for optimizing rehabilitation and its arrangement can be derived.

Disclosure: No conflict of interest disclosed.

Fortbildung

Psychoonkologie: Akzeptanz von Tod und Endlichkeit

V464

Communication about death and dying

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Communication about death and dying requires a confrontation with one´s own death experiences and death-related immaginations and the associated feelings in order not to transfer one´s own fears to the patient. In addition to empathy, honesty, authenticity, acceptance and respect, the willingness to listen and show understanding for feelings are important. The affected person determines the pace, a phase of repression can be a necessary psychological aid. Information can reduce anxiety. Hope should not be destroyed, it helps the patient to endure the situation. If possible, relatives should be involved in order to avoid isolation through an unequal level of knowledge.

Disclosure: No conflict of interest disclosed.

V465

Early intergration of palliative care

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Is there a link between "acceptance of death and finiteness" and the ongoing discussion about early integration of palliative care (EIPC)? Is ultimately "acceptance of death" a goal of "early integration"? Acceptance has many aspects, insightful discussed by Zimmermann who has argued that acceptance of dying among other things also has to do with the interests of carers and institutions (Zimmermann, C. 2012). Some endpoints of EIPC-studies may be regarded as having a dual view on the trajectory of care ("aggressiveness of care", ER visits, medication use in the last phases of life), acceptance representing the "correct" attitude to death for the individual and also advantageous for institutions and society. Many years earlier earlier Kübler-Ross had described the state of acceptance as "an existence without fear or despair". Therefore, the influence of EIPC on parameters like anxiety and distress might be worth looking at. In general, the impact of EIPC in the forms tested so far is possibly overestimated (Schuler, U. S. 2019). For example, both randomized studies by Temel et al. e.g. did not show a significant reduction in anxiety in the respective intervention groups. The impression of seemingly significant effects of EIPC in some domains may be due to rather vague definitions of endpoints, which allowed for several ways of data aggregation and therefore constitute an approach closely related to multiple testing.
1 Schuler, U. S. (2019). "Early Integration of Palliative and Oncological Care: Con." Oncol Res Treat **42**(1-2): 19-24.
2 Zimmermann, C. (2012). "Acceptance of dying: a discourse analysis of palliative care literature." Soc Sci Med **75**(1): 217-224.

Disclosure: No conflict of interest disclosed.

Fortbildung

Prostata: fortgeschrittenes hormonsensitives Karzinom

V468

The role of surgery in advanced prostate cancer

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Mindestens 10% aller neu diagnostizierter Patienten mit Prostatakarzinom (PCa) haben einen lokal (T3-T4 N0 M0) oder regional fortgeschrittenes PCa (T3-T4 N1 M0). Aufgrund der in den letzten Jahren zu beobachteten „Stage-Migration" werden die Zahl dieser Patienten weiter zunehmen. Die Prognose ist gegenüber Patienten mit klinisch lokalisiertem Tumor deutlich schlechter. Die Therapie dieser Hochrisiko-Patienten ist insbesondere zu Rolle der chirurgischen Therapie in Diskussion. Aus überwiegend retrospektiven Studien gibt es mehr und mehr Hinweise, dass ein multimodaler Therapieansatz (radikale Prostatektomie, adjuvante Strahlentherapie +/- antiandrogene Therapie) mit einem besseren Outcome gegenüber einer singulären Therapie vergesellschaftet sein könnte. Die multimodale Therapie beim lokal/regional fortgeschrittenen PCa hat sich durchaus schon in der Praxis etabliert. Randomisierte, prospektive Studien (z.B. SPCG-15) werden zeigen, ob sich dies in einem nachweisbaren Überlebensvorteil niederschlägt.
Ebenfalls in der Diskussion ist der Stellenwert der lokalen Therapie beim primär metastasierten PCa. Kürzlich konnte ein STAMPEDE-Arm zeigen, dass die lokale Bestrahlung der Prostata bei diesen Patienten zu einer signifikanten Verbesserung des progressionsfreien Überlebens führte. Bisher ist unklar, ob diese Ergebnisse einen Analogschluss für die chirurgische Therapie erlauben. Kleinere, retrospektive Studien weisen in diese Richtung.

Disclosure: No conflict of interest disclosed.

V469

Role of radiation therapy

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Advanced prostate cancer is a systemic disease and thus generally treated with androgen deprivation therapy ± further systemic treatment options. Radiation therapy can be utilized to treat symptoms, prevent complications arising from tumor progression, prolong progression free survival and even enhance overall survival in selected groups of patients.
During this session, scenarios when radiation therapy may have a role in the management of advanced prostate cancer will be highlighted together with the supporting evidence from clinical trials.

Disclosure: No conflict of interest disclosed.

Freier Vortrag

Chronisch myeloische Leukämie

V476

Genotypes of the gene encoding the membrane transporter SLC22A4 are associated with molecular relapse-free survival after discontinuation of imatinib therapy in patients with chronic myeloid leukaemia

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Introduction: The single nucleotide polymorphism (SNP) rs460089 (G/C) located in the promotor of *SLC22A4* (transporter hOCTN1) was identified as a prognostic factor for the outcome of chronic myeloid leukaemia patients treated with imatinib (IM) first line (Jaruskova et al. JEC-CR 2017). Patients with GC genotype had significantly higher probability of achievement of major molecular response (MMR, BCR-ABL≤0.1% IS) compared to patients with GG. We investigated differences in the outcome after IM cessation in EURO-SKI patients according to the genotypes of the SNP rs460089.

Methods: DNA analysis was performed by TaqMan SNP genotyping assay using StepOnePlus RQ-PCR System (Thermofisher Scientific). In addition to the inclusion criteria defined for prognostic analysis in Saussele et al. (Lancet Oncology 2018), all patients with interferon pre-treatment were excluded. Data on sex, duration of IM treatment, of deep molecular response and age at time of IM discontinuation as well as molecular status at 6 months thereafter were available for 178 patients. Logistic regression was used to investigate factors affecting MMR maintenance at 6 months. Level of significance was 0.05.

Results: Of 178 patients, 106 (60%) maintained MMR 6 months after TKI stop. GC genotype was identified in 64 patients, GG in 96 and CC in 18. Most beneficial for MMR maintenance was genotype GC (72%, 95% confidence interval (CI): 60-82%), followed by CC (61%, CI: 38-80%) and GG (51%, CI: 41-61%). Overall, genotype was associated with MMR maintenance (p=0.0335) with a significantly higher odds ratio (OR) for maintenance for GC vs. GG (2.451, CI: 1.247-4.819, p=0.0093) but not for CC vs. GG (1.507, CI: 0.539-4.216, p=0.4343). Only duration of TKI treatment was significant (OR: 1.157, CI: 1.014-1.319, p=0.0303) when added to genotype in multiple regression. The OR of GC vs. GG was slightly modified to 2.311 (1.164-4.588, p=0.0166).

Conclusions: We suppose that the GC genotype is associated with sufficient intracellular concentration of IM allowing more efficient targeting of CML cells during IM treatment. This resulted in a higher proportion of patients who sustained MMR after TKI stop compared to patients with GG. Longer duration of imatinib treatment increased the probability of MMR maintenance also in patients with GG. Frequency of CC was low and outcome in between GC and GG. SNP rs460089 may provide an independent prognostic factor for molecular maintenance.

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V477

Primary results of the phase 4 BYOND study of bosutinib for pretreated chronic phase (CP) chronic myeloid leukemia (CML)

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Introduction: The tyrosine kinase inhibitor (TKI) bosutinib (BOS) is approved for patients (pts) with Philadelphia chromosome (Ph)+ CML resistant/intolerant to prior therapy and newly diagnosed pts in CP.

Methods: The ongoing phase 4 BYOND study (NCT02228382) is further evaluating efficacy and safety of BOS (starting dose 500 mg/d) for pts with TKI-resistant/intolerant CML. Primary endpoint in pts with Ph+ CP CML is cumulative confirmed major cytogenetic response (cMCyR) by 1 y.

Results: Of 163 pts who received BOS, 156 had Ph+ CP CML. In the Ph+ CP CML group, 52% of pts were male; median age was 61 y. 83 (53%) pts were resistant to ≥1 prior TKI and 73 (47%) intolerant to all prior TKIs. As of 1 y after last enrolled pt (median follow-up 30.4 mo), 56.4% remained on BOS. Median BOS duration was 23.7 mo and median dose intensity 313 mg/d. In TKI-resistant vs intolerant pts, median BOS duration was similar (23.4 vs 25.3 mo), but median dose intensity was higher (406 vs 292 mg/d). Of 144 evaluable pts with a valid baseline assessment, cumulative cMCyR by 1 y was 71.5% (95% confidence interval [CI] 63.4-78.7). Cumulative and achieved molecular response (MR) rates are shown in the Table. Of 10 pts with baseline mutations, 3 (30.0%) achieved at least major MR (MMR). 10 deaths occurred (5 on treatment); 1-y overall survival rate was 98.0%. No pt progressed to accelerated/blast phase on treatment. 25.0% discontinued BOS due to adverse events (AEs) and 5.1% due to insufficient response. Most common treatment-emergent AEs (TEAEs) of any grade were diarrhea (87.8%) and nausea (41.0%) and of grade 3/4 were diarrhea (16.7%) and increased alanine aminotransferase (ALT; 14.7%). The only TEAE leading to discontinuation in >5% of pts was increased ALT (5.1%).

Conclusions: A substantial proportion of pretreated pts achieved or preserved MMR and deep MR with BOS, further supporting its use for TKI-resistant/intolerant Ph+ CP CML. The most common reason for permanent treatment discontinuation was AEs, reinforcing the importance of appropriate therapy management. In this context, the BODO study (NCT02906696) is evaluating a run-in dose escalation schedule to improve tolerability.

Tab. 1. Cumulative MR rates

Cumulative rate any time on treatment, % (95% CI)	Ph+ CP CML		
	Total	TKI-Resistant	TKI-Intolerant
Evaluable, n	149	76	73
MMR	71.8 (63.9–78.9)	61.8 (50.0–72.8)	82.2 (71.5–90.2)
MR^4	57.0 (48.7–65.1)	46.1 (34.5–57.9)	68.5 (56.6–78.9)
$MR^{4.5}$	46.3 (38.1–54.7)	36.8 (26.1–48.7)	56.2 (44.1–67.8)
No baseline MMR, n	79	48	31
MMR	59.5 (47.9–70.4)	45.8 (31.4–60.8)	80.6 (62.5–92.5)
MR^4	38.0 (27.3–49.6)	22.9 (12.0–37.3)	61.3 (42.2–78.2)
$MR^{4.5}$	30.4 (20.5–41.8)	16.7 (7.5–30.2)	51.6 (33.1–69.8)

Disclosure: Andreas Hochhaus: Expert Testimony: Pfizer, Bristol-Myers Squibb, Incyte, Novartis
Frank Giles: Employment or Leadership Position: Actuate Therapeutics Inc, Epigene Therapeutics Inc; Advisory Role: Epigene Therapeutics Inc, Novartis; Stock Ownership: Epigene Therapeutics Inc

V478

Accumulation of DNA damage and alteration of the DNA damage response in chronic myeloid leukemia

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Purpose: The accumulation of DNA damage and the alteration of the DNA damage response (DDR) are critical features of genetic instability that is presumed to be implicated in BCR/ABL1-mediated blastic transformation of chronic myeloid leukemia (CML). The aim of our study is to analyze underlying mechanisms of genetic instability with regard to DNA damage, DNA double-strand break (DSB) repair and DDR signaling during blastic transformation of CML.
Methods: Immunofluorescence microscopy of γH2AX is performed so far for quantification of DSB in mononuclear cells (MNC) of 6 healthy individuals, 3 chronic phase (CP)-CML patients with a deep molecular response to tyrosine kinase inhibitors (TKI), 2 CP-CML patients, 1 accelerated phase (AP)-CML patient and 2 blast phase (BP)-CML patients. In addition, immunofluorescence microscopy of γH2AX/53BP1 is used for semi-quantification of error-prone DSB repair. Furthermore, immunoblotting of p-ATM, p-ATR, p-CHK1, p-CHK2 and p-TP53 is intended to be performed in MNC of CML patients in comparison to MNC of healthy individuals.
Results: Our analysis reveals an increase in numbers of γH2AX foci in MNC of CP-CML (2.2 γH2AX foci per MNC ± 0.8; mean ± standard error of mean) and AP-/BP-CML patients (4.3 γH2AX foci per MNC ± 0.9) as compared to the number of γH2AX foci in MNC of healthy individuals (1.0 γH2AX foci per MNC ± 0.1) and in MNC of CP-CML patients with a deep molecular response to TKI (0.9 γH2AX foci per MNC ± 0.0) (Figure 1 A and B). Analysis of co-localizing γH2AX/53BP1 foci in MNC suggests progressive activation of error-prone nonhomologous end-joining repair mechanisms during blastic transformation in CML. Signatures of DDR proteins in MNC of CML patients are currently awaiting further evaluation.
Conclusions: In summary, our preliminary data provide evidence for an accumulation of DNA damage in MNC of CP-CML patients towards AP-/BP-CML patients. We hypothesize that increased DNA damage and error-prone DSB repair may be critical mechanisms of blastic transformation in CML.

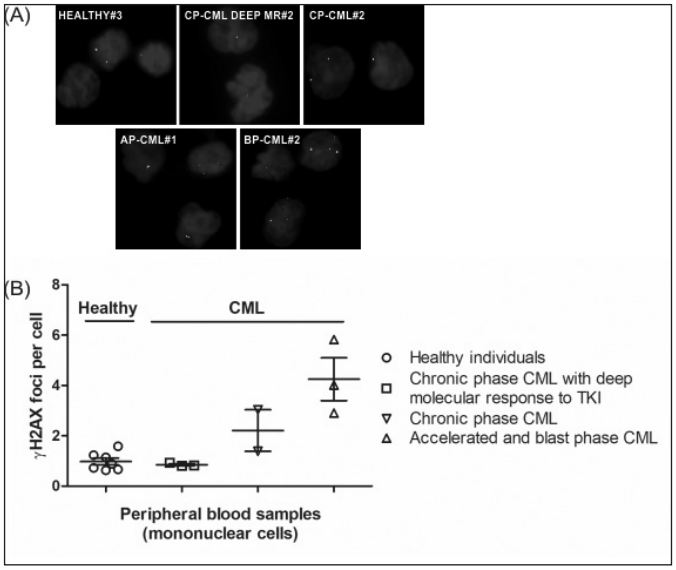

Fig. 1. Analysis of γH2AX foci in mononuclear cells of healthy individuals and CML patients

Disclosure: No conflict of interest disclosed.

V479

Dasatinib (DAS) versus Imatinib (IMA) in patients (pts) with chronic myeloid leukemia in chronic phase (CML-CP) who have not achieved optimal responses to 3 months (mo) of IMA treatment: 2-year update of the DASCERN study

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Introduction: Achievement of BCR-ABL1 ≤10% on the International Scale (IS) at 3 mo with a tyrosine kinase inhibitor (TKI) is optimal according to European LeukemiaNet (ELN) 2013 recommendations, yet one-third of first-line (1L) IMA pts fail to achieve this. In DASCERN, pts with suboptimal responses to 1L IMA who switched to DAS early (at 3 mo) had significantly higher major molecular response (MMR) at 1 year (y) than pts who remained on IMA (29% vs 13%; P=0.005). 2-y results are reported here.
Methods: DASCERN (CA180-399/NCT01593254) is a randomized, open-label phase 2b trial in adults with CML-CP with complete hematologic response but BCR-ABL1 >10% IS at 3 mo after treatment with 400 mg IMA once daily (QD). Pts were randomized 2:1 to receive 100 mg DAS QD or continue on IMA. After randomization, pts in the IMA arm who met ELN 2013 failure criteria and without DAS-resistant mutations crossed over to DAS. The primary endpoint was the rate of MMR at 12 mo after day 1 of 1L IMA. Secondary endpoints include time to MMR and $MR^{4.5}$ (BCR-ABL1 ≤0.0032% IS), progression-free survival (PFS), and overall survival (OS). Tertiary endpoints include safety and molecular response over time.

Results: All 260 pts (DAS 174, IMA 86) had ≥2 y of follow-up; 203 (79%) were continuing in the study. Median age was 37 y (range 18-82; 95% were < 65); 73% were Asian. Baseline pt characteristics were balanced between treatment arms. To date, 45 IMA-randomized pts (52%) crossed over to DAS (44 due to IMA failure). Cumulatively, 141/219 pts (64%) on DAS and 35/86 (40%) on IMA achieved MMR by 2 y. In the intent-to-treat population, 2-y PFS and OS were 96% (95% confidence interval [CI] 92, 98) and 98% (95% CI 94, 99) for pts randomized to DAS and 95% (95% CI 88, 98) and 97% (95% CI 90, 99) for pts randomized to IMA. In pts randomized to IMA who crossed over to DAS, PFS and OS were 93% (95% CI 80, 98) and 96% (95% CI 83, 99). Safety was consistent between 1 and 2y; 16 pts (9%) on DAS developed pleural effusion. Twelve pts (7%) randomized to DAS and 4 pts (5%) randomized to IMA discontinued due to toxicity.
Conclusions: In DASCERN, pts who switched to DAS early, after suboptimal responses to IMA, had significantly higher MMR at 2 y. Safety profiles were also consistent. These data further emphasize the need for early monitoring/intervention for pts who do not receive a 1L second-generation TKI and suggest that switching to DAS in such instances will increase total MMR numbers.

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Giuseppe Saglio: No conflict of interest disclosed.

V480

Impact of comorbidities on outcome with second and further line TKI treatment in patients with chronic myeloid leukemia

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Since introduction of tyrosine kinase inhibitors (TKI), life expectancy of patients (pts) with chronic myeloid leukemia (CML) has been similar to normal population. Meanwhile, overall survival (OS) is determined more by comorbidities at diagnosis than by CML itself. The impact of comorbidities at the time of switching to 2nd line therapy is unknown.
In CML IV, 1401 pts evaluable for Charlson Comorbidity Index (CCI) were analyzed at the time of switching to 2nd line TKI therapy. Pts with stem cell transplantation were excluded for this analysis. We analyzed the impact of the CCI (not considering age) at switching time on OS, progression-free survival (PFS), reason for treatment change and the type of TKI. A multistate model with the transitions "switch -> progression" and "switch -> death without progression" was estimated.
307 of 1401 pts switched to 2nd line TKI therapy. Switching was observed between 0.1 and 10.6 years after diagnosis. Median age at switch was 58 years. Age at diagnosis might be a prognostic factor for the hazard of switching (HR: 1.01, p = 0.065). The reasons for switching were treatment failure (n=165 [53%]), drug intolerance (n=137 [44%]) and others (n=11 [3%]). Treatment was switched to either dasatinib, nilotinib or bosutinib in 156 (50%), 154 (49%) and 3 pts (1%), respectively. CCI at diagnosis was 2 in 233 pts, 3 in 45 pts, 4 in 29 pts, 5-6 in 4 pts, >= 7 for no pts At switching, CCI was 2 in 198 pts, 3 in 55 pts, 4 in 35 pts, 5-6 in 16 pts, > =7 in 3 pts 46 pts had a CCI change: mainly from CCI 2 to 3 or 4 (n=27). OS ten years after switch was 68% (95% confidence interval: [56-78%]). 60 pts died during the observation period. The risk for death without prior progression was mainly influenced by the CCI at diagnosis (HR: 1.6, 95% CI: [1.1-2.2] per point, p = 0.015), the CCI at switch (HR: 1.5, 95% CI: [1.1-2.2] per point, p = 0.022) and age at switch (HR: 1.1 CI:[1.0-1.1] per year, p = 0.005). For the hazard to progression, only the age at switch had a significant effect (HR: 1.1 CI:[1.0-1.1] per year, p = 0.002.
44 of 307 pts had a change of CCI during their disease course before switching. The presence of comorbidities is an independent prognostic factor for OS in pts receiving 2nd line treatment for chronic phase CML regardless of the reason of treatment switch. If the use of a specific 2nd generation TKI has additional and differential impact on outcome has to be further investigated.

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Susanne Saussele: Financing of Scientific Research: Novartis, BMS, Pfizer, Ariad/Incyte; Expert Testimony: Novartis, BMS und Ariad/Incyte

V481

Long-term outcome after transplantation in patients with chronic myeloid leukemia from HLA-compatible unrelated donors

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Introduction: Allogeneic hematopoietic stem cell transplantation (alloSCT) is curative therapy for chronic myeloid leukemia (CML), but its long-term outcomes regarding graft sources are not well described.
Results: Here the outcomes of CML after alloSCT with bone marrow (BM, n=134) were compared to those of peripheral blood stem cell (PBSC, n=172) in the HLA-compatible unrelated donor setting. Patients were transplanted in 1st CP (Bone marrow transplantation (BMT), n=100, and Peripheral blood stem cell transplantation (PBSCT), n=103), in >1st CP (BMT, n=24, and PBSCT, n=52) and in blast crises (BMT, n=10, and PBSCT, n=17). Median follow-up were 54 months after BMT and 106 months after PBSCT. No significant differences were found in the incidence of acute and chronic graft-versus-host disease (GvHD) between both study-groups. The 5-year estimated probability of hematological relapse was 11% for patients in 1st CP CML and 49% for patients in advanced disease after BMT (p< 0.001) and 18% for patients in 1st CP and 22% for patients in advanced disease after PBSCT (p= n.s.). The estimated probability for 10-year overall survival (OS) for patients in 1st CP and patients in advanced stages of CML were 58% and 20% after BMT and 59% and 52% after PBSCT, respectively (not significant for 1st CP and p< 0.0001 for advanced stages). In the multivariate analysis patient age (age > 40 years), disease stage, acute GvHD, chronic GvHD and immunprophylaxis with use of ATG influenced OS significantly. For leukemia-free survival, the following risk factors were significantly in the multivariate analysis, graft source, patient age, gender constellation, disease stage, acute GvHD and chronic GvHD.
Conclusions: This large trial show significant difference between transplant recipients who received PBSC and those who received BM from unrelated donor. These finding may influence the selection of a graft source for alloSCT from unrelated donor.

Disclosure: No conflict of interest disclosed.

Freier Vortrag

Lungenkarzinom II

V482

Efficacy and safety of nintedanib + docetaxel in lung adenocarcinoma patients (pts) following treatment with immune checkpoint inhibitors (ICIs): updated results of the ongoing non-interventional study (NIS) VARGADO (NCT02392455)

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Introduction: Nintedanib (Vargatef®) is an oral triple angiokinase inhibitor of VEGF-, PDGF- and FGF-receptors approved in the EU and other countries in combination with docetaxel for treatment of locally advanced, metastatic or locally recurrent NSCLC of adenocarcinoma histology after 1st line chemotherapy. Data are sparse regarding efficacy and safety of nintedanib in adenocarcinoma pts who had been pre-treated with ICIs.
Methods: This interim analysis included 32 pts with locally advanced, metastatic or locally recurrent lung adenocarcinoma who received nintedanib and docetaxel in 3rd line following ICIs in 2nd line within the ongoing NIS VARGADO (cohort B); it updates and extends data previously presented at ESMO IO 2018.
Results: Median age was 60 years (range: 45 - 76), 21/32 pts (65.6%) were men, and 22/32 pts (68.8%) were ECOG PS0/1. 7/32 pts (21.9%) had brain metastases, and 25/32 pts (78.1%) were current or former smokers. 1st line chemotherapy treatments included pemetrexed (23/32 pts, 71.9%), cisplatin (20/32 pts, 62.5%), carboplatin(16/32 pts, 50.0%), bevacizumab (9/32 pts, 28.1%), vinorelbine (5/32 pts, 15.6%), paclitaxel (2/32 pts, 6.3%), and docetaxel (1/32 pts, 3.1%). 2nd line treatments included nivolumab (21/32 pts, 65.6%), pembrolizumab (7/32 pts, 21.9%), and atezolizumab (3/32 pts, 9.4%). Under nintedanib and docetaxel, 12/24 pts (50.0%) developed a partial response and 7/24 pts (29.2%) showed stable disease; DCR was 79.2% (19/24 pts). Median PFS was 7.1 months (95%CI 2.9 - 8.2). Treatment emergent adverse events (TEAEs) grade ≥3, serious TEAEs, and TEAEs leading to discontinuation were observed in 18/32 pts (56.3%), 16/32 pts (50.0%), and 12/32 pts (37.5%), respectively.
Conclusions: In this updated analysis, nintedanib in combination with docetaxel showed clinically relevant efficacy and an adequate safety profile in stage IIIB/IV lung adenocarcinoma pts following treatment with chemotherapy and ICIs. Data highlight the potential clinical benefit of rational treatment sequencing with anti-angiogenic therapy after ICIs.

Disclosure: Christian Grohé: Advisory Role: Membership on Advisory Boards
Rolf Kaiser: Employment or Leadership Position: Employee Boehringer Ingelheim Pharma GmbH & Co. KG; Honoraria: Yes, Boehringer Ingelheim

V483

Treatment patterns of EGFR mt+ NSCLC IV patients: real world data of the NOWEL network

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Introduction: The percentage of pts switching from 1st gen TKI in 1st line to 3rd gen TKI in 2nd line seems to be low with 30% and it is questionable whether these data represent real world treatments. Therefore, we investigated the treatment pattern and especially the attrition rate between 1st and 2nd line therapy in EGFR mt+ pts from the NOWEL network.
Methods: A retrospective study of 1539 pts with non-squamous NSCLC IV was accomplished. 965/1536 (63%) pts were tested for EGFR mt+ between 2009-2018. 148/965 (15%) pts with an EGFR mt+ were identified. To calculate PFS and OS we used Kaplan Meier methods and the log rang test for p-values.
Results: Baseline characteristics of 148 EGFR mt+ pts: median age 65 yrs; 64% female (n=95/148); 64% never/light smoker (n=94/148). 135/148 pts (91%) carried an EGFR mt+ either del19 (n=81) or L858R (n=55). 144/148 pts were treated with TKI on 1st or 2nd line (after chemotherapy) and 4 pts received no therapy at all. 14/144 pts are still on 1st line, 9 pts were lost to follow-up and 3 pts died while on 1st line therapy. We identified 118/144 candidates for 2nd line therapy (because of progression on 1st line TKI) and only 84/118 (70%) pts received a 2nd line therapy. 30% (36/118) of pts did not receive a 2nd line therapy because of bad PS (n=26), pts refusal (n=2), fast progression (n=6) and death (n=2). After accessibility of 3rd gen TKI 72 pts were candidates for 2nd line treatment and 51/71 pts (71%) received a 2nd line therapy. MOS of pts receiving 2nd line therapy after access to 3rd gen TKI was 35 mo for pts with 2nd line therapy vs. 10 mo without 2nd line (p< 0.000). 32/51 pts (63%) were tested for T790M and 20/32 (62%) were T790M+. Highest T790M testrate in one center was 22/28 (79%). 16/20 (80%) T790M+ pts received 3rd gen TKI for 2nd line therapy. MOS of pts receiving 3rd gen TKI (n=31) was 51 mo vs. 25 mo for pts without 3rd gen TKI (p< 0.002).
Conclusions: In real world, a significant number of pts treated with 1st or 2nd gen TKI do not reach 2nd line therapy even with broad accessibility of 3rd gen TKI. Reasons for not receiving 2nd line therapy are in most cases deterioration of PS, death and no testing for T790M in a minority of cases. These data are important for the interpretation of the OS data of the FLAURA study as they reflect real world treatment algorithms in dedicated German lung cancer centers.

Disclosure: Julia Roeper: Financing of Scientific Research: Roche, Boehringer Ingelheimer, Astra Zeneca
Frank Griesinger: Advisory Role: Astra Zeneca, Boehringer Ingelheim, Novartis, Pfizer, Roche, BMS, MSD, Celgene, Lilly, Takeda, Siemens, Abbvie, Bayer; Financing of Scientific Research: Astra Zeneca, Boehringer Ingelheim, Novartis, Pfizer, Roche, BMS, MSD, Celgene, Lilly, Takeda, Siemens, Abbvie, Bayer; Expert Testimony: Astra Zeneca, Boehringer Ingelheim, Novartis, Pfizer, Roche, BMS, MSD, Celgene, Lilly, Takeda, Siemens

V484

Mechanisms of acquired resistance to first-line osimertinib: preliminary data from the phase III FLAURA study

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Introduction: In the Phase III FLAURA study (NCT02296125), osimertinib showed superior efficacy compared with standard of care (SoC)

EGFR-TKIs in patients (pts) with previously untreated EGFRm advanced NSCLC. Here, we report preliminary data on mechanisms of acquired resistance to osimertinib in pts who progressed during the FLAURA study.
Methods: Pts with previously untreated EGFRm (tissue, ex19del/L858R) advanced NSCLC (N=556) were randomised 1:1 to osimertinib 80 mg once daily (QD; n=279) or SoC EGFRTKI (n=277, gefitinib 250 mg QD or erlotinib 150 mg QD). Paired plasma samples were collected at baseline and following RECIST progression and/or treatment discontinuation up to March 2018. Plasma samples were analysed using next generation sequencing (NGS, Guardant Health; Guardant360 73 gene panel or Omni 500 gene panel).
Results: In the osimertinib and SoC EGFR-TKI arms, respectively, 113/279 (41%) and 159/277 (57%) pts had experienced a progression event and/or discontinued treatment and had paired plasma samples analysed by NGS. Only pts with detectable plasma EGFRm (ex19del/L858R) at baseline were evaluable for this analysis: 91/113 (81%; osimertinib) and 129/159 (81%; SoC). In the osimertinib arm, there was no evidence of acquired EGFR T790M and the most common acquired resistance mechanism detected was MET amplification (amp; 14/91; 15%), followed by EGFR C797S mutation (6/91; 7%); other mechanisms included HER2 amp, PIK3CA and RAS mutations (2-7%). In the SoC arm, the most common resistance mechanisms were T790M mutation (60/129; 47%), MET amp (5/129; 4%) and HER2 amp (3/129; 2%).
Conclusions: In this paired sample preliminary analysis of a subpopulation of pts who had experienced disease progression and/or discontinued treatment, heterogeneous resistance mechanisms were detected with first-line osimertinib. Most commonly being MET amplification and EGFR C797S mutation observed. In line with previous analyses, T790M was acquired in approximately 50% of SoC-treated pts, and none of the osimertinibtreated pts; no unexpected resistance mechanisms were observed in osimertinib-treated pts. Exploration into novel acquired mutations is ongoing.
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Disclosure: Helge Bischoff: Advisory Role: Astra Zeneca, Boehringer Ingelheim, BMS, Celgene, Lilly, MSD, Otsuka, Roche; Financing of Scientific Research: Astra Zeneca, Boehringer Ingelheim, BMS, Celgene, Lilly, MSD, Otsuka, Roche; Expert Testimony: Astra Zeneca, Boehringer Ingelheim, BMS, Lilly, MSD, Roche Christian Meyer zum Büschenfelde: No conflict of interest disclosed.

V485

Real-world evidence: interim analysis of efficacy in 628 patients with stage IIIB/IV non-small cell lung cancer (NSCLC) treated with Nivolumab after prior chemotherapy in a national, prospective, non-Interventional study (ENLARGE-Lung)

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Introduction: We report interim data from patients with advanced NSCLC treated with second-line (2L) nivolumab in routine clinical practice in accordance with the German market authorization approval. The registrational trials of nivolumab in 2L NSCLC have demonstrated significantly longer overall survival (OS), higher response rates, and favorable safety profile relative to docetaxel. These real-world data complement results obtained in clinical trials.
Methods: Adult patients were recruited in 2 stratified cohorts (squamous and non-squamous histology) from 79 cancer care facilities in Germany, both office and hospital based and are being followed for 5 years from index date until death, withdrawal of consent, loss of follow-up/record or end of study. The primary endpoint is OS estimated using the Kaplan-Meier method. Baseline characteristics are reported using descriptive statistics. With the database lock on October 31, 2018, this interim analysis reports data on 628 patients observed for at least 3 months since last patient enrolled.
Results: Among the 628 stage IIIB/IV NSCLC patients who had previously received chemotherapy, the median follow-up was 7.5 months; 64.0% were male; median age was 65.0 years (40-87 years), 14.0% were ≥75 years old; 34.4% of patients had squamous histology; 84.0% were smokers; 22.2% had brain metastases, and ECOG performance status 0-1/2/≥3 was 74.4/9.9/15.1%, respectively. The median OS was 12.0 months (95% CI: 10.4-13.2 months); OS rates at 6 months and 1 year were 75.0% and 49.7%, respectively.
Conclusions: Data on patient characteristics including subgroups of interest (ECOG >1, brain metastases, age ≥75 years) and the efficacy of nivolumab are presented. These real-world data reflect treatment with nivolumab in routine clinical practice in Germany and provide information complementary to that from randomized clinical trials. The real-world OS of NSCLC patients treated with 2L nivolumab is similar to that reported from phase 3 registrational clinical trials CheckMate 017 and 057 confirming similar efficacy of nivolumab in routine clinical practice.

Disclosure: Martin Sebastian: Advisory Role: AbbVie, AstraZeneca, BMS, Boehringer-Ingelheim, Lilly, Medio-lanum, MSD, Novartis, Pfizer, Roche, Takeda; Financing of Scientific Research: AbbVie, AstraZeneca, BMS, Boehringer-Ingelheim, Lilly, Medio-lanum, MSD, Novartis, Pfizer, Roche, Takeda; Other Financial Relationships: BMS, Pfizer Christian Schumann: Advisory Role: AstraZeneca, Boehringer Ingelheim, BMS, Merck, Pfizer, Roche; Financing of Scientific Research: AstraZeneca, Boehringer Ingelheim, BMS, Merck, Pfizer, Roche; Expert Testimony: AstraZeneca, BMS, Merck, Pfizer, Roche

V486

CheckMate 384: phase 3b/4 trial of Nivolumab (Nivo) 480 mg Q4W vs 240 mg Q2W after ≤12 months of Nivo in previously treated advanced NSCLC

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Introduction: Nivo is approved as 240 mg Q2W in the EU and Japan and 240 mg Q2W or 480 mg Q4W in the US and Canada for second-line treatment of advanced NSCLC. Pharmacokinetic modeling in various tumors predicts that exposure, efficacy and safety can be maintained with less frequent Q4W dosing, which may provide a more convenient treatment option. We present an interim analysis of efficacy and safety from CheckMate 384 (NCT02713867), an international, open-label, randomized phase 3b/4 trial evaluating less frequent Nivo dosing (480 mg Q4W vs 240 mg Q2W) in patients with advanced NSCLC and prior Q2W Nivo treatment.

Methods: Patients (N = 329) with previously treated histologically confirmed stage IIIB/IV or recurrent NSCLC, ECOG performance status 0-2, and prior treatment with Nivo 3 mg/kg or 240 mg Q2W for ≤12 mo, with ≥2 consecutive assessments of complete / partial response or stable disease, were randomized 1:1 to Nivo 480 mg Q4W or 240 mg Q2W over a 30-min infusion. Co-primary endpoints: post-randomization progression-free survival rates (PFS) at 6 months (mo) and 1 year (y). Secondary endpoints included safety. Due to treatment landscape changes in NSCLC, statistical analyses were amended for a reduced sample size. One-sided 95% CIs were generated to compare PFS rates; presented data analyses are descriptive.
Results: Of 166 and 163 patients randomized to 480 mg Q4W and 240 mg Q2W, 164 and 161 patients were treated, respectively. Median follow-up was 9.5 mo (480 mg Q4W) and 10.2 mo (240 mg Q2W). Baseline characteristics were balanced between treatment arms. Stratified PFS rates post-randomization were comparable between treatment arms at 6 mo and 1 y (Table). Safety profiles were similar; any grade treatment-related adverse events (TRAEs) and TRAEs leading to discontinuation were reported in 48% vs 61% and 6% vs 9% of patients with 480 mg Q4W vs 240 mg Q2W. No treatment-related deaths were reported.
Conclusions: Nivo 480 mg Q4W showed similar efficacy and safety to 240 mg Q2W in patients with disease control on Nivo, supporting the potential use of 480 mg Q4W as a more convenient dosing option for second-line NSCLC treatment.

Tab. 1.

Table. Stratified PFS post-randomization (by histology and response pre-randomization)		
	480 mg Q4W (n = 166)	**240 mg Q2W (n = 163)**
Median, mo	12.1	12.2
HR (one-sided 95% CI)	0.96 (NA–1.29)	
Rate, %		
6 mo	75	80
1 y	53	53
NA, not applicable		

Disclosure: Niels Reinmuth: Other Financial Relationships: Investigator for BMS
Eric Pichon: Other Financial Relationships: Investigator for BMS

Freier Vortrag

Tumor-/Zellbiologie I

V489

Only hematopoietic stem and progenitor cells from cord blood are susceptible to malignant transformation by MLL-AF4 translocations

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Introduction: *MLL* rearrangements play a crucial role in leukemogenesis. Dependent on age there exist major differences regarding the frequency and main fusion partners of the *MLL* gene. In infants up to 80% of all ALLs are *MLL* leukemias with mainly *AF4* as fusion partner. In contrast, in adults only 10% of all AMLs are *MLL* leukemias with *AF9* as the main fusion partner. Recently, we established a human *MLL*-rearranged (*MLL*r) model based on patients' *MLL-AF4*/*-AF9* translocations in human hematopoietic stem and progenitor cells (HSPCs) derived from cord blood (CB) faithfully mimicking the underlying biology of the disease. Here, we transfer this model into an adult system using HSPCs from adult bone marrow (BM) allowing us to investigate the impact of the cell of origin and fusion partner on disease development.
Methods: We used CRISPR/Cas9 to induce *MLL-AF4*/*-AF9* translocations in HSPCs from human CB and BM. Translocation efficiencies were detected via Sanger sequencing, FISH and karyotyping. *MLL*r cells were characterized by proliferation behavior, surface expression, morphology, *MLL* target gene expression and finally compared to primary patient cells.
Results: Patient-specific *MLL-AF4*/*-AF9* translocations were generated with high efficiency in HSPCs from both CB and BM. Selected cytokine combinations enabled monoclonal outgrowth of translocated cells reaching 100% purity within 30 days for CB and 60 days for BM detected by FISH and karyotyping. Both expressed a myelomonocytic phenotype with CD15, CD64 and specific *MLL* surface marker like CD9. Moreover, both models demonstrated an immature morphology and elevated *MLL* target gene expression comparable to patient cells. Strikingly, all *MLL*r cells presented with indefinite growth potential over one year except for *MLL-AF4* cells derived from BM ceasing proliferation after 100 days. This indicates that *MLL-AF4* cannot immortalize an adult cell of origin under myeloid conditions. This result matches the clinical observation, where the portion of *MLL-AF4* AMLs is negligible.
Conclusions: We successfully introduced *MLL-AF4*/*-AF9* translocations with CRISPR/Cas9 in infant HSPCs derived from CB as well as in adult HSPCs derived from BM. *MLL-AF4* translocation did not result in immortalization when HSPCs derived from BM indicating a specific role of the cell of origin in this disease. Our model faithfully mimics *MLLr* leukemias and serves as an experimental platform to further shed light on the genetic basics of *MLL* leukemogenesis.

Disclosure: No conflict of interest disclosed.

V490

Oncostatin M induced metabolic changes and immune escape in the bone marrow niche

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The cytokine Oncostatin M (OSM) is released from leukemic cells harboring oncogenic mutations (FLT3-ITD, JAK2 V617F) in a STAT5-dependent manner. Since its receptor OSMR is not expressed on HSC but on bone marrow (BM) stromal cells, we assume that OSM acts in a paracrine fashion to support leukemic BM transformation. The impact on stromal cell metabolism and the immune system was investigated.

Cytokine bead arrays were performed on murine BM stromal cell lines incubated with OSM. Bioenergetic (Seahorse) assays investigated key metabolic changes. Intracellular metabolites from OSM treated cells were measured via mass spectrometry. Peripheral blood, spleens and BM specimen from retrovirally transfected BM (OSM vs. empty vector) transplanted Balb/c mice were investigated for lineage changes, T cell exhaustion ($PD1^+/TIM3^+$) and regulatory T cells (Tregs; $CD4^+/FOXP3^+/CD25^{high}$) in flow cytometry.

OSM-treatment induced strongly increased cytokine release from all investigated murine BM stromal cell lines, particularly IL-6. In Seahorse experiments, OSM increased the main parameters of aerobic (i.e. mitochondrial) and anaerobic (i.e. glycolytic) metabolism in the BM stromal cell lines. These metabolic changes were all abolished by treatment with the JAK1/2 inhibitor ruxolitinib. OSM also increased the concentrations of several intracellular metabolites, such as arginine or tryptophan (577.2% [$p< 0.01$]; 335.1% [$p< 0.01$] of untreated control, respectively). OSM overexpressing animals showed lower amounts of T- and B-lymphocytes but increased $CD11b^+/Gr1^+$-myeloid cells compared to controls. Furthermore, OSM animals showed an increased amount of Tregs (2.8% vs. 0.25%, $p< 0.001$) and, in contrast to controls, harbored phenotypically exhausted $CD4^+$- and $CD8^+$-T cells (5.1% [$p< 0.01$]; 2.3%, [$p< 0.001$], respectively).

OSM has been linked to solid tumor progression. However, its role in leukemic expansion remains unclear. We hypothesize, that OSM released from leukemic cells targets the BM niche. By inducing a strongly increased metabolic turnover rate, these cells gain the capacity for strongly increased cytokine and immunoinhibitory metabolite production. These factors induce T cell exhaustion or inhibition and thereby might prevent effective counterbalancing of leukemic cell expansion. Further effects of OSM on the niche, like induction of inhibitory myeloid derived suppressor cells additionally inhibiting antitumor immune response will be investigated in future studies.

Disclosure: No conflict of interest disclosed.

V491

Nr4a1 is implicated in the regulation of immune checkpoints in aggressive lymphomas

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Introduction: In aggressive lymphomas, low expression of *NR4A1* is associated with poor cancer-specific survival and its overexpression suppresses lymphoma cell growth indicating its tumor suppressor properties. The aim of this study was to comprehensively study the function of *Nr4a1* loss in lymphomagenesis.

Methods: Therefore, we intercrossed the *EμMyc* lymphoma mouse model with the *Nr4a1-/-* mouse and monitored them until the onset of disease. Furthermore, we transplanted lymphoma cells of *EμMyc Nr4a1-/-* and *EμMyc Nr4a1+/+* mice into immune-competent C57BL/6 mice and immune-deficient Fox Chase SCID beige mice. Finally, we determined the expression levels of the immune regulatory genes by RQ-PCR in our DLBCL patient cohort with known NR4A1 expression levels.

Results: Loss of *Nr4a1* in the *EμMyc* lymphoma model significantly accelerated lymphomagenesis. RNA-Seq data revealed upregulation of genes implicated in immune regulation (especially immune checkpoint and ligands) in *EμMyc Nr4a1-/-* lymphomas. Transplanting lymphoma cells with or without *Nr4a1* loss into immune-competent mice led to accelerated lymphoma-development and a decreased survival in the absence of Nr4a1 and to no differences in immune-incompetent mice, indicating that the loss of *Nr4a1* results in a suppression of anti-lymphoma immune response. Gene expression analysis of primary and engrafted lymphomas revealed that *Nr4a1* is specifically implicated in the regulation of *Pd1-Pdl1-Pdl2* and *Ctla4-CD80-CD86* axis. Furthermore, flow cytometry analyses demonstrated that tumors transplanted from *EμMyc Nr4a1-/-* mice exhibited a significantly higher percentage of infiltrating T cells. Interestingly, the infiltrating CD8+ T cells displayed higher expressed Pd1 on their surface in transplanted tumors derived from *EμMyc Nr4a1-/-* mice, whereas Ctla-4 has not been investigated so far. In the human setting, we detected a significant negative association of NR4A1 expression levels and the *PD1- PDL1- PDL2-* and *CTLA4- CD80-CD86* in DLBCL confirming our mouse data.

Conclusions: Our data suggest that the tumor suppressive function of *Nr4a1* is mediated by the regulation of Pd1-Pdl1-Pdl2 and Ctla4-Cd80-Cd86 axis in aggressive lymphomas. Thereby, it seems that *Nr4a1* loss significantly contributes to the immune evasion of aggressive lymphomas and that it might act as a potential target for anti-lymphoma therapy.

Disclosure: No conflict of interest disclosed.

V492

Identification of the tumor protein EpCAM as a novel mediator of extracellular vesicle biogenesis

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Introduction: Extracellular vesicles (EV) arise as an emerging field in cell-to-cell communication between tumor cells and their surrounding stroma. Among them, Microvesicles (MV) are a heterogeneous group of vesicles >100 nm in diameter directly budding from the plasma membrane, whereas Exosomes (Exo) originate from endosomal compartments and have a size ranging from 40 to 100 nm. In the tumor microenvironment, MV and Exo are now envisioned as key players to create a favorable tumor niche by transporting proteins, nucleic acids or lipids to surrounding cells. Moreover, tumor cell derived vesicles have recently been identified in the plasma of cancer patients and have been demonstrated as useful prognostic cancer biomarkers. The aim of this study therefore was to identify novel regulators involved in vesicle biogenesis which are responsible for the content and pro-tumorigenic function of tumor EV.
Methods: Syntenin, a previously known intracellular adaptor protein essential for Exo biogenesis, was knocked out by CRISPR/Cas 9. EV were isolated by differential ultracentrifugation and characterized by Proteomics, Western Blot and Nanoparticle Tracking Analysis (NTA) to identify novel interaction partners of Syntenin. Promising candidate proteins were then modulated in their expression by overexpression and knockdown approaches to assess their function in EV biogenesis and tumor progression.
Results: Mass spectrometry identified the tumor protein EpCAM as a novel interaction partner of Syntenin, which was confirmed by surface plasmon resonance spectroscopy. Using siRNA-mediated gene knockdown we confirmed that Syntenin regulates the expression of EpCAM on EV. Interestingly, characterization of the EV secreted by EpCAM knockdown and knockout cells by NTA and Western Blot demonstrated that EpCAM itself alters the composition of both, MV and Exo, suggesting that it is involved in EV biogenesis. Additionally, invasion assays indicated that the regulation of EV content by EpCAM might be important for the pro-invasive phenotype of tumor EV.
Conclusions: In conclusion, our data point towards a novel role of EpCAM in EV biogenesis and suggest that it might additionally be involved in the pro-tumorigenic function of tumor EV. Taken together, these results indicate that the well-known tumor protein EpCAM might not only be useful as a cancer biomarker, but could also functionally support tumor progression through regulation of EV secretion.

Disclosure: No conflict of interest disclosed.

V493

Human monocytes display different levels of CD137/4-1BB expression linked to certain immunometabolic features

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Emerging evidence suggests that monocytes/macrophages (MΦs) play an important role for patients' intrinsic anti-tumor immunity and for immune-based therapeutic approaches. However, anti-tumor activity of monocytes/MΦs is often diminished by tumor-associated mechanisms. Both, blocking immunological checkpoints and triggering costimulatory receptors represent viable options to enhance antitumor immune responses. One very promising costimulatory receptor is CD137 (4-1BB). Despite being well established that agonistic anti-CD137 antibodies promote metabolic fitness and functionality in lymphoid cells, little is known regarding the impact of CD137-signalling on the monocytes' biology.
CD137 expression on human healthy donor-derived monocytes was confirmed by flow cytometry. The monocyte population was dichotomized into a CD137^{high} (75th percentile) and a CD137^{low} (25th percentile) group. A variety of key molecules and functional dyes for different metabolic processes as well as phagocytic activity were assessed by flow cytometry. Furthermore, monocytes were sorted into aforementioned groups and subsequently metabolic flux as well as transcriptome analyses performed. Both monocyte populations display phenotypical and transcriptomic differences with CD137^{high} cells expressing higher CD62L and lower CD16 levels. Moreover, CD137^{high} monocytes depict an increased density of glucose transporters and expression of glycolytic pacemaker enzymes. Metabolic flux analysis performed on sorted monocytes revealed increased glycolytic capacity, glycolytic reserve, respiratory capacity and mitochondrial coupling efficacy. Both, glycolytic activity and mitochondrial coupling efficacy are linked to competent phagocytic activity. As anticipated, CD137^{high} monocytes showed an enhanced phagocytosis of bacteria and of anti-CD20/-CD38 opsonized lymphoma and myeloma cells. Finally, RNAseq revealed a distinct gene expression pattern of CD137^{high} monocytes with, amongst others, enrichment of genes involved in glycolysis, oxidative phosphorylation, and M1 *vs.* M2-polarization.
Taken together, CD137^{high} expressing monocytes comprise a subpopulation of human monocytes characterized by superior metabolic support, enhanced phagocytic activity, and distinct gene expression pattern with enrichment of genes linked to M1 polarization. These results may indicate a potential agonistic effect of therapeutic antibodies in combination with CD137 costimulating agents through the monocyte-/MΦ-compartment.

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V494

Oncogene induced oncostatin M reprograms the stem cell niche promoting leukemic transformation

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Introduction: "Niche hijacking" by leukemic cells has recently been shown to contribute to leukemic cell expansion as well as enhanced survival of leukemic stem cells. However, the factors that mediate this interaction are mainly unknown so far. In previous publications we could demonstrate that STAT5-activating oncogenes like FLT3-ITD induce overexpression of Oncostatin M (OSM) in leukemic cells. Furthemore, OSM overexpression in the murine bone marrow (BM) transplantation model leads to the induction of a myeloproliferative syndrome (MPN).
Methods: We have analyzed the expression of OSM and its receptor OSMR in human and murine cell lines as well as patient samples using qRT-PCR and flow cytometry. The production of inflammatory cytokines by BM stroma cells was assessed using cytokine-specific bead arrays. The impact of OSM on leukemia induction was validated by transplantation of *Osm*-deficient oncogenic murine BM cells into wild type recipient mice.
Results: OSM was found to be overexpressed in cell lines and mouse models of acute myeloid leukemia, chronic myeloid leukemia as well as MPN. Its receptor OSMR however, is not expressed on leukemia cells themselves, but can be found on human and murine bone marrow stroma cells. Treatment of murine BM stroma cell lines with OSM led to a strongly increased release of interleukin-6 and other proinflammatory cytokines. Strikingly, transplantation of FLT3-ITD$^+$ and Bcr-abl$^+$ *Osm*-deficient BM cells resulted in a significantly delayed onset of the leukemic disease compared to wild type BM cells. Furthermore, *Osm* knockout impaired the

onset of the polycythemia vera disease phenotype in Jak2-V617F$^+$ mice as well as the MPN phenotype of FLT3-ITD$^+$ mice.
Conclusions: We demonstrate that OSM is released by STAT5 activating oncogenes like FLT3-ITD, Jak2-V617F and Bcr-abl. However, OSM does not directly influence leukemic cells but rather activates BM stroma cells resulting in an inflammatory phenotype, which in turn favors myeloproliferative expansion of the leukemic cells. As a consequence, *Osm*-deficient oncogenic mouse models display an increased disease latency and an impaired phenotype. We therefore validate OSM as a novel therapeutic target in myeloid leukemic diseases.

Disclosure: No conflict of interest disclosed.

Freier Vortrag

Sarkome

V495

Supportive intervention to improve quality of life (QoL) for patients with soft tissue sarcoma (STS) undergoing palliative treatment: a multicenter, clusterrandomized, controlled trial within the German Interdisciplinary Sarcoma group

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Introduction: The choice of drug treatment in advanced soft tissue sarcoma (STS) continues to be a challenge regarding efficacy, quality of life (QoL) and toxicity. Unlike other cancer types, where integrating patient-reported outcomes (PRO) has proven to be beneficial for QoL, there is no such evidence in patients with STS yet.
Methods: This cluster-randomized multi-center study explored the effect of a comprehensive supportive intervention on QoL in patients with advanced STS undergoing anticancer treatment. Seven hospitals were randomized into control cluster (CG with electronic assessment of PRO) or interventional cluster (IG including ePRO and expert-consensus based treatment recommendations). Outcomes were assessed at baseline, after 3, 6 and 9 weeks and included QoL (measured with FACT-G), symptoms (MDASI), anxiety and depression (HADS), pain intensity and interference (BPI) and survival. The explorative primary endpoint was change of FACT-G total score after nine weeks.
Results: QoL declined less in IG (Δ FACT-G total score: -2.4) than in CG (Δ FACT-G total score: -3.9; $p = 0.765$). The effect size of the intervention on the FACT-G score was d = 0.269 (small effect). Overall mean survival was longer in IG (648 days) than in CG (389 days, $p = 0.110$). Means of progression-free survival were almost identical in IG (249 days) and CG (232 days, $p = 0.899$). FACT-G total score was predicted by each of the following: symptom severity, symptom interference, depression and anxiety. No influence were found regarding age, gender, ECOG, patient-satisfaction, anorexia/cachexia.
Conclusions: This trial adds knowledge to the scarce data about PROs in advanced STS patients. Unlike previous work, it is the first trial that applies an electronic PRO-assessment and remote intervention in STS-patients in a multi-center approach. Overall, the intervention seem to improve several aspects of QoL. Nevertheless, not all outcome dimensions were improved. This trial can serve as the cornerstone for future research.

Tab. 1. Outcome Measures

Patient Reported Outcomes	IC	CC	RC	p-value (between IG and CG)	Direction of the interventional trend
FACT-G total Mean change after 9 weeks	-2.4	-3.9	-3.8	0.955	beneficial
FACT-G physical well-being Mean change after 9 weeks	-1.2	-2.2	-2.1	0.722	beneficial
FACT-G social well-being Mean change after 9 weeks	-1.6	-0.3	0.5	0.193	adverse
FACT-G emotional well-being Mean change after 9 weeks	0.9	-0.1	0.1	0.561	beneficial
FACT-G functional well-being Mean change after 9 weeks	-0.5	-1.3	-2.3	0.536	beneficial
HADS depression Mean change after 9 weeks	0.3	0.2	-0.3	0.419	equivalent
HADS anxiety Mean change after 9 weeks	0.3	-0.8	-0.6	0.710	adverse
BPI average pain Mean change after 9 weeks	0.6	0.2	-0.6	0.788	adverse
BPI pain interference Mean change after 9 weeks	0.4	0.1	-0.2	0.679	adverse
MDASI, symptom severity Mean change after 9 weeks	0.7	0.2	-0.2	0.442	adverse
MDASI, symptom interference Mean change after 9 weeks	1.2	0.8	0.2	0.667	adverse

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V496

Defective homologous recombination DNA repair as therapeutic target in advanced chordoma

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Chordomas are rare tumors of the axial skeleton and skull base with few therapeutic options and no clinically validated molecular drug targets. We performed whole-exome and genome sequencing of tumor and matched germline control samples from 11 patients with locally advanced or metastatic chordoma within the MASTER program. Genomic profiling showed that advanced chordomas are frequently characterized by genomic patterns indicative of defective homologous recombination (HR) DNA repair. First, DNA copy number profiles showed high numbers of structural variants greater than 10 million base pairs in size in the majority of cases. Second, all patients harbored somatic aberrations of at least 2 genes

known to be involved in HR, and 10/11 cases harbored somatic alterations in 3 or more HR pathway genes. For example, 8 patients showed heterozygous BRCA2 deletions, which were associated with heterozygous deletions of ERCC6 in 6 patients and RAD54L in 7 patients, as well as PTEN alterations. Other recurrently altered HR genes included ATR, CHEK2, FANCC, FANCD2, FANCG, RAD18, RAD51B, and XRCC3. Third, pathogenic germline alterations were detected in 3 patients. A heterozygous BRCA2 frameshift mutation, a heterozygous NBN frameshift mutation, and a heterozygous CHEK2 missense mutation were accompanied by somatic deletion of the respective wildtype alleles. Fourth, a mutational signature associated with HR deficiency was significantly enriched in 72.7% of samples and coincided with genomic instability. The high prevalence of an HR deficiency "footprint" in chordoma patients prompted us to explore the clinical efficacy of the poly(ADP-ribose) polymerase(PARP) inhibitor olaparib, which is preferentially toxic to HR-incompetent cells. Olaparib treatment of a patient whose tumor showed a prominent exposure to an HR deficiency-associated mutational signature, a high degree of genomic instability, and 13 heterozygous HR gene alterations halted tumor growth for 10 months. Whole-genome analysis at progression revealed a PARP1 p.T910A mutation predicted to disrupt the autoinhibitory PARP1 helical domain, providing novel insight into the mechanisms of PARP inhibitor resistance. In summary, our study has uncovered a key biological feature of advanced chordoma that represents an immediately actionable therapeutic target and provides a rationale for genomics-guided clinical trials of PARP inhibition in this intractable tumor entity.

Disclosure: No conflict of interest disclosed.

V497

Syngeneic orthotopic soft tissue sarcoma model to study immune checkpoint combination therapies

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Soft-tissue sarcoma represents a very heterogenous group of mesenchymal tumors originating from connective tissues that are classified into subtypes according to their distinct pathological and molecular characteristics. Although the majority of soft tissue sarcomas are sporadic several genetic predispositions and environmental factors have been described to promote their development. Since treatment options like surgery, radiation or chemotherapy are limited, the improvement of treatment is an area of high unmet clinical need. Using a newly established autochthonous soft tissue sarcoma mouse model we want to study the efficacy of immunotherapeutic combination therapies and decipher the molecular mechanisms that are related to response or resistance.

Our soft-tissue sarcoma model is based on the direct injection of sarcoma cell lines into the hindlimb gastrocnemius muscle of mice. The injected cell lines were taken from tumors generated either by Adeno-Cre Virus injection into the hindlimb muscle of mice with conditional $Kras^{G12D}$ and $Trp53^{fl/fl}$ mutations or into conditional $Trp53^{fl/fl}$ mice that were additionally treated with 3-methylcholandrene. Beside the monotherapy with anti-PD-L1 antibodies solitary tumors were also targeted by different combination therapies including anti-angiogenic antibodies or chemotherapeutic approaches. Our preliminary data indicate that sarcoma bearing mice show prolonged survival and response to PD-L1 blockade in combination with anti-angiogenic therapy.

Based on this sarcoma mouse model we are now able to study novel treatment combinations and to perform functional analysis of the tumor microenvironment as well as to investigate the impact of somatic mutations in the tumor cells itself.

Disclosure: No conflict of interest disclosed.

V498

Monocentric analysis to identify clinical prognostic factors for angiosarcoma

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Introduction: Angiosarcoma (AS) is a very rare and aggressive subtype of soft tissue sarcomas (STSs). Hereby, AS represent a very heterogeneous subtype, that can be divided in cutaneous AS (cAS) and soft tissue AS (sAS) as well as in primary and secondary (radiation-associated (RAAS), chronic lymphedema). Whereas sAS have a high risk of metastasis and risk stratification is done analog to other STSs, cAS show a high risk of local recurrence with mutilating growth and no clear prognostic parameters. Current staging classifications lacking histotype-specific validation. Identification of prognostic parameters are urgently needed.

Methods: We performed a comprehensives analysis of patients with the diagnosis AS that were presented or treated at our center between May 1980 to November 2018. Covariates included basic demographic data, tumor characteristics and treatment in order to identify potential prognostic factors.

Results: In 197 AS patients extracted from our institutional database the median age was 62.5 (17-90) years, with a slightly female predominance (54.9% vs 45.1%). The majority of our cases were primary AS (61.1%) followed by RAAS (32.3%) and chronic lymphedema (2.1%). In the group of cAS, the majority were located on the scalp (67.4%) followed by extremity (13%), while sAS were mainly seen in the trunk (76.9%). The median overall survival (mOS) in our cohort was 20 months (±1.6), that differed between cAS (mOS: 31 months (±6.7)) and secondary AS (mOS: 31 months (±5.6)) compared to sAS (19 months (±1.9) and primary AS (15 months (±1.9)). Larger size of the primary was associated with poorer survival (≤5cm: mOS of 31 months) vs >5cm: mOS of 20 months).

Conclusions: The UICC-classification is most likely to underestimate the malignant potential of angiosarcomas. Nomograms and app-based risk classifiers only cover a fraction of patients. We hypothesize that additional factor apart from size and depth are needed to predict survival in AS.

Disclosure: No conflict of interest disclosed.

V499

Long-term response to Nilotinib therapy in Gastrointestinal Stromal Tumor (GIST) harboring pY823D resistance mutation in KIT Exon 17

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We present the case of a 75 year old Caucasian female patient who presented with fulminant gastrointestinal bleeding in 2012. Finally, resection of the jejunum was done to stop hemorrhage. Pathological analysis revealed a GIST characterized by a gain-of function mutation in the c-KIT gene at Exon 11 (c.1651_1671delinsTTC). Considering the low risk of disease progression no adjuvant therapy was performed. Follow-up care was inconspicuous.

In March 2014, a CT scan revealed novel hepatic metastases. Masatinib first line treatment was started within the AB04030 study. A biopsy of the

newly diagnosed hepatic metastasis was done two years later after slow tumor progression had been observed over time. Molecular diagnostics revealed a secondary KIT mutation in Exon 17 (pY823D) which is known to procure resistance to the tyrosine kinase inhibitors Imatinib and Sunitinib in vitro. Therefore hepatic metastases were resected completely. A second line therapy with Imatinib was started assuming that the other tumor manifestations do not harbor the specific Exon 17 resistance mutation and lacking other therapeutic options. Unfortunately, CT scan follow-up showed new metastases after six months. Subsequent therapies comprised the established tyrosine kinase inhibitors Sunitinib for three months and fourth-line Regorafenib for nine months, eventually resulting in progressive disease.
In September 2017, off-label treatment with Nilotinib was started. Efficacy of Nilotinib had been reported for mutations in KIT Exon 17 encoding the activation loop region of KIT-kinase. Regular CT-scans revealed tumor remission followed by stable disease. No relevant adverse events were reported by the meanwhile 81 years old patient who is still under therapy with Nilotinib.
Collectively, the presented case can be seen as a powerful example of rationally applied molecularly targeted therapies and, to our knowledge, represents the first case report of a durable therapy response to Nilotinib for GIST harboring the pY823D resistance mutation in KIT Exon 17.

Disclosure: No conflict of interest disclosed.

V500

Synergistic apoptosis induction in soft-tissue sarcomas by BH3-Mimetic and Bortezomib

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Introduction: Soft-tissue sarcomas (STS) comprise a rare group of mesenchymal malignancies predominantly affecting children and young adults. The heterogeneity of this disease makes it hard to find appropriate therapy options. Today's intensive treatment regimens including multimodal chemotherapy, extensive surgery, and radiotherapy in metastatic diseases are still associated with a poor five-year survival rate of 50%. This highlights the urgency for new efficient therapies. We aimed to develop a combination therapy for the treatment of STS.
Methods: In order to develop a synergistic combination therapy we focused on BH3-mimetic drugs, such as Venetoclax, combined with Bortezomib. The synergistic activity of the treatment combination was validated *in vitro* in various sarcoma subtypes including Rhabdomyosarcoma, Leiomyosarcoma, Liposarcoma, Synovial sarcoma, Chondrosarcoma, and Osteosarcoma.
Results: We show that Venetoclax and Bortezomib synergistically induce cell death in sarcoma cell lines. Proteasome inhibition by Bortezomib enhances the expression of the BH3-only protein Noxa as well as Bok, a homologue of the pore forming Bcl-2 effector proteins Bax and Bak. Enhanced expression of pro-apoptotic Noxa and Bok and simultaneous inhibition of anti-apoptotic Bcl-2 by Venetoclax resulted in efficient apoptosis induction with mitochondrial accumulation of pore forming proteins and phosphatidylserine exposure.
Conclusions: Venetoclax and Bortezomib synergistically induce apoptotic cell death in various sarcoma subtypes. We propose that these drugs synergize by simultaneously inhibiting the anti-apoptotic proteins Bcl-2 and Mcl-1 as well as stabilizing pro-apoptotic Noxa and Bok, thus leading to a predominance of pro-apoptotic factors and high apoptotic priming. This study provides preclinical *in vitro* data for combined treatment with Venetoclax and Bortezomib as a therapeutic option for the effective therapy of STS. In line, a phase 3 clinical trial in relapsed/refractory Multiple Myeloma patients shows higher response rates (but increased risk of death due to sepsis, pneumonia, and cardiac arrest) following Venetoclax, Bortezomib and Dexamethasone combinational treatment (Bellini, NCT02755597).

Disclosure: No conflict of interest disclosed.

Freier Vortrag

Multiples Myelom I

V501

High dose bendamustine and melphalan (BenMel) - a novel conditioning approach before second autologous transplantation in myeloma patients

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Introduction: Consolidation in myeloma patients with high-dose melphalan chemotherapy (Mel HDCT) and autologous transplantation (ASCT) is standard of care since more than two decades. However, definite cure remains exceptional despite intensive treatment, and improving effectiveness of HDCT remains an unmet clinical need. Combining intensified bendamustine with melphalan (BenMel) for high-dose chemotherapy together with ASCT may represent a novel conditioning option for myeloma patients.
Methods: In this single-center prospective study, we analyzed safety and efficacy of combining dose-intensified bendamustine (200 mg/m^2 on days -4/-3) with high-dose melphalan (100 mg/m^2 on days -2/-1) before a second (tandem) ASCT in twelve myeloma patients, who have received Mel HDCT/ASCT1 for consolidation of first-line remission. We compared toxicities, engraftment and duration of hospitalization between standard melphalan conditioning (ASCT1) and BenMel HDCT/ASCT2.
Results: Twelve patients received BenMel conditioning before ASCT2 because of high-risk cytogenetics and/or failure to achieve complete remission (CR) after standard Mel HDCT/ASCT1. Comparing Mel HDCT/ASCT1 and BenMel HDCT/ASCT2, we observed no differences in hematologic recovery and tolerance. Acute renal injury after BenMel conditioning occurred in three (25%) patients, but was reversible in all cases, and there were no treatment related deaths. Cardiac toxicities were observed in two patients (17%) after Mel HDCT/ASCT1, but were not observed following BenMel HDCT/ASCT2. Neutrophil recovery was similar after BenMel HDCT/ASCT2 as compared to Mel HDCT/ASCT1 (day +11 versus day +12), and all patients had complete neutrophil and platelet recovery after BenMel HDCT/ASCT2. Duration of hospitalization was not different after Mel HDCT/ASCT1 compared to BenMel HDCT/ASCT2 (17 days and 18 days, respectively). The CR rates were increasing from 42% after Mel/ASCT1 to 75% after BenMel/ASCT2 (Figure 1). We identified a PFS one year after ASCT2 was 67% and OS was 83%, and the median PFS was 18 months, while the median OS was not reached.
Conclusions: These data suggest that dose-intensified bendamustine with melphalan conditioning is both safe and effective, and warrants a prospective randomized comparison to standard melphalan HDCT in myeloma patients as a conditioning treatment also before ASCT1.

Disclosure: No conflict of interest disclosed.

V502

Novel druggable targets through functional shRNA-based screening for Notch effectors in multiple myeloma cells

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Drug resistance of multiple myeloma (MM) cells and side effects of chemotherapeutic agents remain major challenges in the treatment of MM patients. Further improvement of treatment strategies requires the identification of novel drug targets. Deregulation of Notch1 signaling promotes MM onset, progression, and drug resistance. Although a promising target, inhibition of the Notch pathway through γ-secretase inhibitors is impeded by serious side effects. Therefore, we aim at identifying novel druggable Notch1 downstream effectors by employing shRNA-based high-throughput (HT) functional screening.

We performed genome-wide expression profiling by RNA sequencing. 842 genes were differentially expressed after inhibition of the Notch pathway in MM.1S cells. As targets for two tailored shRNA libraries we chose 40 downregulated and 28 upregulated genes based on strength and consistency of regulation (log2FC; padj < 0.05). Targets comprise enzymes, transcriptional regulators, and growth/migration-associated genes.

Negative functional screens were carried out using U266 cells engineered to stably express Notch1 variants: intracellular Notch (NIC), the active and γ-secretase-independent form, and NΔE, a membrane-bound and γ-secretase-dependent form. Testing NΔE allows for the identification of cytoplasmic Notch interaction partners mediating drug resistance. U266-NIC/NΔE cells were maintained as bulk cultures and used for single-cell cloning. Notch expression levels were determined by flow cytometry analysis and immunoblotting. Viability assays of chemotherapeutic-treated U266 cells showed reduced cell death in the presence of Notch1, confirming its role as survival factor. For screening, U266 cells were transduced with the corresponding shRNA library and cultured under the selective pressure of melphalan, bortezomib or lenalidomide. After six cell cycles the abundance of shRNAs of treated vs. untreated samples was analyzed by HT sequencing. Screen hits hold great potential, as our libraries selectively target subsets of promising genes in view of druggability and relevance, e.g. known key players of MM progression and bone disease such as the Runt-related transcription factor 2 (RUNX2). Selected target genes are further involved in signaling pathways associated with cancer drug resistance, e.g. the Wnt pathway. We will validate screen hits *in vitro* using MM cell lines and *in vivo* using the MM mouse models BALB/c-MOPC315.BM and VK*MYC.

Disclosure: No conflict of interest disclosed.

V503

Mechanical skeletal stimuli cause molecular changes of the extracellular matrix in myeloma bone disease in mice and control dissemination of myeloma cells

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Introduction: Of the patients diagnosed with multiple myeloma (MM), 80% already suffer from MM bone disease, exhibiting osteolytic bone destruction or osteopenia. MM treatment has not yet succeeded in healing bone lesions or regenerating bone even in the absence of active disease. We recently showed in mice that local mechanical loading has anabolic effects and directly affects disease progression and MM dissemination. To evaluate underlying molecular mechanisms, we performed RNA sequencing analysis of cortical bone after mechanical loading. We hypothesized that osteocytes as key orchestrators of the tumor microenvironment modulate the anabolic response and alter tumor biology through extracellular matrix (ECM) changes.

Methods: The 8-week old female Balb/c mice were injected in the left tibia with either syngeneic MOPC315.BM MM cells (36 mice), PBS (36 mice) or were not injected (18 mice). At 14 days after injection, half of the mice from the MM and PBS group and all noninjected mice underwent a single session of tibial compression (-10N) to the left tibia (right tibia as control) and were sacrificed 1h, 8h or 24h following loading (n=5-7 mice/group). The other mice served as non-loaded controls. Total RNA was extracted from cortices of dissected tibiae. RNA sequencing was performed and differential gene expression was analyzed with the EdgeR software package. The Gorilla tool was used for Gene Ontology (GO) enrichment analysis.

Results: Osteocytic gene expression of MM-infiltrated bones compared to PBS-injected bones showed two clearly distinguishable transcriptional profiles. Further, GO analysis of the downregulated MM transcripts revealed that ECM genes were among the most enriched gene sets. Alterations of the ECM affect proliferation, migration and survival of MM cells and have therefore implications for tumor progression and metastasis. Interestingly, anti-angiogenic factors such as Tenascin XB and Collagen Type IV Alpha 1 Chain were part of this gene set. Both factors might be relevant for MM growth. Mechanical loading upregulated the expression of those ECM associated genes, suggesting that osteocytic mechanotransduction could restore the MM-impaired bone matrix.

Conclusions: Our data profile the osteocytic response to tumor and mechanical loading. We identified molecular changes underlying the anabolic adaption and the effects of loading on MM progression. Our study could be the basis for the development of novel targets for treatment of MMBD in patients.

Disclosure: No conflict of interest disclosed.

V504

The BCMA CAR T cell therapy idecabtagene vicleucel (ide-cel/bb2121) in relapsed and refractory multiple myeloma (RRMM): outcomes from phase 1 study support the phase 3 KarMMa-3 study design to compare ide-cel versus standard triplet regimens

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Introduction: New anti-myeloma agents have improved the treatment options for RRMM patients. However, poor overall survival (OS) of 7.9 months was reported in patients with >3 prior therapies. The CRB-401 phase 1 study (NCT02658929) evaluated ide-cel, a BCMA CAR T-cell therapy, in RRMM patients. In the dose-escalation cohort, patients received ≥3 prior therapies including a proteasome inhibitor (PI), immunomodulatory drug (IMiD), or were double-refractory. In the expansion cohort, in addition, patients received an anti-CD38 antibody and were refractory to last therapy (progressive disease at ≤60 days).

Results of the first 33 consecutive patients showed that non-hematologic toxicities, including cytokine-release syndrome and neurotoxicity, were mostly grade 1/2. Objective response rate across all dose levels was 85% (complete response 45%); median progression-free survival (PFS) was 11.8 months (95% CI: 6.2-17.8). All 16 evaluable responding patients were minimal residual disease (MRD)-negative ($\leq 10^{-4}$ nucleated cells) (NEJM 2019). Ide-cel has been granted PRIME eligibility by EMA and breakthrough therapy designation by FDA in RRMM. KarMMa, the phase 2 pivotal study (NCT03361748) has completed accrual (140 patients as of Nov 2018). Informed by these studies, KarMMa-3 (NCT03651128), a phase 3 multicenter randomized trial, is designed to confirm efficacy and safety of ide-cel in earlier treatment lines.

Methods: KarMMa-3 compares efficacy and safety of ide-cel vs standard triplet regimens in RRMM. Eligible patients have received 2-4 prior regimens, including an IMiD, PI, and daratumumab and are refractory to last therapy. Exclusion criteria include prior allogeneic stem cell transplantation, BCMA-targeted therapy, or active infection. Patients are randomized 2:1 to receive either ide-cel treatment that includes lymphodepletion prior to infusion of 150 to 450×10^6 CAR+ T cells, or a standard triplet regimen based on most recent exposure, such as DPd, DVd, or IRd at investigator's discretion. A bridging therapy with a triplet regimen is allowed prior to lymphodepletion in the ide-cel arm. The primary endpoint is PFS. Secondary endpoints include OS, safety, MRD-negative status, and health-related quality of life. Patient accrual is ongoing.
Conclusions: RRMM patients have poor outcomes despite increasing treatments options. The CRB-401 data in patients who received ≥3 prior therapies support investigating ide-cel in earlier treatment lines, as planned in KarMMa-3.

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V505

The Fc-optimized anti-ICAM-1 antibody MSH-TP15 Fc-eng. efficiently recruits immune cells and eliminates malignant plasma cells in vitro and in vivo

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Introduction: Multiple myeloma (MM) is a malignant plasma cell disorder for that no curative therapy exists. Today, the monoclonal antibodies daratumumab and elotuzumab are successfully used in combination regimen for MM treatment, but there remain substantial numbers of patients for which potent novel molecules are required.
Methods: Using phage display and cellular screening, we previously generated a scFv-Fc fusion protein, which recognized intercellular adhesion molecule 1 (ICAM-1/CD54) and prevented MM growth *in vivo*. To further evaluate the antibody's modes of action, human IgG1 antibody variants were generated bearing wild-type (MSH-TP15) or mutated Fc to either enhance (MSH-TP15 Fc-eng.) or prevent (MSH-TP15 Fc k.o.) Fcγ receptor (FcγR) binding. ICAM-1 binding epitope was investigated by flow cytometry with CHO cells expressing truncated ICAM-1 molecules and by cross-blocking with other CD54 antibodies. Functional assays included growth inhibition by MTS and thymidine incorporation. Antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) were investigated in ^{51}Cr-release assays with NK cells and serum, respectively. Antibody-dependent cellular phagocytosis (ADCP) was tested by flow cytometry. *In vivo* efficacy was analyzed in INA-6 MM xenograft models.
Results: Antigen binding studies demonstrated MSH-TP15 binding to ICAM-1 domain 1-2. Furthermore, the antibody Fc variants showed the expected differences in FcγR binding. This translated into efficient recruitment of macrophages for ADCP and engagement of NK cells for ADCC of MM cell lines and patient-derived MM cells predominantly by the Fc-optimized MSH-TP15 Fc-eng.. CDC activity was absent with all tested variants. No direct anti-proliferative effects on MM cells or patient-derived bone marrow stromal cells were observed while in co-culture MM cell growth was inhibited by MSH-TP15. Importantly, both, MSH-TP15 and MSH-TP15 Fc-eng., but not MSH-TP15 Fc k.o., dose-dependently inhibited tumor growth and prolonged survival in MM xenograft models. These results underline the importance of Fc-dependent mechanisms of action of MSH-TP15 *in vivo* as well.
Conclusions: The human, Fc-engineered CD54 antibody MSH-TP15 Fc-eng. exerts potent anti-myeloma activity *in vitro* and *in vivo*. The antibody efficiently recruits immune effector cells and predominantly functions via Fc-mediated mechanisms of action. Therefore, it has promising characteristics for MM immunotherapy.

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V506

Treatment reality of patients with multiple myeloma 2012-2017 in Germany

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Introduction: Survival of patients with Multiple Myeloma (MM) has improved in prospective randomized trials (RCT) due to new treatment options with IMIDS, proteasome inhibitors (PI) and monoclonal antibodies (MAb). Real world data concerning treatment and outcome from unselected patients who receive routine care are not known.
Patients and methods: Multicentre retrospective analysis of 1,000 unselected patients with MM who were treated between 01/12-12/17 in eight community-based oncology group practices in Germany. Data were extracted from patient files into a data base and analyzed statistically using SPSS.
Results: So far 464 patients have been documented, data from 1,000 patients will be presented at the meeting. 44% were female, 56% male. Median age was 70 (35-92). 406 patients (88%) fulfilled CRAB-criteria for cytoreductive treatment. First line treatment consisted of Bortezomib (V)+Melphalan+Prednisone (VMP) in 21%, Bortezomib+Cyclophosphamide+Dexamethasone (VCD) in 15%, V+Dexamethasone (D) in 14%, IMIDS+D in 7% and MP in 2%, 16% received other therapy combinations. 24% were treated with high dose Melphalan and stem cell transplantation. 35% received a doublet, 56% a triplet and 4% a quadruplet as first line therapy. Second line therapy consisted of IMIDS+D in 30%, V+D in 13%, VMP in 8%, VCD in 7%, MAb and MAb combinations in 5%, KRD in 4% and KD in 1%. 13% had high dose Melphalan and stem cell transplantation. Third line therapy consisted of IMIDS+D in 36%, V+D in 11%, MAb and MAb combinations in 11%, Bendamustine in 6%, VMP in 4%, VCD and KRD in 3% respectively and KD in 2%. 6% had an allogeneic stem cell transplantation. 10 of 406 patients (2%) were treated within a RCT. Pts received a median of 2 therapy lines (1-14). 65% had osteoprotective therapy with a bisphosphonate. Median overall survival (OS) of the whole cohort was 78.1 months (0.6-254.6+). OS was strongly dependent on age, comorbidities and ECOG performance status. Median OS of the age cohorts 35-60, 61-70, 71-75 and 76-92 was 111.7 (10.2-254.6+), 95.4 (0.6-201.5), 72.6 (0.6-199.8+) and 48.3 (1.3-111.5) months respectively. This was statistically significant with a p value of $< .001$.
Conclusions: Pts with MM who are treated in routine care receive therapy as suggested by international recommendations. Survival has improved compared to historical controls and is strongly dependent on age, comorbidities and performance status.

Disclosure: No conflict of interest disclosed.

Wissenschaftliches Symposium

Ethik: Off-label Einsatz von Medikamenten

V515

Off label use: Patients' preferences and implications for medical counseling

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Why do cancer patients and their relatives turn to the Cancer Information Service of the German Cancer Research Center to ask about off label use? According to our experience, they are frequently in a situation with no standard treatment available (not any more). Others are looking for alternative treatment options that may be more effective or less toxic than the standard treatment. In general, cancer patients are usually looking for an effective medical treatment for their disease - independent of its classification as off label use or standard treatment.
For doctors, off label use implicates especially high standards in patients' counseling about possible oncological effectiveness and possible risks or side effects. As usual, all important aspects of the medical counseling have to be documented. Another important aspect that has to be discussed with the patient refers to the question whether the medical insurance will cover the costs for the therapy. For cost coverage, doctors have to provide the insurance with a comprehensible, detailed statement to explain why the treatment is medically indicated.

Disclosure: No conflict of interest disclosed.

Wissenschaftliches Symposium

Palliativmedizin: Angehörige und Partnerschaft

V520

Family caregivers of cancer patients - what is the role of the oncologist?

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Cancer does not only affect the patients, but also their families and friends. For one thing, family caregivers represent an important part of the patient`s care system solving as supporter, counselors or even carer. One the other hand, they have own sorrows, questions, problems and needs. Dealing with this double role is often challenging - not only for the family caregivers, but also the patients and heath care professionals. In daily oncology practice, family caregivers are often addressed as important supporter or counselor of the patient, but not as a person who is also affected by the patient`s cancer. In addition, knowledge about the specific problems and needs of cancer patients` family caregivers is not routinely prevalent and health care structures do not include additional space for family caregivers. While, oncology care usually focusses on the patients primarily, in palliative care of advanced cancer patients, improving quality of life of both, patients and their family caregivers, represents central treatment aims. This is based on the knowledge that there are several dyadic effects on psychosocial problems, quality of life and well-being between cancer patients and their family caregivers. Further, improving the family caregivers` psychological situation, their self-efficacy as well as competences and meeting their information and support needs will strengthen the patients` care system persistently.
An overview on problems and needs of cancer patient`s family caregivers of which oncologist should be aware of as well as resulting recommendations for daily clinical oncologist practice will be presented. The role and tasks of oncologists dealing with family caregivers of cancer patients will be discussed.

Disclosure: No conflict of interest disclosed.

V521

Detecting and managing challenging interactions with family caregivers of terminally ill patients

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Family caregivers of terminally ill patients often attend medical consultations, participate in decision-making in the cancer setting. At times, family caregivers' behavior can add complexity to patient care and lead to challenges in the health professional's interaction with family caregivers. Managing complex situations may be even more challenging as family caregivers themselves may perceive that they are acting in the patient's best interest.
Dealing with challenging interactions with family caregivers is a relevant source of stress for health professionals and can cause tension in the healthcare team. In case challenging interactions are not managed well, they may impede the quality of patient-health professional communication, reduce the patient's autonomy, neglect patient's subjective needs or hamper the delivery of effective patient care. Scenarios of challenging interactions with family caregivers, which are often experienced in daily clinical practice, include dominant family caregivers, conflicting treatment preferences of patients and their family caregivers, involvement of large numbers of family caregivers and family conflict/dysfunction.
Yet, health professionals often receive little training on how to facilitate an effective collaboration under these circumstances. Specific skills are needed on how to detect and actively manage complex situations with family caregivers. Knowledge on evidence-based communication strategies and guidelines may help health professionals to proactively respond to challenging interactions and to achieve a constructive partnership with family caregivers.

Disclosure: No conflict of interest disclosed.

Wissenschaftliches Symposium

Neue Therapiekonzepte bei indolenten Lymphomen

V526

Therapy of localised lymphoma

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Radiation therapy of localised low-grade lymphoma has changed over the years. Large field radiation therapy has been exchanged by much smaller radiation volumes in combination with systemic therapy without compromising the efficacy. Additionally, low dose radiation using only two fractions has been used more frequently with low morbidity and high local effectiveness. The talk will focus on those developments and is going to present recommendations for state of the art irradiation of localised low-grade lymphoma.

Disclosure: Klaus Herfarth: Expert Testimony: Studienunterstützuing durch Roche

Fortbildung

Intensivmedizin

V531

Immunotherapy & cytokine storm: intensive care management of immune related toxicities: from outpatient to intensive care unit

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Immunotherapy has become an important tool in hematology and oncology. However, some life-threatening side effects can occur, which are significantly different to the experience in "classical" cancer treatment. The "cytokine release syndrome" (CRS) develops after specific or unspecific activation of immune cells. It was described for the first time as a side effect of an anti-CD3 antibody OKT3 in 1989. Nowadays, it is one of the most relevant side effects of CAR-T cells, bispecific antibodies and some other immunotherapies. The CRS occurs early after administration. The pattern of organ damage is predictable and reminds of sepsis and septic shock. Extreme variants of a CRS can appear as a hemophagocytic lymphohistiocytosis (HLH), a macrophage activation syndrome (MAS) or a capillary leakage syndrome. In contrast to CRS, the most relevant side effects of checkpoint inhibitors often start later during the treatment. The time points, pattern and severity of the manifestations are more unpredictable. Target organs like the lung, skin, liver and bowel reminds sometimes of the graft-versus-host reaction after allogeneic stem cell transplantation. A third group of possible side effects are "on target- off tumor" effects, particularly in specific immunotherapies. Due to the relevance of these new therapies, algorithms for early detection and treatment of these side effects have been developed.

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Fortbildung

Ösophaguskarzinom: Standards und Entwicklungen

V533

What is the best curative treatment approach in oesophageal cancer of different tumor locations?

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Die kurativen Optionen beim Ösophaguskarzinom unterscheiden sich, je nachdem ob der Primärtumor zervikal/im oberen Drittel, intrathorakal oder im ösophago-gastralen Übergang liegt. Für hochsitzende Plattenepithelkarzinome (SCC) ist nach S3-Leitlinie (S3-LL) der AWMF die definitive Chemoradiotherapie (CRT) zu bevorzugen. Diese Empfehlung beruht vor allem auf der hohen Morbidität und Letalität der operativen Resektion und der insgesamt geringen Heilungschance der Patienten mit diesen Tumoren. Zur Radiotherapie können Kombinationen aus einem Platinderivat und 5-FU oder einem Taxan evidenzbasiert eingesetzt werden (Cis/FU, FOLFOX, Carboplatin/Paclitaxel). Der Wert einer Bestrahlungsdosis über 50,4 Gy ist nicht belegt. Intrathorakale SCC sollen mit präoperativer CRT + Operation behandelt werden. Dies ist auf dem Boden zahlreicher Meta-Analysen nachvollziehbar, die den Vorteil der multimodalen Therapie gegenüber primärer Chirurgie nachgewiesen haben. Allerdings ist der Vorteil für eine OP+/-CRT gegenüber definitiver CRT nicht bewiesen. Phase III Studien zeigen lediglich einen Vorteil in der lokalen Tumorkontrolle, jedoch nicht im Gesamtüberleben. Responseabhängige Strategien mit Abwarten nach klinisch kompletter Remission und optional einer Salvageoperation im Verlauf werden von Zentren weltweit zunehmend empfohlen und in der Deutschen S3-LL als Option genannt. Adenokarzinome des ösophago-gastralen Übergangs (AEG) nehmen eine besondere Rolle ein. Für lokal fortgeschrittene Tumoren (T3-4 oder N1-3) ist weiterhin ungeklärt, ob eine perioperative Chemotherapie oder eine präoperative CRT die bestmögliche Therapie darstellt. Retrospektive Daten zeigen keinen Unterschied. Die einzige bisher abgeschlossene Phase III Studie weist auf ein verbessertes OS für die präoperative CRT hin, das jedoch gerade die Signifikanz verfehlt (p=0,055). Es ist daher konsequent, dass weltweit mehrere randomisierte Studien aktiviert sind. In Deutschland soll RACE klären, welche Therapie für lokal fortgeschrittene AEG optimal ist.

Disclosure: No conflict of interest disclosed.

Freier Vortrag

Myelodysplastisches Syndrom II

V538

Patient-individual substance testing of Eltrombopag in a preclinical xenograft model of Myelodysplastic Syndromes (MDS)

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Introduction: Thrombopoietin receptor agonists (TRAs) such as Eltrombopag (EPAG) are currently being evaluated as treatment options for thrombocytopenia in MDS patients. However, there are concerns that TRAs may promote disease progression. Clinical trials have had limitations in being able to distinguish substance-induced from natural disease-related progression. We have established a robust MDS xenograft model, which allows MDS patient-individual substance testing including non-treatment controls. Using this *in vivo* pre-clinical platform, we are interrogating EPAG-induced efficacy on thrombopoiesis of primary MDS samples, potential anti-leukemic effects and clonal composition under treatment.

Methods: $CD34^+$ cells and mesenchymal stroma cells isolated from MDS patient BM were intrafemorally transplanted into NSG mice. Engrafted mice were treated with EPAG or vehicle for 18 weeks. In PB, human $CD41^+$ platelets (PLTs) were absolutely quantified using a bead-based flow cytometric assay. $CD45^+$ BM cells of xenografted patient samples were analyzed by whole exome sequencing (WES) to determine the clonal composition under treatment.

Results: To date, xenografts of n=13 MDS patients have positively engrafted (MDS del(5q)=2, MDS-MLD=2, MDS-EB-1=2, MDS-EB-2=6, MDS-MPN=1) and have received or are currently under treatment with EPAG. Three cases have been completely analyzed. In those three cases, human engraftment increased throughout the whole experiment but was not differentially affected by EPAG. In two cases, EPAG led to an increase of human PLT production. One case was considered a non-responder due to the absence of any detectable human PLTs in all xenografts. In BM smears, increased megakaryopoiesis in EPAG-responsive mice was observed, while blasts were absent in both groups. WES analysis revealed

no significant differences in clonal composition and dynamics of VAFs in CD45$^+$ BM cells between treatment with EPAG or vehicle.
Conclusions: Here, we present first proof of principle data that therapeutic substances can be tested successfully in a pre-clinical xenograft model of primary MDS patient samples. This approach allows for patient-individual, non-treatment-controlled substance testing to enable deciphering substance-specific molecular mechanisms of action from disease inherent events. Further, our preliminary data confirm that EPAG efficaciously stimulates PLT production in MDS patients without adversely affecting the underlying clonal composition.

Disclosure: Nanni Schmitt: No conflict of interest disclosed.
Daniel Nowak: Expert Testimony: Novartis

V539

Disrupted osteoclast differentiation results in myelodysplasia

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Introduction: Differential expression of the hematopoietic master regulator PU.1 ensures balanced maturation of hematopoietic stem and progenitor cells (HSPCs) along all lineages. Likewise, members of the CCAAT enhancer binding protein (C/EBP) family of transcription factors are required to drive myelopoiesis. Osteoclasts are terminally differentiated myeloid cells and part of the bone marrow (BM) microenvironment. While both PU.1 and C/EBPs are involved in osteoclastogenesis little is known about the underlying mechanism.
Methods: We created a knock-in mouse model in which C/EBP family member-induced expression of PU.1 is specifically disrupted (called PU.1$^{Ki/Ki}$ here). This model serves as a tool to study the interaction of these hematopoietic key players. Validation experiments were performed on human serum.
Results: PU.1$^{Ki/Ki}$ mice developed neutropenia and thrombopenia that was paralleled by BM hypercellularity and myelodysplasia meeting diagnostic criteria for murine myelodysplastic syndrome (MDS). Interestingly, changes of PU.1 expression were limited to the monocytic lineage. Most prominently, PU.1 levels were decreased by 50% at the common monocyte progenitor (cMoP) stage. This was associated with increased proliferation of the cMoP population and a shift of mature monocyte subsets towards the Ly6C$^+$ monocyte.
Functionally, PU.1$^{Ki/Ki}$ monocytes showed reduced osteoclast formation potential in an *in vitro* differentiation assay. *In vivo* analysis of murine bones by micro computed tomography (μCT) revealed disorganization of trabecular bone in PU.1$^{Ki/Ki}$ mice as evidenced by decreased trabecular bone fraction (BV/TV) and trabecular number (Tb.N).
RNA-seq identified overexpression of the negative regulator of RANKL-signaling Tmem178 and the enzyme nicotinamide N-methyltransferase (NNMT) in osteoclast precursors. Increased homocysteine serum levels in PU.1$^{Ki/Ki}$ animals confirmed metabolic activity of NNMT. Importantly, we also observed increased homocysteine levels in a cohort of human MDS patients.
Conclusions: While most bone marrow niche studies so far focused on CD45$^-$ cells, such as osteoblasts, our findings provide first evidence that malfunctions of osteoclasts are directly related to myelodysplasia.

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V540

Elucidation of a hypersplicing phenotype in SRSF2 mutant myeloid malignancies

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Recurrent mutations in the splicing factor SRSF2 occur frequently in patients with MDS and secondary AML, and portend a poor prognosis. Their high frequency suggests these mutations drive oncogenesis, yet the molecular explanation for this process is unclear. SRSF2 mutations could directly alter pre-mRNA splicing of a vital gene product; alternatively, a whole network of gene products could be affected.
To determine how mutations in SRSF2 alter its function *in vivo*, we generated hematopoietic cell lines with inducible expression of Flag-tagged SRSF2 WT and MUT. We performed "High-Throughput Sequencing after UV-Cross-Linking and RNA Immuno-Precipitation (HITS-CLIP) and performed RNA deep sequencing (RNA- Seq) on the same cells to correlate RNA binding and splice events. Exon-specific primers were designed around putative molecular targets of both differential binding and splicing.
Remarkably, the majority of differential binding events do not translate into alternative splicing of exons around SRSF2 MUT binding sites. Rather, alternative splice alterations appear to be dominated by indirect effects. SRSF2 MUT targets are enriched in RNA processing and splicing genes, including several members of the hnRNP and SR families of proteins, suggesting a "splicing-cascade" phenotype wherein mutation of a single splicing factor leads to widespread modifications in multiple RNA processing and splicing proteins.
Indeed, we demonstrate that multiple splicing factors, most notably of the hnRNP protein family, are recurrently mis-spliced in diverse SRSF2 MUT cell systems and SRSF2 MUT primary patient samples. By differentiating SRSF2 P95H/WT EML cells down the myeloid lineage, we illustrate that the splice outcomes of the identified target genes are dynamic in nature and influenced by differentiation. Finally, we show that the effects of the SRSF2 mutation on hematopoiesis and lineage skewing are mirrored by the knockdown of hnRNP target genes.
In summary, our data suggests a model, whereby subtle, but broad disruption of splicing sets off a cascade of gene regulatory events that together affect hematopoiesis and drive cancer. These findings provide the mechanistic rationale for studying the generation of neoepitopes in SRSF2 mutant disease and ascertaining the role of immune therapy in exploiting this potential Achilles heel.

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V541

Mesenchymal stromal cell-derived extracellular matrix displays altered structure and impaired functionality in MDS

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Introduction: Myelodysplastic syndromes (MDS) are clonal disorders characterized by ineffective hematopoiesis, peripheral cytopenias and an inherent risk of transformation to acute myeloid leukemia. The bone marrow microenvironment is involved in the deregulation of hematopoiesis. Particularly, the extracellular matrix (ECM) seems to be an interesting player since it regulates stem cell fate through the modulation of growth factor storage and release. Here, we characterized mesenchymal stromal

cell (MSC) derived ECM from MDS patients in comparison to healthy controls.
Methods: MSCs of MDS patients and age-adjusted healthy donors were seeded on poly-octadecene-alt-maleic anhydride and human fibronectin coated glass slides. To yield cell-free ECM structures, cultures were decellularized at day 10 and analyzed by scanning electron microscopy (SEM), sulfated glycosaminoglycans (GAGs) staining (fluorescent LectinWGA and LectinPNA) and quantification (Blyscan assay). Moreover, purified CD34+ HSPCs were cultured on ECM scaffolds for 6 and 9 days, respectively. Subsequently, expansion of adherent and supernatant cells was determined and the phenotype was analyzed by flow cytometry.
Results: ECM from MDS MSCs displayed a denser meshwork of fibers with thicker bundles of fibers. We could detect more abundant GAGs on MDS ECM, present as thin white flakes on ECM fibers or as bigger white sponge-like structures. Lectin staining and confocal imaging demonstrated a higher ECM production in MDS patients. The Blyscan assay confirmed these observations with significantly higher sulfated GAG concentrations in MDS ECM. After seeding purified CD34+ cells, we observed clustered adhesion of HSPCs to the underlying substrate which was more prominent on ECM from healthy MSCs. Whereas after 6 days no significant differences in cell numbers between plastic and ECM cultured HSPCs could be detected, after 9 days significant higher total cell numbers were detected on healthy ECM (18.3-fold vs. 12.1-fold expansion, *p< 0.05) but not on MDS ECM (12.9-fold). The number of adherent cells increased 8.5-fold on healthy and 4.3-fold on MDS ECM. Using flow cytometry, we found ECM scaffolds to maintain CD34+ progenitor cells. Interestingly, the proportion of CD90+ HSPCs was found to be increased by 3.1-fold in the adherent fraction of healthy but only 1.8-fold of MDS MSC ECM after 9 days.
Conclusions: We provide first evidence for structural and functional alterations of MDS MSC derived ECM.

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V542

Impact of somatic mutations on the outcome of patients allografted for MDS or secondary AML

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Introduction: Somatic mutations are central for the pathogenesis of MDS/sAML and seem to influence outcome after allo-SCT. Still, irrespective of TP53 as an undisputed characteristic poor-risk mutation, recent studies revealed heterogeneous results regarding prognostic impact of individual gene mutations after allo-SCT.
Methods: We sequenced pre-transplant samples of 128 pts allografted for MDS/sAML at our institution using the TruSight Myeloid 54-gene panel (Illumina). Of these 128 pts, 55 (43%) received pre-transplant cytoreduction, whereas 73 (57%) received an upfront allo-SCT. Results from mutational analyses were correlated with outcome including response to salvage therapy in pts relapsing after allo-SCT.
Results: Estimated 5-y OS and RFS of the entire cohort was 56% and 42%. A total of 285 mutations were detected corresponding to at least one mutation in 87% of pts (median: 2 per patient, range 0-6). Most frequently mutated genes (≥10% of pts) were RUNX1, ASXL1, SRSF2, DNMT3A, TET2, TP53 and SF3B1. Mutational status of these genes was included into outcome analyses together with mutations found in >5% of pts. In univariate analyses mutations in TP53, SF3B1 (both OS, RFS, CIR), DNMT3A (OS) and NRAS (OS) were associated with poor outcome. Besides age>60 y and complex karyotype (both OS, RFS) especially these "poor risk" mutations and pre-transplant cytoreduction (both OS, RFS, CIR) were significantly associated with worse outcome also in multivariate model. Similar to the non-transplant setting "poor risk" mutations refined the prognosis of pts with complex karyotype with those carrying "poor-risk" mutations having an even worse prognosis. In 41 pts, who had relapsed after a median of 11 months after allo-SCT and were treated with HMA +/- DLI response and survival from relapse were comparable between pts with or without "poor-risk" mutations (detected prior transplant). In contrast, pre-transplant strategy significantly influenced outcome after HMA-based salvage therapy with those pts in the upfront group having a higher likelihood for response and survival.
Conclusions: Mutations in TP53, SF3B1, DNMT3A and NRAS as well as pre-transplant cytoreduction were associated with poor outcome after allo-SCT. In case of relapse after allo-SCT pre-transplant strategy but not "poor-risk" mutations significantly influenced response to and survival after salvage therapy with HMA +/- DLI.

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V543

Targeting R-loops-associated ATR signaling in myelodysplastic syndrome

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Introduction: Somatic mutations in genes coding for splicing factors (e.g. *SF3B1*, *U2AF1* and *SRSF2*) are found in about 50% of patients with myelodysplastic syndrome (MDS). These mutations have been shown to frequently occur early in the mutational hierarchy of the disease making them particularly attractive therapeutic targets. Recent research has revealed an association of splicing factor mutations with elevated levels of R-loops, DNA:RNA intermediates that induce replication stress (RS) and downstream activation of the ataxia telangiectasia and Rad3-related protein (ATR) pathway. The aim of this work was to exploit R-loops-associated ATR signaling as a novel therapeutic concept in MDS with splicing factor mutations and to identify possible novel options for combinatorial therapy.
Methods: We quantified levels of R-loops in primary CD34+ bone marrow cells isolated from MDS patients (n=22) stratified by the presence or absence of splicing factor mutations. Furthermore, we evaluated the direct association of R-loops with induction of RS and activation of associated signaling by analyzing replication fork progression rates and phosphorylation of ATR target proteins. In addition, we assessed the *in vitro* sensitivity of mutant (n=11) and non-mutant CD34+ (n=11) cells towards ATR inhibitors (VE-821 and AZD6738) alone and in combination with splicing modulator Pladienolide B. We also performed these experiments in cord blood-derived CD34+ cells overexpressing *SRSF2*P95H without other MDS-associated cellular alterations.
Results: Our data revealed elevated levels of R-loops in splicing factor mutated CD34+ cells from MDS patients. These caused a delayed replication fork progression indicating stalled replication forks, as well as enhanced phosphorylation of downstream ATR signaling proteins. *In vitro* dose-response studies using ATR inhibitors revealed significantly decreased IC50 values (p< 0.0001) in splicing factor mutated MDS CD34+ cells, which could be further lowered by addition of Pladienolide B at concentrations that didn't affect non-mutant MDS or healthy cells. We also confirmed a direct correlation of R-loops associated ATR signaling with the presence of mutant *SRSF2*P95H by lentiviral overexpression in cord blood CD34+ cells.
Conclusions: Collectively, our results identify ATR as a promising novel therapeutic target in MDS with splicing factor mutations and provide a

preclinical rationale for a combinatorial therapy with splicing modulator drugs.

Disclosure: No conflict of interest disclosed.

Freier Vortrag

Der spezielle Fall

V544

An update on secondary haemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS) - a clinical analysis of 12 cases in Austria

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Introduction: Haemophagocytic lymphohistiocytosis (HLH) is a rare condition characterised by excessive immune activation through dysfunctional downregulation of activated macrophages caused by genetic or acquired background. Secondary causes include malignancies, most commonly lymphoma, autoimmune phenomena, infections and iatrogenic immune suppression. If the underlying disease is rheumatologic, it is referred to as macrophage activation syndrome (MAS). The absence of the negative feedback-signal leads to a pro-inflammatory cytokine storm causing persistent hyperinflammation and tissue destruction, which, when untreated, rapidly result in multiorgan failure and consequently death.
Methods: Retrospective clinical analysis and description of 12 cases from 2013 - 2019 in 3 centres in Austria.
Results: Median age of onset was 57,58 years, 41,6% were females. Within hours or few days after admission all patients could be indicated as critically ill and required intensive treatment measures, although first mild symptoms often appeared weeks in advance. 7 were diagnosed with malignancy-associated HLH, 3 were associated with infections, in 1 patient the cause was unclear. 1 patient suffered from MAS due to adult-onset Still disease. Median HScore was 211,8, leading to a median probability of HLH of 83,11%. 8 patients received an etoposide-containing therapy among others. In the case of MAS, therapy was switched to anakinra and methylprednisolone. 8 out of 12 patients are alive. 4 patients died, 3 after receiving disease-specific therapy, 1 patient without receiving any therapy. The diagnosis was confirmed in autopsy.
Discussion: The presence of persistent unspecific symptoms, high serum ferritin levels, quick aggravation and therapy resistance should be guiding to the diagnosis of HLH/MAS. Rapid application of the required therapy is essential to ensure a positive outcome.

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V545

Splenic rupture after administration of G-CSF. Case report and review of the literature

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Introduction: Splenic rupture is potentially a life-threatening condition. Early diagnosis improves outcome significantly. We present a case of an adult patient with splenic rupture after therapy with granulocyte colony stimulation factor (G-CSF). Literature review was performed to identify patients who are at an increased risk of splenic rupture after G-CSF administration.
Case report: A 24-year-old patient presented to our emergency room (ER) with abdominal pain and signs of hemorrhagic shock. Previously he had been diagnosed with Nodular sclerosis classical Hodgkin lymphoma stage IIA. Due to leucopenia post chemotherapy, he had received two injections of G-CSF (Pegfilgrastim), with most recent dose given five days prior to emergency room visit. This patient had also presented to the ER two days earlier with new onset of nausea and vomiting. He had been dismissed with symptomatic therapy only. On this visit to the ER, his laboratory investigation showed a significant hyperleukocytosis as well as a low hemoglobin. CT scan revealed an intraabdominal bleeding due to splenic rupture. He had denied trauma. An emergency splenectomy was performed. The patient had an uneventful post-operative course. The histopathological examination of the spleen and the associated lymph nodes showed features of extramedullary hematopoiesis but no signs of infiltration by the Hodgkin lymphoma.
Discussion: A literature review identified 28 publications describing heterogenous cases of splenic rupture after administration of G-CSF. The most common complaint was left sided upper abdominal pain followed by clinical signs of shock. Comparing the different cases, neither a common underlying pathophysiological mechanism nor typical risk factors for splenic rupture after G-CSF administration were revealed. There might be different mechanisms leading to the same result of splenic rupture.
Conclusions: Splenic rupture is a rare but potentially lethal complication after G-CSF administration. If diagnosed in time, curative therapy can be initiated. So far, no common risk factors for splenic rupture in this specific setting has been identified. Therefore, doctors treating patients with G-CSF need to be alerted about this possible complication. Additionally, patients who receive G-CSF must be educated about the possibility and clinical signs of splenic rupture. Further research is needed to elucidate the pathophysiological mechanism(s) which leads to splenic rupture after G-CSF-administration.

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V546

Unmasking the true face of Alk-positive anaplastic large cell lymphoma (ALCL)

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A 39-year old female presented with lower back pain for two months and fever. A computerized tomography (CT) of the thorax and abdomen revealed multiple bone lesions. The patient had an unremarkable medical and family history and no occurrence of B-symptoms. Clinical examination showed no abnormalities. All other examinations including bronchoscopy, gynecologic assessment, gastroscopy, colonoscopy and ultrasound of the abdomen revealed no abnormalities. The laboratory results were within normal limits except elevated C-reactive protein (CRP) levels with 56.9 mg/l (normal range < 7.5mg/l). A CT-guided core needle biopsy of an osteolytic lesion of the left os ileum was performed. The histopathologic results showed an infectious or inflammatory process. No malignancies could be diagnosed, however CD30 positive cells were found at low frequency. A second bone biopsy of this lesion revealed metaplastic woven bone with chronic inflammatory infiltration, consistent with chronic recurrent multifocal osteomyelitis (CRMO). The patient was started on bisphosphonates and corticosteroids. Because of refractory pain tumor necrosis alpha inhibitor infliximab was given. MRI scan revealed a fracture of L1. Therefore dorsal stabilizing surgery of L1-L3 was performed. Unexpectedly bone histology revealed an ALK-positive anaplastic large cell lymphoma. 7 months after her first visit the diagnosis was finally made. After pre-phase chemotherapy the patient received six cycles of bi-weekly CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide and prednisone). After the sixth cycle PET-CT showed a

complete response (Deauville-5P-response score 1). The patient has been in complete remission for 18 months.
This case shows the difficulties in diagnosing Alk-positive anaplastic large cell lymphoma due to the variable clinical course including bone infiltration. A major challenge is the histological diagnosis since anaplastic large cell lymphoma may present with expansion of inflammatory cells and few lymphoma cells especially if limited biopsy material is warranted, contributing to delayed diagnosis.

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V547

Large vessel vasculitis as a possible mechanism of vascular side effects of ponatinib

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Introduction: Arterial occlusive events (AOEs) are known side effects of ponatinib, assumed due to rapid development of arteriosclerosis, while the definitive patho-mechanisms are still unclear.[1] We present a case of large vessel vasculitis and discuss this as a possible mechanism.
Patients: A 60-year old Ph+ ALL female was put on ponatinib in subsequent relapse with detection of T315I mutation after two alloSCT and several salvage therapies, including other TKIs. On ponatinib, she achieved a complete molecular remission, but developed symptoms of intermittent claudication. Ultrasound (US) revealed stenosis of bilateral femoro-iliacal and subclavian arteries, with typical pattern for large vessel vasculitis and no arteriosclerosis. After stop of ponatinib and initiation steroids, symptoms improved rapidly, as well as US signs of vasculitis. Due to a meningeal relapse 16 months later, ponatinib was restarted (15 mg/d) and symptoms of claudication recurred. Steroids were administered again and ponatinib was continued, resulting in slight improvement. Three months later, due to abdominal pain, a CT showed a distended caecum (7 cm) and a complete occlusion of the superior mesenteric artery (SMA). The presence of collaterals suggested a chronic stenosis or occlusion. No signs of intestinal arteriosclerosis on CT and no evidence of atrial fibrillation in the patient's history and the current ECG that might suggest a thromboembolic event. Immediate bowel-resection was performed. However, the patient died due to septic complications. The histo-pathological evaluation showed an infarction of the bowel wall but only minimal signs of both arteriosclerosis and inflammation.
Discussion: Large vessel vasculitis as a possible mechanism for AOEs following ponatinib has been described in a patient with cerebral ischemia.[2] In accordance with this report, the present case suggests this patho-mechanism by typical symptoms of claudication and US signs of vasculitis, as well as by rapid improvement after steroids and stopping ponatinib. After re-exposition claudication re-appeared, and the patient finally died from otherwise unexplained ischemic bowel disease. In lack of other obvious reasons, intestinal vasculitis in the context of re-exposition to ponatinib was suspected as a trigger for occlusion of SMA. The missing clear proof of inflammation in histology in our case may be explained by the prior restart of steroids.

References:
1 Cortes JE Blood 2018
2 Mayer Leukemia 2014

Disclosure: No conflict of interest disclosed.

V548

Spontaneous remission of a primary-extramedullary AML in an adult

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Introduction: Isolated extramedullary acute myeloid leukemia (AML), also known as myelosarcoma or chloroma is a rare finding and usually requires treatment analogous to AML. There are about 100 case reports of spontaneous remission of untreated AML. Only three of those deal with myelosarcoma, all of which were pediatric cases.
Here we describe a case of spontaneous remission of extramedullary AML in an adult woman.
Case report: A 59-year-old female patient presented in March 2018 with complaints of numerous skin nodules. A prior skin biopsy suggested infiltration by myeloid blasts, findings that were confirmed by repeat-biopsies from different skin locations, all of which of displayed infiltration by myeloid blasts with myelomonocytic differentiation.
Peripheral blood exhibited anemia and neutropenia. Cytology and flow cytometry of blood and bone marrow showed no evidence of leukemia, whereas histological examination of the trephine biopsy showed only a few myeloid cell clusters with a proliferation of atypical myelomonocytic blasts among an otherwise unremarkable complete maturation of all cell lines. These findings taken on their own would thus not have been sufficient to establish the diagnosis of AML.
All histological and cytological specimen were transferred for referral pathological analysis, which established the diagnosis of AML (FAB M4) in light of the extramedullary Manifestation. Molecular testing revealed NPM1-, DNMT3A- and TP53-mutations.
Before induction therapy could be initiated, the patient's skin changes resolved spontaneously. Simultaneously the blood works normalized and a repeat bone marrow examination failed to show any AML related findings. Thorough questioning revealed that the skin changed resolved following UV exposure during a tanning bed visit. Concurrently the patient had suffered a mild upper respiratory tract infection, which might also have triggered an immunological response.
We decided to forego chemotherapy and instead opted for active surveillance. The patient remains in a complete cytological and molecular (NPM1) remission as of May 2019.
Conclusions: To our knowledge, this is the first case of a spontaneous remission of primary extramedullary AML in an adult patient. The underlying mechanisms, i.e. immune stimulation or a direct effect of UV radiation warrant further investigation.

Disclosure: No conflict of interest disclosed.

V549

Clonal evolution in eltrombopag-resistant aplastic anemia indicated by a novel mutation in transcripts of the thrombopoietin-receptor MPL: a case report

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Introduction: Thrombopoietin (TPO), acting through its receptor c-MPL, is required for hematopoietic stem cell maintenance and megakaryopoiesis. Mutations in TPO and MPL are related to familial aplastic anemia (AA). The TPO receptor agonist elthrombopag has become standard of care for AA patients refractory to immunosuppressive therapy.
Methods and Results: In Apr 14 the diagnosis of vSAA (Gran PNH clone size 4.4% (FLAER)) was confirmed in a 71-year-old female pat (normal karyotype (46,XX) with no evidence of somatic EZH2, ASXL1, or TP53-mutations). Prior to transference she received darbepoetin alfa and

G-CSF, in addition to CsA following a short course of eltrombopag as she remained transfusion dependent for pRBCs and PLTs. At initial presentation in our Department (Sep 14), she presented with fungal pneumonia due to severe neutropenia, requiring antimycotic and antibiotic treatment prior to initiation of hATG/CsA. In Nov 2014 she was hospitalized due to re-occurrence of fungal pneumonia despite voriconazole prophylaxis. Thus, granulocyte transfusion therapy was considered, resulting in rapid improvement. Prior to salvage rATG/CsA - May 15, a subsequent bone marrow (BM) and cytogenetic analysis was performed in Apr 15, ruling out MDS/AML (Gran PNH clone size 90% (FLAER)). A switch to eltrombopag was mandatory due to sustained refractoriness in June 15 and continued until Nov 15, resulting in no hematopoietic response. In consideration of refractoriness, danazol was initiated in Nov 15 and maintained until Aug 16. Refractoriness was confirmed by BM biopsy revealing an aplastic marrow (June 16). However, a mutation panel involving candidate-gene mutations for AA was performed, identifying exclusively a p.Arg514Lys mutation in transcripts of the TPO receptor MPL, which was retrospectively excluded by analyzing BM samples taking in May 15 prior to eltrombopag. Subsequent recurrent hospitalizations were mandatory due to infectious complications with a second indicative granulocyte transfusion regimen in Jan 16. In Nov 16 she died due to septicemia.
Conclusions: Clonal evolution in AA is highest among refractory patients and can be observed in 10-15%. The occurrence of an acquired, apparently homozygous mutation in MPL following eltrombopag might represent a novel mechanism in refractory AA conferring an escape mechanism by cryptic clones and progression to advanced disease states preserving allogeneic stem cell transplantation as the only curative treatment.

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Freier Vortrag

Nierenzellkarzinom

V552

Molecular correlates differentiate response to atezolizumab (atezo) + bevacizumab (bev) vs sunitinib (sun): results from a Phase III study (IMmotion151) in untreated metastatic renal cell carcinoma (mRCC)

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Background: Atezo + bev demonstrated improved PFS vs sun in pts with untreated mRCC expressing PD-L1 in Ph II (IMmotion150) and Ph III studies. Biomarker analyses in IMmotion150 suggested that T effector/IFNγ (T_{eff}) and Angiogenesis (Angio) gene expression signatures (GEs) were associated with differential outcomes with atezo + bev and sun. We conducted genomic analyses to validate these GEs with clinical outcomes in IMmotion151 and evaluated their association with MSKCC risk groups and sarcomatoid histology.
Methods: Tumour GE analysis was performed by RNASeq in 823 pts from IMmotion151. Associations of T_{eff} and Angio GEs with clinical outcome were evaluated at pre-specified expression level cutoffs identified in IMmotion150. PD-L1 status on immune cells was assessed with the SP142 IHC assay.
Results: IMmotion151 met its co-primary endpoint, demonstrating improved PFS with atezo + bev vs sun in PD-L1+ patients (HR, 0.74 [95% CI: 0.57-0.96]; $P = 0.02$) across MSKCC groups. PFS was also improved in pts with sarcomatoid histology (HR, 0.56 [95% CI: 0.38-0.82]). High T_{eff} GE was associated with PD-L1 expression by IHC and longer PFS in atezo + bev vs sun pts (HR, 0.76 [95% CI: 0.59-0.99]). High Angio GE was associated with improved PFS in the sun arm (HR, 0.59 [95% CI: 0.47-0.75]) but did not differentiate clinical activity between atezo + bev vs sun (HR, 0.95 [95% CI: 0.76-1.19]). Atezo + bev improved PFS vs sun in the low Angio subset (HR, 0.68 [95% CI: 0.52-0.88]). Angio GE was higher (P=4.28e-06) in favourable vs intermediate/poor MSKCC risk groups. PD-L1+ prevalence was higher (63% vs 39%) and Angio GE was lower (P=4.73e-16) in sarcomatoid vs non-sarcomatoid tumours.
Conclusions: These prospectively tested biomarker results validate molecular signatures that differentiate clinical outcomes with VEGF inhibition and immunotherapy in 1L mRCC. Moreover, these data identify tumour genomic profiles associated with prognostic risk groups and sarcomatoid histology. Findings from this study further our understanding of the biology of kidney cancer and inform future strategies to enable personalized therapy in mRCC pts.

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Robert J. Motzer: Advisory Role: Paid consulting: Pfizer, Novartis, Genentech/Roche, Merck, Incyte; Expert Testimony: Bristol Myers Squibb, Pfizer, Novartis, Eisai, Genentech/Roche

V553

Renal cell carcinoma in kidney transplant recipients - descriptive analysis and overview of a major German transplant center

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Introduction: Allogenic kidney transplantation (ktx) is associated with an increased risk for cancer-related death. Herein, renal cell carcinoma (RCC) is among the three most frequent causes of cancer related death. Also, an association between end-stage renal diseases (ESRD) and kidney cancer is known. However, there is a lack of data characterizing RCC associated with ESRD and ktx. This large retrospective single center analysis especially aims to identify prognostic and predictive clinicopathologic characteristics for disease outcome.
Methods: 5250 patients with ktx (oberservation period 01/1970-08/2017) were identified. Clinical and pathologic data were evaluated from the electronic hospital information system, retrospectively. Time to recurrence was calculated from time of diagnosis of RCC to secondary renal tumor or metachronous metastatic disease. Overall survival was calculated from time of diagnosis of RCC to death or last follows up.
Results: 124/5250 kts patients with RCC (2.36%) were identified. 43 (33.9%) RCC cases were diagnosed before and 81 cases after ktx (60.1%; incidence 1.2%). Predominantly, RCC stages were locally restricted (pT1=82 [66.1%], pT2=6 [4.8%], pT3=8 [6.4%], n.a.=28 [22.6%]). Overall, metastatic recurrence was noted in 4.8% and second primaries in 12.8% of pts. Post ktx patients with RCC showed an inferior overall survival (OS) compared to RCC pts. prior to ktx (median OS: 12.7(95%-CI: 10.5-14.8) years vs. 23.0(95%-CI: 10.5-14.8) years, log-rank p=0.001). In multivariate analysis tumor stage and hemoglobin were identified to be independently associated with OS. Furthermore, tumor grading was identified to predict recurrence.
Conclusions: This study allows more precise insights into the topic of RCC in the context of ktx. Most importantly, combining the prognostic value of tumor staging and hemoglobin with the predictive value of tumor

grading, our data suggest that a risk adapted approach for early transplantation is feasible. Therefore, patients with G1/2 tumors may be listed for immediate transplantation.

Disclosure: No conflict of interest disclosed.

V554

Von-Hippel-Lindau deletion causes mesenchymal transition in kidney collecting duct cells

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Introduction: Clear-cell renal cell carcinoma (ccRCC) is the most common form of kidney cancer. It is characterized by a loss of function mutation of the von-Hippel-Lindau tumour suppressor (VHL). Alongside the renal nephron, cells are exposed to increasing concentrations of NaCl and urea. In the collecting duct, osmolality can reach up to 1200 mosmol/kg, generating a hyperosmolar environment. It has previously been shown, that VHL deficient and ccRCC harboring mice express a phenotype of polyuria, which is caused by a hypoosmolar environment in the nephron (Schönenberger et al., 2016). This implicates a physiological function of VHL in the collecting duct segment. Most research however, that discusses the effects of VHL deletion has been conducted with renal cancer cell lines such as 786-0, Caki or RENCA, which harbor various other specific mutations. Within this study we analyzed the impact of VHL deletion, using healthy renal collecting duct cells.
Materials and methods: We created a VHL deficient mpkCCD cell line by using CRISPR/Cas9. Single clones with functional VHL deletion were selected. The knockout was confirmed by western blotting. Cell morphology studies were performed, using the immune fluorescence method. The gene expression experiments were conducted with qPCR. Proliferation and migration assays were performed with cells cultivated at 300 and 600 mosmol/kg.
Results: We successfully generated single clones harboring dysfunctional VHL. This was associated with stable Hif1a expression. VHL deficient mpkCCD cells undergo drastic morphological and functional changes. We observed the partial loss of tight and adherens junctions. KO of VHL is also associated with higher migration and lower proliferation potential compared to wildtype cells. The expression of AQP-2 is a specific marker of the collection duct epithelial cells. We observed total loss of APQ-2 expression in our single clones. Taken together, this data indicates that lack of VHL induces a mesenchymal phenotype.
Conclusions: Since the mpkCCD cells only lack active VHL, we are able to conclude a direct link between the loss of function of VHL and the cancerous differentiation of epithelial cells. Furthermore, we propose that proliferation and migration of VHL-mutated mpkCCD cells is supported by a hypoosmolar environment and can be reduced significantly by hypertonicity. Therefore, our results might be useful for further research and novel treatment strategies in the future.

Disclosure: No conflict of interest disclosed.

V555

Changes in treatment of advanced renal cell carcinoma: first results from the prospective, national research platform CARAT for patients with mRCC in Germany

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Introduction: For patients (pts) with advanced or metastatic renal cell carcinoma (mRCC), approval of novel therapies led to continuous changes in treatment options. The prospective Tumour Registry Renal Cell Carcinoma (TNK) analysed treatment and outcome of these pts treated across Germany from 2007-2017. CARAT is the successor registry, which continues to assess longitudinal real world clinical outcome, enriched by patient-reported outcomes (PROs) and decentralized biobanking. Today, we introduce CARAT and report on current changes of the treatment landscape in mRCC in Germany.
Methods: Since Dec. 2017 150 pts. have been enrolled in CARAT, which expands the previous TNK (recruitment 2007-17, 1500 pts). CARAT is an observational, prospective, open, multicentre clinical research platform with a target enrolment of 1000 pts by 150 sites. Pts with mRCC who start 1st-line medical anti-cancer treatment are eligible. Treatment characteristics, clinical outcome and physician-reported factors on treatment decision making and biomarker testing are collected. Overall survival (OS) is assessed by the KM-method. Changes of the treatment landscape are depicted descriptively.
Results: By April 2019, >1650 pts with mRCC have been recruited. Median age is 68 years. The majority (60%) had intermediate risk (MSKCC) at start of 1st-line. Median OS for pts with start of 1st-line 2007-2017 is 19 months (>60% events). If selected by trial eligibility criteria, the median OS is 27 months. Pts who started treatment in 2018 mostly received pazopanib (38%) or sunitinib (34%). Since the approval (May 2018) 18% are treated with cabozantinib. Preferred 2nd-line treatment has changed from sorafenib/temsirolimus (35%/21%, 2007-09), everolimus (33% 2010-12), everolimus/axitinib/sunitinib (29%/19%/18%, 2013-15) to nivolumab (>60% since 2016). The impact of all these new treatment options on OS will be analysed.
Conclusions: Pts in routine care in Germany are older and have inferior prognosis than trial-eligible pts. CARAT complements the results of RCTs with important prospective data on clinical and PROs for pts with mRCC in routine care. CARAT will show how the choice of treatment changes over time, which sequences are applied and investigate the effectiveness in a "real world" setting. The long-term design allows evaluating the impact of novel therapy approvals. For the first time, these data will be combined with PROs and a decentralized biobank for future translational research.

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Viktor Grünwald: Stock Ownership: MSD, AstraZeneca, BMS; Financing of Scientific Research: Pfizer, BMS, Roche, Novartis, EISAI, Ipsen, EUSAPharm, MSD, AstraZeneca, MerckSerono, Lilly, pharmaMar, Nanobiotix, Janssen; Expert Testimony: Pfizer, BMS, Ipsen, EUSAPharm, MSD, Novartis, AstraZeneca

V556

Evaluation of safety, tolerability and activity of Axitinib in patients (pts) with advanced or metastatic renal cell carcinoma (mRCC) in routine clinical practice: the STAR-TOR registry

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Introduction: Axitinib (AXI), an oral tyrosine kinase inhibitor, is approved in the EU for the treatment of pts with mRCC after failure of prior therapy with sunitinib or cytokines. A pivotal study had demonstrated significantly increased progression-free survival (PFS) with AXI compared to Sorafenib (6.7 vs. 4.7 months (mo); one-sided $p < 0.0001$, log-rank). Here we present preliminary data from a non-interventional post-approval study.

Methods: A German multicenter registry for pts with mRCC (NCT00700258) was amended in October 2012 with regulatory and ethic committee´s approval to include pts treated with AXI. Objectives are the evaluation of the safety profile, the tolerability and anti-tumor activity of AXI as well as the profile, comorbidity and characteristics of pts and the sequence of systemic therapies in pts with mRCC. Inclusion criteria are histologically confirmed mRCC treated with AXI and written informed consent.

Results: From November 2012 to February 2019, 73 study sites recruited 204 AXI pts. Characteristics: 71.3% male, median age 69.0 years (28.0-84.0), median Karnofsky index 80% (50-100%). Histological subtype: 78.9% clear cell only, 21.1% other histological entities. In 52.5% of pts AXI was used as second-line therapy, in 23.5% as third-line treatment and in 21.6% as fourth-line and beyond (n=204). 5 pts were treated in first-line. Median number of prior therapies was 1 (0-5). 108 pretreated pts were evaluable with regard to MSKCC criteria: 13.9% favorable, 34.3% intermediate and 51.9% poor risk. Drug related adverse and serious adverse events were observed in 56.4% and 19.1% of pts, respectively. They were observed in the following categories (incidence ≥ 10%): gastrointestinal disorders (37.7%), general disorders (21.1%), skin and subcutaneous tissue disorders (14.2%), metabolic and nutritional disorders (11.3%), nervous system disorders (10.3%). Abnormalities in investigations (i.e. decreased weight, abnormal laboratory findings etc.) were observed in 10.8% of pts. Median PFS of the total AXI cohort was 5.6 mo, median PFS for the subgroup of second line pts (n = 107) was 4.8 mo. Overall survival for all 204 pts was 16.1 mo.

Conclusions: These data show that AXI seems to be an effective therapy option for mRCC pts in second and higher therapy lines in the routine clinical setting. Toxicities were generally manageable, and the reported incidence was lower compared to published phase III data. PFS and OS were in the expected range.

Disclosure: Lothar Bergmann: Advisory Role: BMS, Ipsen, Novartis, Pfizer, Roche, Eusa; Expert Testimony: BMS
Michael Woike: Employment or Leadership Position: Pfizer Pharma GmbH

V557

CheckMate 214 patients who discontinued first-line Nivolumab + Ipilimumab or sunitinib due to treatment-related adverse events

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Introduction: The phase 3 CheckMate 214 trial demonstrated superior efficacy for nivolumab + ipilimumab (NIVO+IPI) versus sunitinib (SUN) in advanced renal cell carcinoma (aRCC), though more patients discontinued NIVO+IPI versus SUN due to treatment-related adverse events (TRAEs). This is a post hoc analysis of outcomes in patients who discontinued NIVO+IPI or SUN due to TRAEs.

Methods: Patients with untreated clear cell aRCC were randomized 1:1 to NIVO 3 mg/kg + IPI 1 mg/kg every 3 weeks for 4 doses and then NIVO 3 mg/kg every 2 weeks, or SUN 50 mg daily for 4 weeks on, 2 weeks off (6-week cycles). This analysis includes all patients who discontinued due to TRAEs reported during ≤100 days after last study dose through August 7, 2017. Minimum follow-up for efficacy was 30 months (median, 32.4 months).

Results: Of 550 NIVO+IPI randomized patients, 135 (25%) discontinued due to TRAEs (increased alanine aminotransferase, diarrhea, and increased aspartate aminotransferase were most common, all 3%); of 535 SUN randomized patients, 64 (12%) discontinued due to TRAEs, all preferred terms were < 2%. Objective response rate (ORR) per investigator (47% vs 33%), complete response (CR) rate (12% vs 3%), and 30-month overall survival (OS) probability (69% vs 59%) were higher, and OS was longer (hazard ratio, 0.70 [95% confidence interval, 0.42-1.15]) in patients who discontinued NIVO+IPI versus SUN. Outcomes in patients who discontinued NIVO+IPI due to TRAEs were similar to all NIVO+IPI intent-to-treat (ITT) patients (ORR per investigator [41%], CR rate [11%], 30-month OS probability [64%]).

Conclusions: Discontinuation of first-line NIVO+IPI due to TRAEs did not result in inferior efficacy compared with ITT patients, and outcomes in patients who discontinued NIVO+IPI due to TRAEs were better than in SUN patients who discontinued due to TRAEs.

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Hans J. Hammers: Employment or Leadership Position: N/A; Advisory Role: BMS, Pfizer, Exelixis, Merck, Armo Biosciences, Novartis; Stock Ownership: N/A; Honoraria: N/A; Financing of Scientific Research: N/A; Expert Testimony: BMS, Merck; Other Financial Relationships: N/A; Immaterial Conflict of Interests: N/A

Freier Vortrag

Hämatopoetische Stammzellen

V558

Loss of the fanconi anemia-associated protein NIPA causes bone marrow failure

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Inherited bone marrow failure syndromes (IBMFS) are a heterogeneous group of disorders characterized by defective hematopoiesis, impaired stem cell function and cancer susceptibility. Diagnosis of IBMFS presents a major challenge due to the variety of phenotypes. Therefore, novel, clinical relevant biomarkers are urgently needed.

Our study identifies NIPA as an IBMFS gene, which is significantly downregulated in some patients with hypocellular refractory cytopenia of childhood (RCC), a provisional entitiy of MDS in the young. Mechanistically, we show, that NIPA is a major player in the Fanconi anemia (FA) pathway, which binds FANCD2 and regulates its nuclear abundance, thereby preventing Mitomycin C hypersensitivity and being essential for a functional DNA repair/FA/BRCA axis. In a knockout mouse model, *Nipa* deficiency leads to major cell intrinsic long-term repopulation defects of hematopoietic stem cells (HSCs), with impaired self-renewal in serial transplantations and myeloid biased differentiation. Unresolved DNA damage in *Nipa* deficient HSCs causes increased sensitivity to cell death and leads to progressive, age-related loss of the HSC pool. Induction of replication stress triggers the phenotypic reduction and functional decline of murine HSCs, resulting in complete bone marrow failure and death of the mice with 100% penetrance.

Taken together, our study adds NIPA to the short list of FA-associated proteins, thereby emphasizing its impact as potential diagnostic marker and/or possible target in diseases characterized by hematopoietic failure.

Disclosure: No conflict of interest disclosed.

V559

Comparative analysis of clonal hematopoiesis of multipotent stem cells in healthy elderly in blood and bone marrow

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Introduction: The identification of clonal hematopoiesis of indeterminate potential (CHIP) in healthy elderly individuals has added a significant new layer of understanding to the development of emerging myeloid neoplasms. Likely due to limited sample availability, all major studies that initially described CH were exclusively performed using peripheral blood (PB) cells of healthy donors. However, additional information about bone marrow (BM) involvement could assist in individual risk prediction. Furthermore, analysis of the BM of CH carrying individuals is necessary to elucidate the cells of origin and pathomechanisms leading to the preferential selection of these mutation carrying clones.

Methods: We therefore collected paired PB and BM from a cohort of n=17 otherwise healthy elderly patients undergoing hip replacement surgery and performed targeted deep sequencing of BM, PB and mesenchymal stromal cells using Illumina Myeloid Panel sequencing on a HiSeq Illumina platform. Primary hematopoietic fractions were sorted and identified mutations were confirmed with independent deep amplicon sequencing.

Results: We found clonal contribution to hematopoiesis in either PB or BM in 35% of cases with the most frequently detected mutations affecting TET2 and DNMT3A. Correlation of the variant allele frequencies in both compartments showed, that in the majority of cases CH was present at comparable levels in both BM and PB. Furthermore, multilineage involvement of CH clones was present in all examined cases in myeloid, erythroid and even lymphoid compartments and was also confirmed in primitive hematopoietic stem cells (HSC). Notably, as early as 4-6h upon surgery a reactive rise in peripheral WBC could be observed in the routine blood counts. Importantly the amplitude of this stress leukocytosis was significantly reduced by a 0.72 fold in subjects with CH.

Conclusion: In conclusion, our study confirms the emergence of CH clones at the level of the hematopoietic stem cell compartment with similar level of clonal expansion in blood and BM. We present first evidence that the presence of CH clones in the bone marrow of healthy individuals may have impact on the reactive capacity of the hematopoietic system upon response to exogenous stressors.

Disclosure: No conflict of interest disclosed.

V560

In vitro rejuvenation of hematopoietic stem and progenitor cells via extracellular vesicles

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Introduction: Hematopoietic stem cell transplantation represents the only effective therapy for many hematologic disorders including leukemia. However, the number of potential donors is limited by their age, since aged hematopoietic stem and progenitor cells (HSPCs) show reduced regeneration capacity as well as lineage skewing. The phenotype of HSPCs is modulated by their microenvironment in the bone marrow (BM), e.g. by extracellular vesicles (EVs) derived from mesenchymal stromal cells (MSCs). By transferring small RNAs, proteins and lipids they are capable of changing the gene and protein expression of recipient cells. The EV content can be modulated by several drugs making their therapeutic opportunities even more promising. Here, we examined the effects of MSC-EVs on the phenotype of physiologically aged HSPCs.

Methods: Human CD34+ HSPCs of young and old healthy donors were isolated with immunomagnetic beads. EVs were purified from BM MSCs thatwere treated with the mTORC1 inhibitor Rapamycin or the PI3K inhibitor LY294002 beforehand by a column-based method and characterized by Western Blot and Nanoparticle Tracking Analysis (NTA).After incubation of HSPCs with EVs, we analyzed gene expression by quantitative real-time PCR as well as their clonogenic capacity in CFU assays.

Results: The EVs of MSCs from young and old donors were isolated after serum-free incubation for 2-3 days. We could successfully detect the exosomal marker proteins CD63 and CD81 by Western Blot. The average concentration was $2{,}1*10^{10} \pm 0{,}2*10^{10}$particles/ ml with a peak at 163,6 ±7,7 nm (n=7), what confirms that the isolated particles mainly represent exosomes and microvesicles. Moreover, NTA reveals that Rapamycin and LY294002 which either inhibit or stimulate autophagy do not alter the EV yield significantly at the chosen concentrations. First results from

the incubation of HSPCs with EVs for 3 days confirm that genes highly expressed in young HSPCs such as Akt1 (1,5-fold) are upregulated by EVs derived from young MSCs and downregulated by EVs of old donors. Furthermore, an increase in autophagy is indicated by the upregulation of several genes including Beclin-1 (1,8-fold) and Sirtuin-1 (1,4-fold). The CFU assays confirm the maintenance of the clonogenic potential after EV treatment.
Conclusions: Our results suggest that the phenotype of HSPCs can be modulated via MSC-derived EVs. Therefore, EVs may represent an appealing method to improve stem cell transplantations.

Disclosure: No conflict of interest disclosed.

V561

The effects of cryopreservation on viability and function of autologous hematopoietic stem cell products

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Introduction: Resulting from routine cryopreservation of autologous mobilized peripheral blood stem cells (PBSCs) at the Institute of Transfusion Medicine and Immunology in Mannheim, stem cells products stored for more than 20 years have become available. The Paul Ehrlich Institute (PEI) requires hematopoietic stem cell products to meet a number of quality criteria prior to transplant. Here we present the implications of long-term cryopreservation on PBSC function in vitro with additional consideration of clinical data.
Methods: Reference samples (n=46) that had been cryostored in vapor-phase nitrogen at a temperature of < -130°C after controlled-rate freezing were analyzed. The retrospective data of patient's diagnosis, mobilization therapy, age, and clinical outcome were evaluated and correlated with the duration of cryostorage. In order to assess vitality, differentiation patterns, and $CD34^+$ and $CD45^+$ cell count, initial data were compared to prospective results of recently thawed cells by flow cytometry and colony forming assay (CFA). An apoptotic population was defined by flow cytometry through forward/side scatter using standard protocols.
Results: The duration of cryopreservation ranged from 34 to 278 months, with a mean and median of 153.5 months. $CD34^+$ cell concentration of the stem cell products measured by recently thawed cells ranged from 129 cells/µl to 6,476 cells/µl with a mean of 1,924 cells/µl and showed a vitality of 88% on average. The number of $CD34^+$ cells were measured at a mean of 4.8 $x10^6$ per kg body weight (bw) (IR: 1.2 $x10^6$ - 6.0 $x10^6$ /kg bw). Colony forming units averaged 2.1 $x10^5$/kg bw. Neither $CD34^+$ cell count, nor viability and function of PBSCs showed a negative correlation in respect to the duration of cryopreservation or the donor's age.
Conclusions: This comprehensive analysis of multiple variables affecting HSC function indicates the underestimated scope of stem cell products after long-term cryostorage. We demonstrate that HSC were able to survive up to 23 years under constant conditions without significant deterioration of cell viability and functionality. Ongoing studies are currently focusing on potential signs of cellular senescence in long-term stored stem cell products.

Disclosure: Svea Löwhagen: No conflict of interest disclosed.
Patrick Wuchter: Advisory Role: Membership on Advisory Boards for Sanofi.

V562

Monitoring of the immunometabolic profile of reconstituting leukocytes upon autologous peripheral blood stem cell transplantation

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Introduction: The field of immunometabolism has been of emerging interest exploring the connection between the immune cells' metabolism and function. Metabolic changes are associated with the activation of immune cells, e. g. a switch from a respiratory to a glycolytic phenotype. In this project we aim to investigate the metabolic demands of a recovering immune system in patients receiving autologous peripheral blood stem cell transplantation (autoPBSCT) upon high dose chemotherapy (HDC). HDC followed by autoPBSCT is a well-established treatment option for patients suffering from multiple myeloma or lymphoma; both patient groups are included in our study.
Methods: Blood was collected from patients at three time points: before HDC (TP1), at leukocyte recovery (>1000 leukocytes/µl), 10-15 days after autoPBSCT (TP2), and during post-treatment evaluation, 30-45 days after autoPBSCT (TP3). Absolute leukocyte counts were determined ex vivo by bead-normalized FACS. Screening of the metabolic phenotype of leukocytes in reconstitution (T cells, NK cells and monocytes) was performed using multicolor flow cytometry on cryopreserved PBMCs. Fluorescent cell barcoding method enabled us to stain samples of all three time points in one tube in order to minimize interference factors.
Results: As anticipated, we observed highly proliferative, reconstituting immune cell populations (T cells, NK cells, monocytes) at TP2 displaying an enhanced expression of glycolytic features such as the glucose transporter GLUT1 and HK2, glycolysis´ rate limiting enzyme. Furthermore, indicators for fatty acid oxidation (i.e. CPT1α) and amino acid transport proteins (i.e. CD98) were upregulated suggesting an overall increased metabolic activity. However, PGC1α, co-transcriptionally regulating mitochondrial biogenesis, was found reduced in all reconstituting leukocyte subsets (T cells, NK cells, monocytes) at TP2, despite the increased expression of one of its regulators, i.e. the co-stimulatory CD137 (4-1BB). In contrast to elevated metabolic markers PD-1 expression, a mediator of immunometabolic anergy, was steadily increasing during the course of our analyses.
Conclusions: Taken together, our data demonstrates metabolically active reconstituting immune cells regardless of the underlying disease. Next, we want to functionally validate these findings and correlate them with the patients' clinical course (e.g. time to leukocyte recovery, infectious complications, and early relapse).

Disclosure: No conflict of interest disclosed.

Freier Vortrag

Rehabilitation

V563

Cognitive dysfunction and return to work in patients with breast cancer: Final results from the NeuroCog FX Study

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Introduction: Patients with breast cancer often complain of impaired mental performance. Etiologically, not only tumor therapy, but also a multitude of psychosocial factors seem to play an essential role. The influence of objective or subjective cognitive deficits on gainful employment after oncological rehabilitation is yet unclear.
Methods: As part of an oncological rehabilitation, a neuropsychological examination was conducted in 396 breast cancer patients, using a computer-assisted test battery (NeuroCog FX). In addition, the subjective assessment of cognitive performance, depressive symptoms and health-related quality of life were assessed by means of standardized questionnaires (EORTC QLQ-30, PHQ9, FEDA). A socio-medical follow-up survey was carried out 6-9 months after the rehabilitation measure.
Results: Neither the objective neuropsychological test data nor the clinical and therapeutic factors (apart from a positive nodal status) showed a statistical significant correlation to re-employment after rehabilitation (p>.05). On the other hand the subsequent loss of gainful employment correlated significantly with subjective cognitive deficits (p< .001), depressive moods (p< .001) and impaired quality of life (p=.004), which were already perceived during rehabilitation. Positive factors influencing gainful employment were: occupation prior to cancer diagnosis (p< .001), continued employment (p< .001), white-collar worker (p=.007) and step-by-step reintegration (p< .001).
Conclusions: The subjective assessment of one´s own performance significantly influences future employment. Patients with unfavorable prognostic factors can be identified already during a rehabilitation measure and given appropriate therapies or support offers. This is important not only for social health professionals but also for oncology specialists.

Disclosure: No conflict of interest disclosed.

V564

Multiprofessional teamwork in oncological rehabilitation and the use of volitional strategies improve the outcome of rehabilitation and promote aftercare of cancer patients

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Introduction: Oncological rehabilitation focuses lifestyle problems like physical activity and nutrition also than functional problems like fatigue or return to work after cancer disease. In different studies we investigated teamwork effects and the use of volitional strategies for a better outcome of rehabilitation and more sustainability in aftercare for cancer patients.
Methods: In different randomized studies we focused sustainability of lifestyle interventions to control physical activity and nutrition by volitional strategies. We also developed different modules like "fatigue management" and "job perspective" for return to work in rehabilitation team. We evaluated the processes and the modules themselves for outcome and sustainability.
Lifestyle interventions were randomly assigned to a control (CG) or intervention group (IG) including 2 measurement points later to assess intentions, volitional strategies and also exercise levels or nutritional effects. The management modules were developed with team accompanied by expert interviews and group interviews with cancer patients. Therefore we used sequential control group designs with an intervention (IG) and a control group (CG).
Results: Volitional strategies and teamwork in oncological rehabilitation focusing the lifestyle problem physical activity (PA) increase level of PA in cancer patients (IG) on average 120 min/week higher than in CG (p< .05, d=0.63) in the 12 month follow-up. Also health related quality of life (QL) is more increased in IG than CG (p< .001, d=0.53). Cancer patients receiving an additional nutritional module in rehabilitation can reduce BMI (p< .001) or increase fruit consumption (p< .001) significantly in the 6 month follow-up. Developing management modules in oncological rehabilitation in team are valued as meaningful by cancer patients and team members. We see synergetic effects. Exchange and communication within the team were promoted. Patients felt better prepared for fatigue management (p< 0.001) and return to work (p< 0.05).
Conclusions: Lifestyle strategies like physical activity or nutrition will be improved sustainably until 12 months after rehabilitation by volitional strategies and teamwork in rehabilitation.
Module development promotes cooperation in the rehabilitation team and enhances outcomes in oncological rehabilitation like fatigue management or return to work for cancer patients and also promote aftercare.

Disclosure: Birgit Leibbrand: Employment or Leadership Position: Ärztliche Leitung Salzetalklinik, Vorstandsmitglied VfR Norderney; Expert Testimony: Drittmittel VfR Norderney
Heike Kähnert: Expert Testimony: Drittmittel VfR Norderney

V565

Physical fitness and body composition in breast cancer patients with different nutritional regimes

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Introduction: Breast cancer (BC) patients are commonly advised to adhere to a "healthy diet". However, this diet has not been defined yet. The aim of this study therefore was to evaluate the effect of 3 different diets on physical fitness and body composition in breast cancer patients to detect the most supportive diet for BC patients.
Methods: 152 BC patients, included in this prospective study, could choose between 3 different diets. They received intense training and advice during 3 weeks of rehabilitation and were instructed to adhere to their diet for 20 weeks in total. Proportion of macronutrients in energy percent (fat/protein/carbohydrates) were: Ketogenic diet (KD) 80/16/4 (n= 29), Low-Carb diet (LC) 50/20/30 (n=92) and western diet (WD) 30/15/55 (n=31). Dual-Energy x-ray (DXA) and spiroergometry were performed at start (t0) and after 20 weeks (t20) to analyse body composition and physical fitness. Data were analyzed by non-parametric Kruskal-Wallis test or Mann-Whitney-U-Test.
Results: From t0 to t20 muscle fat relation increased [2.1/2.4 (KD), 1.6/1.77 (LC) (p=0.02) and 1.65/1.75 (WD)] and visceral fat decreased [10.0/7.9kg (KD), 14.3/12.6kg (LC) and 12.7/12.1 (WD)] in all diet groups. At t0, total fat was lowest with KD (21.8kg) (p< 0.001) and the muscle/fat relation (2.3) was significantly higher than with LC (1.8) and WD (1.9). Here, subgroup analysis based on food questionnaires revealed, that 14/31 patients had used KD, 8/31 LC and only 7/31 WD before the study while 14/92 in the LC group hat used LC before and the 31/31 patients started from WD. With regard to physical fitness, both, Vo2/kg at VT2 (anaerobic threshold) [KD (+2.93), LC (+0.64) and WD (+0.48]) and Vo/kg Max [KD (+2.51), LC 1.43 and WD(+2,49)] increased between t0 and t20.
Conclusions: All three groups improved in body composition and physical fitness attesting the efficacy of the multimodal rehabilitation interven-

tion. However, KD proved to be best for positive changes in muscle/fat relation and physical fitness in breast cancer patients over a period of 20 weeks. One reason for this surprising result might be that ketone bodies such as ß-hydroxybutyrate may act as "super fuel" improving energy efficiency which is especially important in cancer patients.
Although still controversially discussed among oncologists, our results strongly support further studies to evaluate the therapeutic potential of a KD as nutritional regime for BC patients.

Disclosure: No conflict of interest disclosed.

V566

Work-related medical rehabilitation in cancer survivors: results from a cluster randomized multicenter trial

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Introduction: Work is a central resource for cancer survivors impacting health and quality of life. Effective multidisciplinary rehabilitation programs supporting the return to work have become increasingly relevant for cancer patients. In Germany, work-related medical rehabilitation programs consider treatment modules of work-related diagnostics, work-related functional capacity training, psychosocial groups, and intensified social counseling. Our study investigated the effectiveness of work-related medical rehabilitation as compared with conventional medical rehabilitation in a cluster randomized multicenter trial (German Clinical Trial Register: DRKS00007770).
Methods: In total, 484 patients with cancer, aged 18 to 60 years, were recruited in four rehabilitation centers. Patients at a center who started their rehabilitation in the same week represented a cluster. These clusters were randomly assigned using computer-generated randomization schedules to intervention group (IG; work-related medical rehabilitation) or control group (CG). The primary outcome was role functioning 12 months after completing rehabilitation as assessed by the corresponding scale of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30). Secondary outcomes were other quality of life domains and return to work.
Results: Analysis of delivered dose of treatments indicated a successful implementation of work-related medical rehabilitation. 379 patients, 197 in the IG, were included in the analysis of the 12-month follow-up. Overall, there was a difference of 16 hours in the dose of treatments between IG (79 hours) and CG (63 hours). There was no significant difference between IG and CG in the primary outcome (role functioning: b=3.69; 95% CI: -2.01-9.39; p=0.204) and secondary outcomes. Return to work rates were 72% and 75% for the IG and CG.
Conclusions: Despite effects at the end of rehabilitation and the 3-month follow-up work-related medical rehabilitation in cancer survivors had no long-term effect on quality of life and return to work as compared with medical rehabilitation.

Disclosure: No conflict of interest disclosed.

V567

Determine the "minimum clinical important difference" (MICD) in 1- and 24-hour pad test for the evaluation of postprostatectomy urinary incontinence during oncological rehabilitation?

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Introduction: The 1- (1hPT) and 24-h Pad Test (24hPT) are used as objective diagnostic methods for the assessment of postprostatectomy stress urinary incontinence. The aim of this study was to determine the "minimal clinical important difference" (MCID) and the test-retest reliability of the 1hPT and 24hPT.
Methods: 93 patients (mean age 64.0 years) were examined performing a 1hPT and 24hPT at the beginning and at the end of a three-week inpatient rehabilitation. The Pearson correlation was used for the statistical evaluation of the retest reliability. Values from 0.7 indicate a good repeatability of the test. The MCID was determined using distribution-based methods (intra-class coefficient (ICC), standard error of the mean (SEM), half standard deviation (0.5 SD)).
Results: The data of all 93 patients could be evaluated. The test-retest reliability resulted in a value of 0.85 for the 1hPT and a value of 0.88 for the 24hPT.
Conclusion: The results show that the 1hPT and the 24hPT have a very good test-retest reliability in everyday clinical practice. The minimum clinical difference (MCID) for urine loss reduction that is considered to be significant is between 9.5g to 12.6g for the 1hPT and between 82.1g to 85.7g for the 24hPT.

Disclosure: No conflict of interest disclosed.

Tab. 1. Urine loss 1hPT and 24hPT before and after 21 days of rehabilitation

parameter	Baseline (g) mean (SD)	after 3-weeks (g) mean (SD)	difference (g)	%	P value within group after 3-weeks
1h - Pad-Test	22.6 (31.2)	8.5 (13.2)	14.1 (25.3)	37.6	P<0.001
24h - Pad-Test	242.9 (269.6)	126.7 (171.1)	116.14 (171.3)	52.2	P<0.001

Tab. 2. Determination of the MCID by means of ICC, SEM, 0.5 SD

parameter	ICC	SEM	0.5 SD
1h - Pad-Test	0.55	9.5	12.6
24h - Pad-Test	0.77	82.1	85.7

V568

Influence of individualized sensorimotor training on the sense of balance and the reaction time of patients after radical prostatectomy?

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Introduction: The combination of classical continence training with oscillation rod training is an established concept in the rehabilitation of patients with post-prostatectomy incontinence (1). The aim of this study was to figure out if the sensorimotor training using an oscillating rod, originally used for incontinence therapy, also has a positive influence on the sense of balance and the reaction time in patients after radical prostatectomy.
Methods: 47 patients (Ø 64.3 years) after radical prostatectomy were examined. All study participants completed a standard therapy program, consisting of classical continence training, sensorimotor training, endurance training and a moderate strength training. The sense of balance and the reaction time were measured using Microswing Balance Test (MBT) and Traffic Light Test (TLT) at the beginning and at the end of rehabilitation. The urinary incontinence was evaluated with the 1-h and 24-h test pad.
Results: The following results (pre-post-comparison) were obtained:

1 highly significant improvement of postural stability ($p < 0.001$)
- stability right side from 51% to 57%
- stability left side from 53% to 59%
- overall stability from 52% to 58%

2 highly significant improvement in reaction time, by Ø 12 milliseconds($p < 0.001$)
3 significant improvement of 1-hour pad test (21.2g auf 9.4g ($p < 0.05$))
4 highly significant improvement of 24-hour pad test (218.1g auf 135.1g ($p < 0.001$))

Conclusion: A significant improvement of the sense of balance and the reaction time was shown. Therefore, could be concluded, that not only the continence apparatus but also the local and deep back and abdominal muscles as well as the sensory control of the arms, legs and stabilization of the trunk benefit from oscillation rod therapy.

Reference:

1. Heydenreich M, Puta C, Gabriel H, Zermann D, Oscillating pole treatment-a new effective treatment option for postprostatectomy urinary incontinence. Oncology Research and Treatment; 2016.

Disclosure: No conflict of interest disclosed.

Expertenseminar

E19: Inspektion im Prüfzentrum

V569

Investigator site inspection

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Any site involved in a clinical trial may be subject to inspection, such as the investigator sites, any laboratory used for clinical trial analyses and the sponsor's premises. GCP site inspections were much more frequent than sponsor inspections. Inspections may be conducted on a routine basis, or may arise as a result of a specific trigger. Inspections may be conducted on ongoing or completed studies and may be announced or unannounced. The legal framework does not distinguish between academic versus commercial trials. Deficiencies are classified into three categories; critical, major and minor. A summary for the criteria for judging deficiencies as critical, major or other are detailed.

This expert seminar wants to provide tips for a successful investigator site inspection. After a short induction refering to the clinical trial regulation 536/2014, the ICH GCP E6(R2) addendum, and the "4. Änderungsgesetz arzneimittelrechtlicher und anderer Vorschriften», key findings of inspections are reported.
On the basis of an updated criteria cataloque of the DGHO Workshop "AMG" the seminar hands out numerous advices how to prepare for a GCP inspection by the German health authorities.

Disclosure: No conflict of interest disclosed.

Expertenseminar

E20: T-NHL: Periphere T-Zell Lymphome

V570

Peripheral T cell lymphomas - bridging the gap between pathophysiological understanding and all day treatment

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Introduction: Peripheral T-cell lymphomas (PTCL) comprise molecular and clinical heterogeneous diseases with an aggressive clinical course and poor prognosis. 1/3 of patients are primary refractory after CHOP treatment and 1/3 of patients will relapse in the course of the disease. Prognosis in relapsed or refractory setting without stem cell transplantation is devastatingly poor. Understanding the molecular basis of PTCL evolved tremendously within the last decade. Based on these findings, many new therapies are currently investigated.
Methods: Literature-based review.
Results: For most PTCL subtypes, current consent of front-line treatment is anthracycline-based chemotherapy and, depending on the PTCL entity, autologous stem cell transplantation, reaching long term remissions in about 50% of patients. Treatment of some PTCL entities is substantially different. In ENKTL highest remission rates can be achieved with combination treatment with radiation and chemotherapy in localized and asparaginase-based chemotherapy in disseminated disease. Mainstay of T-PLL treatment is alemtuzumab and allogeneic stem cell transplantation. Unfortunately, about 30% of patients with PTCL will face primary refractory disease. For relapsed or refractory disease allogeneic stem cell transplantation is often the only option for long term disease control. New treatments tested to date, such as HDAC-inhibitors do not sufficiently improve survival. Deeper understanding of the underlying pathophysiological mechanisms of many PTCL subtypes identified new potential therapeutic targets such as JAK-STAT signaling, T-cell receptor signaling, DNA-methylation or check point inhibition, leading to trials with new drugs and drug combinations. The antibody drug conjugate brentuximab vedotin is EMA-approved for relapsed ALCL and in combination with chemotherapy will soon be approved in the first line setting. In relapsed and refractory PTCL, PI3K-inhibitors such as duvelisib achieve responses in about 50% of cases.
Conclusions: The current management of most PTCL is based on chemotherapy and stem cell transplantation concepts. In the near future, more effective treatments may lead to better therapy outcomes in many PTCL entities.

Disclosure: Thomas Weber: Financing of Scientific Research: Takeda

Wissenschaftliches Symposium

Update Infektionen in der Hämatologie und Onkologie

V584

Lung infiltrates in febrile neutropenia

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Lung infiltrates (LI), including infections and other differential diagnoses, are frequent complications in patients with high-risk neutropenia. These patients have a higher risk of treatment failure and mortality compared to those with fever of unknown origin (FUO) or other clinically documented infections. Therefore, the AGIHO provided the 2019 updated guidelines on diagnosis and antimicrobial therapy. Multi-slice or high-resolution CT scan is the diagnostic method of choice; conventional chest radiograph plays no role for diagnosis. If LI are detected, a bronchoalveolar lavage should be performed. Transbronchial biopsies are not recommended. If a tissue sample is required, CT-guided side-cut percutaneous biopsy, video-assisted thoracoscopy or open-lung biopsy should be used. In microbiologically documented cases, Gram-negative bacteria and pathogens resistant to beta-lactam antibiotics, e.g. moulds, *Pneumocystis jirovecii* or viruses are predominant. However, enterococci, coagulase-negative staphylococci or *Candida* spp. are not causative pathogens. Response to broad-spectrum antibiotics is less than 30%, whereas the addition of mould-active antifungals increases response rates to up to 75%. Anti-pseudomonal beta-lactam antibiotics, as used for FUO in these high-risk patients, should be administered 1st-line, while voriconazole, isavuconazole or liposomal amphotericin B (L-AmB) are the preferred pre-emptive antifungals. Patients under current azole prophylaxis should be switched to L-AmB. Fungal PCR and *Aspergillus* galactomannan should be used for diagnosis of invasive aspergillosis. If *A. fumigatus* is isolated, *in vitro* testing for azole resistance should be ordered. Patient with no antifungal prophylaxis should receive isavuconazole or voriconazole. In hospitalized patients in this setting, antiviral agents, macrolide antibiotics, aminoglycosides or fluoroquinolones should only be given based upon conclusive microbiological findings. If *Pneumocystis* pneumonia is suspected due to the radiological LI pattern and new LDH elevation, treatment should be initiated promptly, also before bronchoscopy. Persistent fever, progressive or newly emerged LI and rising inflammatory parameters after 7 days of treatment typically indicate the need for repeated microbiological diagnostics and changing the antimicrobial treatment regimen. A switch to 2nd-line antibiotics such as meropenem may be considered, but is based on weak evidence.

Disclosure: Enrico Schalk: No conflict of interest disclosed.
Georg Maschmeyer: Financing of Scientific Research: Speaker Honoraria: Gilead, Bristol-Myers Squibb, Merck-Serono, Janssen-Cilag, Forum für Medizinische Fortbildung, RS GmbH, MedUpdate GmbH; Other Financial Relationships: Congress Attendance: Bristol-Myers Squibb, Janssen-Cilag

Fortbildung

Sarkome: Therapie 2019

V594

Update 2018/2019: ANNOUNCE & Co

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Soft tissue sarcomas (STS) are a heterogeneous group of tumours arising from the embryonic mesoderm comprising more than 50 different histological entities exhibiting great differences in terms of clinical behaviour, pathogenesis and genetics. In up to 50 % of patients distant metastases will occur and the median overall survival for patients with advanced disease is approximately 12-15 months. As effective targeted treatments are scarce, doxorubicin and ifosfamide - being used for more than 40 years - still remain the backbone of systemic chemotherapy. Trabectedin, pazopanib and eribulin have been introduced into and have enriched the therapeutic armamentarium.
Regarding trabectedin - approved in Europe since 2007 - a large phase III study in the USA comparing trabectedin versus DTIC stressed its sustained activity in STS patients. Even though the primary endpoint, overall survival, was not reached, the results led to global FDA registration in October 2015 for the treatment of patients with leiomyosarcomas and liposarcomas. The anti-angiogenic compound pazopanib has been tested in a large EORTC phase III trial (PALETTE) demonstrating a significant advantage regarding PFS prolongation of about three months in favour of pazopanib versus placebo for certain STS subtypes excluding liposarcomas resulting in its approval in USA, Europe and Japan in 2012. The phase III trial of eribulin met its primary endpoint of an overall survival benefit of two months (13.5 versus 11.5 months) in favour of eribulin compared to DTIC in pretreated patients with advanced leiomyosarcomas or adipocytic sarcomas. The final approval of eribulin in early 2016, however, is restricted to pretreated liposarcoma patients. Olaratumab, a fully human anti-PDGFRα monoclonal antibody, has been tested in a phase Ib/II trial in combination with doxorubicin demonstrating an overall survival benefit of roughly 12 months (26.5 versus 14.7 months). However, results of the phase III trial (ANNOUNCE) demonstrated that the study did not meet its primary endpoint in the full study population or in the leiomyosarcoma sub-population; there was no difference in overall survival between the study arms for either population. Other interesting candidates being tested in phase III study concepts such as selinexor or carotuximab as well as ongoing national and international trials of interest will be presented in this update.

Disclosure: Bernd Kasper: Advisory Role: Bayer, Clinigen, Eisai, Lilly, Roche; Financing of Scientific Research: Bayer, Lilly, Novartis, PharmaMar, Pfizer; Expert Testimony: PharmaMar

V595

Status of the S3 guideline on adult soft tissue sarcomas and the certification process of sarcoma centers

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The treatment landscape in sarcomas is complex and an interdisciplinary is a key component of patient management. After a long haul we started the process to homogenize the treatment approach in adult soft tissue sarcomas (STS) in Germany in 2017. It is a unique endeavor, which will create a template for treatment of highly diverse diseases across multiple disciplines.
In parallel, we started the process to develop the certification process for sarcoma centers within the German Cancer Society. After a pilot phase, a first set of centers was able to achieve certification and introduces a level of visability in this rare diseases.

Disclosure: Viktor Grünwald: Employment or Leadership Position: UK Essen; Advisory Role: Lilly; Stock Ownership: AstraZeneca, BMS, MSD; Financing of Scientific Research: Lilly, PharmaMar; Expert Testimony: Novartis; Other Financial Relationships: Ipsen

V596

Baseline Results of the German Health Services Research Study PROSa - quality of care and patient reported outcomes

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Introduction: Sarcoma treatment challenges clinical care and research because of a complex diagnostic and treatment algorithm and a high disease burden. There is scarce knowledge about the real-world situation of sarcoma care in Germany such as compliance to treatment guidelines and the quality of care. Little is known about quality of life (QoL) and other patient-reported outcomes (PRO).

Methods: We established a nationwide study-network and conducted a prospective cohort study. 1308 adult patients with incident or prevalent sarcoma were recruited between 09/2017 and 01/2019 in 60 participating institutions. Clinical data on patient- and institutional-level and PRO via standardized and self-developed questionnaires were collected at 0, 6 and 12 months. Study data were managed using REDCap electronic data capture tools.

Standards of care were identified through established guidelines and with the help of expert consultations. We examined the implementation of the following standards: Case review by multidisciplinary tumor-board, biopsy before therapy, local CT or MRI scan, thoracic or abdominal CT scans before therapy, the quality of surgical margins, psycho-oncological care and social care.

For the measurement of patient reported outcomes, we used established validated instruments. In baseline we assessed Quality of Life (EORTC QLQ-C30), psychological distress (PHQ 4), pain (BPI), physical activity (BSA) and treatment decision making (CPS).

Results/Aims: Baseline clinical data collection closes in 05/2019. Final baseline results will be presented at the conference.

With regard to health services research we aim to identify potential factors associated with non-guideline adherence. On an institutional level those might for example include: numbers of patients treated per year, existing certifications and type of medical facility. On a patient level those might include: gender, socio-economic-status and age.

With regard to PRO we aim to identify potential factors associated with changes in QoL and other PRO.

Conclusions: PROSa will provide detailed information on the quality of care and guideline adherence in Germany as well as PRO. The study supports the identification of potentially insufficient healthcare structures as well as potential vulnerable groups. Ultimately, it might contribute to an optimization of healthcare service for adult sarcoma patients.

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V597

TRK-inhibition in sarcoma: How do I find the correct patient?

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TRK fusions result from chromosomal translocations involving the NTRK1, NTRK2 or NTRK3 genes. They have been identified across a broad range of tumor types in adults and children. TRK fusions are very common in infantile fibrosarcoma, cellular congenital mesoblastic nephroma, and secretory breast cancer. However, TRK fusions have also been detected in a wide variety of other cancers, including undifferentiated sarcoma, melanoma, glioma, papillary thyroid cancer, and even acute leukemia, albeit at much lower frequencies. Selective TRK inhibitors have achieved response rates exceeding 75% in children and adults with TRK fusion cancers, regardless of histology, and have at the same time demonstrated a very favorable safety profile.

While *NTRK* gene fusions were among the first oncogenic translocations identified, they are not yet routinely tested for. TRK fusions might be screened for through a number of diagnostic tests. Immunohistochemistry (IHC) can be performed on formalin-fixed, paraffin-embedded (FFPE) tissue; TRKA, TRKC and pan TRK antibodies are commercially available for clinical use. Outside of the brain, sensitivities and specificities in the range of 95-100% have been reported. The advantages of IHC are fast turnaround time, use of less tissue and lower costs compared with molecular methods. DNA fluorescence in situ hybridization (FISH) has been a standard method of detecting ETV6-NTRK3 fusions in tumors likely to carry them. Its sensitivity is lower than that of IHC and the method is not reliable in tumors harboring ETV6 fusions with non-NTRK partners or non-classical NTRK fusions. Reverse transcription polymerase chain reaction (RT-PCR) is designed to identify only known translocation partners and breakpoints and cannot identify novel breakpoints or novel fusion partners. Therefore, RT-PCR is not used routinely in this context. Next-generation sequencing (NGS) has high specificity with variable sensitivity, provides the most comprehensive overview of a large number of genes and may identify *NTRK* gene fusions as well as other actionable alterations, with minimal tissue needed. In the clinical practice, collaboration between oncologists and pathology lab partners can help determine which tests are appropriate to detect TRK fusion cancers.

Here, we review the literature and provide recommendations for screening indication, screening methods and patient target groups who might benefit from treatment with a TRK inhibitor.

Disclosure: No conflict of interest disclosed.

Fortbildung

CLL: Therapie in der neuen Ära

V600

Treatment after failure of B-cell-receptor-signalling inhibitors

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Signaling through the B-cell receptor (BCR) plays a central role in chronic lymphocytic leukemia (CLL). Inhibitors of the BCR signalling pathway (BCR-I) like Ibrutinib and idelalisib changed the therapeutic landscape of CLL in the last 5 years.

Initially both agents were used predominantly in high-risk disease, either after failure of chemoimmunotherapy (CIT) or presence of del17p and/or TP53 mutation. Recently phase-III trials showed favourable results for ibrutinib compared to CIT as 1st line treatment. Ibrutinb has become the most frequently used drug for CLL in the USA.

Unlike CIT BCR-I have to be given as continuous treatment. Adverse events are a common reason for stopping a BCR-I, notably when used in 1st line. Despite high activity relapse on BCR-I occurs, either as progressive CLL or as high-grade transformation.

The term failure of BCR-I has been used for both resistance and intolerance. Therefore patients with failure of BCR-I are very heterogenous. Therapeutic options depend on the characteristics of the disease, type of failure and patient factors.

Initial reports suggested that patients with failure of ibrutinib had a very poor survival. At that time many patients had a very advanced CLL without any options left. Today most patients treated with BCR-I can receive other highly effective therapies either another BCR-I or venetoclax, an inhibitor of bcl2.

In patients who relapse on BCR-I with suspected transformation PET/CT can identify optimal site for tissue biopsy. Diffuse large B cell lymphoma (DLBCL) is the most common form of transformation. 80% of DLBCL are clonally related to the CLL with poor outcome despite CIT (e.g. R.CHOP).

For patients relapsing with CLL due to resistance to a BCR-I with del17p/TP53 mutation venetoclax seems to be more active than change to another BCR-I. The situation is similar for resistance to BCR-I after failure of CIT.

In high-risk-CLL, resistant to CIT and BCR-I, or clonally related DLBCL allogeneic stem cell transplantation with reduced-intensity conditioning or if available new cellular therapies as CAR-T-cells should be considered in eligible patients.

Patients discontinuing an BCR-I due to toxicity or intolerance can be switched to another BCR-I. In patients with poor compliance and low-risk disease (e.g. IGHV mutated, ibrutinib as 1st line) standard CIT is still an option. Venetoclax combined with an anti-CD20-antibody is highly active time-limited treatment to be considered in this situation.

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Freier Vortrag

B-Zell-Lymphom, indolent

V603

Ibrutinib treatment in Waldenström's macroglobulinemia (WM): follow-up results of the phase 3 iNNOVATE™ study

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Introduction: In iNNOVATE, ibrutinib (ibr) + rituximab (RTX) improved PFS and response vs RTX in treatment-naïve (TN) and previously treated WM patients (pts). In the open-label substudy, single-agent ibr showed sustained responses with manageable toxicity in RTX-refractory WM. Follow-up data from the randomized study (median follow-up, 33.4mo) and substudy (median follow-up, 42.2mo) are reported.

Methods: Pts with confirmed, symptomatic WM requiring treatment (untreated or ≥minor response [MR] to their last RTX-based regimen) were randomized to daily 420 mg ibr (IR) or placebo (R) plus RTX (375mg/m^2/week IV at weeks 1-4 and 17-20). Pts who did not achieve ≥MR or relapsed within 12mo of last RTX therapy received daily 420mg ibr (substudy). Key endpoints were PFS and response rates by investigator assessment, OS, and safety.

Results: Of 150 randomized pts (n=75/arm; median age 69y), 45% were TN. Median treatment duration was 32mo for IR and 16mo for R. Major response rates (≥PR) were 79% vs 33%; ORRs (≥MR) were 95% vs 48% (both $P< 0.0001$). VGPR rates were 25% vs 3%. Major responses with IR were robust and independent of MYD88/CXCR4 genotype; time to major response was 2, 3, and 6mo for MYD88^{L265P}/CXCR4^{WT}, MYD88^{L265P}/CXCR4^{WHIM}, and MYD88^{WT}/CXCR4^{WT}. Median PFS was not reached vs 20.3mo (HR=0.22; $P< 0.0001$); estimated 36-mo PFS was 76% vs 31% and was comparable across genotypes for pts on IR. Estimated 36-mo OS was 93% vs 90%; 32 pts (43%) on R crossed over to IR after PD. Reasons for ibr discontinuation on IR included PD (9%), AEs (7%), and pt withdrawal (11%). The AE profile for IR was consistent with previous reports. Grade ≥3 AEs occurred in 65% vs 56% of pts. With current follow-up, 71% of pts on IR continue ibr. In the substudy, 31 RTX-refractory pts (median age, 67y) received single-agent ibr; 71% had ≥3 prior therapies. With longer follow-up, median PFS was 41mo; estimated 36-mo PFS was 61%. Major response rate was 77%; ORR was 90%. Estimated 36-mo OS was 84%. Treatment was ongoing in 48% of pts. With median 38mo of ibr therapy, no major hemorrhage or atrial fibrillation was reported. Grade ≥3 AEs occurred in 77% of pts; no fatal AEs were reported.

Conclusions: IR showed continued superiority over R regardless of genotypic factors in WM pts. In heavily pretreated, RTX-refractory pts, single-agent ibr was highly active with follow-up >3y. Ibr as single-agent or in combination had a manageable safety profile with no new AEs identified over longer follow-up.

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V604

Activated CXCR4 signaling accelerates TCL-1 driven lymphomagenesis

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Introduction: CXCR4 is a chemokine receptor of the CXC-motif family with multiple essential roles in a widespread set of physiologic processes, including hematopoiesis and homing of immune cells. Activating C-terminal WHIM (warts, hypogammaglobulinemia, immunodeficiency, myelokathexis) syndrome -like mutations are recurrent genetic aberrations in lymphoma. High CXCR4 expression and activating CXCR4 mutations are associated with adverse outcome and impaired efficacy of conventional immunochemotherapy and B-cell receptor targeted therapies in lymphoma.

Methods: Constitutively active CXCR4 signaling was established in two murine models of lymphoma (indolent lymphoma/chronic lymphocytic leukemia-like disease: *Eμ-TCL1;* aggressive B-cell lymphoma: *Eμ-Myc),* by intercrossing to mice harboring the internalization-defective *CXCR4*^{C1013G} WHIM syndrom-like mutation. Double transgenic mice and controls were monitored for lymphoma onset, lymphoma phenotype and disease

presentation. Further, we performed extensive transcriptome analysis as well as comprehensive flow cytometry analysis of surface antigens and CXCR4- and B-cell receptor downstream signaling pathways on pre-malignant B cells and lymphoma samples.
Results: CXCR4 surface expression was increased in *Eμ-TCL1;CXCR4*^{C1013G} mice as compared to *Eμ-TCL1* controls. Activated CXCR4 signaling in *Eμ-TCL1;CXCR4*^{C1013G} mice accelerated disease onset with extensively more malignant CD19^{+}CD5^{+}B220^{low} cells in lymphatic organs as compared to *Eμ-TCL* controls. Furthermore CXCR4 activation by means of heterozygous *CXCR4*^{C1013G} state lead to a more aggressive phenotype with lymphadenopathy observed in 33% of mice, whilst presenting with the same CD19^{+}CD5^{+} B220^{low} CLL-like phenotype like *Eμ-TCL1* controls. In contrast, activation of CXCR4 in *Eμ-Myc* mice (*Eμ-TCL1;CXCR4*^{C1013G}), did not result in disease acceleration. Evaluating transcriptomic results performing GSEA on B cells of *C1013G* mutated mice identified an activation of NF-κB signaling and further pathways associated with CXCR4 activation.
Conclusions: Activated CXCR4 signaling by means of the internalization-defective WHIM-like CXCR4 mutations accelerates lymphomagenesis in a model of indolent lymphoma, but not in aggressive Myc-driven B-cell lymphoma. Furthermore, this study provides insights into crucial CXCR4-dependent signaling pathways and events of CXCR4 activation in vivo.

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V605

A focused RNAi screen identifies MCL1 as potent therapeutic target in mantle cell lymphoma

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Mantle cell lymphoma (MCL) presents as a highly disseminated B-cell malignancy characterized by a t(11;14translocation leading to the overexpression of the cell cycle regulator Cyclin D1. The disease is associated with short responses to current standard therapies and a great need for new therapeutic strategies. Since MCL displays sensitivity to mTOR inhibition, we aimed to dissect the impact of PI3K/mTOR signaling in MCL by conducting a RNAi-based functional screen of the PI3K/mTOR pathway in a mouse model of MCL generated by transduction of Eμ-*myc* transgenic mice with Cyclin D1. Using primary MCL tumor cell lines derived from this model as a platform, we conducted a loss-of-function screen using a custom-generated miR30-based shRNA library of ~1500 shRNAs targeting more than 300 different PI3K related genes in duplicate MCL lymphoma and p19/ARF$^{-/-}$ murine control lymphoma cells. We identified more than 50 genes affecting MCL tumor growth and survival, including the *Mcl1* gene, an anti-apoptotic member of the Bcl-2 family. All shRNAs targeting *Mcl1* scored in the primary screen, and knockdown of *Mcl1* by two different hairpins induced rapid cell depletion. To expand the genetic results, we also tested two recently developed potent BH3-mimetic inhibitors of MCL1. Targeting MCL1 with two preclinical inhibitors (S63845, AZD 5991) led to rapid induction of apoptosis in our primary murine MCL cells, and also in 4 out of 6 human MCL cell lines at nanomolar concentrations. Two of the human MCL lines were resistant (IC50>5μM), although MCL1 was clearly inhibited as evidenced by significant protein stabilization after treatment. Further analysis of apoptosis-related proteins in the resistant lines excluded compensatory regulation of anti- or pro-apoptotic BCL2-family members as effectors of MCL1 independence. Nevertheless, co-targeting of BCL2 (Venetoclax) and MCL1 showed synergistic effects in all tested cell lines, suggesting an added benefit of combined inhibition of MCL1 and BCL2 in MCL.
In summary, using an unbiased shRNA screen of more than 300 genes contained in the PI3K pathway, we were able to identify a range of novel targets in Cyclin D1 driven lymphoma cells. The BCL2 family member MCL1 emerged from the screen as a potent vulnerability in our MCL model, and subsequent preclinical testing in primary tumors and human MCL cell lines using 2 small molecule inhibitors confirmed MCL1 inhibition as a promising new therapeutic approach in MCL.

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V606

Derivatives of the endogenous CXCR4 inhibitor EPI-X4 suppress oncogenic MAP kinase signaling in Waldenström's macroglobulinemia

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Background: Waldenström's Macroglobulinemia (WM) is a rare indolent B-NHL. Current therapy approaches with Ibrutinib have demonstrated a major role of mutations in CXCR4 for the pathobiology of WM. Interplay of the Bruton tyrosine kinase (BTK) and CXCR4 lead to activation of the MAP kinase pathways resulting in inferior response to the BTK inhibitor Ibrutinib. The CXCR4 mutation S338X has been shown to enhance ERK activation in WM with constitutive phosphorylation upon Ibrutinib therapy as one of the Ibrutinib resistance mechanisms in WM patients. Thus, innovative approaches to counteract growth promoting effects of mutated CXCR4 are needed in WM. We recently demonstrated that a novel naturally occurring peptide EPI-X4 (Endogenous Peptide Inhibitor of CXCR4) cleaved from ubiquitously present albumin counteracts WM growth and migration in vitro and in vivo. We now demonstrate that EPI-X4 acts in a cell intrinsic way by blocking downstream signaling.
Results: First, WM cells harboring different WHIM-like CXCR4 mutations were generated. Using flow cytometry, we observed an increase in ERK phosphorylation at Tyr204 (ERK1) and Tyr187 (ERK2) in WM mutant cells compared to the wild-type control, with CXCR4$_{S339fs/365X}$ having the most prominent effect. When adding the CXCR4 antagonists AMD3100 or Opt#2 (an optimized EPI-X4 derivate) to the cells, CXCL12-induced ERK phosphorylation of all CXCR4 mutants was reduced in a dose-dependent manner. Reduction in ERK phosphorylation was accompanied by significant changes in cell death and migration. The indicated mutant cell lines showed an increase of apoptosis (up to 90% compared to the control) and an impaired migration ability of 63% and 95% respectively, when treated with the first and second generation of EPI-X4 derivatives. Also in vivo, the reduction in ERK phosphorylation was paralleled by anti-lymphoma activity with prolonged survival of NSG xenografts transplanted with WM cells by 26 days (median survival control 54,5 days versus 80,5 days for WSC02, respectively). In parallel, we treated three different WM cell lines with EPI-X4 and performed proteomic analysis using tandem mass spectrometry. These results are currently being analyzed and will be presented.
Conclusions: CXCL12/CXCR4 interaction triggers BTK phosphorylation and downstream MAPK signaling. The naturally occurring EPI-X4 and its optimized derivatives are able to interfere with CXCR4 downstream signaling and impair growth of CXCR4 mutated WM cells.

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V607

First line systemic treatment for mucosa-associated lymphoid tissue (MALT) lymphoma not eligible for H. pylori eradication - do we still need chemotherapy?

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Background: There is no clear therapeutic algorithm for MALT lymphoma patients beyond H. pylori eradication and while recent data on chemotherapy based regimens +/- rituximab (R) have potentially set new standards for patients in need of systemic treatment, it appears of interest to investigate also chemotherapy-free strategies.
Methods: We have assessed MALT lymphoma patients treated upfront with systemic treatment defined as either chemotherapy (= classical cytostatic agents +/- R) or immunotherapy (= immunomodulatory agents or anti-CD20 antibodies) at the Medical University Vienna 1999-2019. Primary endpoint was progression-free survival (PFS).
Results: 159 patients received upfront systemic treatment (median age 65 years) with the median follow-up being 67 months (IQR 33-101). The majority of patients had extragastric disease (80%) but we identified also 32 patients (20%) with H. pylori negative gastric lymphoma. At initial diagnosis, 64% had stage I/IIE and 36% disseminated disease (IIIE/IV) and MALT-IPI predicted low risk in 39%, intermediate risk in 46% and high risk in 15% of cases. Looking at type of first line systemic treatment and outcome, 47% (74/159) received chemotherapy-based regimens and 53% (85/159) immunotherapy including IMiDs lenalidomide/ thalidomide (36%), anti-CD20 monotherapy rituximab/ ofatumumab (27%), macrolides clarithromycin/ azithromycin (27%) and proteasome inhibitor bortezomib (9%). Median estimated PFS for the entire collective was 76 months (95%CI 50-102) and while the overall response rate (90% vs 68%, p< 0.01) and the complete remission rate (75% vs 43%, p< 0.01) was significantly higher in the chemotherapy group, there was no difference in PFS between the chemo- (median 81 months, 95%CI 47-115) and the immunotherapy cohort (median 76 months, 95%CI 50-103) (p = 0.57), suggesting comparable long-term outcome. Interestingly, there was a non-significant trend towards a decrease in relapse rates for immunotherapy, resulting in a lower number of patients in need of second line treatment (39% vs 50%, p = 0.15).
Conclusions: Our data show higher response rates with chemo- compared to immunotherapy, but this did not translate into a superior PFS. Thus, given the biological background of MALT lymphoma being highly depended on the microenvironment and in view of the favorable toxicity profile of novel immunotherapeutic approaches such as IMiDs and macrolides, we suggest that this should be further investigated in clinical trials.

Disclosure: No conflict of interest disclosed.

V608

MAGNIFY: A phase IIIb trial shows promising efficacy in the treatment of relapsed/refractory, indolent non-Hodgkin lymphoma patients with lenalidomide in combination with rituximab (R^2)

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Introduction: Standard treatment is lacking in relapsed/refractory (R/R) indolent NHL (iNHL), as indicated by a median PFS of < 1 y with PI3K inhibitors. Recently, the immunomodulatory agent lenalidomide (L) reported enhanced activity with rituximab (R) as combination R^2, with a median PFS of 39.4 mo in R/R iNHL patients (pts; AUGMENT: Leonard et al. J Clin Oncol; 2019.).
Methods: The global, multicenter, non-registrational, randomized phase IIIb MAGNIFY trial was designed to determine the optimal duration of L (+ R) in pts with R/R FL gr 1-3a and MZL (NCT01996865). R^2 treatment is 12 cycles of L (20 mg/d, d1-21/28) + R (375 mg/m^2/wk cycle 1 and every 8 wk for cycles 3+) followed by 1:1 randomization in patients with stable disease or better to continue with R^2 vs R maintenance. The interim primary endpoint was overall response rate (ORR) by 1999 IWG criteria with induction R^2 in treated, efficacy-evaluable pts with baseline/post-baseline assessments.
Results: At a median 16.7-mo follow-up (range, 0.39-48.8), 370 pts (295 [80%] FL gr 1-3a; 75 [20%] MZL) were enrolled with a median age of 66 y, 83% stage III/IV disease, and a median of 2 prior therapies (range, 1-11; 95% prior R-containing). Efficacy-evaluable pts showed a 73% ORR and 45% CR (Table). Median TTR was 2.7 mo, median DOR was 36.8 mo, and median PFS was 36.0 mo. Of 370 pts, 142 have been randomized and entered maintenance (response also contributed to DOR/PFS). The most common all-grade AEs were 48% fatigue, 40% neutropenia, 35% diarrhea, 30% nausea, and 29% constipation. Grade 3/4 neutropenia was 34%; all other grade 3/4 AEs were < 6%. These results are corroborated by the AUGMENT trial, in which a total of 358 pts with R/R FL gr 1-3a and MZL were randomized to R^2 (n=178) vs placebo/rituximab (n=180), where PFS was significantly improved for R^2 with a HR of 0.46 (95% CI, 0.34-0.62; P< 0.001) and median PFS of 39.4 mo (95% CI, 22.9 mo-NR) vs 14.1 mo (95% CI, 11.4-16.7), respectively.
Conclusion: Lenalidomide improves the efficacy of R, as shown by a clinically-active (with a high CR rate) and well tolerated R^2 therapy in pts with recurrent indolent lymphoma, including those refractory to rituximab.

Tab. 1. Efficacy for induction R2 in R/R iNHL (MAGNIFY)

	ORR, %	CR, %	Median TTR, mo (range)	Median DOR, mo (95% CI)	Median PFS, mo (95% CI)
Overall	73	45	2.7 (1.6-12.0)	36.8 (35.8-NR)	36.0 (26.5-NR)
By histology					
FL gr 1-3a / MZL	74 / 65	46 / 38	2.8 (1.6-12.0) / 2.7 (1.9-11.1)	NR (27.7-NR) / 35.8 (NR-NR)	30.2 (23.0-NR) / 38.4 (26.5-38.4)
By rituximab-refractory status					
Yes / No	63 / 78	40 / 47	2.8 (1.6-12.0) / 2.7 (1.6-11.6)	35.8 (19.2-NR) / NR (36.8-NR)	18.1 (15.5-26.5) / NR (36.0-NR)

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Jeff Sharman: Employment or Leadership Position: leadership for US Oncology; Advisory Role: AbbVie, Acerta, Celgene, Genentech, Gilead Sciences, Pharmacyclics, TG Therapeutics; Financing of Scientific Research: Gilead Sciences; Expert Testimony: Acerta, Celgene, Genentech, Pharmacyclics, Gilead Sciences, Merck, Seattle Genetics, TG Therapeutics, Takeda

Freier Vortrag

Hodgkin Lymphom

V609

B-CAP (Brentuximab Vedotin, Cyclophosphamide, Doxorubicin and predniso(lo)Ne) in older patients with advanced-stage hodgkin lymphoma: results of a phase II intergroup trial By the German Hodgkin study group (GHSG) and the Nordic Lymphoma group (NLG)

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About one third of patients diagnosed with classical Hodgkin lymphoma (cHL) are 60 years or older. They have a poor prognosis, particularly when presenting in advanced stages. In previous trials, older patients did not benefit from intensified regimens in terms of overall survival due to a high toxicity-related death rate. In order to improve tolerability, we developed the B-CAP regimen (brentuximab vedotin, cyclophosphamide, doxorubicin and predniso(lo)ne), incorporating the antibody-drug conjugate brentuximab vedotin into a CHOP- based chemotherapy backbone. We recruited patients with newly diagnosed advanced-stage cHL aged 60 years or older and eligible for polychemotherapy (Cumulative Illness Rating Scale for Geriatrics ≤6 in total and ≤3 per organ system) in five European countries. Treatment consisted of six cycles B-CAP; radiotherapy to Positron Emission Tomography (PET) positive residuals was applied. The primary endpoint was the CT-based objective response rate (ORR; complete [CR] or partial remission (PR]) after six cycles of B-CAP, aiming at excluding an ORR of 60% or less via a one-sided 95% confidence interval. All patients completing interim staging after two cycles were considered eligible.
Between November 2015 and September 2017, 50 patients were recruited, of whom one withdrew consent before start of treatment. Of the remaining 49, 26 patients (53%) were male, 47 (96%) had stage III-IV disease, and the median age was 66 years (range 60-84). One patient died from infection before interim staging, and 48 patients were eligible for the primary endpoint. There were no further treatment-related deaths. The CT-based
ORR was 98% (one-sided 95% CI 90.5%-100%) with 21 patients having CR, 26 patients having PR, and one patient having progressive disease in the restaging after completion of B-CAP therapy. All patients with CT-based CR and 10/26 patients with PR had a negative PET (Deauville < 4), resulting in a complete metabolic response rate of 65%. Dose delivery was high with only two patients stopping treatment after four and five cycles, respectively, due to toxicity. Progression-free and Overall-Survival estimates at one year were 73.9% [95% CI: 61.1% to 86.6%] and 92.6% [95% CI: 84.5% to 100%], respectively.
In conclusion B-CAP is feasible and effective in patients older than 60 years with advanced-stage cHL and should be subject of further research.

Disclosure: Boris Böll: Advisory Role: Baxalta, Celgene, MSD, Mundipharma, Takeda; Financing of Scientific Research: Astellas, Celgene, J&J, Maquet, Miltenyi, MSD, Takeda; Expert Testimony: MSD, Takeda
Peter Borchmann: No conflict of interest disclosed.

V610

Nivolumab and brentuximab vedotin (BV)-based, response-adapted treatment in primary refractory patients (pts) and in pediatric pts with relapsed/refractory (R/R) classical Hodgkin lymphoma (cHL) in the phase 2 CheckMate 744 study

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Introduction: New salvage therapy (Tx) strategies are required for young pts with R/R cHL. CheckMate 744 (NCT02927769) is an ongoing study evaluating risk-stratified, response-adapted Tx using nivolumab (Nivo), BV, and bendamustine (Benda) in children, adolescents, and young adults with R/R cHL. In the standard-risk cohort, the regimen was well tolerated and resulted in high complete metabolic response (CMR) rates prior to consolidation. Here we evaluate this approach in primary refractory pts, and in pediatric pts in CheckMate 744.
Methods: Pts aged 5-30 years (y), after 1 prior Tx without autologous transplantation (auto-HCT), were eligible. Risk stratification was based on stage at diagnosis, time to relapse, B symptoms or extranodal disease at relapse, extensive disease with radiation Tx (RT) contraindicated at relapse, or relapse in a prior RT field. In the standard-risk cohort, pts received 4 induction (IND) cycles with Nivo+BV. Tumors were assessed every 2 cycles by investigators and blinded independent central review (BICR) per Lugano 2014 criteria. Pts with CMR any time after cycle 4 proceeded to high-dose chemotherapy/auto-HCT consolidation. Pts with suboptimal response after IND received 2-4 cycles of BV+Benda intensification (INT). Primary endpoint was CMR rate per BICR any time before consolidation. Analyses in primary refractory pts, and in pts aged ~18 y were post hoc.
Results: At baseline, 31/44 pts (70%) were aged ~18 y and 24/44 (55%) had primary refractory disease. Median follow-up was 43 wk. 10 pts aged ~18 y entered INT; of these, 2 received 4 INT cycles. CMR and objective response rates (ORR) per BICR are shown in the Table.

Tab. 1.

Table. CMR rates and ORR in primary refractory patients and in pediatric patients (aged <18 y) per BICR

n (%)	Overall (n=44)	Primary refractory (n=24)	Pediatric (aged <18 y) (n=31)
After nivolumab + BV induction			
CMR	26 (59)	15 (63)	18 (58)
ORR	36 (82)	19 (79)	25 (81)
Any time prior to consolidation			
CMR	38 (86)	20 (83)	27 (87)

Overall, 12 pts (27%) experienced a grade (G) 3-4 Tx-related adverse event (TRAE). 10/31 pts aged ~18 y (32%) experienced a G3-4 TRAE, most commonly neutropenia (2/31; 6%); no deaths or TRAEs led to discontinuation.

Conclusions: Response-adapted Tx with Nivo+BV achieved high CMR rates after IND in primary refractory pts with cHL. In pediatric pts with a standard risk of relapse, Nivo+BV IND, followed by BV+Benda INT for suboptimal response, demonstrated high CMR rates and favorable safety prior to consolidation.

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V611

Nivolumab plus Doxorubicin, Vinblastine and Dacarbazine for newly diagnosed advanced-stage classical Hodgkin lymphoma: CheckMate 205 Cohort D 2-year follow-up results

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Introduction: Up to 30% of patients (pts) with advanced-stage (AS) classical Hodgkin lymphoma (cHL) are not cured by current front-line therapies (Tx). Promising activity and acceptable safety were reported in newly diagnosed pts with AS cHL treated with nivolumab, an anti-PD-1 immune checkpoint inhibitor monoclonal antibody, followed by nivolumab plus doxorubicin, vinblastine, and dacarbazine (N-AVD) at a 9-mo follow-up of CheckMate 205 Cohort D (NCT02181738). Here, we report efficacy and safety in a 2-y follow-up, including Deauville assessment of response.

Methods: Pts ≥18 y of age with newly diagnosed AS cHL (stage IIB with unfavorable risk factors, III, or IV) received 4 doses of nivolumab monotherapy (240 mg IV every 2 weeks) followed by N-AVD combination Tx for 6 cycles (12 doses). Primary endpoint was safety; secondary endpoints included complete remission (CR) rate per independent review committee (IRC) at end of Tx (EOT) using 2007 International Working Group criteria. Complete metabolic response (CMR) was defined as a Deauville score of ≤3 (PET negative) by IRC in a post hoc analysis. Progression-free survival (PFS) was a post hoc analysis.

Results: Fifty-one pts were treated (median age 37 y); minimum follow-up was 24.4 mo at data cut-off. Other baseline characteristics have been previously described (Ramchandren R et al. EHA 2018). Monotherapy was completed by 49/51 (96%) pts, combination Tx by 45/50 (90%); 48 pts entered follow-up. After 2 combination cycles, CR rate was 51% per IRC (71% CMR) and 71% per investigator; at EOT, CR rate was 69% (75% CMR) per IRC and 80% per investigator. At 21 mo, PFS rate per investigator was 83% (95% CI, 69-91). Overall, 30 (59%) pts experienced grade (G) 3-4 TRAEs, most commonly neutropenia in 21 (41%). The most common G3-4 immune-mediated AE was hepatitis (2 pts, 4%). No G5 TRAEs occurred ≤30 d from last dose; 2 deaths were reported: 1 pt (aged 68 y) died 38 d after last dose due to study drug toxicity; another (aged 85 y) died 451 d after last dose due to disease progression.

Conclusions: With extended follow-up, nivolumab followed by N-AVD demonstrated a 21-mo PFS rate of 83% per investigator, a high metabolic response rate with 75% CMR at EOT per IRC, with no new safety signals. Incorporation of Deauville assessment improved the concordance of CR between IRC- and investigator-assessed responses. Nivolumab followed by N-AVD provides a promising alternative Tx option in newly diagnosed AS cHL.

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Stephen M. Ansell: Financing of Scientific Research: WebMD, Research to Practice; Expert Testimony: Affimed Therapeutics (Inst), Bristol-Myers Squibb (Inst), Merck (Inst), Regeneron (Inst), Seattle Genetics (Inst), Trillium Therapeutics (Inst), Pfizer (Inst).

V612

Everolimus with DHAP (Dexamethasone, high-dose AraC, Cisplatinum) in patients with relapsed or refractory classical Hodgkin lymphoma: a randomized, placebo-controlled phase I/II trial (HD-R3i)

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Introduction: Induction chemotherapy followed by high dose chemotherapy (HDCT) and autologous peripheral blood stem cell transplant (PBSC transplant) is standard of care for transplant-eligible patients with relapsed or refractory classical Hodgkin lymphoma (rrHL). However, approx. 50% of patients relapse and treatment is generally palliative in this situation. As response to induction therapy is predictive of the outcome after HDCT, this trial aimed at improving the response to induction therapy by adding oral everolimus to DHAP (Ever-DHAP).

Methods: We included patients with histologically confirmed rrHL aged 18-60 years in this phase I/II trial. Dosage of everolimus was pre-determined in the phase I part with 10 mg/day in parallel to DHAP for 14 days within each of two cycles. The phase II part started as a randomized controlled trial comparing 50 patients in the everolimus group to 50 patients in a placebo group. The primary endpoint of the phase II part was the CT-based complete remission (CR-) rate after two cycles of Ever-DHAP. This CR-rate would be expected to be ≥ 40% if adding everolimus was effective.

Results: From 7/2014 to 3/2018 we recruited a total of 59 patients in the phase II part. Because of poor recruitment the placebo group was closed in 9/2015 after 9 patients were randomized. Of 50 patients in the everolimus group 2 did not start therapy; 3 additional patients discontinued Ever-DHAP because of toxicity. Nine patients (20%) and 13 patients (28%) needed dose reductions in the first and second cycle of Ever-DHAP, respectively. CTCAE grade IV toxicities occurred in 39 patients (95%) and 27 patients (75%) in cycle 1 and 2, respectively. All grade IV-toxicities were hematological toxicities. PBSC collection was successful in 38/42 documented patients receiving Ever-DHAP (91%). After two cycles of therapy we observed a CT-based CR in 12/45 patients of the everolimus group (27%) and in 2/9 patients of the placebo group (22%). A PET-based CR was achieved by 22/39 patients of the everolimus group (56%) and by 2/8 patients of the placebo group (25%). In the everolimus group 2 patients had progressive disease (4%) and 3 died (7%, not related to Ever-DHAP).
Conclusions: With a CT-based CR-rate of 27% after two cycles of everolimus plus DHAP (PET-based CR-rate 56%), the trial did not meet the primary endpoint. Adding everolimus to time-intensified DHAP is feasible, however, everolimus plus DHAP failed to show an improved efficacy.

Disclosure: Bastian von Tresckow: Advisory Role: MSD, Novartis, Takeda; Financing of Scientific Research: MSD, Novartis, Takeda, Pfizer, Roche, Amgen; Other Financial Relationships: MSD, Novartis, Takeda
Peter Borchmann: Advisory Role: Novartis; Financing of Scientific Research: Novartis

V613

JAK-inhibition with Ruxolitinib in patients with relapsed or refractory classical Hodgkin Lymphoma: a phase II, open label, multicenter clinical trial (JeRiCHO)

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Introduction: Classical Hodgkin Lymphoma (cHL) patients relapsing after high dose chemotherapy (HDCT) and autologous stem cell transplantation (ASCT) have a dismal prognosis and eventually progress also after subsequent administration of brentuximab vedotin (BV) or anti-programmed cell death protein 1 (PD-1)-antibodies. New approaches exploiting specific cHL pathways are warranted in relapsed or refractory (r/r) cHL. In cHL 9p24.1 amplification is a disease-specific structural alteration that induces Janus kinase 2 (JAK2) signaling and increases PD-1 ligand (PD-L1) expression. As the JAK/STAT (signal transducers and activators of transcription) pathway is involved in PD-L1 upregulation (hallmark of cHL), treatment with ruxolitinib as a potent selective inhibitor of JAK1 and JAK2 kinases was evaluated in patients with r/r cHL in this phase II trial.
Methods: JeRiCHO adopted a 2-stage phase II design. If ≥1 overall response (OR) was observed among the 12 patients enrolled in the 1st stage, 25 additional patients would be recruited for the 2nd stage. Patients with r/r cHL requiring treatment after at least 1 therapy regimen were included. 25mg ruxolitinib were administered orally twice daily in 28-day cycles until progression or unacceptable toxicity. Primary endpoint was PET/CT-based OR-rate after 2 cycles. Secondary endpoints included progression free survival (PFS), overall survival (OS) and treatment feasibility.
Results: From 10/2015 to 05/2017 12 qualified patients were enrolled. Patients' median age was 55.5 years, previous HL-therapies were up to 11 (7 HDCT+ASCT, 2 allogeneic SCT, 12 BV). Median treatment duration was 10 weeks, median number of ruxolitinib cycles received was 3. After 2 cycles, PR was observed in 2, stable disease (SD) in 3 and progressive disease (PD) in 6 patients (ORR: 2/11, 18%). Best response to treatment was PR, SD or PD for 3, 2, and 6 patients, respectively. Median PFS was 3.6 months and the 1-year PFS estimate was 8.3%. The 1-year OS estimate was 50.6% (median not reached). Toxicity profile was favorable. 2 deaths were considered HL-related. Detailed data on efficacy, toxicity and treatment administration will be presented.
Conclusions: Ruxolitinib showed modest activity and a favorable side effect profile. However, median PFS was only 3.6 months and no CR was achieved. Even though the formal stopping criterion after stage I was not met, it was decided that the trial would not continue to stage II due to the low response rate.

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V614

The role of autologous stem cell transplantation in primary refractory and relapsed Hodgkin lymphoma - a long-term follow-up single center experience

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Autologous stem cell transplantation (autoSCT) can achieve long-term remission in primary refractory or relapsed Hodgkin lymphoma (r/r HL), however up to 50% of patients show recurrence of disease after autoSCT. As effective new agents are emerging for the treatment of r/r HL, defining patients with a high risk for relapse after autoSCT is becoming essential for a risk-stratified treatment approach. In this retrospective analysis, we investigated the impact of autoSCT in a consecutive, unselected collective of r/r HL patients in the pre-brentuximab vedotin era.
Retrospective follow-up data was available for 66 patients aged 16 to 69 years who underwent autoSCT at the Department of Hematology and Oncology at the University Hospital Tübingen. 62 patients underwent autoSCT for relapsed HL, only 4 patients underwent autoSCT for primary refractory disease. VIPE and DHAP were the most frequently used salvage chemotherapy regimens, but no difference regarding outcome was observed between the two groups. In our cohort, a 5-year overall survival (OS) from autoSCT of 59.5% and a 5-year progression free survival (PFS) after autoSCT of 46.1% was achieved. Patients relapsing after autoSCT had a particular poor outcome, regardless of eligibility to undergo allogeneic stem cell transplantation (alloSCT), partly due to a high transplant related mortality of 45% attributed to alloSCT. 5 patients (7.6%) in our cohort developed and died from secondary malignancies during the observation period. Multivariate analysis revealed early relapse (< 12 months) after initial therapy and the presence of B-symptoms at relapse as independent risk factors associated with a higher risk for relapse and an inferior PFS and OS. Other clinical factors associated with an inferior survival included the presence of extranodal disease and failure to achieve a complete response to salvage chemotherapy. In our study, we evaluated recently published prognostic models for r/r HL patients undergoing autoSCT. While the *Bröckelmann* and *Hahn* score correlated well with the risk for relapse in the first years following transplantation, the *Josting* score did not correlate with outcome in our cohort.
Our study shows that autoSCT can achieve long-term remission in r/r HL and strengthens its role for the treatment of these patients. We could confirm previously described risk factors for relapse after autoSCT and validated previously published prognostic scores in our independent "real world" patient cohort.

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Freier Vortrag

Palliativmedizin

V615

Course of health-related quality of life including psychological burden in patients with incurable cancer - results of a prospective longitudinal multicenter cohort study of the Arbeitsgemeinschaft Palliativmedizin (APM)

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Introduction: During the course of incurable cancer, the intensity of palliative care has to be adjusted to the individual demands. However, it is unclear, when patients (pts) with incurable cancer experience the highest need for palliative support.
Methods: We conducted a prospective, non-interventional, longitudinal multicenter study aiming to assess physical and psychological distress as well as need for palliative care of cancer patients at diagnosis of an incurable stage (T0), and after three (T1), six (T2) and twelve months (T3) follow-up. Pts were asked to answer validated questionnaires (FACT-G, SEIQoL-Q, PHQ-4, modified SCNS-SF 34, Distress Thermometer). Treating physicians provided medical information.
Results: Within two years (Oct 2014 to Oct 2016), 502 pts with incurable cancer participated in the study (281 male, 219 female, 2 unknown; mean age 64.2 years; median ECOG PS 1 (T0)). Underlying diagnoses were: lung (219 pts), gastrointestinal (156 pts), head and neck (55 pts), gynecological cancer (57 pts) and malignant melanoma (15 pts). Highest distress levels and lowest quality of life were measured at the beginning of the incurable disease trajectory. In addition, compared to patients still being alive at the next follow-up visit, patients who died before the next follow-up visit had shown a significantly higher distress level (at least 1 scale unit difference on distress thermometer; T0: 5.25 vs 6.24, T1: 4.17 vs 6.32, T2: 4.09 vs 5.18), a significantly lower health-related quality of life (at least a difference of 11 at FACT-G total score values; T0: 70.80 vs 58.96, T1: 74.59 vs 56.29, T2: 77.42 vs 65.73) and significantly higher levels of anxiety and depression symptoms (at least a difference of 1.5 at symptom score; T0: 4.28 vs 5.76, T1: 3.23 vs 5.52, T2: 2.83 vs 4.50).
Conclusions: We observed significantly higher physical and psychological distress and worse health-related quality of life in patients who died before the next follow-up visit compared to surviving patients with incurable cancer. This finding indicates increased palliative care needs upon progression of the underlying cancer and towards end of life. However, it should be recognized that patients have the highest scores of distress and lowest quality of life at the time of first diagnosis, indicating a high palliative care need especially at the beginning of the trajectory of incurable cancer.

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V616

Advanced cancer patients' "last wishes" at initiation of specialist palliative care

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Introduction: The last weeks or months of life represent a crucial time for advanced cancer patients (pts) and specific wishes may emerge. An early recognition of these wishes by healthcare providers might serve as a guide in conducting goals-of-care conversations and tailoring individual care. This multicenter study explored wishes among cancer pts at initiation of out- or inpatient specialist palliative care (SPC).
Methods: Within a 12-months period, cancer pts entering SPC were recruited consecutively. Pts completed a survey including an open-ended question concerning "last wishes". Descriptions of wishes were analyzed using inductive qualitative content analysis to identify main themes. All transcripts of wishes were than coded for presence or absence of each of the themes identified. Univariate and multivariate logistic regression analyses were conducted to investigate factors associated with having a wish.
Results: Of 386 pts (52% male, median age 71, 67% outpatient SPC), 220 expressed having a specific "last wish" (68%). Nine main themes of wishes emerged, with desire to travel or visit specific places being the most prevalent one (32%). Further themes were to accomplish soothing or daring activities (17%), to live longer or regain health (17%), to spend quality time with family and friends (15%), to achieve better quality of life (14%), to experience conditions attributed to a "good death" (6%), and to turn back time, to solve things before dying and others (each 2%). According to univariate regression analyses, low education (p=.019, OR 1.836), inpatient SPC (p=.001, OR 2.393), screening result of suspected anxiety/depression (PHQ-4; p=.005, OR 2.095), and higher numbers of practical (p=.005, OR 1.474), emotional (p=.015, OR 1.173) and physical problems (p< .001, OR1.194) were significantly associated with having a wish. Multivariate stepwise regression analysis revealed low education (p=.001, OR 1.974,), inpatient SPC (p=.006, OR 2.216) and higher numbers of physical problems (p< .001, OR 1.192) to independently increase the likelihood of having a wish.
Conclusions: Oncologists should ask pts about their "last wishes" to discuss their individual priorities. These conversations could be used as a simple strategy to support pts consider health decisions. In case of unrealistic wishes, oncologists may help by either suggesting more realistic goals to pts or take these wishes as an inducement to discuss coping with end-of-life issues.

Disclosure: No conflict of interest disclosed.

V617

Experiences with death and dying among refugees in two venues in Germany

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Introduction: In Germany during the last 5 years the number of refugees grew by more than a million people characterized by different age groups, both sexes and various origins. Our aim was to explore different characteristics of refugees regarding age, sex and country of origin and their experiences with death and dying in general.
Methods: A cross-sectional study from May 2016 to May 2017 was performed enrolling 193 participants seeking refuge in Germany. Participants were asked 50 objective questions from a multilingual questionnaire (each question in Arabic, English and German). The interviews took place in Rostock and Bremerhaven, Germany in different locations as refugee camps, private homes, doctor`s offices or other places by an interviewing party of two Rostock based medical students who speak native Arabic and German and highly fluent English. Age was categorized in 3, sex in 2 and origin in 2 groups.
Results: Of the 193 participants 181 refugees (94 %) had made experiences with accompanying family members or friends in process of dying in various situations, mostly in the country of origin, but also on their way to Europe. Thereby only 54 (28 %) were familiar with the concept of palliative care. Median age of all refugees was 35, with 56% males and 44% females.
Conclusions: Refugees have accompanied relatives and friends in process of dying in various situations. However, the minority is familiar with the concept of palliative care. It appears to be an important chore to introduce modern palliative care concepts to refugees.

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V618

Barriers and motivation of physical activitiy (PA) in patients with cancer related fatigue (CRF)

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Introduction: In order to counteract CRF, PA is recommended for all stages of cancer. Despite the high level of evidence, only 30% of patients with advanced cancer (ACP) are physically active. Currently, only little is known about motivation for and barriers of PA in a palliative setting. This prospective study aimed to identify barriers and motivation to PA in ACP.
Methods: From May 2017 to August 2018, ACP who reported moderate or severe tiredness or weakness were asked to complete a questionnaire (FACT-F, PHQ8, motivation and barriers of PA). A follow up was done after 3 (T1), 6 (T2) and 12 months (T3).
Results: 141 of 440 eligible pts (32.0%) participated in this study. Median age was 60.2 (range 26-83), most pts had cancer of gastrointestinal tract (44; 31.2%), lung (40; 28.4%) or breast (28; 19.9%). At baseline (T0) 31 (22.0%) pts were physically active. Pts´ activity level did not change significantly during follow up (T1: n=23, 24.2%; T2: n=20, 26.0%; T3: n=6, 18.8%). CRF (FACT-F ≤ 34) was detected in 99 (70.2%) pts at baseline. FACT-F showed no significant differences after 3 (mean: 27.4; p=0.142), 6 (mean: 28.2; p=0.331) or 12 (mean: 26.9; p=0.08) months.
Active systemic cancer treatment (n=108; 76.6%), *tiredness* (n=101; 71.6%) and *CRF* (n=99; 70.2%) were the most common physical barriers, without showing significant differences during the follow up period. Predominant psychological barriers were *lack of motivation* (n=71; 50.4%) and *no interest in exercise program* (n=61; 43.3%). Motivation for PA was significantly decreasing during the follow up period (p=0.009). The T3- follow up is still ongoing.
The multiple regression analysis identified the independent variables *interest in exercise program* (β=0.769; p=0.001), *knowledge about the positive impact of PA on quality of life* (β=0.688; p=0.011) and *PA before cancer diagnosis* (β=0.639; p=0.003) as significant predictors of a motivated attitude towards PA. *CRF* (β=-2.032; p=0.008) turned out to be a strong negative predictor.
Conclusions: We identified *active systemic cancer treatment* as most common physical and *lack of motivation* as most frequent psychological barrier of PA. Motivation for PA was significantly decreasing during the follow up period.
The early integration of interdisciplinary programs including psychoeducation, motivational counselling and exercise programs tailored the individuals´ needs and abilities may help ACP to overcome barriers and effectively reduce fatigue.

Disclosure: No conflict of interest disclosed.

V619

Physical and psychosocial symptom burden in inpatient advanced cancer patients at first inpatient palliative care consultation

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Introduction: Many cancer patients have multiple physical and psychosocial symptoms and needs, which are addressed during inpatient palliative care consultations (IPCC). We evaluated patients' self-assessment and palliative care physicians' perspective on these issues at first IPCC in advanced cancer patients.
Methods: Physicians completed the Symptom and Problem Checklist of the German Hospice and Palliative Care Evaluation (HOPE-SP-CL) and pts the Integrated Palliative Care Outcome Scale (IPOS) plus the Distress Thermometer (DT). These evaluations were conducted between August 2015 and September 2018 on regular wards during IPCC in pts with advanced cancer.
Results: 1363 pts (median age 68 years; 46% female; 23% gastrointestinal, 16% lung, 15% gynecologic, 10% urogenital cancer) receiving first IPCC on different wards (oncology 35%, intensive care 11%, other wards (54%) were included. ECOG performance status was 3 in 31% and 4 in 25%. In HOPE-SP-CL (1363 pts), symptoms/problems of at least moderate intensity were weakness (95%), need of assistance with activities of daily living (90%), further care organization (82%), overstraining of family caregivers (78%), fatigue (76%), loss of appetite (76%), tension (67%), and pain (54%). Pts who completed IPOS (167 pts) rated as follows: weakness 97%, impaired mobility 93%, pain 63%, fatigue 61%, loss of appetite 61%, and dyspnea 50% (all at least moderate). Correlation between pts' and physicians' ratings were high in all symptoms (all p< 0.001). Median distress was 8 (range 4-10) with clinically relevant distress (DT ≥5) in 91%. Pts frequently felt anxious or worried (97%) and depressed (93%). Family and friends were considered being worried in 97%. Only 25% of pts declared to have received as much information as they wanted and only 35% felt that problems resulting from their illness had been addressed adequately. In the further course of care, 50% were admitted to the palliative care ward, 23% were discharged home, 19% died on-site, and 8% were admitted to hospice or nursing homes.
Conclusions: At first IPCC, advanced cancer pts presented with high burden caused primarily by a loss of mobility and autonomy, which lead to aggravated physical symptoms, psychosocial problems and distress. Pts complained about deficient information and unsatisfactory support concerning their daily problems.

Disclosure: No conflict of interest disclosed.

V620

Psychological burden and associated factors in advanced cancer patients at initiation of specialist palliative care

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Introduction: Addressing psychological burden is a core component of specialist palliative care (SPC), but systematic data on its severity and associated factors in advanced cancer patients (pts) are limited. This study systematically screened cancer pts entering an in- and outpatient specialist palliative care network for symptoms of distress, depression and anxiety.
Methods: Pts were consecutively recruited within 12 months. At initiation of SPC, participants completed validated screening tools (Distress Thermometer (DT) and PHQ-4) and reported on demographic and care-related characteristics. Univariate and multivariate logistic regression models were used to determine associations between these background factors and psychological burden.
Results: Among 386 cancer pts (52% male, median age 71, 67% outpatient SPC), mean DT was 7.2 (SD 2.1; range, 1-10) with 90% indicating clinically relevant (≥5) and 53% severe (≥8) distress. Distress did not differ between pts entering outpatient SPC (M=7.2; 90% ≥5; 51% ≥8) and inpatient SPC (M=7.3; 89% ≥5; 57% ≥8) (all p≥.05). Univariate regression analyses showed significant effects of childlessness for severe distress (DT ≥8). Regarding symptoms of depression and anxiety, mean scores were 5.2 for PHQ-4 (SD 3.6; range, 0-12), 2.9 for PHQ-2 (SD 2.0; range, 0-6), and 2.3 for GAD-2 (SD 1.9; range 0-6). Patients screened for suspect mood disorders (PHQ-2/GAD-2 ≥3) were 51% for depression and 35% for anxiety. For pts entering outpatient vs. inpatient SPC, rates were 48%/56% for depression and 35%/34% for anxiety (all p≥.05). Univariate regression analyses revealed that younger pts (depression and anxiety), pts with statutory health insurance only (depression and anxiety), childless pts (depression) and those low educated (anxiety) were more likely to be screened for mood disorders. However, childlessness and low education did not retain significant on multivariate stepwise regression analyses for suspect depression or anxiety.
Conclusions: Irrespective of out- and inpatient care, psychological burden appears to affect a substantial part of cancer pts when entering SPC. Cancer pts should be routinely screened for psychological burden, e.g. using ultra-brief measures (DT and PHQ-4), with special attention being paid to younger pts and those with statutory health insurance only.

Disclosure: No conflict of interest disclosed.

Expertenseminar

E22: Komplementäre Medizin

V621

Complementary Medicine

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Methods of complementary (accompanying and supplementary methods) and alternative (instead of conventional methods) medicine are widely used in oncology.
Complementary medicine often is accepted without critical appraisal as it allegedly is in agreement with patients´ desire for a "soft" treatment, may support mentally and will for sure do no harm. Most often, oncologists leave the field to other "specialists" for naturopathy, without there being any consent on quality of the counseling or treatment. In contrast, with evidence based knowledge on the most often used methods of complementary and alternative medicine, oncologists may integrate counseling in their communication without much effort. In fact, nutrition and physical activity are the methods with highest evidence concerning most side effects of cancer therapy. Moreover, discussion of complementary methods would help to reduce side effects from natural substances and interactions between cancer therapies and complementary therapies.
Complementary medicine comprises a wide variation of different methods and substances. For some substances, evidence from clinical as well as preclinical studies is sufficient to provide evidence-based recommendations. For others evidence is heterogeneous, scarce or not available. With respect to holistic methods which often combine different approaches most studies are difficult to interpret as the effect of the components are not clear and may in part be even contra-productive even in case of traditional usage. Moreover, methods as yoga etc. are not clearly defined. Additionally, they often depend on the instructor. Accordingly, study results have to be interpreted cautiously. Is the control group adequate and is the intervention precisely described and was the study multi-centered? In fact, the control group is decisive, as most complementary methods provide some attention or care to the patient. An equivalent should be provided in the control group.
Side effects as well as interactions are the main risks of complementary medicine besides omitting or delaying conventional treatment. Unfortunately, data on these risks are scarce. Therefore, physicians and nurses should be attentive to all effects and symptoms of their patients.
If we conceive complementary medicine as the answer to the question of patients and caregivers, what they may contribute to improving the situation, complementary medicine has the potential to activate and empower patients and to increase adherence to cancer therapies and quality of life.

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Wissenschaftliches Symposium

Kolon- und Rektumkarzinom: Therapieansätze 2019

V626

Palliative therapy of colorectal cancer - stratification for molecular markers - trials

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For the palliative systemic therapy of colorectal cancer, patients are grouped according to a set of biological and clinical markers. Key biomarkers include mismatch-repair deficiency, Kras and Nras exon 2-4 sequencing and Braf assessment. Clinically, ECOG performance status and frailty are important.
In this presentation, we are going to focus on utility and applicability of predictive markers of treatment benefit. We will look into recent trials investigating established and putative biomarkers used in the setting of clinical care. In addition, we will catch a glimpse of new predictive markers and tests, such as drug phenotyping and CyTOF, which are currently in development.

Disclosure: Andreas Wicki: Expert Testimony: Swiss Tumor Profiler Research Consortium

Wissenschaftliches Symposium

Hodgkin-Lymphom: Stellenwert und Mechanismus von PD1-Blockade

V632

PD-1 Blockade - Signatures of Response and Resistance

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Hodgkin Reed Sternberg cells in classical Hodgkin lymphoma (cHL) harbor as a disease-defining alteration the gain of 9p/24.1/PD-L1/PD-L2 with increased expression of the encoded PD-1 ligands, constituting the genetic basis for PD-1-mediated immune escape in this disease. In fact, PD-1 blockade has demonstrated durable high overall response rates and the optimal clinical algorithm for PD-1 blockade is currently explored in clinical trials. Despite the clinical success and the high response rates, our current insights into the mechanism of action for PD-1 blockade in cHL warrants further studies. The high response rates and frequent 9p24.1 copy gains are contrasted by additional pervasive genetic alteration that reduce the antigen presentation via HLA-class I and class II and abolish the ability to present tumor-associated antigens suggesting a non-CD8-mediated mechanism of action. This presentation will highlight the current state-of-the-art regarding i signatures of response and resistance of PD-1 blockade.

Disclosure: No conflict of interest disclosed.

V633

Scientific symposium: Hodgkin's Lymphoma: status and mechanism of PD-1 blockade "From third to second line: concepts and discussion"

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Programmed death cell protein-1 (PD-1) receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. This checkpoint mediated immune evasion was established as a hallmark of classical Hodgkin Lymphoma (cHL) pathogenesis with the identification of amplifications of the 9p24 gene locus resulting in constitutive expression of PD-1 ligands PD-L1/2 in more than 85% of cHL patients. The evaluation of inhibitors (Is) targeting PD-1 has demonstrated impressive remissions in relapsed/refractory (r/r) cHL patients even though the mechanisms of action are not yet fully understood; in phase I trials with pembrolizumab/nivolumab, 66%/87% of patients achieved objective responses (complete responses 16%/22%), tolerability was excellent. Currently, PD-1-Is are approved for 3rd-line therapy of r/r cHL after high-dose chemotherapy (HDCT) + autologous stem cell transplantation (ASCT) (if eligible) and therapy with brentuximab vedotin (BV).
After 1st-line therapy about 15% of cHL patients relapse and standard of care is salvage chemotherapy (CT) followed by HDCT and ASCT in transplant eligible patients. Unfortunately, this approach has a high second failure rate and is very toxic. Clinical research was focused on improving 2nd-line therapy by treatment intensification including second salvage therapies, tandem ASCT and consolidation with BV. However, still half of all patients fail to reach long-term remissions with any of the new approaches and acute and long-term toxicity remains high due to the use of HDCT. Consequently, the challenge is to improve efficacy while reducing toxicity, which can hardly be achieved with chemotherapy. Therefore, PD-1-Is are currently introduced in 2nd-line therapy of r/r cHL. As PD-1 blockade alone might be a curative option for few patients only, current trials evaluate the combination of PD1-Is with BV or with established CT. These new combinations aim at improving the efficacy of re-induction regimes and potentially even replacing HDCT.
For patients not eligible for HDCT and ASCT, synergistic effects of CT with PD-1-Is may facilitate an effective therapy with limited toxicity and might thus also allow to increase the response and cure rate 2nd-line for this difficult to treat patient population.
Overall, these ongoing trials represent a paradigm shift in the treatment of r/r cHL patients from conventional genotoxic chemotherapy to an immunotherapy targeting PD-1 as the biological hallmark of this malignancy.

Disclosure: Sarah Gillessen: No conflict of interest disclosed.
Peter Borchmann: Financing of Scientific Research: BMS, MSD; Expert Testimony: MSD

Wissenschaftliches Symposium

Migrationsmedizin

V639

Haemoglobinopathy

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"Haemoglobinopathy" (HP) is an overarching term referring to a group of inherited disorders of blood in which there is either defective synthesis of globin chains (thalassaemia) or a structurally abnormal haemoglobin (Hb) (Hb variants), or a combination of both. It results from mutations and/or deletions in the globin genes.
It has been estimated that around 7% of world's population are carriers. HPs are endemic in certain regions of the world, like the Middle East, Mediterranean area or Africa with an incidence of 2.5% to 25%. However, increased levels of cross-border migration resulting from socio-political problems such as wars, terroristic attacks or famine has led to spreading of carriers of Hb disorders to non-endemic parts of the world making it one of the major global health issues.
In suspected people initial diagnosis and screening of Hb disorders includes complete blood count with red blood cell (RBC) parameters (MCV, MCHC, MCH, RDW, etc) and Hb electrophoresis. Advanced testing including genetic analysis is required for confirmation of the diagnosis and/or identification of compound cases, as well as for cases with high clinical and laboratory suspicion of HP and normal electrophoresis.
While some heterozygous carriers might be completely asymptomatic and are diagnosed during a routine check-up or family screening of an index case, others might present with indistinct symptomatology, like fatigue and lassitude.
Diverse clinical manifestations usually differ according to the genetic severity of the disease, ranging from absence of symptoms to profound anaemias that might be fatal unless treated accordingly.
Complications are mostly linked to the consequences of ineffective erythropoiesis, extramedullary haematopoiesis, chronic haemolytic anaemia, hypoxia and life-long transfusion; and include skeletal deformities, tumoral masses, thrombosis, iron-overload and hemosiderosis associated organ dysfunction, and, in cases with therapeutic splenectomy or autosplenectomy, increased susceptibility to infections.
Treatment is supportive in most patients and involves life-long regular RBC transfusion, iron chelators, splenectomy and hydroxyurea. Allogeneic stem cell transplantation is the only available curative treatment option for selected patients. Novel therapies including fetal Hb inducers and gene transfer are eagerly awaited.

Disclosure: No conflict of interest disclosed.

Fortbildung

Die optimale Therapiesequenz bei indolenten Lymphomen

V642

The optimal sequence of treatment in indolent lymphoma: follicular lymphoma

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Patients with follicular lymphoma usually have a good prognosis with a 10-years survival of approximately 80% and a disease-specific survival up to 90%. In many cases, the treatment does not start before symptoms occur ("watch and wait"). In contrast to a monotherapy with monoclonal antibodies, chemoimmunotherapy and maintenance with antibodies prolong to progression free survival up to 10 years. Patients with long duration of response (e.g. > 5 years) may benefit from another chemoimmunotherapy. Patients with progression within the first 24 months after chemoimmunotherapy (POD24) have an inferior survival. In these patients, more intensive concepts like high-dose chemotherapy and stem cell transplantation should be discussed. Whenever possible, these patients should be treated within clinical trials. In future, chemo-free strategies might play an important role. The PI3Kδ Idelalisib is approved for patients not responding to two prior therapies. Another PI3K inhibitor - Copanlisib - is approved in USA in patients who failed two prior therapies. The combination of lenalidomide and rituximab was not superior to a chemoimmunotherapy in first line treatment in a randomized phase-III trial; however, in relapsed patients this combination has been approved in USA based on two randomized trials (AUGMENT, MAGNIFY). Many other drugs, including immunotherapies and CAR-T cell therapies, are under investigation. The identification of patients with high medical need and new drugs will improve the therapeutic options in future.

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Freier Vortrag

AML II

V653

FlowSOM: implementing an R-based evaluation strategy for flow cytometry-based measurable residual disease (MRD) diagnostics in AML

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Introduction: Patients with acute myeloid leukemia (AML) frequently relapse due to chemorefractory AML cells persisting after intensive chemotherapy at levels below the 5% morphological detection threshold (measurable residual disease, MRD). MRD has been established as an important prognostic factor for relapse-free and overall survival, making it highly relevant for post-remission treatment stratification.
Multiparametric flow cytometry (MPFC)-based MRD measurements are applicable in more than 95% of AML patients, while still offering a sensitivity of 10^{-4} to 10^{-5}. However, MPFC MRD assessment is usually performed by scatterplot-based manual, two-dimensional analysis of high-dimensional data. This leads to a loss of information and significant inter-observer variability in MRD diagnostics. We therefore aimed to establish a computational, unsupervised data analysis based on the FlowSOM algorithm.
Methods: FlowSOM clusters similar events (cells) into nodes. These nodes are then arranged in a minimal spanning tree, again according to likeliness. Overclustering enables the visualization of high-dimensional data, and subpopulations can be detected that are otherwise often overlooked. FlowSOM analysis identifies aberrant (sub-)populations of cells by comparison with healthy bone marrow data. Nodes with high percentage of aberrant events are termed "nodes of interest" (NOI) to further simplify MRD analysis after clustering.
Results: Healthy reference FlowSOM trees were established by merging flow data of 11 and 17 healthy donors, respectively, measured in two separate MPFC panels. We systematically varied parameters defining NOI to ensure reliable identification of aberrant events. FlowSOM-based identification of MRD events was then followed by three different MRD calculation approaches. After establishing the analysis protocols, healthy bone marrow was spiked with patient-derived AML cells (0%, 0.05%, 0.1%, 0.5% and 5%). Using the FlowSOM analysis approach, we were able to distinguish and correctly assign the different MRD levels when performing investigator-blinded analyses of these samples. When applied to patient samples (n=15), FlowSOM analysis yielded results hinting at MRD positivity that were considered MRD negative by conventional analysis.
Conclusions: We have set up a comprehensive FlowSOM-based protocol for the detection of MRD in AML. We will further validate this protocol using a larger cohort of AML patients with known outcomes (n = 57).

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Marion Subklewe: Financing of Scientific Research: BeckmanCoulter

V654

Genomic profiling in acute myeloid leukemia with complex karyotype

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Acute myeloid leukemia (AML) is characterized by abnormal clonal expansion of undifferentiated malignant cells, which interferes with normal hematopoiesis. A stratification of patients in risk groups is based on cytogenetics and detection of molecular events as described in the 2017 European LeukemiaNet (ELN) recommendations. While many genomic changes can be captured by conventional molecular methods within 48 hours to guarantee a genotype-based treatment strategy, the results of conventional karyotyping, which is still needed to determine many "high-risk" AML cases, are available after 5 to 7 days at the earliest. However, for more effective application of new drugs, one of which was recently approved for high-risk subsets of AML, it is crucial to establish karyotype analysis in the shortest time possible.
Using GridION and Oxford Nanopore (ONT) technology we established karyotyping based on shallow whole genome sequencing with library prep and bioinformatics analysis within a timeframe of 24 hours. The effective throughput, 10-15 GB from 1 flowcell, was sufficient to achieve 3-fold whole genome coverage (range 2.5-3.6) and to reproduce results of conventional karyotyping in 20 AML patients. Sequencing results describe the genomic changes, especially in patients with high genomic instability, more precisely with a resolution of approximately 1 Mb. Additional analyses to understand the sensitivity of the test in respect to clonality of tumors are underway.
While the discovery of structural variations in ONT sequencing with shallow coverage remains a challenge, we established also a transcriptome protocol to allow the analysis of fusion genes in a similar timeframe of 24 hours. Using direct RNA sequencing we could achieve 1.2 million reads,

corresponding to 0.8 GB data, on a single flowcell. In several test runs, the throughput of a 20 hours run was sufficient to detect a balanced translocation t(9;22) resulting in the expression of the fusion gene *BCR-ABL1* in the cell line K-562 (fusion gene supported with 6-8 reads of high quality). While a study of a larger AML patient cohort by ONT technology is currently ongoing, Nanopore technology provides the opportunity to rapidly characterize AML at the genomic level, which is needed for improved genotype-based treatment strategies. Feasible within 24 hours, parallel low coverage whole genome and transcriptome analysis allows identification of high-risk AML during the initial diagnostic work-up.

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Lars Bullinger: Advisory Role: Bristol-Myers Squibb, Daiichi Sankyo, Janssen, Novartis, Pfizer; Financing of Scientific Research: Amgen, Bristol-Myers Squibb, Celgene, Janssen, Jazz Pharmaceuticals, Novartis, Pfizer, Sanofi, Seattle Genetics; Expert Testimony: Bayer

V655

Activating JAK-mutations confer resistance to FLT3 kinase inhibitors in FLT3-ITD positive AML in vitro and in vivo

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Introduction: Internal tandem duplication (ITD) mutations of FLT3 are found in 30% of AML patients and are associated with poor prognosis. The clinical benefit of FLT3 tyrosine kinase inhibitors (TKIs) could be elaborated recently which led to the FDA approval for midostaurin in combination with standard chemotherapy and gilteritinib for relapsed/refractory disease. Therefore the need to detect and target resistance mechanisms against TKIs is strong. Our study concentrated on resistance mechanisms other than secondary FLT3 mutations.
Methods: Drug resistant sublines were generated by exposure of stably transfected BA/F3 FLT3-ITD cells to FLT3 kinase inhibitors (TKIs). These sublines were selected for further analysis by PCR, Western-Blot (WB) and IP. Samples from patients with FLT3 mutated AML after FLT3 inhibitor treatment were analyzed for mutations in FLT3 and JAK1-3.
Results: In a cell based screen with Ba/F3 cells expressing FLT3-ITD, we detected a JAK1 V658F mutation in in 6 out of 23 TKI resistant cell lines without secondary FLT3 mutations. This mutation led to reactivation of the STAT5 pathway via phosphorylation of IL-3 receptor beta chain. A knockdown of JAK1 or additional treatment with a JAK inhibitor resensitized the cell lines to TKI treatment. We screened samples from 136 patients from 3 centers with FLT3 mutated AML before and after treatment with FLT3 inhibitor for secondary mutations in the FLT3 and JAK family genes. In 13 patients, secondary FLT3 mutations were identified as mechanism mediating TKI resistance. In 6 patients, mutations within the JAK family were found that were either detectable at relapse only or displayed with increasing allele frequencies after TKI treatment. Variants included five bona fide activating mutations in JAK1, JAK2 and JAK3. All of these mutations are either known oncogenes or were tested by us to transform Ba/F3 cells. The remaining variant corresponded to a JAK3 splice site mutation of unknown significance in a sample at relapse. In Ba/F3 cells expressing FLT3-ITD and each of the five JAK-family activating variants, the resistance to FLT3-TKIs was overcome by dual FLT3- and JAK inhibition.
Conclusion: These results suggest that patients with FLT3 mutated AML resistant to FLT3 TKIs should be examined for activating JAK mutations as they might benefit from dual JAK and FLT3 inhibition.

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V656

Sirtuin 7 (SIRT7): influence factor in healthy aging and age dependent myeloid stem cell disorder development

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Introduction: Alterations within the hematopoietic system influence longevity and development of age-related myeloid stem cell disorders like AML, CML, and MDS. A reduced expression of histone deacetylase sirtuin 7 (SIRT7) in older murine hematopoietic stem cells results in reduced longevity and increased proliferation. Here, we sought to investigate age-dependency of SIRT7 in humans and the relevant pathomechanisms in myeloid stem cell disorders.
Methods: SIRT7 was investigated in human mononuclear cells of 169 healthy people, 78 CML-, 50 MDS-, and 113 AML-patients. Furthermore, various disease specific cell lines including CML-, MDS-, and FLT3-wild type or FLT3-ITD mutated AML cell lines were investigated. SIRT7 overexpression in THP-1 cells was done by generation of pseudoviral particles and cell transduction. THP-1 monocyte differentiation was induced by PMA and monitored by flow cytometry. SIRT7, C/EBPα, β and ε gene expression was measured by quantitative real-time PCR and protein levels by western blotting. Effects of C/EBPα, β and ε in SIRT7 promoter region were investigated by luciferase reporter gene assays and chromatin immunoprecipitation.
Results: SIRT7 expression in mononuclear cells of healthy people decreased with higher age. Low SIRT7 levels were found in CML-, AML-, and MDS-patients. SIRT7 expression increased with positive treatment response and decreased at progress or relapse. Targeted driver mutation inhibitions in CML (BCR-ABL) or AML (FLT3-ITD) also resulted in increased SIRT7 levels (monitored in patient samples and cell lines). Furthermore, SIRT7 expression increased in time of PMA-mediated monocyte differentiation of THP-1 cells. SIRT7 overexpression in THP-1 cells resulted in cell differentiation marker increase too. In general, BCR-ABL, FLT3-ITD and cell differentiation associated SIRT7 expression was positively regulated by C/EBPα, β and ε binding to two different C/EBP binding sides within the SIRT7 promoter.
Conclusion: SIRT7 is important in human hematopoietic cell aging and longevity. It might act as an important tumor suppressor and biomarker for treatment response monitoring in myeloid stem cell disorders that needs to be further evaluated.

Disclosure: No conflict of interest disclosed.

V657

Impact of somatic mutations on response in patients > 60 years old with newly diagnosed AML treated with response-adapted sequential Azacitidine and induction chemotherapy: results of the DRKS00004519 trial (RAS-AZIC) of the East German study group (OSHO)

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Molecular genetics determine the outcome and highlight the need for personalized treatment in AML patients (pts). In the multicenter RAS-AZIC study of the OSHO, 112 pts ≥60 years (y) with newly diagnosed AML received induction with Azacitidine (AZA) followed by a bone marrow (BM) blast count-adapted sequential treatment with AZA or intensive chemotherapy (IC) [fig.1]. With a TRM of only 8.9%, an overall remission

rate (ORR) of 64% was achieved on day 90. The impact of the mutational profile per NGS on remission is presented.

Patients and methods: Baseline BMs of 79 pts, who signed translational informed consent, were analyzed by NGS using the NEOmyeloid panel of NEO New Oncology (A Siemens Healthineers Company, Germany). This hybrid capture-based assay comprises 43 genes. Results were correlated to clinical data.

Results: Median age was 69 y. Secondary AML was present in 38%. ELN 2010 genetic risk stratification was int-II and adverse in 24% and 27% respectively. ORR on day 90 was 67% (CR/CRi 57%, PR 10%). A median of 3 mutations (mut) per pt were found. Only 3 pts had none. Mutations in DNMT3A (34%), ASXL1 (25%), RUNX1 (24%), SRSF2 (23%), and TET2 (23%) were most frequently detected [fig.2]. Interestingly, 72% of SRSF2 mut were associated with ASXL1 and/or RUNX1 mut. Response correlated strongly with the established genetic risk groups and less with other somatic mut. CR/CRi in favorable and int-I was 72% irrespective of the presence of high risk mut such as ASXL1 and RUNX1. In int-II and adverse risk pts, CR/CRi was 50%. Nevertheless, response adapted therapy seems to overcome the negative impact of high risk mut. CR/CRi was achieved in 66% of pts with TP53 mut.

Conclusions: Despite a very high frequency of high risk mut in this elderly cohort, a BM blast count-based sequential approach mitigates the negative impact, at least partially, of these mut on response.

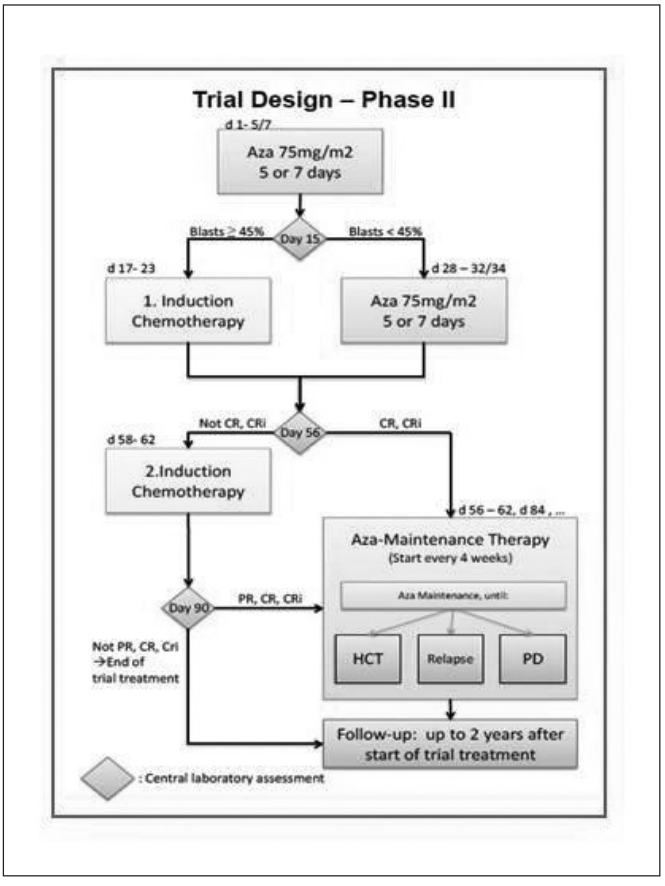

Fig. 1.

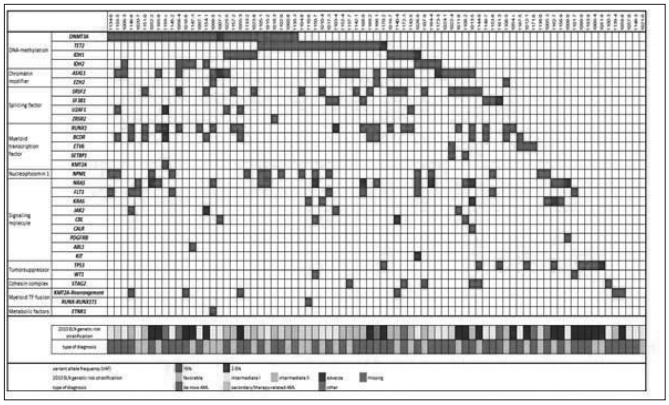

Fig. 2. Mutational profile per NGS

Disclosure: Nadja Jäkel: No conflict of interest disclosed.
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V658

The microRNA miR-196b acts as a tumor suppressor in Cdx2 driven acute myeloid leukemia

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Acute myeloid leukemia (AML) is characterized by high mortality, underlining the necessity for identifying tumor suppressors which counteract the leukemogenic potential of bona fide oncogenes such as the homeobox genes *HOXA9* and *CDX2*. The microRNA miR-196 was shown to cleave *HOXB8*, characterizing it as a putative tumor suppressor in HOX-driven AML. However, it has been postulated that miR-196 acts as oncogene in MLL- rearranged leukemias. Here we first show that miR-196b originates from a non-coding transcript in the HOXA9-10 locus and that its expression is driven by a *HOXA9* independent promoter. We identified two novel non-coding transcript variants encoding the miR-196b hairpin precursor sequence expressed from the HOXA9-10 locus in BM HSPCs: MF139050, 486 basepairs (bps), longer transcript and MF139051, 396 bps, shorter transcript. MF139051, a splice variant of the MF139050 transcript, lacked 90 bps of the exon 1 sequence of the *HOXA9* transcript and showed 99.47% homology to MF139050. Both transcripts displayed high homology to other vertebrates and particularly to mammalian species. We further demonstrate that in cytogenetically normal AML the balance between miR-196b expression and the expression of its target *HOXA9* is grossly shifted towards *HOXA9*, resulting in a 93-fold higher ratio between the expression values of *HOXA9* to mature miR-196b compared to normal $CD34^+$ BM. Retrovirally engineered overexpression of miR-196b significantly delayed leukemogenesis in a murine model of *Cdx2* induced leukemogenesis and impaired leukemic growth of human NPM1-mutated and HOX gene positive human AML. This tumor suppressive activity of miR-196b was accompanied by targeting genes associated with stem cell self-renewal and MAPK pathways. Taken together, these data indicate that miR-196b can act as a potent tumor suppressor in AML, suggesting that this microRNA has dichotomous functions in leukemia, dependent on the genetic background of the disease.

Disclosure: No conflict of interest disclosed.

Freier Vortrag

Diagnose und Therapie der Infektion

V660

Chlorhexidine dressings for prevention of central venous catheter-related bloodstream infections in patients with haematological malignancies: a matched-pair analysis from the SECRECY registry

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Introduction: Data on prevention of central venous catheter (CVC)-related bloodstream infections (CRBSI) in adult patients with haematological malignancies using chlorhexidine dressings (CHD) are derived from a few small randomized controlled clinical trials using inconsistent endpoints and hardly reflect real-life experience in this setting.
Methods: Short-term, non-tunnelled CVC in adult patients with haematological malignancies with CHD were compared with standard non-CHD dressing. Data were derived from SECRECY (DRKS00006551), a multi-centric CRBSI registry. Jugular and subclavian vein CVC with ≥1 day *in situ* were considered, using the 2012 AGIHO/DGHO CRBSI definition; only *definite* (dCRBSI) and the composite of *definite* and *probable* CRBSI (dpCRBSI) were analysed. Patients were matched for diagnosis, sex, complicated CVC insertion, anatomic insertion site, coated CVC and neutropenia at CVC insertion. Primary endpoint was cumulative dCRBSI probability at day 14 (dCRBSI14).
Results: In a total of 2323 CVC from 6 centres, 944 (40.6%) CHD were used, *n*=831 were matched. Median CVC time *in situ* was 15 days (interquartile range [IQR] 8-23); dCRBSI occurred at a median of 14 days (IQR 11-23), dpCRBSI after 13 days (IQR 10-18). In the CHD group, 32 (3.9%) dCRBSI and 89 (10.7%) dpCRBSI occurred, compared to 59 (7.1%) dCRBSI and 101 (12.2%) dpCRBSI in the non-CHD group. Neutropenia was present at CVC insertion in 294 (17.7%) patients; 884 (53.2%) were high-risk CVC. We found no statistically significant differences for dCRBSI14 (3.7% *vs.* 4.9%; hazard ratio [HR] 0.79 [95%CI 0.44-1.40]; *p*=0.41), or for dCRBSI incidence at day 14 (2.4/1000 CVC days *vs.* 2.9/1000 CVC days; *p*=0.50) comparing the CHD group and the non-CHD group. The median dCRBSI onset was also not different (day 11 [IQR 8.5-12] *vs.* day 11 [IQR 8-12.5]; *p*=0.60). The cumulative overall dpCRBSI probability was also not significantly different with 22.6% in the CHD group compared to 57.3% in the non-CHD group (HR 0.87 [95%CI 0.65-1.16]; *p*=0.33). This resulted in a comparable overall dpCRBSI incidence of 6.7/1000 CVC days *vs.* 7.6/1000 CVC days (*p*=0.41) in both groups.
Conclusions: In this large multi-centric analysis, CHD had no benefit for preventing CRBSI in adult patients with haematological malignancies.

Disclosure: No conflict of interest disclosed.

V661

Quantification of Letermovir serum levels in a routine clinical setting using a new high-performance liquid chromatography method

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Introduction: Letermovir is a new antiviral drug approved for prophylaxis of cytomegalovirus (CMV) infection and disease in CMV-positive adult allogeneic hematopoietic stem cell transplant recipients. Coadministration of OATP1B1/3 inhibitors (e.g. cyclosporine) or inducers of metabolizing enzymes may result in subtherapeutic exposure. Interindividual genetic differences increase these effects.
Since knowledge of Letermovir exposure in daily clinical practice is scarce, we established a high-performance liquid chromatography (HPLC) assay for quantification of Letermovir. Serum concentrations were determined in daily clinical practice and correlated with the presence of CMV DNA in blood.
Methods: A simple, rapid and sensitive method using HPLC with a diode-array detector (DAD) was developed and validated for the quantification of Letermovir in human serum using Sorafenib as internal standard. After pretreating samples by liquid-liquid extraction, separation was achieved on a X-Terra RP-18 column (Dimension 150 x 2.1mm, 5µm) using gradient elution. Samples were eluted at a flow rate of 0.3ml / min throughout the 20-minute run. Detection was at 260 nm using UV wavelength mode. Presence of CMV DNA was monitored by PCR routinely.
Results: The calibration curve was linear (r > 0.99) in a concentration range of 25 - 5000 ng / ml for Letermovir. The HPLC assay showed a high rate of accuracy and precision (intraday variability: -9.21 to 12 % (accuracy) and 0.31 to 3.75 % (precision); interday variability: -2.6 to 6.9 % (accuracy) and 3.74 to 7.41 % (precision)).
The analysis of 22 untimed samples of 9 patients (8 male / 1 female, age range 37 - 69 years) showed a mean concentration of 5,187 ng / ml (median 4,573 ng / ml, standard deviation 3,565 ng / ml, range 525 - 11,452 ng / ml). No patient demonstrated onset of active CMV replication under Letermovir when samples were obtained. One patient with fatal outcome was given Letermovir as an off-label treatment for severe necrotizing CMV esophagitis and showed a mean concentration below average of 1,218 ng / ml.
Conclusions: The newly developed HPLC method is useful for the determination of Letermovir concentrations. Samples of a small cohort of patients analyzed in a routine clinical setting demonstrated considerable interindividual variability. All measured concentrations were above the EC50 of Letermovir. Monitoring the concentration of Letermovir could help to prevent over- or underexposure.

Disclosure: Nora Isberner: No conflict of interest disclosed.
Hartwig H. F. Klinker: Advisory Role: AbbVie, BMS, Gilead, Hexal, Janssen, MSD; Financing of Scientific Research: AbbVie, BMS, Gilead, Hexal, Janssen, MSD; Expert Testimony: Abbvie, BMS, Gilead, Janssen, MSD

V662

Acyclovir resistant herpes simplex virus stomatitis in patients with relapsed acute myeloid leukemia after allogeneic hematopoietic cell transplantation

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Introduction: Despite antiviral prophylaxis patients undergoing allogeneic hematopoietic cell transplantation (aHCT) are at risk to develop Herpes simplex virus (HSV) reactivations, particularly stomatitis. Here we report on management and outcome of AML patients who relapsed after aHCT and developed severe acyclovir (ACV) resistant HSV-1 stomatitis.

Methods: As part of our institutional guidelines all patients suffering from HSV stomatitis without clinical improvement after one week of i.v. high dose ACV were tested for ACV-resistance, either by cell culture or sequencing. All patients with documented ACV-resistance were treated topically with 3% cidofovir solution (rinsing of the oral cavity) and 1% cidofovir gel (lips). In addition, patients without clinical response to topical therapy received foscavir i.v. (40mg/kg, 3x/d).
Results: Among 214 patients who received aHCT at our institution between 07/2010 and 04/2019 six developed ACV-resistant HSV-1 stomatitis, all WHO stage IV. Only two of them developed HSV-stomatitis during or shortly after the acute phase of aHCT. The remaining patients had a common clinical feature: All suffered from relapse of AML after aHCT. The relapses occurred 1.5 (P1), 3 (P2), 7 (P3) and 11 (P4) months after aHCT, respectively. HSV stomatitis occurred during therapy of the relapses by 5-azacytidin (P1), FLAG-IDA (P2 & P3) or the 2nd aHCT (P4). ACV-resistant stomatitis was treated locally with cidofovir solution and gel. After one week of local therapy no (P1-3) or limited response (P4) was seen. In P1-3 a systemic therapy by foscavir was added for at least one week. This antiviral salvage therapy led to a complete response in P3, a partial response (down staging to WHO II) in P2 and no change in P1. P4 experienced a complete response after 4 weeks of topical therapy. Whereas P1 died after a 5-week persistence of HSV-stomatitis, the other patients cleared virus replication (HSV-PCR neg. swabs) after 8 (P2), 5 (P3) and 6 weeks (P4), respectively. All affected patients needed parenteral nutrition and systemic opiate therapy for at least 4 weeks. Only P4 survived. P1-3 died due to refractory AML.
Conclusions: ACV-resistant HSV-stomatitis is a severe complication in AML patients relapsing after aHCT. It causes severe impairment of the clinical condition and QL. The response rate to local therapy by cidofovir seems to be low. Thus, it has to be considered whether these patients should be treated upfront systemically by foscavir.

Disclosure: No conflict of interest disclosed.

V663

Central nervous system disorders after hematopoietic stem cell transplantation - a prospective study of the Infectious diseases working party of EBMT

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Introduction: Limited data are available on neurological disorders in patients who underwent hematopoietic stem cell transplantation (HSCT).
Methods: We performed a prospective study to evaluate types and characteristics of central nervous system (CNS) disorders in patients after HSCT.
Results: The study included 163 episodes of CNS disorders occurring either after autologous (n=10, 6%) or allogeneic (n=153, 94%) HSCT. CNS infections accounted for 58 (36%) of these neurological disorders whereas proven or probable infections (n=34) included fungi (n=10, 29%), viruses (n=12, 35%), *Toxoplasma* spp. (n=9, 27%) and bacteria (n=3, 9%). Non-infectious neurological disorders (n=105, 64%) frequently encompassed metabolic/drug-induced abnormalities (n=28, 27%) or vascular events (n=22, 21%). Median onset times were later for infectious (day +101, range day 3-740) *vs* non-infectious neurological disorders (day +50, range day 0-609; p=0.009). Recipient *Toxoplasma* spp. seropositivity was more frequently reported for neurotoxoplasmosis than for other CNS infection types (100% *vs* 46%, p=0.003). Absence of cerebrospinal fluid pleocytosis despite a normal or increased peripheral blood white blood cell count was identified in 26% of CNS infections. Moreover, 33% of CNS infections were accompanied by an unremarkable cranial CT scan. Rates of normal cranial CT scans were higher for viral (58%) than for fungal (14%), toxoplasmic (22%) or bacterial (40%) CNS infections (p=0.06). An abnormal MRI of the neurocranium despite an unremarkable cranial CT scan was found in 22% of viral CNS infections but in none of the patients with CNS aspergillosis or neurotoxoplasmosis. Seizures were most frequent in patients with metabolic/drug-induced disorders (68%), whereas paraplegia/hemiplegia or need of mechanical ventilation (32% each) occurred most frequently in patients with cerebral vascular events. Mortality rates 30 days after onset were significantly higher for fungal (87%) *vs* non-fungal CNS infections (40%, p< 0.001). Likewise, mortality rates were significantly higher for cerebral vascular events than for other non-infectious CNS disorders (86% *vs* 34%, p< 0.001).
Conclusions: Our prospective study shows that CNS disorders are common after HSCT. Diagnostic findings in these diseases might differ between patients after HSCT and immunocompetent hosts. Therefore, special awareness and timely initiation of adequate diagnostics is crucial to improve the prognosis of these patients.

Disclosure: No conflict of interest disclosed.

V664

Evaluation of human herpes virus 6 (HHV6) infections and chromosomal integration of HHV6 after allogeneic hematopoietic stem cell transplantation

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Introduction: Human herpes virus 6 (HHV6) reactivation after allogeneic stem cell transplantation (alloSCT) may be associated with significant morbidity and mortality.
Methods: Epidemiology of HHV6 infections and their impact on outcome after alloSCT were retrospectively analyzed in 689 patients consecutively transplanted 2015-2018. Chromosomal integration (ciHHV6) in donor and patient was investigated for viral loads ≥1e4 copies/mL to evaluate therapeutic necessities.
Results: 53 HHV6 infections occurred (7.69%; encephalitis (1), gastroenteritis (42), dermatitis (2), hepatitis (2), pneumonitis (2)). In 40/689 patients (5.81 %), HHV6 viremia was detected. 6/40 (15%) patients had HHV6 viral loads ≥1e4 copies/mL and were analyzed for chromosomal integration of HHV6 (ciHHV6). To this end, each a blood sample from the donor and a blood sample from the patient before alloSCT were screened for the presence of HHV6. In 3 of these 6 patients, excess copy numbers of HHV6 were detected as a consequence of engraftment with cells from the donor who had genomic integration of HHV6, and not as a consequence of viral reactivation. Donor viral loads ranged from ≥2e5-1.5e6 copies/mL for HHV6-A (n=2) and -B (n=1). On the other hand, 3 patients with high viral loads showed genomic integration of HHV6-A (n=1) and -B (n=2) before alloSCT, and no HHV6 could be detected in

blood samples from the donor. HHV6 infections were not associated with other virus infections e.g. EBV reactivation, or CMV status of the subjects. Engraftment did not differ after alloSCT between the HHV6-infected and non-infected groups (15.17±9.65 days vs 13.41±4.3 days). Age did not differ between the groups (mean age 53.49 ±14.77 vs 55.3±13.78 years). The occurrence of graft-versus-host disease (acute OR: 3.54; 95%CI: 1.75-7.15; p=0.0004; chronic: 2.56; 95% CI: 1.46-4.54, p=0.001) and HHV6 infection after alloSCT showed a statistically significant association with each other. Although 21 subjects with HHV6B infection died (39.6% of infected), neither HHV6 reactivation nor infection was a risk factor for death (p=n.s., log rank test).
Conclusions: In this series of alloSCT recipients with elevated blood viral loads of HHV6, 7.5% patients were ciHHV6. Active HHV6 infection with replicative viremia could only be detected in one patient. Screening of the donor for chromosomal integration of HHV6 (ciHHV6) before initiation of antiviral therapy is advised.

Disclosure: No conflict of interest disclosed.

V665

Single center real-world data on Letermovir prophylaxis for cytomegalovirus reactivation after allogeneic hematopoietic cell transplantation

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Introduction: Reactivation of cytomegalovirus (CMV) still contributes substantially to morbidity and mortality after allogeneic hematopoietic cell transplantation (alloHCT). Letermovir significantly reduced the incidence of CMV reactivation in a pivotal phase III trial (NEJM 2017;377:2433). It is neither nephro- nor myelotoxic. We adopted letermovir prophylaxis according to the label as standard policy in our institution: After engraftment letermovir was initiated in seropositive recipients and continued until CMV reactivation or day +100. The purpose of this study was to analyse if the favorable trial results could be reproduced under real-world conditions.
Methods: The study cohort was formed by the first seropositive 35 patients who received letermovir prophylaxis at our institution (between March and August 2018). Comparison was done with a control cohort transplanted between August 2017 and March 2018 before the advent of letermovir. Both cohorts were matched for donor type source of stem cells, CMV donor/recipient sero-status, application of ATG and underlying disease. CMV viremia was monitored by quantitative PCR twice a week during the inpatient period and weekly thereafter. Patients reactivating CMV prior to engraftment were not considered as event in both groups.
Results: There were no major side effects of letermovir intake observed. The cumulative rate of CMV reactivation on day +100 in the letermovir cohort was 14% (95%CI 1-45%) and thus significantly lower than in the control group (58% (95%CI 42-71%); HR 0.23 (0.10-0.51); p=0.0003). For the control patients median time to reactivation was 53 days and not reached for the letermovir patients. The cumulative number of days on valganciclovir before d +100 was 151d for the letermovir cohort vs 689d for the the control cohort. There were 5 hospitalizations for foscavir administration in the control group and no hospitalizations in the letermovir group. There were 2 deaths before d +100 in the letermovir group compared to 3 deaths in the control group.
Conclusions: This observational study in a real-world setting confirms the safety and efficacy of letermovir for the prophylaxis of CMV reactivation in seropositive patients after alloHCT. Although letermovir seemed to lower the need for therapeutic foscavir and valganciclovir enormously, larger samples with longer follow-up are needed to assess the impact of letermovir prophylaxis on overall and non-relapse mortality as well as on resource consumption.

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Michael Schmitt: Employment or Leadership Position: Universitätsprofessor Uni HD; Advisory Role: MSD, Gilead, Janssen, Novartis; Stock Ownership: Mitgründer der TolerogenixX GmbH, Heidelberg; Honoraria: RHAMM, Markierung von HSC mit GFP; Financing of Scientific Research: Hexal, Teva; Expert Testimony: Novartis, Theranostics/Mallinkrodt; Other Financial Relationships: Reisekosten von Novartis, MSD, Hexal, Janssen, Teva, Pierre Fabre

Freier Vortrag

ALL

V666

Blinatumomab for minimal residual disease (MRD) in adults with b-cell precursor acute lymphoblastic leukemia (BCP-ALL): median overall survival (OS) not reached at 5 years for complete mrd responders

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Introduction: In a single-arm study (BLAST; NCT01207388) in adults with BCP-ALL and MRD, 78% (88/113) of patients (pts) achieved a complete MRD response after 1 cycle of blinatumomab. Here, we report the final OS analysis among adults with a >5 years of follow-up after blinatumomab treatment.
Methods: The BLAST study enrolled adults in first (CR1) or subsequent (CR2+) hematologic complete remission after ≥3 intensive chemotherapy blocks, with MRD ($\geq 10^{-3}$) ≥2 weeks after the last chemotherapy. All pts received blinatumomab 15 μg/m^2 per day for up to 4 cycles. Complete MRD response was defined as no target amplification, with a minimum sensitivity of 10^{-4}. After MRD response assessment (end of cycle 1), pts could undergo allogeneic HSCT at any time. Kaplan-Meier estimates of OS were determined after 5-year follow-up. A conditional landmark of 45 days (end of cycle 1) was used for subgroup analyses by complete MRD response.
Results: Of 116 pts with MRD who received blinatumomab, OS was evaluated for 110 pts with Philadelphia chromosome-negative (Ph$^-$) BCP-ALL and < 5% blasts at enrolment, including 74 received HSCT in continuous complete remission (CCR) after blinatumomab. With a median follow-up of 59.8 months (mos), median OS was 36.5 mos (95% CI: 22.0-not estimable [NE]). At 5 years, outcomes with or without HSCT in CCR were as follows: alive without relapse, 40.5% vs 19.4%; relapse, 23.0% vs 72.2%; and death without relapse, 36.5% vs 8.3%. Analyses of OS by complete MRD response in cycle 1 (n=107) excluded pts with no central MRD assay (n=1) or inadequate MRD test sensitivity (n=2). Median OS was not reached (95% CI: 29.5 mos-NE) for complete MRD responders (n=84) and 14.4 mos (95% CI: 3.8-32.3) for MRD nonresponders (n=23; log-rank p=0.002). Estimated 5-year survival was 43% overall (95% CI: 34%>52%) and 50% for complete MRD responders (95% CI: 39%>60%). Among HSCT recipients in CCR, median OS from HSCT was not reached (95% CI: 25.7 mos-NE) for complete MRD responders (n=61) and 16.5 mos (95% CI: 1.1-NE) for MRD nonresponders (n=10; log-rank p=0.065). Among all pts with MRD in CR1, regardless of HSCT, median OS was not reached (95% CI: 29.5 mos-NE) for complete MRD responders (n=60) and 10.6 mos (95% CI: 2.7-39.7) for MRD nonresponders (n=13; p=0.008).

Conclusions: The final, 5-year OS results of this multinational study provide further support for long-term OS benefits associated with blinatumomab treatment in adults with BCP-ALL and MRD.

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Ralf Bargou: Advisory Role: Amgen, Novartis, AstraZeneca, GEMoaB, Pfizer; Honoraria: holds a patent for blinatumomab, and reports patent royalties from Amgen; Financing of Scientific Research: Amgen, Novartis and GEMoaB; Expert Testimony: Amgen

V667

RNA-Seq pipeline identifies novel molecular subgroups and targetable alterations in high-risk acute lymphoblastic leukemia patients

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The landscape of molecular subtypes in acute lymphoblastic leukemia (ALL) is increasingly complex with >60 recurrent gene fusions in up to 20 molecular subtypes in B-cell precursor ALL alone. Response to induction therapy, as assessed by minimal residual disease (MRD), is the strongest prognosticator in ALL. It identifies patients with a poor response to conventional therapy and an overall inferior outcome.
To perform molecular subgroup allocation and define selected driver events in high risk ALL patients within a turn-around time of 6-8 weeks, we have established an RNA-Seq based analysis pipeline. Sequencing libraries were prepared from diagnostic bone marrow mononuclear cells and were sequenced (2x75 bp) on a NextSeq system to obtain ~30 Mio reads/sample.
Analyzing 330 retrospectively collected ALL samples as reference cohort, we identified 18 molecular ALL subtypes by distinct gene expression profiles and corresponding driver alterations. For *IGH-BCL2* and *IGH-CEBPE* gene fusions, which had been previously cytogenetically described in rare BCP-ALL cases, we observed new subgroup-defining gene expression profiles. We identified a novel subgroup ('PAX5-plus ALL'; n=19/250 BCP-ALL) defined by bi-allelic genomic alterations in the B-lymphoid transcription factor *PAX5* and strong enrichment of *CDKN2A* deletions and RAS-activating mutations.
To evaluate our pipeline in a diagnostic setting within the context of GMALL studies, we prospectively analyzed high risk Ph-negative patients with molecular poor response to induction therapy ('molecular failures', n=17). All but one of these 17 patients could be allocated to the described molecular subtypes. Of these, 8 belonged to the high-risk Philadelphia-like subtype (Ph-like) and 3 of these Ph-like cases harbored *ETV6-NTRK3* gene fusions. ETV6-NTRK3 was shown to cause highly aggressive leukemias in a murine model, amenable to specific inhibition with clinically available NTRK-inhibitors. Two other Ph-like patients harbored ABL1-class gene fusions (*EBF1-PDGFRB, FOXP1-ABL1*), which have shown sensitivity towards tyrosine kinase inhibitor treatments in reported cases.
Transcriptome sequencing based on our newly established pipeline provided subgroup allocation of ALL samples by coherent identification of driver alterations and gene expression profiles. It identified targetable alterations in a subset of prospectively analyzed high risk patients, which might direct additional treatment based on targetable lesions.

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Interim results of a multicenter, single-arm study to assess Blinatumomab in adult patients (pts) with minimal residual disease (MRD) of B-precursor (BCP) acute lymphoblastic leukemia (GMALL-MOLACT1-BLINA)

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MRD is defined as the detection of leukemic cells in bone marrow below the microscopic threshold in hematological complete remission (CR). Pts having persistent/recurrent MRD after induction/consolidation therapy are at a high risk for relapse. In these pts, therapies should prevent hematologic relapse, reduce MRD load and provide a bridging strategy to allogeneic hematopoietic stem cell transplantation (HSCT).
Blinatumomab is an antibody construct that redirects $CD3^+$ T cells to $CD19^+$ target cells, resulting in a serial lysis of $CD19^+$ B cells. In a study in 116 pts with MRD $\geq 10^{-3}$, 78% achieved complete MRD response (Gökbuget N et al., Blood 2018). MolAct1 evaluates the efficacy and tolerability of Blinatumomab in MRD^+ ALL.
Adults (≥ 18 yrs) with $CD19^+$ BCP ALL in CR after ≥ 3 chemotherapies with MRD $\geq 10^{-4}$ were eligible. Blinatumomab 28 µg/day was given by continuous 4-wk infusion, followed by a 2-wk break (1 cycle). Responders could receive up to 4 cycles or undergo HSCT after ≥ 1 cycle. Complete MRD response (MRD negative, sensitivity of $\geq 10^{-4}$ after 1 cycle) was the primary endpoint. MRD was centrally assessed by allele-specific quantitative real-time PCR for clonal rearrangements of immunoglobulin or T-cell receptor genes. Positive MRD $< 10^{-4}$, not quantifiable (quant.) was defined as MolNE1 (molecular not evaluable), quant. MRD $< 10^{-4}$ as MolNE2 and not quant. MRD positivity as MolNE3.
35 pts were treated and 33 were evaluable for MRD after cycle 1. 24 pts (69%) had molecular failure, 11 (31%) molecular relapse. 23 pts (70%) had a complete MRD response, 7 pts (21%) MolNE (2 MolNE1, 1 MolNE2, 4 MolNE3), 3 (9%) molecular failure. 31 pts had ended treatment, 6 (18%) due to relapse, 1 (3%) due to neurotoxicity, 23 (70%) for subsequent HSCT and 1 pt received maintenance. Follow-up after HSCT is available in 18 pts; 14 pts are in continuous remission, 2 relapsed, 2 died in CR.
Results from previous trials were confirmed with an MRD response rate of 79%. A complete MRD response was achieved in 70% of the pts. 70% were transferred to HSCT with promising outcomes. The trial will be amended to include pts with low positive MRD.
This study was supported by Amgen Inc.

Baseline characteristics	n (%)
Total number of pts	35 (100)
Median age (Range)	45 (18-73) yrs
CR in which blinatumomab was given	
First CR	34 (97)
Later CR	1 (3)
Baseline MRD levels	
$\geq 10^{-2}$	7 (20)
$\geq 10^{-3} < 10^{-2}$	18 (51)
$\geq 10^{-4} < 10^{-3}$	10 (29)
Median follow-up of surviving pts	223 d (28-625d)

Fig. 1. Baseline characteristics

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V669

CD20 expression and treatment response to Rituximab in B-cell precursor Acute Lymphoblastic Leukemia - research project within the GMALL08/2013 trial

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Introduction: Rituximab (R) application in B cell precursor ALL (B-ALL) is often restricted to patients (pts) with ≥20% leukemic CD20 expression, but the biological plausibility of this arbitrary cutoff is unclear. As the addition of R contributes to improved remission duration in *BCR-ABL1*-negative B-ALL, R is administered to all *BCR-ABL1* negative B-ALL irrespective of the leukemic CD20 expression in the GMALL08/2013 trial. In parallel, we compare leukemic CD20 expression at diagnosis/after prephase, correlate it to early MRD response and investigate CD20-related (sub)clonal diversity.
Methods: Standardized quantification of CD20 expression was performed in initial blood/BM and after the dexamethasone-containing prephase (day 6) by flow cytometry (FCM) in a 3-Tube (T1-3) antibody panel. CD20 median fluorescence intensity (MFICD20) of blasts and percentages of CD20+ blasts/all blasts (%CD20+) were correlated to MRD values of clonal immune gene rearrangements at therapy day 22 (after induction/1 dose R) measured by RQ PCR. MRD response was defined as MRD decrease to $< 10^{-4}$, MRD persistence as detection of quantifiable MRD $\geq 10^{-4}$. Clone diversity studies were done by cell sorting, MLPA, FISH and NGS methods.
Results: FCM results of 105 B-ALL pts were evaluated. In 52 paired initial/day 6 blood samples leukemic CD20 expression significantly increased after prephase in n=43 c-/pre-B-ALL (T1/2 p< .0001, T3 p=.004 for MFICD20 and p< .0001 for %CD20+, Wilcoxon signed rank test) but not in n=9 pro-B-ALL.
In 37 paired blood/BM initial samples, the %CD20+ blasts was significantly higher in blood in n=30 c-/pre-B-ALL (*p*< .0001, Wilcoxon signed rank test) as were the MFICD20 values (T1-3: p< .0001, p=.0003, p=.0008) but not in n=7 pro-B-ALL.
Highest initial %CD20+ blasts was significantly higher in 31 MRD Responders compared to 47 MRD Persisters (p< .0001, Mann-Whitney test), also when excluding n=12 worse-responding pro-B-ALL and comparing sole n=66 c-/pre-B ALL MRD Persisters vs Responders (*p*=.0015).
Finally, only 2/61 (3%) pts showed subclonal differences in CD20+ vs CD20- sorted blasts.
Conclusion: We found significant differences in leukemic CD20 expression between initial blood/BM and initial/after-prephase blood in pts with c-/pre-B-ALL challenging the conventional eligibility criteria for CD20-targeted treatment. MRD Responders had higher CD20 expression compared to MRD Persisters. (Sub)clonal diversity seems not to be dependent on CD20 expression.

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V670

Expression of CD38 as a potential therapeutic target in adult acute lymphoblastic leukemia (ALL)

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Introduction: Therapeutic targeting using monoclonal antibodies has entered clinical routine in B-lineage ALL, but this is not established in T-ALL. CD38 is of interest since several therapeutic antibodies are available.
Methods: Using flow cytometry, we prospectively evaluated CD38 expression in newly diagnosed adult ALL within the GMALL study. Positivity was considered when >=20% cells showed antigen expression above the fluorescence intensity of negative controls. ALL-subtypes were grouped into T- (pre-T: CD2-, surface CD3-, thymic: CD1a+, mature T: CD2+, surface CD3 +/-) and B-lineage (pro-B: CD10-, common: CD10+, Ig-, pre-B: cytoplasmatic IgM+, mature B: surface Ig+).
Results: Overall, 226 specimens (bone marrow 151, blood 72, pleural effusion 3) were tested. In T-ALL, 45 (98%) of 46 specimens showed strong expression of CD38 across all subtypes (Figure 1). In B-lineage ALL, the percentage of CD38+ specimens ranged from 92% in common ALL to 100% in mature ALL with a larger variation in positivity compared to T-ALL (Figure 2). We also compared the CD38 expression in residual, normal T-cells with that of leukemic cells in T-ALL samples containing >=10% residual T-cells. In 6 of 7 T-ALL samples, the percentage of CD38+ cells was higher in leukemic cells compared to residual T-cells (Figure 3).
Conclusions: CD38 is frequently expressed in adult ALL with a more intense expression in T-ALL. In T-ALL, CD38 expression was usually higher on leukemic cells compared to residual T-cells, which makes profound T-cell depletion through antibody-mediated CD38-targeting less likely.

Disclosure: No conflict of interest disclosed.

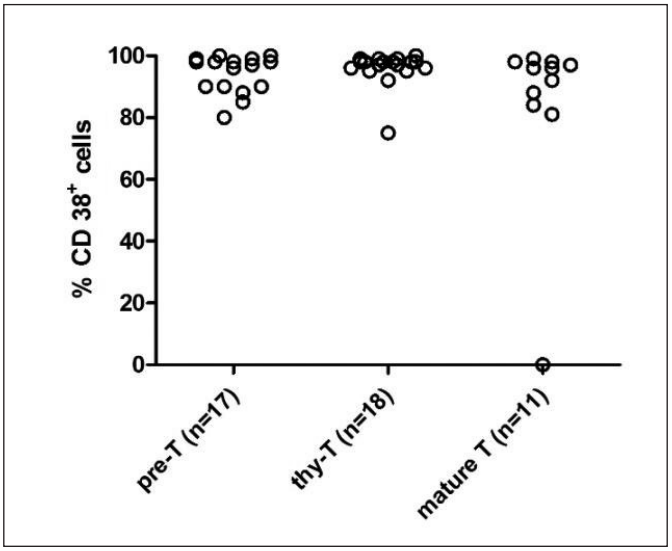

Fig. 1.

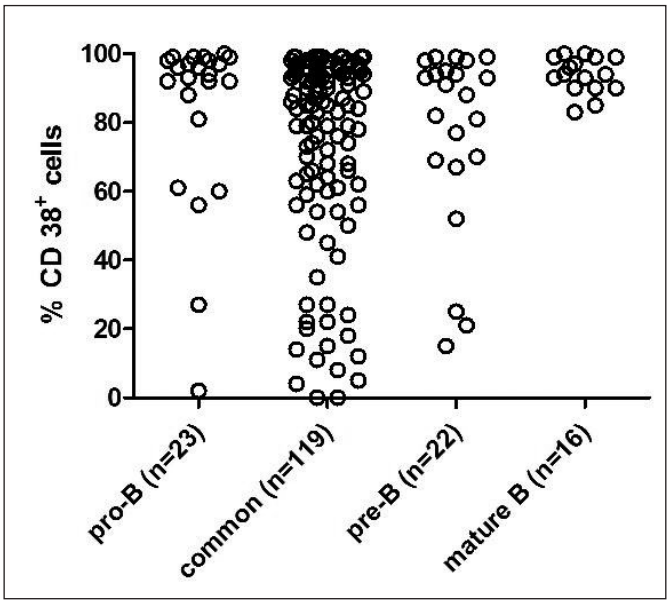

Fig. 2.

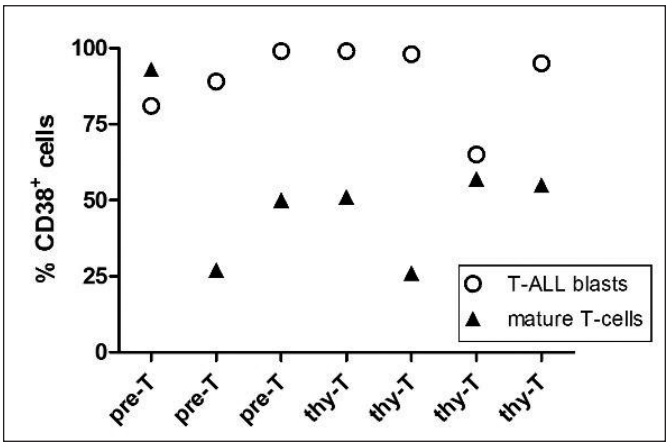

Fig. 3.

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Combined inhibition of PI3K and SYK enhances synergistically the gene expression modulation in BCR dependent and independent B-lymphoblastic leukemia cell lines

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Introduction: SYK is a key proximate kinase of the B-Cell-Receptor (BCR) and frequently associated with hematological neoplasm and aberrant B-cell regulation. Previously, we reported synergistic effects (Bliss) on cell biologic parameters such as proliferation, metabolic activity and apoptosis combining the SYK inhibitor Entospletinib (Ento) with PI3K pathway specific inhibitors in acute lymphoblastic leukemia cell lines. Interestingly, in BCR independent pro-B-ALL cells also a pronounced unexpected inhibitory effect was observed. Herein, we investigated the underlying gene regulation mechanisms by whole transcriptome analysis.
Methods: B-ALL cell lines (BCR+/pre-B-ALL NALM-6, BCR-/pro-B-ALL SEM & RS4;11) were exposed to Ento as mono substance or in combination with four different PI3K pathway inhibitors. Whole transcriptome analyses were performed for selected samples. Bioinformatical analyses were carried out via in-house pipeline (incl. DESeq2, WikiPathways). Downstream analyses included differential expression and pathway analysis. A rank-rank matrix of the top 100 regulated genes and the most enriched pathways was analyzed.
Results: Transcriptome analyses revealed 313 (fold change range: -6,6 - 3,9) significantly deregulated genes after Ento and 258 (fold change range: -2,8 - 3,4) genes after BKM-120 (BKM) application. The combined application led to synergistically enhanced gene modulation (1042 significantly deregulated genes; fold change range of -6,68 - 4,95). Pathway association revealed that these genes are mainly involved in metabolism, BCR signaling, calcium-, cytoskeleton-, cell cycle-, apoptosis-, hormone- and oxidative stress- signaling, matching our previous cell biologic findings. Combination of Ento and BKM regulated exclusively several genes. Genes as CALML, STX1B, LINC00163, NRG3 and JCHAIN were found to be up-regulated whereas genes as HIST1H4E, DYNC1I1, WNT10B, ANGPT4, IL1R1, CD86, FSCN1 and CD40 were down-regulated.
Conclusions: In the BCR independent cell line SEM BCR/PI3K signaling itself is only marginally affected. The BCR independent inhibitory effect appears more likely to be regulated by cell proliferation and development, calcium regulation and apoptosis induction pathways. The exclusively gene modulation by combined exposition of Ento and BKM identifies mainly cell-growth, -migration, -proliferation, cell cycle arrest, apoptosis, transcription regulation and DNA repair as the potentially underlying biological processes.

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Freier Vortrag

Sonstige Themen

V672

T cell receptor next-generation sequencing reveals cancer-associated repertoire metrics and reconstitution after cytotoxic therapy in patients with hematological and solid tumors

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The dynamics of immunoaging and the onset of immunoparesis in healthy humans has been controversially discussed over the past decades. Even more debatable is the situation in cancer patients and especially the role of chemotherapy on immunodiversity and T cell regeneration. Next-generation immunosequencing technology has opened up avenues to precisely study T cell repertoire metrics over time. Here, we used this technology on 99 blood samples from 95 healthy donors and 248 blood samples from 215 cancer patients generating a set of 347 T cell repertoires containing 8.8 million individual T cell receptor rearrangements. This analysis clearly showed that decline of T cell diversity and increase in T cell clonality is a continuous process beginning in healthy individuals over 40 years of age. Untreated patients with hematological cancers involving primary or secondary lymphoid tissues or patients with solid cancers showed blood T cell repertoires with significantly lower diversity and higher clonality as compared to age-matched healthy control individuals. Interestingly and independently of the age group studied, post chemotherapy the blood TCR repertoire diversity could be regenerated to pre-treatment age-specific levels. Even patients with hematological cancers over the age of 70 years who received T cell toxic therapies recovered their pre-treatment T cell diversity with only a slight trend towards increased post-treatment clonality. Moreover, the post-treatment T cell repertoire showed low to none overlap to the respective pre-treatment T cell repertoire suggesting rebound thymic activity rather than recovery of T cell counts by peripheral expansion only. Taken together, these data suggest that human TCR repertoire metrics gradually deteriorate over age, but age-specific TCR metrics can be largely restored after T cell depleting therapy even in elderly patients with cancer through generation of new T cell clones.

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V673

How to avoid anglicisms in German scientific presentations

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It´s been a steady evolution of the German scientific language since Paul Ehrlich talked about "Zauberkugeln". Today, a similar scientist would refer to them with the anglicism "targeted therapies". Several developments have led to this predominance of English terms: The rise of the English language as "lingua franca" in daily life, and the feeling that whoever speaks English must be especially knowledgeable or innovative. The latter may be the explanation why genuine German inventions like an inflatable saftey bag in cars was dubbed "airbag" instead of, e.g., "Prallsack". The second reason is probably a sort of laziness, inability or lack of understanding that leads the German public to translate English words wrongly. The most striking example is the word "to support" which has a German translation of "unterstützen". However, in the sentence "your computer doesn´t support this programme", the correct term is far from "unterstützen", but rather "funktionieren": "Das Programm funktioniert nicht auf Ihrem Computer" would be the correct German equivalent. Such anglicisms also exist in medicine. I have reviewed the German medical literature from 2007 to 2014 and compiled a list of anglicisms that you will hear throughout DGHO 2019. I realise that certain English terms are an enrichment for the German medical language, but a tendency for unnecessary anglicisms is unequivocal. German native speakers might reverse some of the more drastic derailments. Alas, for others, it is too late. "Evidence-based medicine" is one striking example where the battle is lost. "Evidence" is the English word for "Beweis". In contrast, German "Evidenz" means that there is no need for any "Beweis", because the matter is crystal clear. The simplest translation of "evidence-based", of course, would be "wissenschaftlich", because "Wissenschaft" is always evidence-based, otherwise it wouldn´t be "Wissenschaft". How about GCP in "Ist die Dokumentation GCP-konform?". The German language provides us with "ordnungsgemäß"... Other anglicisms include "gebiast" for "verzerrt", "Armamentarium" for "Arsenal", "händelbar" for "beherrschbar", "präliminär" for "vorläufig", "Reliabilität" for "Zuverlässigkeit", and - one of my favorites - "relabiert" for "rezidiviert". But "relabiert" is a neologism that should get some credit. First, it substitutes another foreign term, and second, it is so close to "gelabert" that it is a hilarious example of how not to integrate English words in our language.

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V674

Tumor board and pathway adherence at comprehensive cancer center Freiburg (CCCF): a cross-section analysis

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Introduction: The increasing complexity of cancer treatment requires multidisciplinary cancer conferences for clinical decision-making. These tumor boards constitute the standard in cancer patient care and are a prerequisite for certification of cancer center in Germany. Although multidisciplinary cancer conferences are internationally recognized as a means for improving patient care, there is little evidence that tumor boards improve patient outcome.
In this study, we examined the quality of tumor board recommendations to translate treatment guidelines into clinical action in cancer patient care.
Methods: In this retrospective observational study, we performed a cross-sectional analysis of tumor board recommendations affecting patients with colorectal cancer discussed in the tumor board of the center for gastrointestinal tumours at the Comprehensive Cancer Center Freiburg (CCCF) from October to December 2016. Following criteria for inclusion and exclusion, 117 tumor board case presentations were identified, which included 234 structured recommendations. As primary objectives, we examined the compliance of tumor board recommendations with clinical pathways and treatment guidelines, and the adherence of clinical actions to tumor board recommendations.
Results: The results of this study showed a pathway compliance of 96 %. However, the tumor board adherence was only 71 %. The two main reasons for not implementing structured tumor board recommendations were the following: In 23 %, medical reasons prevented the implementation, and 24 % of recommended procedures were declined by the patient.
Conclusions: The high adherence of tumor board recommendations to pathways demonstrates faithful translation of treatment guidelines by the interdisciplinary tumor board. In contrast, the comparably low tumor board adherence and the rather high percentage of the patient's wish as the reason for not carrying out the tumor board decision suggest that individual patient values and preferences should be taken into account

and could lead to a higher tumor board adherence and improved decision making process.

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V675

Clinical trial (CT) activities including early phase I & II trials in hematology & oncology (H&O) supported by the Clinical Cancer Research (CCR-) group and Comprehensive Cancer Center Freiburg (CCCF): model for success

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Introduction: Rapid advances in drug development have led to an impressive increase in CTs, but also their complexity. Molecular therapies, including immunotherapies have made the organization and logistics of CTs increasingly challenging. Growing numbers of CTs in Europe have led to the successful implementation of Early Clinical Trial Units (ECTUs) within CCCs.
Methods: We report on the structural and logistic organization of our specialized unit for clinical research.
Results: Our unit is responsible for all CTs conducted in H&O, the acquisition of patient (pt) data within and outside CTs, all supported by our pharmacovigilance team and chemotherapy (CTx) management software (ChemoCompile). In close cooperation with all Principal Investigators (PIs), our CT office coordinates all CT-tasks: first contacts (with sponsors, CROs, ethics, BfArM, PEI), evaluation of CTs, logistics and CRF-documentation. In order to estimate highly realistic pt recruitment, our documentation system (Carat+) is used, which includes demographics, cancer histologies, diagnoses, CTx-regimens, progression and survival. Internal protocol-study-and-review-board meetings allow discussion of newly proposed CTs: therein, all relevant aspects: clinical concepts, pt numbers, feasibility, scientific relevance and regulatory and financial aspects are discussed. In order to enhance pt recruitment, we have implemented various effective strategies: educational programs, cross-linkage to CTx-management and intra-/internet CT quick-search program (QuickQueck©). Entity-specific tumorboards (n=22) are another useful tool to efficiently enrol pts into CTs. Moreover, a core CT group has formed and meets every 3 weeks to solve relevant CT-specific issues. Pts' responses to our CCCF-ECTU have been exceptional: organization, coordination, medical support and CT assistance were rated as excellent. A constant high number in phase I and other trials has been accompanied with high pt numbers being treated within this busy, effective unit.
Conclusions: Our ECTU supports clinical research that is of utmost importance for new drug development. In times of increasingly dense physicians´ schedules and CT-logistics, our CCCF-ECTU-structure proves highly valuable for eager CT performance, serving as an useful example for other sites/CCCs. Our predestined location in the triangle of Germany, Switzerland and France also allows to further expand early CTs to grant pts´ access to novel therapies and cancer medicine.

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V676

CTCAE-conform patient self-reported determation of chemotherapy-induced peripheral neuropathy (CIPN) is feasible in daily routine practice

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Introduction: CIPN is very common in patients treated with oxaliplatin. However documentation of CIPN onset and duration in accordance to CTCAE[1]-critieria of peripheral neuropathy is often incompletly recorded in daily routine practice.
Methods: We used a modified FACT/GOG-NTX-questionnaire[2] (vers.4) in the multicenter NEMO-Trial (non-interventional trial for determination of neurotoxicity with oxaliplatin in patients with colorectal cancer, observation is still ongoing) and evaluated patients questionaires according to CTCAE-critieria before treatment, every 3 months under treatment and every 6 months after completion of treatment for 2 years. We used 9 questions out of 19 to determine CTCAE-grade of peripheral neuropathy. 3 questions were related to each CTCAE-grade, at least one positive answer of these 3 questions determined the highest CTCAE-grade. Results were put in relation to results reported in the MOSAIC-Trial[3].
Results: Out of 183 patients we recieved questionnaires of 180 patients. 43 (24%) patients presented with CIPN before therapy with oxaliplatin, 21 (12%) grade 1, 6 (3%) grade 2, 21 (12%) grade 3. After treatment 144(80%) patients indicated CIPN, 48 (27%) grade 1, 12 (7%) grade 2, 84 (47%) grade 3. In the MOSAIC-trial CIPN was reported after treatment with oxaliplatin in 92% of patients for all grades, 12,4% of patients with grade 3.
Conclusions: We identified a set of questions to determine CIPN according to CTCAE-critieria self-reported by patients. Results of the questionnaire go long with previously reported results from the MOSAIC-trail. CTCAE-conform documentation of CIPN is feasible in daily routine practice using a modified FACT/GOG-NTX-questionnaire. The questionnaire will be demonstrated in detail at the DGHO-meeting.

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V677

Metabolomic profiling of microvesicles in the peripheral blood of glioblastoma patients

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Background: Cancer cells secret high numbers of extracellular vesicles (EV) into extracellular fluids. Especially the larger EVs, the so called microvesicles (MV, diameter 100-1000 nm), budding off directly from the plasma membrane are easily detectable in the peripheral blood. Not only do these MVs contain nucleic acids and proteins specific to the cells of origin, but also a wealth of barely investigated small metabolites. Since cancer cells differ from benign ones with regard to their metabolism, we hypothesized that plasma MV from glioblastoma (GBM) patients, containing various amounts of malignant MV, exhibit a specific profile of metabolites.
Methods: MVs were isolated by differential ultracentrifugation from the peripheral blood of patients with GBM, low grade gliomas (LGG, WHO

II°) and, for comparison, from breast cancer (BC) patients and healthy controls. These MVs were analyzed using a targeted approach on a triple quadrupole mass spectrometer recognizing 180 predefined metabolites (AbsoluteIDQ ®p180 Kit, Biocrates, Innsbruck). Bioinformatical analysis was performed with the free online software *metaboanalyst.ca*.
Results: MVs from 25 GBM, 7 LGG, 22 BC patients and 11 controls were analyzed. Regarding all GBM MV samples, principle component analysis (PCA) and cluster analysis showed a scattered metabolomic pattern. However, within the GBM cohort we detected a subgroup that clustered separately from healthy controls. Quantitative enrichment analysis between MVs from GBM patients and controls revealed differences in tryptophan metabolism and branched-chain amino acid degradation. In contrast, there was no significant difference in the metabolome pattern between the MVs of LGG patients and controls.
A comparative analysis of the MVs of BC and GBM patients revealed no general separation of the two groups. Nevertheless, the previously established subgroup of GBM samples clustered separately from BC samples in the PCA. Heat-map analysis showed a different metabolomic profile for the majority of BC MVs compared to GBM MVs.
Conclusions: Although plasma MVs derive mainly from blood and endothelial cells, the entire mixture contains only minor amounts of tumor-derived MVs. We were able to characterize a subpopulation of GBM patients with a different metabolome profile than healthy controls or BC patients - metabolomic profiling of blood MVs may be a useful tool to identify biomarkers and potential therapeutic targets in GBM and other cancer patients.

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Posterdiskussion

Versorgungsforschung und Ausbildung

P680

Oncology in primary medicine

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Introduction: The incidence of malignomas results in about 476 000 per year according to data of the ZfKD. Primary medicine is in the utmost responsibility to detect early stages of tumorigenesis to open up options of cure to the patient. Thus we investigated the signs and symptoms that lead to the diagnosis of cancer or malignomas of the hematological system in the front situation of primary medicine.
Methods: Patient data were evaluated retrospectively over 12 years from 2007 to 2018. We structured our analysis according to results given by thorough clinical investigation as well as laboratory and morphological results. We developed investigational pathways to increase sensitivity and specificity of pre-apparative results in order to define investigational algorithms leading to correct diagnostic structures.
Results: Our data supports the statistical results in the leading incidence of breast tumor in women and prostate cancer in men followed by colorectal and lung carcinoma as well as increasing incidences of urine bladder carcinomas. We found that exacerbation of herpes zoster as well as the occurance of deep vein thrombosis and lung embolism are significant signs that should lead to full awareness of intensified tumor screening. We evaluated a standardized questionnaire to aquire initial data in the frontline situation to lead to increased screening for malignomas. These algorithms can be used in the term of standardized and digitalized medicine to increase upfront diagnostic safety as well as increase sensitivity in secondary prevention. We demonstrate that thorough questionnaires help to prevent over diagnostics and ensure patients in their wellbeing.
Conclusions: Primary medicine is the leading and initializing part in the diagnosis of tumors. Awareness is important to achieve high level diagnostic discrimination leading to adequate treatment options. Standardized diagnostic pathways are important guiding diagnostic tools and leading to early findings of malignancies in order to increase life expectancy in cancer.

Disclosure: No conflict of interest disclosed.

P681

A mixed-methods study to improve recall and knowledge among haematological cancer patients undergoing transplant procedures and their support persons

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Background: Allogeneic haematopoietic stem cell transplantation (alloHSCT) includes a high risk of mortality and long-term morbidity. When being presented with this treatment option, patients and their support persons commonly have a plethora of information to consider and need to cope with the anxiety and distress related to their disease and potential treatment outcomes. However, strategies are lacking that could help transplant patients and their support persons to understand and "digest" the information provided by their clinicians.
Aims: This study project explores, qualitatively, in a sample of haematological cancer patients (prior to alloHSCT or CAR-T cell therapy) and their support persons, their perceptions of issues relating to the provision of diagnosis, treatment options, and strategies to improve the quality of care (part I). Based on these findings, an intervention will be developed and pilot tested with the aim to improve recall and knowledge among haematological cancer patients and their support persons (part II).
Methods: For part I, semi-structured interviews with haematological cancer patients and their support persons are conducted. Data are analysed using framework analysis. For part II, an intervention will be developed with the help of a multidisciplinary expert panel. The intervention will be pilot tested using a two-arm randomised-controlled trial.
Results: Recruitment and data collection are currently ongoing. Preliminary findings suggest that patients are overwhelmed when being informed about stem cell transplantation which limits their ability to recall, comprehend and use the information provided by their clinicians. This can only partially be compensated by current written information material. Detailed results of part I and a prototype of the intervention will be presented at the conference.
Conclusions: Using robust methodology, this project will provide novel strategies for how to improve care for transplant patients and their support persons. The intervention will be easily modifiable to address other information needs, such as those relating to follow-up or end-of-life care. If effective, the intervention will be accessible and integrated into practice functioning. The project findings will make an important contribution to providing high-quality, patient-centred care which improves patient outcomes, ensures efficient and ethical clinical practice and protects the legal rights of patients.

Disclosure: No conflict of interest disclosed.

P682

Development of a screening method for the assessment and improvement of the needs and quality of life of oncological patients in the daily routine

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Introduction: Complex oncological therapies are an enormous challenge for many patients. Therefore, oncology centers start to employ patient-guides who support patients in coordinating the management of the various facets of the oncological therapy as well as the corresponding supportive therapies. However, patient-guides play only a minor role in the follow-up phase. In addition, they are not used to the routine analysis of needs and quality of life (QoL). As part of the implementation process of a QoL-guide in our interdisciplinary oncological day clinic (ICT), we developed a screening method to specifically assess the patient needs in different areas.
Methods: A mixed-methods study was applied, consisting of a systematic literature search, the conduct of two focus groups (one with patients, the other with health care practitioners), the assembling and adapting of various published measures, and the piloting of the questionnaire in the ICT.
Results: The literature review identified numerous QoL and needs questionnaires. However, most questionnaires were developed for the use in clinical trials, and none of the questionnaires was suitable for our purposes. In order to gain a better understanding of the QoL deficits and needs of our patients, a focus group with 13 patients (different tumor types such as breast, brain, colon or haematological) identified 158 needs and the focus group with 16 health care practitioners (physicians, nurses, psycho-oncologist, physiotherapist …) identified a total of 175 needs. Many of the identified needs were overlapping and could be grouped in 14 clusters, such as medical information, psycho-oncology, social-medical aspects, or physical complaints. These clusters were addressed by 25 needs items of the questionnaire, and were supplemented with questions on symptom burden and performance. All questions were adapted from existing questionnaires, and references were adequately made. Currently, the questionnaire is used and validated in clinical routine in our ICT.
Conclusions: Addressing patients` concerns and QoL is increasingly being recognized as an important component of oncological care in the treatment and follow-up phase. The employment of a QoL-guide is a crucial step to implement these principles in clinical routine, and an adequate needs measure is an indispensable tool to provide quality-assured QoL diagnostics and therapy.

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P683

The relevance of cancer related fatigue in neuroendocrine neoplasia patients

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Introduction: Cancer-related fatigue (CrF) is a common accompanying syndrome of a neoplastic disease and can manifest before, during and after therapy. CrF has a debilitating effect on a patient's life situation and well-being by symptoms as sleeplessness, chronic fatigue, severe pain, brain-fog and depression like symptoms. This state can persist for years even after successful treatment of the prior tumor disease. Diagnosis is made by the criteria according to Cella, although this appears not to be adequate in many cases.
Aim: The aim of the survey was to determine how many patients with neuroendocrine neoplasia (NEN) suffer from CrF, what impact on quality of life and different aspects of everyday life. A further goal was to determine whether there are any clinical factors related to the occurrence of CrF like grading or choice of therapeutics, and whether there are any helpful supporting strategies.
Methods: The national German support Group "Netzwerk NeT e.V." in cooperation with the Charité conducted the first survey regarding fatigue in NEN patients. The survey was mainly conducted online entirely anonymous through a link ("Survey Monkey") and in part through a printed version sent by post (and resent anonymously).
Results: Between 6/2017 and 9/2017 the survey was started online 686 times and was finished in 69 % (470) of the cases. 51 printed versions returned by post. After evaluation of completeness and plausibility 487 questionnaires were included into further analysis.
Nearly 60 % of the participants reported to experience fatigue right now or have been affected by it in the past. 203 (41 %) fulfilled the diagnosis criteria postulated by Cella; 77 (38 %) of them are not receiving any cancer related therapy now.
There were no differences between G1/G2 and G3 grade in current fatigue severity. Further there was a strong negative correlation between quality of life (including working ability) and experienced fatigue. 41 (14 %) also met the canadian criteria for chronic fatigue syndrome. The full statistical analysis will be presented on the meeting.
Conclusions: We could show that fatigue is a common and severe accompanying symptom in NEN patients with detrimental effects on quality of life and working ability. The symptom variety indicates that CrF is a heterogeneous illness and patients need to get adjusted to their energy level, and need multimodal, personalised therapy.

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P684

Increasing use and acceptance of Rituximab biosimilars in a network of office based oncologic practices in Germany

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Introduction: Rituximab was the first monoclonal antibody to be approved for therapeutic use and became an integral part of the current treatment of NHL and CLL. In 2017 the first rituximab biosimilars were approved by EMA based on broad comparability exercises with the reference product. However, while there are clinical studies with rituximab biosimilars in FL there is no data yet for the extrapolated indications. We aimed to display current real world data of rituximab containing therapy regimens including biosimilars.
Methods: Data were collected using Oncotrace software in office-based oncologic practices in Germany. Statistical analyses were done with SPSS by Onkotrakt AG. In total, 61 physicians across 19 centers recorded data for 1432 patients between July 2017 and December 2018.
Results: In the analyzed group are 808 (56.4%) male and 624 (43.6%) female patients, mostly elderly with 58.2% between 60 and 80 years. 1028 patients were diagnosed with NHL and 404 with CLL. Among patients with NHL there were 279 (19.5%) FL, 193 (13.5%) DLBCL and 556 (25.5%) other lymphomas included. In total, 30 distinct rituximab-containing protocols were reported (12 protocols used other CD20 antibodies). Overall 1188 rituximab-containing protocols were recorded, 427 (35.9%) used MabThera® (21 (4.9%) s.c.), 575 (48.4%) used biosimilar rituximab (334 Rixathon® and 241 other rituximab biosimilars), and 221 (18.6%) did

not specify rituximab brand name. Biosimilar rituximab was used in all indications and in 52.6% of the cases in extrapolated indications (58.8% DLBCL, 46.1% CLL). Within the observation period, the proportion of biosimilar rituximab prescriptions increased from 12.3% (July 2017) to 76.7% (December 2018).
Conclusions: Here, we describe the use of rituximab biosimilars and changes in prescription patterns for the treatment of NHL and CLL. The strength of this investigation is that, in a relatively short timeframe, we have collected real-world data depicting treatment protocols. We have found increasing usage of biosimilar rituximab among patients with NHL and CLL. Our results suggest increasing acceptance of biosimilars, even in extrapolated indications. To date, data regarding effectiveness and safety have not been captured by the database but this could be an interesting future investigation.

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Andra Kuske: Employment or Leadership Position: Ist Angestellte der Hexal AG

P685

Longitudinal evaluation of palliative care needs in patients with metastatic lung cancer by oncology nurse navigators

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Introduction: Oncological guidelines recommend the early integration of palliative care for patients with metastatic lung cancer. For needs assessment and quality management screening tools like the IPOS questionnaire (Integrated Palliative care Outcome Scale) have been validated. Apart from physical symptoms, the IPOS measures patients' psychosocial issues like mood, concerns, family anxieties etc. Using not only closed but also open-ended questions, the IPOS gives patients the possibility to state their main problems besides preformed answer options. Usually, the assessment is performed by a palliative care team. At our institution, we introduced the IPOS as part of a new oncology nurse navigation program for patients with metastatic lung cancer.
Methods: 153 patients with metastatic lung cancer were assessed using the IPOS. Monthly follow-up sessions also provided longitudinal information. Following a quantitative approach, we formed IPOS subscales for patients' physical and emotional status. Descriptive analysis on subscale and on item level were performed both for cross-sectional and longitudinal data. Furthermore means comparisons of specific patients' characteristics were computed. Finally open-ended questions were analysed and classified into different groups of symptoms.
Results: In general, patients' physical symptoms are on an average low level and decreasing over time. Those patients who died during the period of observation show a significant higher level of physical symptoms. In contrast, emotional burden is on average reported on a medium level and constant over time. In the means comparison, especially women and patients closer to death show a significant higher mean value of emotional strain. When mentioned in open-ended questions, main emotional concerns evolve around topics of therapeutic success, disease progression and general fears about the future.
Conclusions: The introduction of a palliative care screening tool like the IPOS by oncology nurse navigators is feasible. It provides important information about unmet needs in specific groups of patients and facilitates early integration of palliative care.

Disclosure: No conflict of interest disclosed.

P686

Information and support needs of family caregivers of advanced cancer patients planned to be discharged from hospital - a pilot study

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Introduction: Discharge from hospital often represents a challenge for advanced cancer patients, their family caregivers (FCs) and the multiprofessional care team that aims to provide most helpful support.
Methods: In this pilot study, 22 FCs (52% female, 73% spouses/partners, mean age 59 years) of advanced cancer patients fulfilled the Distress Thermometer (DT), a Scale measuring home-caregiving distress („Häusliche Pflegeskala"; HPS) and a study-specific questionnaire on information and support needs prior to the patient`s discharge from a specialist palliative care ward (T1). Two weeks after discharge, 11 FCs completed a second questionnaire set (T2).
Results: Mean distress was 7.4 (range, 2-10) with significant distress in 90% of FCs (DT≥5) at T1 and similar rates of 7.3 (range, 4-10) with significant distress in 91% at T2. Care-specific burden (HPS) was rated at T1 in mean with 15.6 of 30 (range, 3-30) and decreased to 12.2 at T2 (range, 0-28). Prior to the patient`s discharge (T1), "knowing, which institutions are involved in further care", "knowing that all information are transferred to all further carers", knowing about the patient`s prognosis and further course of disease", "knowing to contact whom in cause of new symptoms", and "knowing who to contact in case of extensive symptoms or emergencies" were the most frequent needs of FCs (all 100%). However, the least frequently met needs were "information about when symptoms have to be expected" (79%), "information about which new symptoms have to be expected" (79%), "nursing training for patient home care" (78%), "information about how to talk with the patient" (78%), and "knowing my responsibility concerning detection and treatment of symptoms" (78%). Retrospectively, preparation prior to admission was insufficient especially for "information about when symptoms have to be expected" (78%), "being prepared for death, dying and bereavement" (70%), "information about which new symptoms have to be expected" (67%), "knowing who to contact in case of extensive symptoms or emergencies" (56%), and knowing the patient´s medication and each indication" (50%).
Conclusions: Discharge planning in advancer cancer patients has to include information about probable course of disease and occurring symptoms, medication, practical trainings, and preparation for death and dying.

Disclosure: No conflict of interest disclosed.

P687

Kinaesthetics - a tool to improve quality of life and patient autonomy in oncological care

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Patients with oncological and chronic diseases often have long therapies behind them that are accompanied by restrictions of their ability to move. They are often confronted with their increasing weakness and the loss of control over their physical activities, which are experienced as a burden, and their living space is often limited to their bed. Their own ability to move and body image therefore get lost. An additional problem is pain during movements.
The central aim within the Kineasthetics programme is the development of health and improvement of the quality of life. Considering different understandings of development of health it is targeted at supporting the affected person in their everyday life and in sequences of movement to encourage the patient's intrinsic activity. A qualitative support by the care-taker is only possible if they are aware of their own movements. Kineasthetics supports the mindfulness about breathing and pain. As part of

a pilot study it was demonstrated that patients had less pain after a major operation if Kinaesthetics movements had been considered. Moreover, the oxygen saturation became significantly higher. With the same principles as mentioned above, oncological patients can be supported to move with less pain. Kineasthetics is a tool to analyze the situation and the sequences of movement of the affected person and make adjustments accordingly. Affected people are enabled to carry out small movements and therefore gain awareness of their remaining abilities and to further develop them. Especially through slow and differentiated exercises of movement strain is reduced. Inner processes are activated as well. The goal is to create the interaction between care-taker and patient in a way that the preservation of intrinsic activity and stimulation of the quality of life are key. Therefore the self-efficacy expectations are supported. The workshop will demonstrate this concept. By self-experience of exercises movements can be analyzed and reflected on in order to find alternative solution paths.

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P688

How perform nurses psychosocial screening with the distress thermometer in cancer patients? An evaluation four years after implementation

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Introduction: Caring for distressed cancer patient is an important issue. Since health professionals can assess moderate and severe distressed patients with an appropriate instrument, we implemented the screening with the distress thermometer (DT) throughout the Comprehensive Cancer Centre Zurich in 2012. Since then, nurses perform the screening of every cancer inpatient at admission.
Methods: We wanted to identify the adherence to our screening protocol with a descriptive retrospective study from 2012 to 2016. We also interviewed nurses and nursing experts of wards with high and low screening rates about their experience of their daily screening practice in three focus group interviews.
Results: 32 % (N= 7034) of 22 112 oncologic cases have been screened at admission. 10% (N=676) of the screenings could not be performed because patient did not want to fill in or were not able because of cognitive problems, fatigue or foreign language. Screeningrate increased over the years from 26 % to 33,4%. Wards with oncologic patients mainly had a significant higher screening rate than others.
47 % (N=2984) of the screened cases were assessed as severe or moderate distressed and of them 24,8% (N=739) wished a referral to psychooncological service, 20,7 % (N=618) to social service and 11,1% (N=331) to spiritual care. Yet, 10,2% (N= 304) had an appointment with a psychooncologist and 42,6% (N=1272) to the social service during their stay. However, over the years psychosocial referrals increased from 8,3% (N=43) to 17,5% (N=142). 44 % of the distressed patient were screened a second time during their stay.
In the focus groups interviews, we showed nurses these results and asked for their interpretation. They experienced screening as helpful if they could use it in a situation-specific way. However, they experienced problems with the given screening time point at admission, as well as the rejection of the screening through patients and the psycho-oncological referral. Preliminary data of the focus groups interviews will be presented.
Conclusions: Screening is useful in recognizing distress among patients, but screening practice and our screening protocol needs to be reconsidered. Nurses and even patients seem to have some problems about timing and usage.

Disclosure: No conflict of interest disclosed.

P689

APACHE II is superior for prediction of ICU survival after allogeneic HSCT

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Introduction: Patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT) have a high morbidity and mortality, especially if treatment in an intensive care unit (ICU) is required. The primary objective of the current study was to identify new clinical and biological predictors and validate new and established prognostic factors associated with ICU, hundred day and 1-year mortality for allogeneic HSCT patients admitted to ICU during peri-transplant period.
Methods: We performed a retrospective single-center study analyzing clinical and laboratory parameters as well as prognostic scores measured during first 24h after ICU admission. Of 544 adult patients who underwent allogeneic HSCT between 2010 and 2017, 78 (14.3%) were admitted to ICU during peri-transplant period (d-7 to d+30).
Results: The ICU, 100d and 365d survival rates were 56.4 %, 42.3% and 23.1%, respectively. Cox regression analysis demonstrated significant differences in ICU survivors vs non-survivors for the clinical parameters invasive mechanical ventilation (p=0.010), renal replacement therapy (p=0.013), urine output (p=0.006), mean arterial pressure (p=0.001) and amount of norepinephrine (p=0.007). Additionally, the following prognostic scores SOFA (p=0.017), APACHE II (p< 0.001), APACHE IV (p=0.002) and SAPS II (p=0.025) also showed to be useful in prediction of ICU survival. In contrast, PICAT score was not significantly changed (p=0.113). An elevated level of Lactate was associated with poor survival on ICU (p< 0.001). Procalcitonin (PCT) level at admission was not significantly changed between ICU survivors and non- survivors, but patients admitted to ICU before and close around the transplantation date had higher PCT levels than in later course of transplantation (r^2= 0.253). Urine output in 24 hours after admission to ICU of 365d survivors was 4055ml (IQR 2048-5015) and of 365d non-survivors 1290ml (IQR 588-2350). The urine output was the most significant clinical and laboratory parameter (p< 0.001) in 365d mortality analysis with an AUC of 0.79 (0.66-0.92, 95% CI).
Conclusions: In our cohort the APACHE II score showed best discriminative power predicting ICU mortality. The newly developed PICAT score was not valuable predicting mortality on ICU as well as short-and long-term survival. For the development of a prognostic score for critically ill allo-HSCT patients, the inclusion of urine output and lactate should be highly considered.

Disclosure: No conflict of interest disclosed.

P690

Dysregulation of Interleukin-6 in critically-ill neutropenic cancer patients

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Introduction: Interleukin-6 (IL-6) is pleitropic cytokine which plays an important role in inflammatory processes. It is involved in many conditions that are accompanied by an inflammatory reaction. e.g. rheumatoid arthritis, cancer, sepsis, and cytokine release syndrome. The aim of this study was to gain insight into the regulation of IL-6 in critically-ill patients with a particular focus on patients with a malignant disease. We chose to study critically-ill patients because this patients population has a high prevalence of inflammation.
Methods: In this retrospective observational study we investigated the association of blood IL-6 levels with clinical parameters and outcome in 148 consecutive patients admitted to a medical ICU of the University Hospital of Cologne. The data were collected by reviewing the medical records of the patients.

Results: In the univariate analysis there was a positive association between the type of underlying disease, the presence of fever on the day of ICU admission, a clinical diagnosis of sepsis, neutropenia, TISS, SAPS, length of ICU stay and the plasma concentration of IL-6. The ICU mortality was increased in patients with higher IL-6 levels. Among the laboratory values cortisol levels, lactate, CRP and PCT levels were positively correlated with IL-6 levels. Gender, age, leukocyte counts, immunosuppressive medication, and chemotherapy within the last 30 days were not significantly associated with IL-6 levels. In the multivariate analysis only fever, CRP, PCT, and neutropenia were significantly associated with IL-6 serum concentration.
Conclusion: Taken together, our study showed that high IL-6 levels are associated with a worse prognosis. Not surprisingly, we found that fever and increased levels of inflammatory markers were correlated with IL-6 levels. Surprisingly, our analysis revealed that neutropenia is associated with very high levels of IL-6. This finding indicates that neutropenia is accompanied by a dysregulation of IL-6 production. Furthermore, our results suggest that the biology of neutropenic sepsis differs sepsis in non-neutropenic patients. This could have important implications for the managment of neutropenic patients with infections. Therefore further research is needed to better understand why neutropenic patients develop a dysregulation of IL-6 and whether therapeutic targeting of IL-6 in neutropenic patients is of clinical value.

Disclosure: No conflict of interest disclosed.

P691

Sustained complete remission with Ruxolitinib in a patient with refractory hemophagocytic lymphohistiocytosis: a case report

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Background: Hemophagocytic lymphohistiocytosis (HLH) is a rare life-threatening immune-mediated hyperinflammatory disease which can be primary due to an underlying genetic disorder or secondary to infections, malignancies or autoimmune diseases. A regimen incorporating etoposide and dexamethasone (HLH-94 protocol) is the current standard therapy but optimal salvage for refractory cases is unknown. Subsequent allogeneic stem cell transplantation improved outcomes in children with primary HLH. More recently, it has been shown that the JAK1/2 inhibitor ruxolitinib might be a valuable second-line therapy.
Case report: A 31 year old Caucasian patient with fever (starting two weeks prior to admission), ascites, splenomegaly and worsening leukopenia was transferred to our tertiary center for further workup of suspected HLH. His past medical history was unremarkable. His family history was negative for consanguinity or HLH. At admission, the patient presented with spiking fevers (up to 40°C), hypoxemia, tachypnea (30-40 breaths per minute) and tachycardia (120-140 beats per minute). The laboratory workup (WBC 2.89G/L [normal: 4.4-11.3]; AST 954U/L [≤35]; fibrinogen 71mg/dL [210-400]; ferritin 13,730ng/mL [30-150]; sCD25 >20,000pg/mL [458-1997]; triglycerides 654mg/dL [≤150]) was compatible with HLH and bone marrow biopsy showed features consistent with hemophagocytosis. Treatment according to HLH-94 was commenced. An extensive workup for infections and malignancies failed to find a causal illness. Flow cytometry of cellular expression of perforin, SLAM26 associated protein, XIAP or CD107a showed normal results. A genetic investigation did not reveal any known predisposing germline mutations. Worsening pancytopenia and signs of active HLH led to initiation of salvage therapy with anakinra, corticosteroids and intravenous immunoglobulins. Since the patient again failed to respond, ruxolitinib (5mg BID) was started on day 84 after admission. Initially, spiking fevers persisted but blood counts started to normalize within the first week and ferritin as well as sCD25 levels continuously declined. The patient's condition improved in the second week and ruxolitinib dose was increased stepwise (final dose: 20mg BID). The patient could be discharged in the fifth week. Six months later, the patient still shows no signs of HLH relapse under ruxolitinib maintenance.
Conclusions: Ruxolitinib rapidly induced a sustained complete remission in an adult patient with refractory HLH.

Disclosure: No conflict of interest disclosed.

P692

Competence-based catalogue of learning objectives for professionalism and communication skills training for physicians in care of oncologic patients

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Introduction: Effective communication skills (CS) have been positively attributed to patient satisfaction and clinical outcomes. CS can be improved by communication skills training (CST). Throughout Germany, CST has been implemented in medical school curricula and actor-based training is widely used. CST is mandatory for board certification of oncologists in some countries e.g. Switzerland. However, few oncologic training sites in Germany offer obligatory and structural CST for medical personnel (physicians in training, board certified physicians, or other health care staff). The federal ministry of health demands within the national cancer act (Nationaler Krebsplan) to implement mandatory CST for health care workers caring for oncologic patients. As physicians do not only act as medical experts and communicators but also fill the roles of being collaborators, leaders, health advocates, scholars, and professionals, known as CanMEDS roles, we propose that professionalism skills should be added to classical CST.
The aim of this project was to compile a competence-based catalogue of learning objectives for professionalism and communicative skills (PCS), to set up a blueprint for PCS training (PCST) and to identify the interfaces between undergraduate and postgraduate education.
Methods: A literature and internet research was performed to identify communicative learning objectives for PCS in oncology and to collect information on PCST in under- and postgraduate education. Interviews (focus groups and single) were conducted with physicians (training or trained in urology and hematology/ oncology), nurses, oncology nurses and welfare workers to identify areas of need regarding PCS. We then defined the level of expected competence for each learning objective.
Results: We identified learning objectives that could be assigned to 4 areas of professionalism and communication (general and specific communication skills in oncology, organization development and risk management, interprofessional collaboration and ethical leadership). A curriculum encompassing 80 teaching units was compiled as blueprint and is currently piloted in the Dept. of Urology at the University Hospital Düsseldorf (KomMent).
Conclusions: We propose a curriculum blueprint for PCST for physicians in care of oncologic patients that meets the requirements of the national cancer act and that could be transferred to other training sites throughout Germany.

Disclosure: No conflict of interest disclosed.

P693

A digital microscopy teaching module for myelodysplastic syndromes - a pilot project for a high quality, innovative and interactive tool for training hematologists

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Introduction: Hematology trainees are required to be competent in the evaluation of blood and bone marrow smears. Laboratory centralization and reduced capacity of continuing education lead to decreased access of training. There is an urgent need for teaching capacity and qualified education for unskilled and advanced trainees in bone marrow morphology. Digital microscopy (DM) allows a whole slide once scanned, to be visualized, navigated and annotated at different magnifications on a digital viewing platform and therefore offers the opportunity to overcome the limitations by realizing new modes of training. As a proof of concept we established a digital course on myelodysplastic syndromes (MDS).
Methods: Blood and bone marrow smears of several MDS-subtypes were scanned using a high resolution high speed camera and were hosted on a central server. 8 patient cases were created. Each case is presented with a condensed description of medical history, clinical findings and lab results. The respective DM-slide is integrated in the presentation including a detailed report of the diagnostic findings. Terms and definitions of the report are linked to single pathological cells in the smear and vice versa with annotation of single cells or defined areas in the DM-slide linked to the appropriate term in the report. Further explanations and comments were added including diagnostic, therapeutic and prognostic information.
Results: The DM-MDS course is offered to post-graduate hematologists. Accessibility to the course and the digital image bank is possible for all digital communication devices (smartphone, tablet, PC/Mac etc.). The image quality of blood and bone marrow smears was equivalent to light microscopy. Navigation on the complete digital slides is easily possible with no relevant time delay even in high power fields.
Conclusions: This proof-of-principle DM-MDS course demonstrates that incorporation of DM for post-graduate education of hematologist is feasible and offers an innovative technical and didactic platform for contemporary training. Feedback data of users about the DM-MDS course will be obtained to evaluate benefits and further needs of the training platform. The high image quality, easy accessibility and versatility of the DM platform facilitates its implementation into a wide range of e-learning settings including teaching different occupational groups, self-assessments and exams.

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Posterdiskussion

B-Zell-Lymphome

P694

BRAF inhibitor treatment in hairy cell leukemia: a long-term follow up study

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Introduction: BRAF inhibitor (BRAFi) treatment is an effective treatment approach in refractory/relapsed hairy cell leukemia (HCL). However, relapses after BRAFi treatment occur frequently and knowledge about retreatment is scarce. In this case series, we report our real-world experience on the long-term outcome of 27 HCL patients with BRAFi treatment.
Methods: Patients were treated in seven different European centers (Heidelberg, n=10; Caen, n=9; Munich, n=3; Innsbruck, n=2; London, n=1; Basel n=1; Erlangen, n=1) from 2011 to 2018. Clinical baseline and follow-up data were collected by chart review.
Results: The majority of patients were heavily pretreated before the first course of BRAFi (median of 3 prior treatment lines; range, 0-12 lines). BRAFi treatment induced a complete hematologic remission (CHR) in all patients. In accordance with previous studies, the remission was not durable after cessation of BRAFi with a median time to retreatment of 12.1 months (95% CI, 9.4-15.6 months). In total, 23 patients needed retreatment during the observation period. 17 patients were retreated with at least one further course of BRAFi. A rapid recovery of blood counts was observed during all 33 BRAFi retreatment courses. Five patients received more than three BRAFi courses (range, 4-6). The median duration of all completed BRAFi courses was 3.8 months (range, 1.7 - 20.2 months). Median response duration after the second course of BRAFi was 10.9 months and was comparable with the response duration after the first BRAFi course (median, 10.9 versus 12.1 months; HR, 1.35; p=0.5, Fig.1). Although we observed that all courses of BRAFi retreatment resulted in a blood count recovery, response duration was significantly shorter after more than two retreatments (HR, 5.27; 95% CI, 2.43-11.4; p< 0.0001). We did not observe BRAFi refractory disease courses as reported in HCL patients with PI3K or KRAS mutations.
Conclusions: BRAFi retreatment is a valuable therapeutic option in r/r HCL patients, but response duration shortens after multiple rounds of BRAFi retreatment. Further studies are necessary to explore if response duration could be improved by BRAFi combination therapies.

Disclosure: No conflict of interest disclosed.

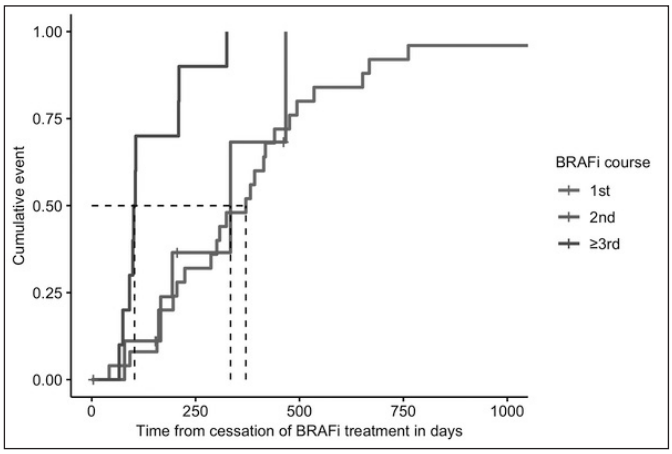

Fig. 1. Kaplan-Meier cumulative event rates of patients after one, two and three or more BRAFi courses

P695

Patients with marginal zone lymphoma: characteristics, treatment reality and outcome data from the German prospective TLN Registry

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Introduction: Marginal zone lymphoma (MZL), a low-grade lymphoma, accounts for 8-12% of all lymphomas, with extranodal MZL of mucosa-associated lymphoid tissue (MALT) being the most common subtype. Prospective evaluations of treatments (thx) and outcome are rare, and MZL-specific thx recommendations are missing. According to SEER, 5-year (yrs) overall survival (OS) is 72% for all MZL in the US, while no data have been published so far for patients (pts) in Germany. Here, we present data of 175 MZL pts treated in German routine care.
Methods: The open, prospective, clinical registry on lymphoid neoplasms (TLN Registry, ClinicalTrial.gov NCT00889798) documented thx of pts with lymphoid B-cell neoplasms by German office-based haematologists. Pts were followed for 5 yrs. Data regarding pts and tumour characteristics, comorbidities, systemic thx and response rates, date(s) of progression(s) and death were recorded. Between 2009 and 2014, a total of 3,795 pts were recruited by 122 study sites. Database cut for the present analyses was August 2018, 31th.
Results: Of 1,049 pts with low-grade NHL recruited at the start of 1-line therapy, 175 were diagnosed with MZL, of whom 58 (33%) were categorized as MALT-lymphoma
Pts were median 69yrs old (range 25-89yrs, 61% ≥65yrs), 51% male, 41%/6% with ECOG1/≥2 and 67% with any comorbidities (e.g. 38% hypertension, 11% diabetes, 4% moderate/severe renal disease, 7% heart failure, 5% myocardial infarction). 24% of pts had B-symptoms, 29% elevated LDH at start of 1st-line.
Overall, between 2009-2014 Bendamustine+rituximab (BR) was the most commonly applied thx (75%), cyclophosphamide+doxorubicin+vincristine+prednisone+rituximab (R-CHOP) was used in 8% and other regimens in individual cases only (each ≤4%).
Objective response rate as assessed by the local physicians was 81%, with documented clinical (unconfirmed) complete remission rate of 33%.
With median follow-up of 60 months, median progression-free (PFS) and OS were not reached. 4yrs PFS rate was 72% (95%-CI 64-78%) and 4yrs OS rate was 80% (95%-CI 73-86%). 17% of pts had so far started a 2-line thx, of whom 30% received a re-treatment with BR. 18% of pts had been lost to follow-up.
Conclusions: In German routine practice, the BR-combination was the most commonly applied 1-line regimen for patients with MZL; furthermore, a re-treatment with BR was also the most frequently used choice in 2-line. Outcome data in Germany compare well with published real-world data in the US.

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Norbert Marschner: Employment or Leadership Position: iOMEDICO; Advisory Role: Roche, Mundipharma, AMGEN; Stock Ownership: iOMEDICO; Financing of Scientific Research: Roche, Mundipharma, AMGEN; Expert Testimony: iOMEDICO

P696

Antiphospholipide syndrome in frequently association with splenic marginal zone lymphoma

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Introduction: Splenic marginal zone lymphoma (SMZL) is a rare, indolent B-cell lymphoma, accounting for < 2% of lymphoid neoplasms. Patients typically present with splenomegaly, whereas peripheral lymphadenopathy is quite uncommon. Bone marrow (BM) is regularly involved. When present in peripheral blood (PB), the lymphoma cells are typically small and reveal short, fine cytoplasmic projections. Approximately 20% of patients show an autoimmune manifestation, including cytopenias, cold agglutinin disease, acquired von Willebrand disease, or angioedema. As shown here, an antiphospholipide syndrome (APS), another autoimmune antibody-mediated condition characterized by thrombotic events, is also not uncommon in SMZL. In this series of cases with SMZL, we demonstrate that splenectomy is a very effective treatment for SMZL and its associated complications.
Methods: We retrospectively analyzed the clinical course of SMZL patients, diagnosed between 2011 and 2018 in our institution. Diagnosis of SMZL based primarily on examination of PB and BM (cytology, histology, immunotyping) and was finally confirmed in all patients by histology of the splenectomy specimens.
Results: 7 patients (male, n=1; female, n=6), aged 50-64 years, were diagnosed with SMZL. All patients had splenomegaly (median 17.5 cm; range, 14-30 cm). Percentage of BM infiltration at diagnosis ranged between 1-50%, PB was always involved. The median white blood cell count was 11,260/µL (range 2,450-75,000/µL), containing 14-90% lymphoma cells. All but one patient were anemic (median hemoglobin 9.5 g/dL). Five patients revealed APS (cardiolipin antibodies and/or lupus antikoagulant), three of them had falsely prolonged prothrombin time (INR 4.8, 2.4 and 2.3, respectively) and presented initially with a thrombotic event (mesenterial vein thrombosis, n=1; deep femoral vein thrombosis, n=2). Four patients had to be treated immediately, 3 patients after a watch & wait period of 1-3 years. All patients were treated by splenectomy, which stabilized the clinical situation in all cases. PB count completely normalized and APS disappeared within 3-15 months (median 10 months). One patient relapsed 3 years after splenectomy and died on bleeding complications due to recurrent APS.
Conclusions: APS should be excluded in all SMZL, especially in cases with history of thrombotic events. Splenectomy is an effective first-line treatment in SMZL, even for patients with a considerable involvement of BM and/or PB or APS.

Disclosure: No conflict of interest disclosed.

P697

Autologous stem cell transplantation in first remission significantly prolongs progression-free and overall survival in mantle-cell lymphoma (MCL)

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Introduction: Mantle cell lymphoma is an aggressive lymphoma with a short remission duration after standard therapies. We report here the long term efficacy results of the only randomized trial comparing consolidation with myeloablative radiochemotherapy and autologous stem cell transplantation (ASCT) to α-interferon maintenance (IFN).
Methods: Between September 1996 and March 2004, 269 patients up to 65 years of age from 129 institutions were randomized to either ASCT or IFN after induction with CHOP without or with rituximab (R), or mitoxantrone-chlorambucil-prednisone. R-CHOP was used in 31% of 232 patients.
Results: After a median follow-up of 14 years, 93 patients in the ASCT arm and 81 patients in the IFN arm, respectively, were evaluable for the intention to treat analysis of progression-free survival (PFS) and overall survival (OS) after response to induction treatment. Clinical characteristics were comparable in both treatment groups with a median age of 55 years (34-65), 82% stage IV and 73% low, 20% intermediate, and 7% high risk according to MIPI. In patients receiving ASCT, the median PFS was 3.3 years compared to 1.5 years in the IFN arm ($p < 0.0001$). In addition, median OS was significantly prolonged in patients receiving ASCT (7.5 years compared to 4.8 years; $p = 0.019$). Adjusting for MIPI score and addition of rituximab, the hazard ratios for ASCT vs. IFN were 0.50 (95% CI, 0.36-69) for PFS and 0.66 (0.46-0.95) for OS.
Cox regression analyses were performed to evaluate the differential effects of ASCT versus (vs.) IFN on PFS and OS according to induction treatment with Rituximab, adjusting for MIPI score. For patients treated without Rituximab the PFS hazard ratio for ASCT (n = 52) vs. IFN (n = 54) was 0.40 (0.26-0.61), in comparison to 0.72 (0.42-1.24) for patients treated with Rituximab (ASCT n = 41, IFN n = 27). A similar observation was made in the OS analysis (without Rituximab: HR ASCT vs. IFN was 0.52 (0.33-0.82), with Rituximab: HR 1.05 (0.55-1.99)).
Conclusion: After a prolonged median follow up of 14 years the mature results of our trial confirm a significantly prolonged PFS and OS after ASCT in first remission. However, in the subset of patients treated with rituximab there was only a non-significant trend for PFS and no difference in OS, potentially due to the reduced statistical power of this subgroup analysis. In the current study generation, the substitution of ASCT by the BTK inhibitor Ibrutinib is evaluated.

Disclosure: No conflict of interest disclosed.

P698

Transformation of follicular lymphoma to precursor B-cell lymphoblastic lymphoma in a 72-year old woman - a case report

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Introduction: Histological transformation of follicular B cell lymphoma to high-grade aggressive non-Hodgkin lymphoma, mainly diffuse large cell lymphoma, is reported in around 10-20% of patients at 5 years and associated with a poor prognosis. We present the rare case of a 72-year old women with transformation of follicular lymphoma to B-cell lymphoblastic lymphoma (B-LBL).
Case report: Initial diagnosis of follicular lymphoma grade IIIa was made in 05/2014 when our patient presented with lymph node swelling on both sides of the diaphragm and bone marrow infiltration (Ann Arbor stage IVa, FLIPI: high risk). She received six cycles of immunochemotherapy (R-CHOP), followed by two years of maintenance with rituximab. Treatment resulted in a complete response. A small swelling on the forearm was identified 9 months after discontinuation of rituximab maintenance. Histopathology revealed a precursor B-LBL, CT scan did not show further enlarged lymph nodes. The solitary lesion was completely resected and involved field radiotherapy initiated. Unfortunately, our patient relapsed nine month after radiotherapy with extended disease and poor response to salvage therapy with R-GDP. FISH Analysis revealed bcl-2 and Myc aberration (Double Hit) in both follicular lymphoma and LBL. Molecular studies of IgH-Gene-Products showed genetical relation, indicating an uncommon evolution of follicular lymphoma.
Conclusion: The presented patient shows that transformation of follicular lymphoma to B-LBL may rarely occur. The molecular mechanisms involved in this atypical evolution pathway remain to be elucidated.

Disclosure: No conflict of interest disclosed.

P699

Successful treatment with PD-1 checkpoint blocker Nivolumab in a patient with relapsed cerebral PTLD after liver transplantation - a case report

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Introduction: Post-transplant lymphoproliferative disorders (PTLD) occur with an incidence of 1-2% after liver transplantation. PTLD is associated with high mortality: overall survival ranges between 25-35%, and is further reduced for patients presenting with recurrent cerebral PTLD. Due to paucity of data there is no standard treatment algorithm for patients with relapsed cerebral PTLD. New treatment options are urgently needed for those patients.
Case presentation: We present a 71-year-old patient who underwent liver transplantation in 2006 because of alcohol-induced liver cirrhosis. In 2016 he was diagnosed with an EBV-positive PTLD with manifestations in the lung, bone marrow and brain. In addition to reduction of immunosuppression, 8 cycles of rituximab were administered, which resulted in a partial response in the lung but in new cerebral manifestations. The patient received 2 cycles of high-dose methotrexate leading to a complete remission in the lung but only a partial response in the brain. In February 2017, after 2 cycles of intrathecal rituximab, cytarabine and dexamethasone the patient achieved a complete remission. 7 months later new cerebral manifestations became detectable. Almost all neoplastic cells expressed PD-L1. Due to limited alternatives we started treatment with the anti-PD-1 antibody Nivolumab (3 mg/kg, repeated only every 3-5 weeks) and rituximab. The patient responded with an improvement of his neurological symptoms. In February 2018, there was the only episode of acute liver transplant rejection quickly manageable by an increase of his immunosuppression, whereas Nivolumab was not paused. At the beginning of this year, still formally on Nivolumab treatment, the patient died after a new relapse of his PTLD.
Conclusions: The most feared complication of immune checkpoint inhibitors (CPIs) in solid-organ transplant recipients is a fatal allograft rejection. On the other hand, CPIs have revolutionized the treatment of many cancer entities. There is a limited number of cases of liver transplant recipients published. Although fatal organ rejection is not to be underestimated and no robust biomarkers predicting organ failure have been identified so far, there are still cases of good allograft tolerability despite significant anticancer efficacy. To our knowledge, we report here the first case of a

patient with recurrent cerebral PTLD after liver transplantation who was successfully treated with Nivolumab without severe allograft rejection.

Disclosure: No conflict of interest disclosed.

P700

An uncommon presentation of sporadic Burkitt lymphoma as an acute pancreatitis in an adult: a case report

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Introduction: Burkitt lymphoma (BL) is a highly aggressive B cell non-Hodgkin lymphoma (NHL). It comprises 30 % of pediatric lymphomas and < 1 % of adult NHL in western countries. Three clinical variants namely endemic, sporadic, and immunodeficiency-associated are recognised. Although they are histologically identical, there are differences in epidemiology, clinical presentation, and genetic features between them. Bone marrow and CNS involvement occurs in approximately 30 and 15 % of cases, respectively.
Case presentation: This presentation reports a rare case of sporadic form of Burkitt leukemia clinically manifesting as a pancreatitis in an immunocompetent adult male, which demonstrated an aggressive behavior and diffuse extranodal involvement. A 24-year-old male presented with abdominal pain and diarrhea for several weeks. Shortly after, the patient was hemodynamically unstable and transferred to the ICU. Initial computed tomography findings and laboratory results suggested a necrotizing pancreatitis (Lipase 1833 U/l, LDH 1455 U/l). Because of the complicated course, it was decided to undertake an endoscopic ultrasound-guided fine-needle aspiration biopsy from the stomach. Initial histopathological examination of the lesion suggested a DLBCL. Pt. was allocated to R-CHOP regimen and received one cycle resulting in a short improvement of symptoms. Within a few days the proliferation parameters increased again (Lipase 5032 U/l, LDH 25346 U/l). Further immunhistochemical and molecular cytogenetic diagnostics confirmed a BL. A bone marrow biopsy showed 92% of lymphoblastic infiltration. This was possible only after consulting 3 departments of pathology and 2 departments of human genetics simultaneously. Immediate treatment according to GMALL-B-ALL/NHL protocol for BL was started. The patient is currently in block B2 and has a complete clinical, cytologic as well as molecular genetic remission.
Conclusions: Since a wide array of causes can be attributed to pancreatitis, it is necessary to consider malignancies as one of the important differential diagnosis, so as to facilitate the need for appropriate and prompt diagnosis and treatment. While delay in diagnosing BL may allow to hinder successful therapeutic outcomes, early diagnosis of the disease plus appropriate therapy can ensure significant cure rates.

Disclosure: No conflict of interest disclosed.

P701

A case report about atypical symptoms of a 57yrs old patient - intravascular high malignant B cell lymphoma - a rare disease with variable symptoms and poor prognosis

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We report about a 57yrs old obese male patient which showed major B-symptoms in October 2017. He suffered from fever, night sweats and a weight loss about 20 kg. Already known diagnoses were obesity, hypertension, diabetes and hyperuricemia. Different diagnostic step did not lead to a successful diagnosis. The LDH was highly elevated and the patient showed a skin eczema at the lower abdomen. A biopsy was taken from the eczema and the histopathological analysis revealed an eczematous chronic dermatitis and atypical intravascular proliferation of blastoid B cells. This proliferation was consistent with an intravascular large B cell lymphoma. Due to a pronounced hepatomegaly a further biopsy was taken from the liver which confirmed the intravascular infiltration of the B cell lymphoma. The additional staging with FDG-PET-CT showed positive signals at the skin lesion and hepatic lymph nodes. The bone marrow was not infiltrated. Therefore, we diagnosed an Ann Arbor stadium IV with IPI: 3. Due to the known high rate of relapses and the risk of involvement of the CNS a prophase with vincristine, prednisone was started as initial treatment. This followed a systemic prophylaxis with MTX (1500 mg/ qm.Subsequently, the patient was treated with 8 cycles of R-CHOEP, which was well tolerated. At the end we applied again a prophylactic treatment with MTX. The initial staging after treatment and the further controls with FDG-PET-CT showed no indication of the relapse.The intravascular high malignant B cell lymphoma is a rare disease which is probably often not diagnosed. Therefore, precise diagnostic and intense therapy are necessary to treat the disease. Due to the rareness of this disease a register for such patients were desirable.

Disclosure: No conflict of interest disclosed.

P702

High-dose chemotherapy followed by autologous stem-cell transplantation in patients with secondary CNS lymphoma: data from the prospective multicenter registry for secondary CNS involvement in malignant lymphoma

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Introduction: Secondary central nervous system involvement of lymphoma (SCNSL) is a rare (< 5%) complication of systemic disease. The prognosis of SCNSL is considered to be poor with median overall survival (OS) of less than 6 months. The optimal management for SCNSL is yet to be defined.
Methods: Since 2011, a prospective multicenter international registry for SCNSL is being conducted. Patients with secondary CNS involvement of indolent or aggressive Non-Hodgkin lymphoma (confirmed histologically or cytologically) with or without systemic involvement at the time point of CNS involvement are eligible. Since July 2011, 235 patients were included. Here, we present data of the first 181 patients with April 2018 as data cutoff.
Results: Median age was 63 years (range 23-86 years). 31 patients (17%) had CNS involvement at initial diagnosis and 150 (83%) at relapse. In 180 patients with available data, first-line therapy (defined as therapy at diagnosis at CNS involvement) was given to 177. 83 patients (46%) received a combined systemic and intrathecal chemotherapy, 72 (40%) systemic

therapy alone, 3 (2%) radiotherapy (RT) alone, 14 (8%) a combination of RT and systemic and/or intrathecal therapy, 2 (1%) intrathecal therapy alone and 3 patients (2%) best supportive care only. Systemic chemotherapy was high-dose methotrexate-based in 139 patients (79%) and high-dose cytarabin-based in 100 (56%). Systemic rituximab was given to 111 patients (63%). Regarding all 181 patients, median progression-free survival (PFS) was 7.9 months (95% CI 6.1-9.7), and median OS 14.5 months (95% CI 8.1-21.0). As consolidation therapy within the first-line regimen, 56 patients (32%) received high-dose chemotherapy followed by autologous stem-cell transplantation (HD-ASCT). Therapy regimens were mainly (77%) carmustine- and thiotepa-based with or without etoposide and/or rituximab. 12 patients (7%) received HD-ASCT as part of further relapse therapy. In the first-line HD-ASCT group, median PFS was 13.2 months (95% CI 1.4-25) and median OS was 30 months. One-year OS in the first-line HD-ASCT group was 66% compared to 43% in patients without first-line HD-ASCT (HR 0.54, p < .05).
Conclusions: We here report a large series of patients prospectively registered to analyse therapeutic approaches for SCNSL. The data suggest that intensive systemic (immune-) chemotherapy may improve the outcome of SCNSL patients as compared to historical controls, particularly if HD-ASCT can be applied.

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P703

The distinct spectrum of lymphomas in patients diagnosed with common variable immunodeficiency (CVID) is preceded by autoimmunity and lymphoid hyperplasia

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Introduction: Patients with common variable immunodeficiency (CVID) have a 7-8x increased risk of developing a lymphoid neoplasm. Little is known about the frequencies of distinct lymphoma subtypes in CVID and the complex biologic factors involved in their development.
Methods: We retrospectively reviewed 21 lymphoid neoplasms occurring in the context of CVID and CVID-like disorders. We correlated clinical, both germline and somatic genetic as well as histopathological findings.
Results: Median age at diagnosis of lymphoma was significantly younger in CVID patients (median 38 years) compared to the general population (median 67 years, Smith et al. 2015). The most prevalent B-cell lymphoma subtypes were marginal zone lymphoma (MZL), diffuse-large B-cell lymphoma (DLBCL) and Hodgkin lymphoma. DLBCLs were EBV associated in 3/7 cases while EBV-association of DLBCL is < 4% in the general population. EBV+ DLBCL showed expression of PDL1 and PD1 suggesting a tolerogenic tumor environment. Among the Hodgkin lymphomas all were EBV+ mixed cellularity classical subtype. Germline CTLA4 mutation were present in 3/4 patients with Hodgkin lymphoma. T-cell lymphomas were less frequent and mostly T-cell large granular lymphocytic leukemia (T-LGLL). The prognosis of the CVID patients was predominantly determined by the underlying lymphoid neoplasm while toxicity of treatment had a minor impact. Median time between onset of first symptoms attributed to CVID and lymphoma was 14 years. Non-infectious inflammatory, autoimmune manifestations and lymphoid hyperplasia (splenomegaly, non-malignant lymphadenopathy) preceded the lymphoma in the majority of patients.
Conclusions: This study summarizes the largest detailed analysis of lymphomas in patients with CVID. Our data illustrate that an inflammatory environment facilitates the development of a distinct spectrum of lymphoid neoplasms in CVID. The spectrum of lymphomas differs in several aspects from the general population and most likely reflects pathogenetically relevant factors due to the underlying immunodeficiency.

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Posterdiskussion

Multiples Myelom II

P704

A retrospective, single centre analysis of overall-survival and progression-free survival in 644 patients with multiple myeloma treated with high-dose chemotherapy with autologous stem cell transplantation

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Introduction: The standard 1st line therapy for patients with Multiple Myeloma (MM) at an age of less than 65 years is melphalan-based high-dose chemotherapy with autologous stem cell transplantation (ASCT). Still, this treatment modality is also used in patients of older age, particularly for those without relevant comorbidities. In the light of lacking guidelines, we were interested in the impact of ASCT on outcome of those elderly patients.
Methods: In our retrospective single centre study, we included 644 patients (38% females) with MM who received ASCT between December 1994 and October 2017. In particular, we assessed the influence of age, type of induction and maintenance therapy on overall survival (OS) and progression-free survival (PFS).
Results: At the time of ASCT, the median age of our patients was 57 years (27-75 years) with a proportion of 19% (125 patients) of greater than 65 years. After a median follow-up of 55 months (3-309), 269 patients (41%) were still alive, while the median OS was 91 months (81-101). There was no difference in OS between the younger and elderly patients (94 vs 81 months, p=0.212). PFS was also not different between these groups (37 vs 32 months, p=0.395).
Bortezomib-based induction (310 patients, 48%) did not significantly improve OS neither for the younger (115 vs 91 months, p=0.1) nor the elderly patients (86 vs 70 months, p=0.5).
The PFS was significantly longer for the entire group of patients and the younger ones receiving Bortezomib (41 vs 33 months, p=0.004 and 41 vs 34 months, p=0.01 respectively). The difference in PFS in the elderly group was not statistically significant (40 vs 27 months, p=0.1).
Maintenance therapy was administered to 454 patients and significantly improved both OS (88 vs 27 months, p< 0,0001) and PFS (38 vs 25 months, p< 0.0001). With regard to the type of maintenance, Lenalidomide (150 patients, 23%) was superior to all the other modalities (Thalidomide and miscellaneous 271 patients) with an OS of 98 months vs 82 months and PFS of 45 months vs 23 months.
Conclusions: In our retrospective evaluation, we could demonstrate that ASCT is an efficacious and safe treatment in elderly patients. An improvement of PFS and a trend for OS could be shown independent of age since

the use of new treatment modalities with Bortezomib during induction and Lenalidomide as maintenance therapy. Therefore, ASCT should be recommended for elderly patients with MM.

Disclosure: No conflict of interest disclosed.

P705

The revised myeloma comorbidity Index (R-MCI) in comparison with other comorbidity indices (CI) as a new approach for predicting overall survival (OS) and reducing treatment complications in multiple myeloma (MM) patients (pts)

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Introduction: MM affects elderly pts with heterogeneous health status. Although novel treatment options have improved progression-free- (PFS) and OS, elderly pts appear to benefit to lesser extends. To verify therapy endurance, incorporation of comorbidity, at best via easily assessable MM risk score(s), have proven as relevant, rather than via age and physician perceptive alone. We analyzed the accuracy of 5 comorbidity indices (CIs) in predicting OS and PFS for MM pts.
Methods: We performed this prospective study for 347 consecutive pts treated at our center, analyzing the R-MCI, IMWG-, CCI, Mayo- and MRP-scores (Table 1). Based on each CI, pts were divided into 3 risk groups (low-, intermediate-, high-risk), except for the CCI with low- and high-risk group only. OS and PFS were estimated by Kaplan Meier Method and compared via log rank test.
Results: Pt characteristics were typical for tertiary centers with a median age of 65 years (yrs). All 5 CIs could divide pts into risk groups with significantly different OS ($p < 0.05$). For the R-MCI, the difference in 3-yrs-OS for high- and low-risk group was 43%, that for IMWG- and Mayo-scores were 37% and 70%, respectively. With 25% (CCI) and 20% (MPR) differences, both latter scores seemed least accurate for prediction of OS. For the MRP, the 3-yrs-OS rate for high risk (59%) exceeded that of intermediate pts (50%), moreover, this group comprised low numbers (n=8). In analogy Δ 3-yrs-PFS amounted to 48% for the R-MCI vs. 40% and 59% for IMWG and Mayo, respectively. Again the CCI and MPR showed lowest PFS differences (Table 1).
Conclusions: This is the first large prospective comparative analysis of 5 eagerly discussed CIs. According to our analysis, best results for OS and PFS prediction were obtained via R-MCI, IMWG and Mayo-scores. The results of this analysis reinforce the multifunctionality and convenience of using one MM-CI, like the robustly tested and repeatedly validated R-MCI. Further unique features of the R-MCI are the pro- and retrospective applicability in daily clinics, a user-friendly homepage and the future perspective of extended use, e.g. for tailoring therapies, which is currently investigated.

Tab. 1. Prospective comparative results of 5 comorbidity indices, including OS and PFS results

Risk Scores	Revised Myeloma Comorbidity Index (R-MCI)	International Myeloma Working Group (IMWG)-frailty index	Charlson Comorbidity Index (CCI)	Mayo Risk Score	UK Myeloma Research Alliance Risk Profile (MRP)
Risk parameters used within respective score	eGFR Lung function KPS Frailty **Age** +/- Cytogenetics	ADL IADL CCI **Age**	19 categories with differently associated weight	ECOG-PS NT-proBNP **Age**	ECOG-PS ISS CRP **Age**
Reference	Haematologica 2017;102:910-21	Blood 2015;125:2068-74	J Chronic Dis. 1987;40:373-83	Am J Hematol. 2016;91:1129-34	Lancet Haematol.2019; :e154-66
3-yrs-OS **Low-risk** **Intermediate-risk** **High-risk** ***p-value***	 90% 76% 47% *<0.0001*	 95% 81% 58% *<0.0001*	 90% - 65% *<0.0001*	 92% 69% 22% *<0.0001*	 79% 50% 50% *0.0105*
3-yrs-PFS **Low-risk** **Intermediate-risk** **High-risk** ***p-value***	 68% 43% 20% *<0.00001*	 73% 41% 33% *<0.0001*	 58% - 38% *0.0008*	 59% 37% - *<0.0001*	 51% - 24% *0.0115*
Retrospective **Prospective** **External validation**	+ + +	+ in Engelhardt 2016*	+ - -	+ - -	+ - -
Advantages	- Time-effective - Pro-& retrospectively assessable	- Well published + internationally tested	- Long known and used	- Time-effective to assess	
Disadvantages		- Not retrospectively assessable - No clear distinction between low- and intermediate-risk groups - Time consuming to assess	- Not MM-specific - Time consuming to assess	- No 'CI', rather than combined risk combo with NT-proBNP (according to amyloidosis Mayo risk assessment)	- No distinction between intermediate- and high-risk group - Low observation number in intermediate group - Complicated algorithm

Abbreviations: eGFR: estimated glomerular filtration rate; KPS: Karnofsky Performance Status; ADL: Activity of daily living; IADL: Instrumental Activity of daily living; PS: Performance Status; ISS: International Staging System; CRP: C-reactive protein; yrs: years; OS: overall survival; PFS: progression free survival, UKF: University of Freiburg Medical Center

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P706

CD200-expression on multiple myeloma cells reduces T cell-mediated cytotoxicity

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Introduction: Cancer treatment with checkpoint inhibitors has led to major improvents for patients suffering from malignancies such as melanoma, lung cancer or Hodgkin's lymphoma. However, in multiple myeloma (MM), early clinical trials with PD-1 inhibitors have observed only limited rates of tumor regression. Therefore, we sought to analyze the role of CD200 which represents another less well-characterized potential immune checkpoint. CD200 is expressed in a variety of hematological cancers including MM, yet also on a variety of immune effector cells, although its physiological role remains elusive. We tested the functional relevance of CD200 for T cell-mediated cytotoxicity against MM cells *in vitro*.
Methods: Expression of CD200 on primary MM cells was analyzed with flow cytometry from routine bone marrow aspirates of MM patients. CD200- MM cell lines MM.1S, L363, and U266 were transfected using a Sleeping Beauty transposon vector system to stably express CD200. The CD200+ cell lines were co-cultured in different ratios with CD3+ T cells purified from healthy donors by negative selection and activated with CD3/CD28 beads. MM cell survival rates were measured by flow cytometry and compared to those of the respective CD200- cell lines co-cultured accordingly. In addition, we tested the potential impact of CD200 expression on anti-MM activity of MM-specific CD4+ and/or CD8+ CAR T cells directed against the MM-specific target SLAMF7.
Results: Strong CD200 expression was detected in ca. ¾ of primary MM cases (n=43), whereas CD200 was not present in any of the tested MM cell lines (n=9). Therefore, we stably expressed CD200 in MM cell lines

MM.1S, L363, and U266 via transfection of a Sleeping Beauty transposon vector system for further analysis. Co-culture of activated primary CD3+ T cells with CD200- MM cell lines reduced MM cell survival in varying degrees compared to co-culture with non-activated controls. In contrast, CD200+ cell lines attenuated T cell-mediated cytotoxicity resulting in up to 2-fold increased MM cell survival. However, co-culture of SLAMF7-directed MM-specific CAR T cells with CD200- or CD200+ MM cell lines showed that CD200 expression did not appear to overcome the cytotoxic effects of the CAR T cells.
Conclusions: Expression of CD200 on MM cell lines reduced cytotoxic effects mediated by primary T cells, but did not appear to overcome the anti-MM activity of SLAMF7-directed CAR T cells *in vitro*.

Disclosure: No conflict of interest disclosed.

P707

Daratumumab as salvage therapy in relapsed/refractory multiple myeloma patients after allogeneic stem cell transplantation

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The human monoclonal anti-CD38-antibody daratumumab is approved as second line therapy either as single agent therapy or in combination with lenalidomide or bortezomib for the treatment of patients with relapsed/refractory multiple myeloma (MM). Besides Fc-dependent immune effector mechanisms its anti-myeloma activity seems to be mediated by improving host-anti-tumor immune response. Data addressing its value as a salvage therapy regime for patients relapsing after allogenic stem cell transplantation (allo-SCT) are missing.
From April 2016 till November 2018 a total of 22 patients (male, n=11) with the median age of 64 years (40-72) received daratumumab as a salvage therapy for relapse of MM after allo-SCT. Daratumumab was started at a median of 19 months (0-43) after relapse/progress and patients received a median of 2 salvage lines (0-4) in this period. Daratumumab was initiated as monotherapy in all patients. In 14 patients, combination therapy with an IMiD (n=11) or a PI (n=3) was started when progress or no response to monotherapy was observed. Data on immune reconstitution prior to the first and after 3 infusions of daratumumab were available in 6 of 22 patients (27%).
The median number of infusions was 18 (3-38). 20 adverse reactions were observed in 13 of 22 (59%) patients which were mostly mild or moderate (CTC 1-2, n=19). Three patients developed late onset infections, no cases of GvHD occurred. With a median follow-up of 28.2 months after the first infusion 9 of 22 patients remain alive (1-year OS 62.3% [CI 41.2-79.6%]). One patient died due to pneumonia and another one in neutropenic sepsis after chemotherapy for secondary malignoma. All other patients died with PD. 13 of 22 patients responded (59%; PR, n=3; vgPR, n=8; CR, n=2) to the therapy with daratumumab +/- IMiD/PI. The responses occurred at a median of 41 days (7-245) after the first infusion and lasted for 8.4 months (0.5-30.4). 3 patients only responded after start of combination therapy. Ongoing responses are observed in 3 patients. The median PFS was 3.4 months (CI 0.4-6.4). A decline in the percentage of Treg- and NK-cells after 3 infusions of daratumumab was observed regardless of the treatment response.
Daratumumab shows efficacy and an acceptable toxicity profile in patients with relapsed/refractory MM after allo-SCT. Further studies are needed to investigate the role of a combination therapy with an IMiD or a PI in this setting and evaluate effects on the immune profile.

Disclosure: No conflict of interest disclosed.

P708

The receptor tyrosine kinase Mer promotes multiple myeloma progression and osteolytic bone disease

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Introduction: Previous data supports an oncogenic role of the TAM family receptor tyrosine kinase Mer in Multiple Myeloma and other cancers. Here we report a thus far unrecognized dual role of Mer in mediating myeloma progression and perturbing bone homeostasis. Our data provides a rationale for using Mer inhibitors for the treatment of Multiple Myeloma and its associated bone disease.
Methods: We utilized the potentially clinically applicable Mer inhibitor R992 (gift from Rigel, San Francisco, USA) which is specific for Mer in the lower nanomolar range and reaches sufficient plasma levels in mice after oral application.
Results: Our experiments could show that Mer exerts an antagonistic function in bone cells via activation of osteoclasts by promoting pro-osteoclastogenic p38 MAPK pathway and inhibition of osteoblast differentiation.
Overexpression of the Mer ligands Pros1 and Gas6 in the JJN3 mouse model led to a severe osteolytic bone phenotype with decreased bone volume (n=6/6/6; $p< 0.05$) and trabecular thickness (n=6/6/6; $p< 0.05$). Histological analysis by TRAP staining showed increased osteoclast number (n=6/6/6; $p< 0.01$).
Importantly, oral administration of 60 mg/kg of the Mer inhibitor R992 BID to mice reduced myeloma bone disease. µCT analysis of proximal tibia metaphyses revealed increased bone volume, trabecular number and trabecular thickness (n=7/7, *$p< 0.05$, *$p< 0.05$ and *$p< 0.05$). *In vitro* myeloma - bone cell co-cultures confirmed the ability of Mer inhibitors in preventing the myeloma-mediated osteoblast inhibition and osteoclast differentiation.
Furthermore, R992 reduced tumor burden in a systemic myeloma xenograft mouse model. The λ light chain concentration and the $CD138^+$ MM cell load was reduced 2-fold in R992 treated U266 mice compared to placebo treated mice 8 weeks after injection (n=5/5, *$p< 0.05$ and n=5/5, *$p< 0.05$, respectively). Importantly, treatment with R992 resulted in a significant prolongation of overall survival by 15 days in the U266 model (median OS 73 vs. 88 days (n=13/12, *$p< 0.05$).
Conclusions: Our study revealed the antagonistic function of Mer in bone cells in the pathological Gas6 and Pros1 mediated crosstalk between myeloma cells and bone-specific cells during osteolytic bone disease. Importantly, we have accumulated substantial preclinical evidence for Mer inhibitors as therapeutic agents against Multiple Myeloma and its associated bone disease by reversing the myeloma-mediated effects on bone cells.

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P709

Impact of whole body vibration exercise on bone turnover and physical performance in patients with monoclonal gammopathy of undetermined significance

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Introduction: Multiple Myeloma (MM) bone disease is a major cause of morbidity and mortality in patients due to osteolytic bone destruction or osteopenia with symptoms of severe pain and fractures. There is accumulating evidence that even patients with monoclonal gammopathy of undetermined significance (MGUS) have an increased fracture risk due to deregulated bone turnover. We evaluated whether whole body vibration exercise (WBV) is effective in patients with MGUS with respect to bone turnover and physical performance as shown in patients with osteoporosis.

Material and methods: Between May and June 2018, fifteen MGUS patients (62.5 ± 7.8 yr; body mass index, 28.7 ± 4.35 $kg \cdot m^{-2}$; n=9 female) were enrolled in a prospective clinic trial for evaluation of WBV effects. Three out of fifteen patients were diagnosed with smoldering MM. Over twelve weeks participants performed WBV two times per week for 30 minutes. Ten out fifteen patients extended training additional twelve weeks. Bone density parameters of quantitative computer tomography (qCT) and serum biomarkers such as Dickkopf1 (DKK1), sclerostin, alkaline phosphatase (ALP), procollagen type 1 N-terminal propeptide (P1NP) as indicators of bone turnover were primary end points. Secondary end points included measures of functional and activity testing, M-protein levels, and quality of life.

Results: There was a significant increase in cortical thickness (21.2 mg/cm^3; P=0.016) at the tibia over 24 weeks in females, whereas no increase was observed in the entire cohort. At 24 weeks of WBV training, a significant decrease in the bone turnover parameters such as DKK1 (8.02 pmol/l, P=0.012), ALP (P=0.006), P1NP (P=0.027) and an increase of sclerostin (P=0.015) were detected. Measures of physical functioning revealed significant differences in Chair Rise Test (P=0.001), Handgrip strength (P=0.032), Timed up and go (P=0.001) and 6-minute Walk Test (P=0.001) between time points before and after 24 weeks of WBV training. There were no exercise-related events or skeletal fractures.

Conclusions: WBV exercise in patients with MGUS and smoldering MM led to improvements in physical functioning and bone density parameters, particularly in females. WBV further mitigates increased bone turnover. DKK1 levels correlate with the extent of bone disease in patients with MM. The results of this pilot study require further investigations on the impact of exercise training on bone density and bone turnover in patients with MM.

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P710

Identification of novel interactors of CD147/MCT1 as mediators of resistance to immunomodulatory drugs in multiple myeloma

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Introduction: Cereblon (CRBN) is the target for immunomodulatory drugs (IMiDs) such as thalidomide and its derivatives lenalidomide and pomalidomide, which are key therapeutics for hematologic malignancies such as multiple myeloma (MM) and del(5q) myelodysplastic syndrome (MDS). Previously, CRBN has been described to stabilize the two transmembrane proteins basigin (CD147) and monocarboxylate transporter 1 (MCT1). By competitively interfering with this process, IMiDs destabilize the transmembrane proteins, thereby mediating their various anti-tumor and teratotoxic activities. In contrast to IMiD-sensitive myeloma cells, IMiD-resistant cells display unaffected CD147 and MCT1 levels upon IMiD treatment. So far, it has remained elusive how CD147/MCT1 conserve their mature, tumor-promoting state in IMiD-resistant MM cells.

Methods: CD147/MCT1 interactors were identified in an unbiased screen combining tandem affinity purification with mass spectrometric analysis from IMiD-sensitive versus IMiD-resistant cell lines. Binding was ascertained via immunoprecipitations and subsequent western blotting. MM cell lines were treated with IMiDs or shRNA constructs, proliferation was assessed and protein expression was analyzed by immunoblotting and flow cytometry.

Results: Here, we identify hypoxia-upregulated protein 1 (HYOU1) as a novel interactor of CD147/MCT1, which specifically binds CD147 in IMiD-resistant MM cells and demonstrates high expression levels in the resistant setting. The endoplasmic reticulum (ER)-localized chaperone HYOU1 is a member of the HSP70 superfamily and has previously been implicated in different cancers by stabilizing oncogenic proteins such as VEGF in breast cancer. Immunoprecipitation experiments confirmed interaction between HYOU1 and CD147. Loss of HYOU1 impaired MM cell proliferation and survival and showed reduced CD147 protein abundance on the cell surface and in whole cell extracts. Furthermore, overexpression of HYOU1 stabilized the CD147/MCT1 complex and conserves CD147/MCT1 expression in Lenalidomide treated MM cells.

Conclusions: Taken together, HYOU1 is a novel interactor of CD147 which positively affects cell survival in MM. HYOU1 is specifically enriched in IMiD-resistant MM cells and may serve as a mediator of IMiD resistance by replacing CRBN activity towards CD147.

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P711

Use of the revised multiple myeloma (MM) comorbidity index (R-MCI) for decision support in therapy (Tx) intensity and to reduce (or at best entirely avoid) Tx-induced side effects, serious adverse events (SAE), Tx-discontinuation and -endurance in MM patients (pts)

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Introduction: MM Tx has improved greatly with a large amount of variable Tx lines with substantial benefit on pt outcome. Considering the varying risks of SAEs and depending on pts' constitution, our hypothesis is that Tx application according to an objective risk score rather than physician judgement alone improves Tx-efficacy and avoids -toxicities and -discontinuation. The R-MCI is a successfully and repeatedly validated MM-specific risk tool. We here evaluated the relationship of the R-MCI with physicians´ Tx decisions and feasibility of the R-MCI for future decision support.

Methods: We performed this initially retrospective assessment in 205 MM pts treated at our center, rating them into fit, intermediate-fit and frail via R-MCI according to prior studies. Tx was not yet modified according to the R-MCI, but is in a prospective group discussed in our interdisciplinary MM-tumorboard (iTB).For every Tx regimen, 1 key substance was determined with its standard dose, according to NCCN/EMN-guidelines. Any decrease in dose intensity was counted as dose reduction (DR). SAEs were rated using the Common Terminology Criteria (CTC) AE V5.0. We assessed infectious, pulmonary, cardiac and renal CTCs ≥3-5.

Results: Fit pts had short Tx-duration (~6 mos induction), including 1 or 2 stem cell transplantations (SCT), low rates in initial DR (16%) and few CTCs 3-5 (4/49 pts). Intermediate-fit and frail pts had longer mean induction Tx duration (112 and 137 days (d) vs. 67d in fit pts), lower SCT rates (0.25/pt in frail pts), increased DRs (28% and 58%), but despite DR, substantial CTCs (64/132 and 29/24 pts). Median time to 1.CTCs was much shorter in frail and intermediate- than fit pts with 24d, 23d and 60d, respectively. Reasonable dose adaptations seemed to relate to the R-MCI, but potential for improvement remained (2 deaths at induction), likely due to the fact that neither Tx-DR was rigorously enough performed nor according to the R-MCI.

Conclusions: The precise comorbidity assessment seems relevant to achieve even more favorable Tx results, less DRs, low SAEs and high quality of life, the latter demonstrated by our group to be preserved in pts responding to MM-Tx, including after allo-SCT. This analysis will be compared with MM pts, in which Tx is adapted to the R-MCI via our iTB and may verify pts´ need for strictly tailored Tx. The R-MCI is compelling to be prospectively used to achieve these goals, possibly further verified in a randomized clinical trial.

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P712

Elotuzumab plus pomalidomide and dexamethasone for relapsed/refractory multiple myeloma (RRMM): efficacy results after additional follow-up of the phase 2, randomized ELOQUENT-3 study

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Introduction: Overall survival (OS) is poor for patients (pts) with RRMM. In the primary analysis (minimum follow-up [FU]: 9.1 months [mo]) of the ELOQUENT-3 study (NCT02654132), the anti-SLAM7 immunostimulatory monoclonal antibody elotuzumab plus pomalidomide (pom) and dexamethasone (dex; EPd) showed a 46% reduction in the risk of progression or death and a favorable trend in preliminary OS versus pom/dex (Pd) in pts with RRMM. We assessed efficacy and safety data after extended FU (non-prespecified).

Methods: Adult pts, including pts from Germany, with ≥2 prior lines of therapy (LoTs), including lenalidomide (len) and a proteasome inhibitor (PI; prior pom not permitted), who had MM that was refractory to last therapy and either refractory or relapsed and refractory to len and a PI, were randomized 1:1 to receive EPd or Pd in 28-day cycles until disease progression or unacceptable toxicity. Primary endpoint: investigator-assessed progression-free survival (PFS). OS was a secondary endpoint.

Results: In all, 60 pts were randomized to EPd and 57 to Pd. Median (range) age was 67 (36-81) years. Median (range) number of prior LoTs was 3 (2-8); 68% (EPd) and 72% (Pd) of pts had MM that was refractory to len and a PI. At clinical data cut-off (29 Nov 2018, minimum FU 18.3 mo), 90 PFS events (EPd: 40; Pd: 50) had occurred. PFS rates (EPd vs Pd) were 43% vs 20% (12 mo) and 34% vs 11% (18 mo). In this updated assessment, after 48 (EPd: 20; Pd: 28) of the 78 (62%) deaths required for the final analysis, OS curves continued to diverge, with a 46% reduction in the risk of death with EPd vs Pd (HR 0.54; 95% CI, 0.30-0.96; Figure).

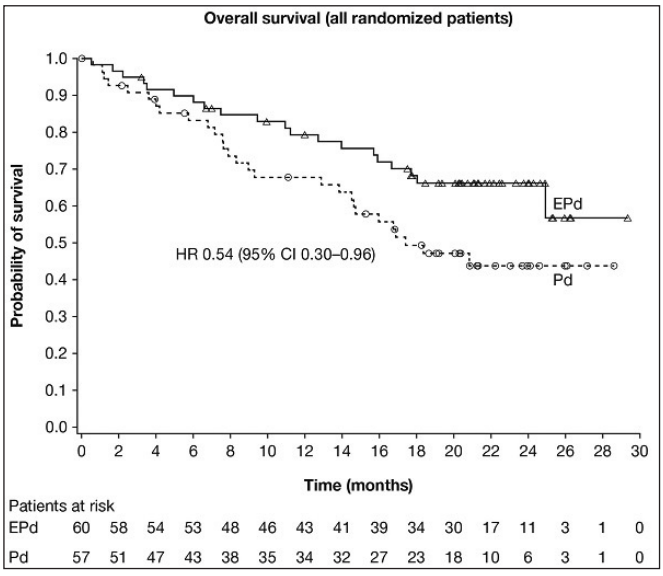

Fig. 1.

Median (95% CI) OS was not reached (24.9-not estimable [NE]) with EPd and was 17.4 mo (13.8-NE) with Pd. OS rates (EPd vs Pd) were 79% vs 68% (12 mo) and 68% vs 49% (18 mo). Safety was consistent with the primary analysis.
Conclusions: In this extended FU of ELOQUENT-3, EPd demonstrated sustained and clinically relevant PFS and OS benefits vs Pd, with no new safety signals. These data support the long-term favorable efficacy-safety profile of EPd and suggest this regimen could be a standard of care for pts with RRMM after failure of len and a PI.

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Jesús San-Miguel: Advisory Role: Scientific advisory board: Amgen, Bristol-Myers Squibb, Celgene, Janssen, Novartis, Sanofi, Takeda

P713

MyLife: longitudinal assessment of health-related quality of life in patients with multiple myeloma in Germany - first patient-reported outcomes data from MYRIAM, the prospective, national, intersectoral cohort study for treatment and outcome of myeloma patients

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Introduction: Patient (pts)-reported outcomes (PRO), have become a key focus in clinical research: In oncology, quality of life (QoL) is frequently a secondary endpoint of trials. Evaluation of PROs to measure morbidity are also increasingly considered highly relevant in benefit assessments. However, data on PROs in routine care are still exceptionally rare and their collection remains a challenge. The aim of MYRIAM with its PRO module MyLife is to close this gap for multiple myeloma (MM) pts.
Methods: As part of MYRIAM, 1.000 MM pts starting their 1- or 2-line systemic treatment will be recruited and fill-in the EORTC QLQ-C30+MY20 and Brief Pain Inventory at baseline, every 3 months (ms) for the first 2 years (yrs) and every 6 ms thereafter (MyLife). Data for the MM-specific risk score (Revised Myeloma Comorbidity Index, R-MCI), are also collected. Disease characteristics, treatment and outcome data are collected for a maximum of 5 yrs (or until death). The study was approved by local ethics committees and is registered at clinicaltrials.gov (identifier: NCT03308474). Here, we present data of the first annual interim analysis (database cut (dbc): April 30th, 2018).
Results: The first pt was recruited in 09/2017. At 1.dbc, 171 pts had been enrolled by 52 sites, of whom 87 pts (51%) were enrolled before start of their systemic treatment (eligible for MyLife). Of these, 90% agreed to participate in MyLife. Half of the pts were male. 76% (n=59) were enrolled at start of 1-line treatment. Median pts age at start of 1- and 2-line was substantial with 71 and 77 yrs, respectively.
At dbc, 90% (as yet: n=70) had returned baseline questionnaires. Overall, mean global health status of pts was markedly lower than in the non-MM reference population, and somewhat lower than in the historic reference MM population (43, 72 and 56 points, respectively). MyLife pts seemed somewhat more impaired than the historic MM reference population (albeit data is from 2008), in role (45 vs. 60) and emotional functioning (56 vs. 71), insomnia (47 vs. 29) and dyspnoea (36 vs. 26). These differences will be presented and discussed at the meeting.
Conclusions: To our best knowledge, MyLife is the first longitudinal QoL assessment for MM pts in daily practice. It provides essential insight into MM pts' view on relevant issues and will place data into context to historic and general populations. This will gain valuable insights how to improve QoL measures in routine care of MM pts further.

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P714

Mass spectrometry-based identification of a BCMA-derived T-cell epitope for antigen-specific immunotherapy in multiple myeloma

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The B-cell maturation antigen (BCMA) is selectively expressed by cells of the B-lineage, including multiple myeloma (MM) cells, and constitutes a feasible target for immunotherapy. BCMA is being evaluated as target for immunotherapeutic approaches in MM, such as CAR T cells and bispecific antibodies, demonstrating promising clinical results. Cytotoxic T cells bearing BCMA-specific T-cell receptors represent an alternative approach to target MM. For such approaches, the identification of naturally presented BCMA-derived peptides as T cell target structures is indispensable. Previously, we characterized the immunopeptidome of MM by mass spectrometry-based analysis of naturally presented HLA ligands from 7 primary MM samples and 5 MM cell lines. Here, we evaluated this data for BCMA-derived antigens and identified 3 HLA class I-restricted peptides from the intracellular domain of BCMA. One HLA-B*18-restricted ligand $P(BCMA)_{B^*18}$ shows MM-associated representation in 17% (2/12) of our MM cohort with an allotype-adjusted frequency of 67% and was additionally identified on benign B-lineage cells only (1/5 B-cell (20%), 2/17 lymph node (12%) samples) according to our extensive benign immunopeptidome database (149,297 peptides from 17,093 proteins, 404 samples of various tissues).
For immunological characterization we performed *in vitro* artificial APC-based priming experiments using naïve $CD8^+$ T cells from healthy volunteers (HVs, n=10). Induction of tetramer-positive T cells with frequencies ranging from 0.1-7.9% was observed, demonstrating the immunogenicity of $P(BCMA)_{B^*18}$. To assess the functionality of $P(BCMA)_{B^*18}$-specific T cells we performed intracellular cytokine staining (ICS) and observed IFNγ and TNF production as well as upregulation of the degranulation marker CD107a upon peptide stimulation. Cytotoxicity assays using the induced polyclonal peptide-specific T cells of HVs revealed antigen-specific cell lysis of autologous peptide-loaded cells. Moreover, using T cells from an MM patient we demonstrated the induction of multifunctional $P(BCMA)_{B^*18}$-specific cells with frequencies of 0.2-4.1% $CD8^+$ T cells. In addition, antigen-specific cell lysis of autologous peptide-loaded cells and $P(BCMA)_{B^*18}$-presenting MM1S cells was detected using polyclonal $P(BCMA)_{B^*18}$-specific cells of the MM patient.
Taken together, we identified a naturally presented BCMA-derived T-cell epitope, which constitutes a promising target for T cell-based immunotherapeutic approaches in MM.

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P715

Phase 3 randomized study of Daratumumab plus lenalidomide and Dexamethasone (D-Rd) versus lenalidomide and Dexamethasone (Rd) in patients with newly diagnosed multiple myeloma (NDMM) ineligible for transplant (MAIA)

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Introduction: Lenalidomide-based therapies are a standard-of-care (SoC) for patients (pts) with transplant-ineligible NDMM. Daratumumab (D) is a CD38-targeted mAb. In the phase 3 POLLUX study, D-Rd reduced the risk of disease progression or death by 63% vs Rd alone in MM pts with ≥1 prior line of therapy. We report results of the prespecified interim analysis of the phase 3 MAIA study that evaluated D-Rd vs Rd in transplant-ineligible NDMM.

Methods: Pts ineligible for autologous stem cell transplant were randomized 1:1 to Rd ± D. Stratification was based on ISS stage, region, and age. All pts received Rd ± D (28-day cycles) until disease progression or unacceptable toxicity. R: 25 mg PO QD on Days 121; d: 40 mg PO on Days 1, 8, 15 and 22 ± D 16 mg/kg IV QW for C12, Q2W for C3-6, and Q4W C7+. The primary endpoint was progression-free survival (PFS). Key secondary endpoints included overall response rate, minimal residual disease-negativity rate (10^{-5}), and safety.

Results: A total of 737 pts were randomized (D-Rd: 368; Rd: 369). Key baseline characteristics were balanced between groups. The median (range) age was 73 (45-90) y (44% were ≥75 y). At a median follow-up of 28 months, the hazard ratio for PFS was 0.55 (95% CI, 0.43 to 0.72; P < 0.0001), representing a 45% reduction in the risk of disease progression or death for patients treated with D-Rd (Figure). D-Rd resulted in deeper responses, with a complete response or better rate of 47.6% for D-Rd arm vs 24.7% for Rd and a very good partial response or better rate of 79.3% vs 53.1% respectively (both P < 0.0001). 19% of pts have died and follow-up for OS is ongoing. Higher rates (≥5% difference) of grade 3/4 pneumonia, neutropenia, and leukopenia were observed with D-Rd. The safety profile of D-Rd is consistent with previous studies of D. The complete data set will be presented with additional efficacy endpoints.

Conclusions: D-Rd in pts with transplant-ineligible NDMM significantly reduced the risk of progression or death by 45%. There are no new safety signals using D-Rd in NDMM. These data together with the phase 3 ALCYONE study support the addition of D to SoC in pts with transplant-ineligible NDMM.

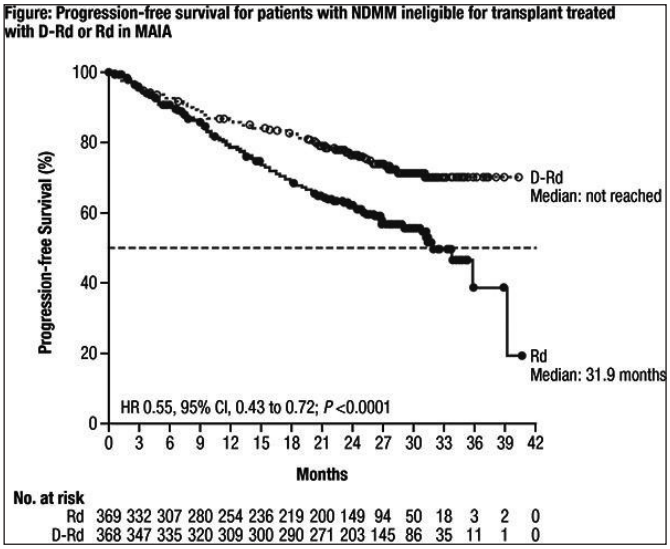

Fig. 1.

Disclosure: Katja Weisel: Advisory Role: Advisory board: Amgen, Adaptive Biotech, BMS, Celgene, Janssen, Juno, Sanofi, Takeda; Financing of Scientific Research: Amgen, BMS, Celgene, Janssen, Takeda; Expert Testimony: Amgen, Celgene Sanofi, Janssen (institution)
Saad Z. Usmani: Advisory Role: Consulted for Abbvie, GlaxoSmithKline, Celgene, Amgen/Onyx, Takeda/Millennium, Sanofi, Seattle Genetics, Skyline, Merck, and Janssen. Served on speakers bureaus for Celgene, Amgen, Janssen, Sanofi, and Takeda; Expert Testimony: Celgene, Amgen/Onyx, Takeda/Millennium, Sanofi, Seattle Genetics, Skyline, Merck, Janssen, Array BioPharma, and Pharmacyclics; Other Financial Relationships: Received travel expenses from Janssen, Celgene, Amgen, and Takeda.

P716

Ixazomib maintenance therapy following autologous stem cell transplantation significantly prolongs progression-free survival in patients with newly diagnosed Multiple Myeloma: phase 3 TOURMALINE-MM3 trial

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Introduction: Maintenance therapy post-transplant can prolong disease control and potentially survival in newly diagnosed multiple myeloma (NDMM). Only lenalidomide is approved for this indication but is associated with second primary malignancies (SPMs) and tolerability issues. There is a need for an oral proteasome inhibitor (PI) maintenance therapy that can be administered long-term, improve depth of response without cumulative/lateonset toxicity, and improve convenience for patients.

Methods: The phase 3, double-blind, placebo-controlled, multicenter TOURMALINE-MM3 study (NCT02181413) compared weekly ixazomib vs placebo maintenance in NDMM patients with at least a partial response to PI or immunomodulatory drug-based induction therapy plus single transplant. Patients were randomized 3:2 to ixazomib (n=395) or placebo (n=261) on day 1, 8, and 15 of 28-day cycles for ~2 years or until progressive disease/toxicity. The initial 3 mg ixazomib dose was escalated to 4 mg from cycle 5, if tolerated in cycles 1-4. Primary endpoint was progressionfree survival (PFS).

Results: Patient/disease characteristics were well-balanced between groups. At data cut-off, after a median follow-up of 31 months (54% PFS events), there was a 28% reduction in risk of progression/death with ixazomib vs placebo, corresponding to a 39% improvement in PFS (median 26.5 vs 21.3 months; hazard ratio 0.72; 95% confidence interval [CI] 0.58-0.89; p=0.0023). Ixazomib maintenance led to higher rates of deepened response vs placebo (relative risk 1.41; 95% CI 1.10-1.80; p=0.0042). 12% vs 7% of ixazomib vs placebo patients converted from minimal residual disease-positive to -negative status. With ixazomib vs placebo, 7% vs 5% of patients discontinued treatment due to adverse events (AEs); 42% vs 26% had grade ≥3 AEs; 27% vs 20% had serious AEs; 1 patient vs 0 died on-study. The most common grade ≥3 AEs were infections (15% vs 8%), gastrointestinal disorders (6% vs 1%) and neutropenia (5% vs 3%). Peripheral neuropathy rates were 19% vs 15%; SPM rate was 3% in both arms.

Conclusions: Based on these findings, ixazomib maintenance is a valuable option in responding patients post-transplant.

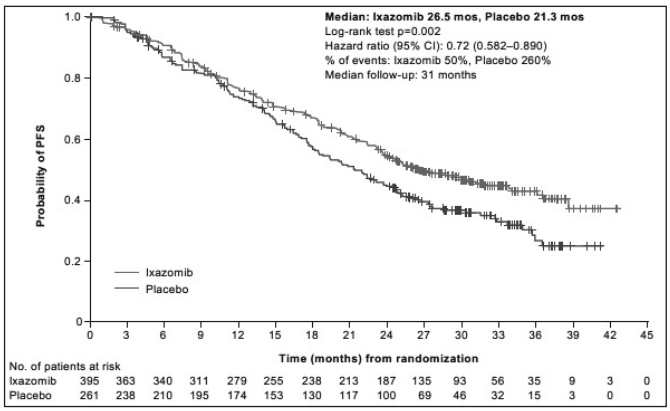

Fig. 1. PFS with ixazomib maintenance therapy vs placebo in the TOURMALINE-MM3 phase 3 study

Disclosure: Katja Weisel: Advisory Role: Amgen, Adaptive Biotech, BMS, Celgene, Janssen, Juno, Sanofi, Takeda; Financing of Scientific Research: Amgen, BMS, Celgene, Janssen, Sanofi, Takeda; Expert Testimony: Amgen, Celgene Sanofi (Institution)
S Vincent Rajkumar: No conflict of interest disclosed.

Posterdiskussion

Myelodysplastische Syndrome

P717

Systematic comparison of clonal advantage by genetic barcoding of stem cells with haploinsufficiency for Del(5q) MDS candidate genes

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Del(5q) Myelodysplastic Syndrome (MDS) is a malignant clonal disorder of hematopoiesis arising in hematopoietic stem cells (HSCs). In this disease, HSCs acquire a deletion of the long arm in one copy of chromosome 5 (i.e. haploinsufficiency of 5q). HSCs with 5q haploinsufficiency gain a clonal advantage in the bone marrow resulting in out-competition of normal hematopoiesis. A critical, yet unsolved question remains: how does genetic haploinsufficiency contribute to the clonal dominance of HSCs and to malignant transformation. We systematically investigated the role of haploinsufficiency for three candidate genes in the common deleted region on chromosome 5 (*Csnk1a1*, *Egr1* and *Apc*) alone and in combination with each other. We further explored the involvement of β-catenin as a downstream target of *Apc* and *Csnk1a1* in clonal stem cell growth. We employed a novel lentiviral genetic barcoding strategy in murine models for the candidate genes to introduce genotype and cell-specific barcodes into HSCs, which were subsequently competitively transplanted into wildtype recipient mice (N=10) in a first and a secondary transplant. We observed engraftment and stable high chimerism of barcoded HSCs through two consecutive transplantations. The barcoded progeny was reliably detected in peripheral blood lineages. We observed that 5q- clones had the potential to outcompete wildtype clones (7 of 10 mice). Especially, *Csnk1a1* and *Egr1* haploinsufficient HSCs expanded oligoclonally and dominated over other genotypes. This clonal advantage was enhanced in a secondary transplant, hinting towards an advantage in stem cell function. We furthermore showed that the clonal advantage of *Csnk1a1* haploinsufficient HSCs is dependent on β-catenin level, since the combination of *Csnk1a* haploinsufficiency with *β-catenin* knockout did not prove to be advantageous, nor the combination of *Csnk1a1/Apc* haploinsufficiency. Last, we detected a striking T-lymphocyte lineage bias in stem cells with *Csnk1a1/Egr1* double haploinsufficiency. In conclusion, we demonstrated the feasibility of dissecting clonal stem cell advantage in del(5q) MDS by genetic barcoding. The method allowed us to reliably track different genotypes in a direct competitive transplantation with single clone resolution within one microenvironment. Further, this approach allowed us to deconstruct the clonal advantage, clonal stability and relative contribution to different hematopoietic lineages of 5q- candidate genes over time.

Disclosure: No conflict of interest disclosed.

P718

Molecular and cytogenetic analysis of MDS patients undergoing therapy with hypomethylating agents: correlation of sequential comprehensive genetic profiles with clinical course and response

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Introduction: To date, the only curative therapy for pts with myelodysplastic syndromes is allogenic stem cell transplantation. A standard therapeutic option for high-risk pts are demethylating agents (HMA). We focused on frequent monitoring pts during HMA treatment using molecular genetic and cytogenetic techniques in order to identify cytogenetic and molecular mutations characterizing founder- and subclones and delineate their distinct responses to HMA.
Methods: We included 22 high-risk MDS pts treated with HMA. To allow frequent genetic follow-up during treatment, in addition to bone marrow, also immunomagnetically enriched CD34+ peripheral blood cells were analyzed. The median observation time was 452 days (range: 258-905) and the median number of sequential genetic analyses for each patient was 8 (range: 3-11). Genetic analyses included banding analysis, fluorescence in situ hybridization (FISH, 10 probes) and next generation sequencing (NGS, 54 genes). At least 50% reduction in variant allele frequency (VAF) or FISH clone size was defined as genetic response.
Results: In our cohort, during HMA-therapy, 5/6 *TP53* mutations decreased in VAF. Monosomy 7 decreased in 4/7 cases, in two it remained stable and in one it emerged under therapy. Mutations in *ASXL1* remained stable in most of the cases (8/11), decreased in two and increased in just one patient. Mutations in *RUNX1* remained stable in 4/8 pts, decreased in two, increased in one and in one case we discovered two *RUNX1* mutations: one decreased and one emerged during the observation period. Mutations in *IDH2* remained stable in 2/3 pts and decreased in one. Mutations in *IDH1* were stable in one and in 2 pts they emerged. Mutations in *TET2* were stable in 4 pts, decreased in 2 and newly emerged in one patient.
Conclusions: We could objectify the response of aberrant clones during treatment with HMA, as well as the increase or even the acquirement of new clones. Mostly molecular or cytogenetic abnormalities that are known to be associated with poor prognoses emerged during the treatment, as for example *NRAS* mutations in 2 pts. The exception were mutation of *TP53*: They responded very well to HMA (5/6 *TP53* mutations). In summary, we could show that clones can be reliably followed over time using molecular and cytogenetic methods applied on peripheral blood during treatment with HMA. Differential patterns of response could be delineated and were found to be associated with the genomic profile of individual pts.

Disclosure: Paolo Mazzeo: No conflict of interest disclosed.
Detlef Haase: Expert Testimony: Forschungsunterstützung Celgene

P719

The deregulation of inflammatory cell-death in the bone marrow of patients with MDS, CMML and sAML

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Myelodysplastic syndromes (MDS) are characterized by an inflammatory microenvironment in the bone marrow (BM) and deregulated cell-death. Whereas apoptosis is increased in the BM of patients with early stage MDS, disease progression is associated with an acquired resistance to apoptosis. Necroptosis (regulated necrosis) is a form of programmed cell death that promotes inflammation with RIPK3 (Receptor-interacting serine/threonine-protein kinase 3) being a central player in the necroptotic signalling pathway. We aim to characterize the necroptotic capacity in the BM of patients with MDS, CMML (Chronic Myelomonocytic Leukemia) and secondary AML (sAML). Furthermore necroptotic signalling is correlated with symptom burden and stage of disease. Pharmacological inhibition of RIKP1 and RIPK3 is used to gain insight into the dependence of MDSD BM cells on necroptotic signalling.

Therefore we analyzed necroptotic signalling in bulk bone marrow and the subset of CD34+ stem/progenitor cells of patients with MDS, CMML and sAML *in vitro*. BM aspirates were collected from 11 patients with MDS, 14 patients with CMML and 10 patients with sAML.BMMNCs were isolated, followed by intracellular staining for RIPK3. Protein expression was quantified via flow cytometry after staining for $CD34^+$stem/progenitor cells. 12 age-matched healthy control samples were obtained from hip replacement surgery. Furthermore BMMNCs were treated with specific inhibitors of RIPK1 (Nec1s, 30μM) and RIPK3 (GSK 843A, 1 μM) for 72h. Short term viability analysis was performed by flow cytometry using Annexin V and 7AAD after gating on $CD34^+$cells. For long-term viability analysis BMMNC (1×10^4) were plated in duplicates in methylcellulose. Colony forming capacity was assessed after 14 days.

We found that protein expression of RIPK3 was significantly elevated in sAML when compared to early stages of MDS, CMML and healthy controls. In a short-term viability assay treatment with GSK and Nec1s did not affect BMMNC survival. However, inhibition of pro-necroptotic signalling significantly increased colony forming capacity after 14 days in patients with early MDS.

We conclude that necroptotic signalling mediated by RIPK3 can be detected in the BM of patients with MDS and CMML. Disease progression to sAML is associated with an increased expression of RIPK3.

Disclosure: No conflict of interest disclosed.

P720

Isolated der (1;7) fits well in the intermediate risk group of the cytogenetic scoring system for myelodysplastic syndromes

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Introduction: The prognostic impact of common cytogenetic aberrations in MDS is defined by the new comprehensive cytogenetic scoring system for MDS (Schanz, 2012). Various efforts are being made to clarify the prognostic impact of rare cytogenetic abnormalities (Schanz, ASH, 2015). Also for the unbalanced der(1;7)(q10;p10), which results in trisomy 1q and deletion 7q (del(7q)), there still exists uncertainty regarding its prognostic classification. Therefore, we aimed to clarify the prognostic impact of der(1;7) on an international homogenous and well-documented data base.

Methods: Within an international collaborative we collected 63 pts with isolated der(1;7). Clinical data were compared with those of 12 pts with isolated del(7q) and 41 pts with isolated monosomy 7. We included MDS (N=100), CMML (N=7) and oligoblastic AML (< 30% blasts, N=9). The participating centers provided karyotypes and clinical data for all pts.

Results: In our cohort of pts with isolated der(1;7) the median overall survival (OS) was 26 months (range: 17-63). Risk for death did not significantly differ between der(1;7) and del(7q) (hazard ratio (HR): 0.91, CI: 0.41-2.02), however it was significantly higher in monosomy 7 (HR: 2.53, CI: 1.43-4.46). Median AML free survival with death as competing event was not reached in our der(1;7) cohort. The risk for AML transformation with death as competing event was significantly increased in del(7q) vs der(1;7) (HR: 3.89, CI: 1.23-12.26) and in monosomy 7 vs der(1;7) (HR: 5.88, CI: 2.48-13.96). Regarding blood counts, most noticeable was a distinctive thrombocytopenia observed in der(1;7) (plt: 77 G/L, range: 3-432) as well as in monosomy 7 (plt: 58 G/L, range:4-586, P=0.04), which was less pronounced in del(7q) (plt: 146 G/L, range: 28-496, P=0.04).

Conclusions: Although pts with der(1;7) show a very low risk for AML transformation, they have an intermediate OS only. The reduced OS might thus be related to the profound cytopenia observed in these pts. As far as we know, we characterized the largest cohort of pts with isolated der(1;7) in MDS until know. Based on a sufficient data set, our data show that assigning der(1;7) to the intermediate risk group in the cytogenetic scoring system is justified.

Disclosure: No conflict of interest disclosed.

P721

First results of the EUROPE-Trial: validation of a new predictive model of response to romiplostim in patients with IPSS low risk myelodysplastic syndrome (MDS) and thrombocytopenia

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Introduction: In about half of patients with lower-risk Myelodysplastic Syndrome (LR-MDS), thrombocytopenia is present at the time of diagnosis. Available data suggest efficacy of thrombopoietin receptor agonists (TPO-RA) like romiplostim in a still poorly defined subset of patients.
Methods: The multicenter phase II EUROPE trial within the EMSCO network investigated the impact of endogenous thrombopoietin (TPO) level and platelet transfusion events (PTE) on the efficacy of romiplostim (750µg SC qw) in patients with LR-MDS (IPSS low/int-1, < 5% BM blasts). Patients were eligible if baseline platelet counts were ≤30 Gpt/L or ≤50 Gpt/L in case of bleeding history. According to a previously published model of response to TPO-RA (Sekeres BJH 2014), patients were assigned into 3 different cohorts (cohort A: TPO< 500 ng/l, PTE< 6 units/past year; cohort B: TPO< 500 ng/l, PTE≥6 units or TPO≥500 ng/l, PTE< 6 units, cohort C: TPO≥500 ng/l, PTE≥6 units). Primary endpoint of the study was hematologic improvement of platelets (HI-P) after 16 weeks of treatment. The here presented intention-to-treat analysis included all patients who attended at least one treatment visit and were available for HI-P evaluation after a maximum of 16 weeks romiplostim treatment.
Results: Between 2015 and 2019 a total of 74 patients with a median age of 74 years and a median platelet count of 25 Gpt/L (range 1-50 Gpt/L) were included in 24 trial sites in Germany, France and the Czech Republic. Patient distribution to the three pre-defined response cohorts was 50(A), 19(B) and 5(C). 72 patients received at least one cycle of romiplostim with a median of 13 cycles; treatment is still ongoing in 7 patients. Reasons for premature study discontinuation before week 16 in 22% of patients (n=16) were investigator/patient decision (n=7), adverse events (n=6), withdrawal of informed consent (n=1), disease progression (n=1) or death (n=1). HI-P for at least 8 weeks according to IWG 2006 criteria was observed in 31 of 72 patients (43%) patients. Moreover, the rate of HI-P lasting for at least 8 weeks was notably higher in cohort A (49%) compared to patients in cohort B (39%) or C (0%). Treatment-emerging serious AEs included pulmonary embolism (n=1), AML progression (n=1), subacute stroke (n=1), mucocutaneous bleeding (n=1) or varicella zoster infection (n=1).
Conclusions: These preliminary results of the EUROPE trial confirm, that romiplostim treatment is highly effective in a subset of lower-risk MDS patients.

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Uwe Platzbecker: Expert Testimony: The EUROPE trial has received funding from Amgen.

P722

A new, simple prognostic system for complex aberrant myelodysplastic syndromes and secondary AML

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Introduction: Complex aberrant karyotypes (CK, ≥3 cytogenetic aberrations, CA) are associated with an unfavorable prognosis and an increased AML transformation rate in MDS. However, even MDS with CK (CK-MDS) are heterogeneous in terms of genetic profile and prognosis. Mutations in *TP53* (*TP53*^{mut}) are the most frequent gene mutations in CK-MDS and are prognostically unfavorable. Whether the bad prognosis is completely independent from the karyotype is a matter of debate. Recently, we demonstrated that a higher number of CA as well as *TP53*^{mut} are associated with increased risk in CK-MDS (Haase, 2019). We here aimed to develop a better differentiating prognostic system for the still heterogeneous subgroup of CK-MDS/sAML, taking into account clinical parameters and the *TP53* status.
Methods: We included 125 pts with MDS (N=92), CMML (N=3) and sAML after MDS (N=30), all with CK. The number of CA was determined by banding analysis. In addition, all pts were characterized by FISH analysis of the *TP53* locus in 17p13 and *TP53* mutation analysis. Molecular karyotyping demonstrating copy number-neutral loss of heterozygosity (CN-LOH) was available in 36/125 pts.
Results: In our cohort, the presence of an abnormal *TP53* gene (either mutation, and/or deletion, and/or CN-LOH) had the greatest impact on overall survival (OS, HR: 2.35) in the multivariate model (Cox regression). Other strong adverse prognostic factors were anemia (HR: 2.33), marrow blasts ≥20% (HR: 2.01) and ≥5 CA (HR: 1.60, Fig.1A). Based on the three parameters with the greatest impact on OS, a simple provisional prognostic system was created. One scoring point each was assigned to a *TP53* alteration, anemia and blasts ≥20%. Regarding OS, the resulting four risk groups separated very well (Fig.1B).
Conclusions: Based on the *TP53* status (mutation and/or deletion), the presence of anemia and the blast count, the individual risk of CK-MDS and sAML can be estimated. This will allow to better tailor treatment decisions for individual pts with CA. The development of an analogous scoring system restricted to MDS only is on the way.

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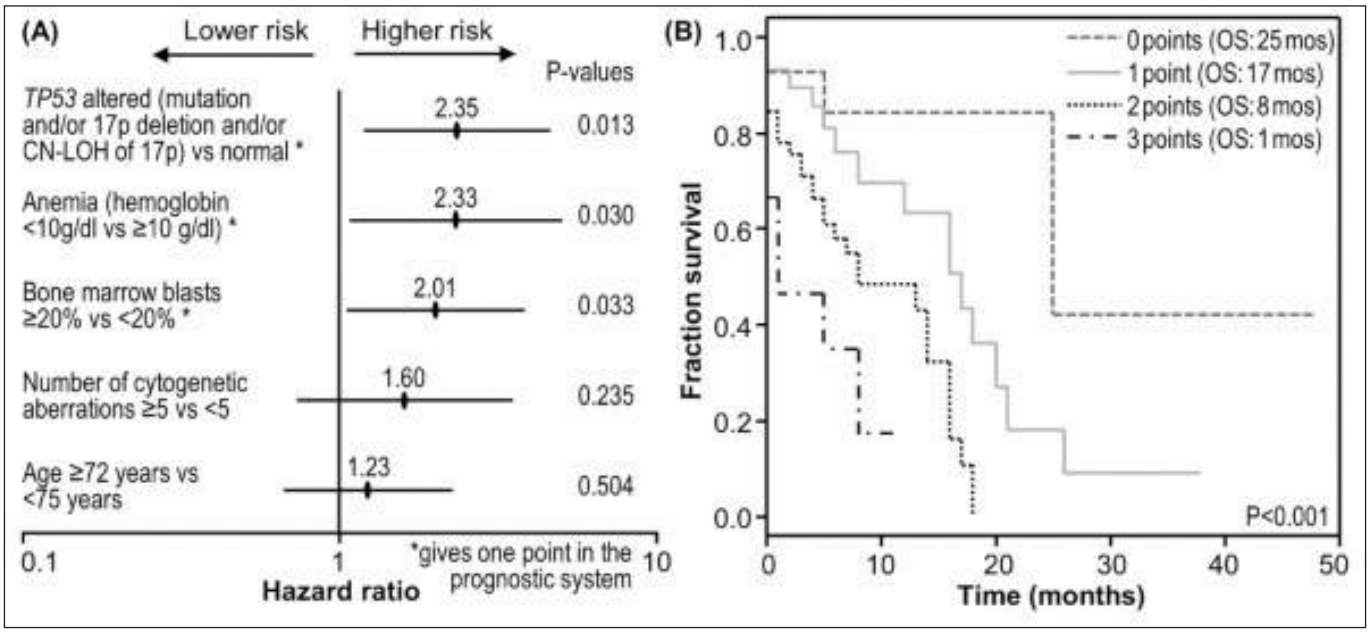

Fig. 1. Multivariate model (A) and survival of the risk groups of the proposed prognostic system (B)

P724

Clonal evolution in high-risk MDS and secondary AML treated with venetoclax and azacitidine

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Introduction: There is an urgent need for novel therapeutic strategies for patients with high-risk MDS and secondary AML that are ineligible for intensive treatment and resistant to hypomethylating agents (HMA). Recently, the combination of venetoclax and HMAs emerged as a promising treatment option. However, mechanistic insights considering genetic und functional mechanisms determining response and resistance are scarce.
Methods: To monitor the genetic basis of clonal evolution in MDS, we performed repetitive cytogenetics and next-generation sequencing. Alongside, we performed BH3-profiling to dissect the functional relevance of anti-apoptotic BCL2-family members.
Results: We here report a case of a secondary AML, initially successfully treated with venetoclax but later rapid progression upon combination with azacitidine. The 79 year-old patient was diagnosed with sAML in 2016. Initially, he showed a normal karyotype and IDH2 mutation. Upon induction and consolidating therapy, he achieved a CR, but relapsed within one year with MDS EB-2. Cytogenetics now revealed a karyotype evolution with trisomy 21 and del 7q. Besides the known IDH2 mutation, NGS now identified additional mutations in SRSF2, RUNX1 and DNMT3A. The patient was successfully treated with 12 cycles of azacitidine, but gained a pathogenic NRAS-mutation and ultimately progressed. After transient cytoreductive treatment, the patient again progressed with hyperleukocytosis. At this point, a venetoclax ramp-up was initiated and the patient showed a rapid response. Alongside, BH3 profiling revealed a strong BCL2-dependence of the malignant clone. Next, azacitidine was added to venetoclax. Unfortunately, the patient now progressed rapidly. Surprisingly, cytogenetics and NGS did not show changes in the genetic alterations of the malignant clone. Furthermore, NGS of the BCL2 gene did not reveal mutations that might confer resistance to venetoclax. In contrast, BH3 profiling now showed a functional switch from BCL2- towards MCL1-dependence, explaining acquired resistance to venetoclax.
Conclusions: The BCL2-inhibitor venetoclax is a promising treatment option for patients with high-risk MDS and AML and combination strategies may enhance the efficacy. However, further genetic and functional studies are needed to understand mechanisms of interactions determining response and resistance some of which might be unknown and on a functional, non-genetic basis as shown in this case.

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P725

Type of applied therapy and outcome of dysplastic CMML patients

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Introduction: Prognosis of dysplastic CMML patients (pts) is poor. There are no causative therapy options available besides allogeneic hematopoetic stem cell transplantation (aHSCT).
To elucidate how dysplastic CMML pts are actually treated and what treatment outcome is like, we screened the Duesseldorf MDS registry for dysplastic CMML pts and analysed those with regard to disease risk, therapy and outcome.
Results: We identified 237 dysplastic CMML pts with a median age of 70 years (25-96), 65% were male. According to the WHO-classification 29.5% were classified as CMML 0, 48.5% as CMML 1 and 22% as CMML 2. CPSS was available for 93 pts: 34 (37%) belonged to the low risk-, 26 (28%) to the intermediate 1-, 30 (33%) to the intermediate 2- and 3 (2%) pts to the high risk group. According to the Düsseldorf Score (n=189), 20 pts (11 %) were low risk, 122 (64%) intermediate risk and 47 (25%) high risk. Seventy-eight pts (33%) underwent disease specific therapy, therapy-options were divided into 6 groups and first line therapy was as follows: 1. hypomethylating agents (n=13), 2. low dose cytoreductive therapy (n=26), 3. induction chemotherapy (n=7), 4. aHSCT (n=5), 5. growths factors (n=12), and 6. other (n=15).). At therapy start white blood cell count (WBC) was known for 49 pts, 17 (35%) pts had >13.000/µl WBC of those 6 had already developed AML and another 8 were treated at AML evolution with normal or unknown WBC. At AML evolution 3 received HMA, 6 low dose cytoreduction and 5 induction chemotherapy as first

line therapy. In total, 12 pts received aHSCT at any timepoint. Regarding CPSS risk groups 38% of low risk pts were treated. 69% of intermediate 1 risk pts, 63% of intermediate 2 risk pts and 66% of high risk pts. Thirty-nine pts received second line therapy. Median time from diagnosis until treatment start was 2.8 months (ms) (0-136). Estimated overall survival of all pts was 27.6 ms (CI 20.9-34.8), of pts who were treated 23 ms and of not treated pts 31 ms. High risk pts who underwent aHSCT had a better survival as compared to the differently treated pts, whereas other treatment modalities did not increase survival probability significantly.
Conclusions: Therapy of patients with dysplastic CMML is not targeted but often triggered by disease progression to a proliferative type of CMML (WBC >13000/µl) or by disease progression to AML. A large proportion of patients receives best supportive care only including transfusion, primarily in the low risk groups.

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P726

Azacitidine is removed effectively by hemodialysis

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Azacitidine (AZA) represents a standard therapy in Myelodysplastic Syndromes (MDS) and in acute myeloid leukemia (AML).
There is limited data so far on the use of AZA in patients with renal impairment. A study by Laille demonstrated, that AZA may be safely used in this group of patients. For hemodialysis patients there are only a few case reports for application of AZA and to our knowledge it has never been investigated to which extent AZA is removed by hemodialysis or in particular hemodiafiltration.
We report a 52 year old patient who was diagnosed with MDS RAEB2 in 03/2015. At this time the patient was already on hemodialysis (since 03/2013). The cause for his end stage renal disease was likely toxicity related to a platin-containing polychemotherapy, which he received in 1995 for a mixed testicular cancer (seminoma and embryonal carcinoma, pT-4N4M1). Further relevant comorbidities were psoriatic arthritis treated with Etanercept from 2010 to 2015 and COPD IV° after longstanding nicotine use comprising 60 packyears.
Therapy with AZA was initiated 12/2015 at a dose of 75 mg/m² s.c. d1-7, q28d, but was switched to the i.v. route due to local adverse effects (pruritus and hematomas at the injection site). The blood concentration of AZA was determined on a non-dialysis and a dialysis day 0, 15, 30, 45 and 75 minutes after begin of dialysis / administration. During dialysis drug concentration was measured in hemodiafiltratate in parallel.
On non-dialysis day, AZA peak plasma level was 729 ng/mL 15 minutes after administration, which is in accordance with the literature, and area under the concentration-time curve $AUC_{0\text{-}75min}$ was 20947 ng x min/mL. On dialysis day, peak plasma concentration was 56% less (322 ng/mL) and reductions at the same extend were found at all later time points. Dialysate concentrations of AZA were about one third of those in plasma. The AUC of AZA in dialysate was calculated after adjusting dialysate concentrations for the dilution effects of dialysate flow plus substituate volume. $AUC_{0\text{-}75min}$ in plasma and dialysate was 9744 and 8767 ng x min/mL , respectively. These results suggest that the amount of AZA is substantially decreased during dialysis, most probably mainly through diffusion. However, a small amount may be also bound to the filter membrane.
To the best of our knowledge this is the first demonstration, that AZA is substantially removed during hemodialysis. Therefore, we suggest the administration of AZA after dialysis.

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P727

Paraneoplastic autoimmune phenomena in chronic myelomonocytic leukemia: successful treatment with 5-azacytidine and corticosteroids

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Introduction: Chronic myelomonocytic leukemia (CMML) is a clonal hematopoietic disorder with overlapping myeloproliferative and myelodysplastic features. The association of autoimmunity and hematopoietic stem cell disorders either as predisposition or as paraneoplastic syndrome is well known. Treatment is not standardized. A patient with a complex clinical phenotype and successful treatment is presented.
Methods: Clinical case report and review of literature
Results: Here we present the case of a 73- year old patient with CMML-1 diagnosed in 2016, who initially presented with tendinitis of the Achilles´ heels. Cytogenetics revealed a deletion of chromosome Y. A V617F mutation in Jak2 and a BCR-ABL fusion transcript were excluded. He was started on hydroxyurea with good symptom control of the tendinitis over 2 years. In 2018, he developed acute heart failure due to acute perimyokarditis with pericardial and pleural effusions. After exclusion of an infectious cause, corticosteroids (CS) were initiated leading to full cardiac recovery. Shortly thereafter, the patient suffered from immobilizing lumbago and disabling pelvic pain, arthralgia and pustulous skin lesions. Magnetic resonance imaging revealed edema of the back and pelvic muscles. Simultaneously, laboratory results showed aggravating leucocytosis and thrombocytopenia without AML transformation. The overall picture was consistent with a paraneoplastic autoimmune syndrome. CS-pulse therapy was started and treatment with 5- azacytidine was initiated. Molecular genetics showed a ASXL-1, EZH2, p53 and IDH 1 mutation, indicating high risk disease. After eleven cycles of 5-azacytidine the 75- year old patient is scheduled for reduced conditioning allogeneic hematopoietic stem cell transplant. By treatment with 5-azacytidine, complete remission of the paraneoplastic autoimmune phenomena was achieved.
Conclusions: Paraneoplastic autoimmune phenomena can emerge in the course of CMML. Here, serositis, dermatitis and tendinitis/myositis produced a disabling complex clinical phenotype, which responded to combined immunosuppression with demethylating treatment with 5-azacytidine.

Disclosure: No conflict of interest disclosed.

P728

Giant "pseudo-smudge" cells and severe dyserythropoiesis in the bone marrow of myelodysplastic syndromes (MDS): a unique clinical and cytomorphological entity

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Introduction: Myelodysplastic syndromes (MDS) display a very heterogeneous disease. While cytogenetic and molecular genetic aberrations play an important role in diagnosis, prognostication and also for therapeutic decisions, some specific cytomorphological features like ring sideroblasts, excess of blasts and hypolobulated megakaryopoiesis can also be highly predictive for the patients outcome and may help in therapeutic decisions. There are still cytomorphological characteristics which haven´t been described before and appear to be associated with a very aggressive course of the disease.

Case description: In 2018 a 56-year old male patient and in 2019 a 43-year old female patient presented with severe pancytopenia. Both patients showed intellectual deficiencies, but no signs for Dyskeratosis congenita. In both patients bone marrow cytomorphology displayed a prominent dysplastic erythropoiesis and excess of blasts, MDS-EB2 according to WHO 2016. Cytogenetic analysis revealed high-risk cytogenetics.
The striking findings in these patients were the dysplastic findings on erythropoiesis with multinuclearity reminding of congenital dyserythropoietic anemia (CDA), highly increased atypical mitotis, karyorrhexis as well as giant "pseudo-smudge" cells with blue nuclei. Pure erythroid leukemia (AEL) could be excluded. The male patient underwent early alloSCT but died in relapse. The female patient is planned for alloSCT.
Conclusions: These MDS cases show a very distinct clinical and cytomorphological entity which is associated with high-risk cytogenetics and an aggressive course of the disease, so that already even before the results of cytogenetics, upfront intensive therapy including allogeneic stem cell transplantation for suitable patients should be planned.
The typical finding of giant "pseudo-smudge" cells might be a sign for disrupted normal apoptosis and also for massive proliferation and ineffective erythropoiesis. The multinuclearity, micronuclei as well as severly increased atypic mitosis and karyorrhexis might be due to chromosomes and/or chromosome fragments that have been detached from the metaphases so that the genetic material is placed disorganized outside the main nucleus. These cytomorphological finding as seen here have not been described before and appear to display an own entity. It is not yet part of the morphological manifestations of dyserythropoiesis of WHO 2016.

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P729

Stable complete hematological remission in a patient with refractory cytopenia with multilineage dysplasia (RCMD) treated with more than 90 cycles of azacitidine

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Introduction: Myelodysplastic syndromes (MDS) are a group of bone marrow disorders characterized by ineffective hematopoiesis, peripheral blood cytopenias and an increased risk of transformation to acute myeloid leukemia (AML). In recent years the demethylating agents azacitidine and decitabine have been increasingly used to treat higher-risk MDS because they prolong overall survival and lower the risk of progression to AML.
Case presentation: We report the case of a 72-year-old man, who was diagnosed as having RCMD with intermediate I risk profile according to the international prognostic scoring system (IPSS) in 2001. One year after diagnosis we treated the patient with erythropoiesis-stimulating agents (ESAs) because of transfusion-dependent anemia. For a long period, the patient solely received best supportive care (BSC) which aims to alleviate the negative effects of cytopenia and to improve the quality of life. Because of increasing demand for blood products and decreasing platelet levels, we commenced therapy with 5-azacitidine (75 mg/m2 per day subcutaneously for days 1-7 of every 28-day cycle). At that time a repeat bone marrow examination showed a progression of RCMD to RAEB-2 (refractory anemia with excess blasts). After the 18th cycle with 5-azacitidine the patient showed a hematological response, with transfusion independence and with no recurrent febrile episodes. In the most recent bone marrow biopsy we observed cytological, histological, cytogenetic as well as molecular complete remission of RAEB-2 and the patient's blood analysis had also been normalized. Although we occasionally interrupted the treatment because of surgical procedures, the patient did not lose the response to demethylating therapy and still remains in complete remission after 90 cycles of azacitidine.
Conclusions: This case report indicates that a subset of patients who belong to the intermediate I risk category of IPSS, benefits from prolonged treatment with hypomethylating therapy.
Our experience demonstrates that long treatment with azacitidine in hematological feasible and perhaps responsible for the favorable patient outcome.

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P730

Erythropoiesis-stimulating agents for the treatment of myelodysplastic syndrome-related anemia

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Introduction: Myelodysplastic syndromes (MDS) are clonal hematopoietic stem cell disorders. Anemia is common in MDS, affecting >50% of patients at presentation and up to 90% of patients at some point during the course of the disease. We summarize the latest knowledge on the treatment of anemia in MDS, and in particular the use of erythropoiesis-stimulating agents (ESAs).
Methods: Published literature of anemia treatment in MDS was reviewed, including factors that are predictive of response to treatment and available guideline recommendations.
Results: Several options are available for the treatment of anemia in patients with cancer, including red blood cell (RBC) transfusions, iron supplementation and ESAs. RBC transfusions have been commonly used for many years in cancer patients, including MDS; however associated complications include excess morbidity, hemochromatosis, hemolytic reactions, and transmission of biological pathogens. Erythropoiesis-stimulating agents (ESAs) have been used for >20 years to correct anemia in MDS. Several factors are predictive of a response to ESAs in MDS patients, including endogenous erythropoietin (EPO) levels < 500 U/l, marrow blast < 10%, IPSS low to intermediate-1, diagnosis of refractory anemia, and normal karyotype. Patients with higher-risk MDS are generally not considered for ESA therapy because of poor responses, short survival times and the frequent use of hypomethylating agents and stem cell transplantation, which require RBC transfusion support. Hence ESAs are commonly used to treat anemia in lower-risk MDS patients, and efficacy and safety has been demonstrated in clinical trials (involving >2500 patients) and several meta-analyses. The most recent guidelines from ESMO recommend (Grade 1A) that ESAs should be considered in MDS patients with symptomatic anemia, Hb < 10 g/dl, IPSS risk low to intermediate-1 or very low to intermediate, < 2 RBC transfusions/month and/or serum EPO < 500 IU/l. Despite clinical practice and their recommendation in guidelines, for many years use of ESAs in MDS was not licensed, until the recent approval in Europe of epoetin alfa and biosimilar epoetin alfa for use in this patient population.
Conclusions: Anemia commonly affects patients with MDS. ESAs have been used for many years to treat anemia in cancer patients, and are recommended in clinical guidelines for use in lower-risk MDS patients. Several epoetin alfas are now approved in Europe for use in this population.

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Posterdiskussion

Allogene Stammzelltransplantation

P731

Recipient mast cells are critically involved in the development of dermal sclerodermatous chronic graft-versus-host disease

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Background: Allogeneic hematopoietic stem cell transplantation (allo-HCT) is a potentially curative treatment for patients with malignant neoplasms or inborn defects of hematopoiesis. Benefits of allo-HSCT are hampered by graft-versus-host-disease (GVHD), which can be debilitating and potentially lethal. In chronic GVHD (cGVHD), inflammation and aberrant wound healing lead to pathological fibrosis across multiple organs, most frequently in the skin, yet the exact pathophysiology is not well-understood. Mast cells (MCs) are primarily known for their role in atopic disease. However, recent studies have demonstrated new roles for MCs, showing that they can be involved in wound healing and in the pathogenesis of fibrotic disease. Given these new paradigms and the MC tropism to skin, alongside their reported role in other fibrotic diseases, we investigated whether MCs may play a role in the pathogenesis of dermal cGVHD.
Methods: Cells: MCs were grown ex vivo from murine bone marrow. Transplant: 8 Gy radiation, followed by injection of LP/J marrow and splenocytes into C57BL/6J (WT) or B6.Cg-KitW-sh MC-deficient recipients.
Results: Ex vivo, we show that MCs survive and are functional after lethal radiation, such as that used in conditioning prior to HCT. In a murine model of cGVHD WT mice had significantly more cGVHD symptoms than MC-deficient mice as measured by clinical scoring. This scoring correlated with a significant increase in skin pathology, collagen deposition, and expression of pro-fibrotic genes in WT as compared to B6.Cg-KitW-sh mice. Dermal MC numbers were increased in WT mice, but were nearly undetectable in B6.Cg-KitW-sh mice, implying that the MCs that are present were recipient-derived and had survived conditioning. Skin from WT but not B6.Cg-KitW-sh mice was enriched in cGVHD effector cells and in inflammatory cytokines and chemokines. Murine MCs, upon stimulation were sources of many of these factors, production of which was blocked when treated with ibrutinib and ruxolitinib, drugs used in cGVHD treatment. In support of our mouse data, we found increased numbers of tryptase positive mast cells primarily located near the dermal-epidermal junction in patients with cGVHD of the skin.
Conclusions: In summary, we show here a previously unknown role for MCs in the pathogenesis of dermal cGVHD, suggesting that MCs may be targetable to prevent and treat this devastating complication of allo HCT.

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P732

Impact of major complications affecting the central nervous system on the outcome of allogeneic hematopoietic stem cell transplantation: a large retrospective study on 888 consecutive patients

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Introduction: Central nervous system (CNS) symptoms are a frequent observation after allogeneic stem cell transplantation (allo-SCT), characterized by the lack of specific nosological patterns. Toxicity, opportunistic infections, CNS relapse, metabolic disorders, stroke, and psychiatric disorders are differential diagnoses. The origin of the CNS complication will frequently be unclear, even after thorough workup.
Methods: The epidemiology of major CNS complications, i.e. prompting either CNS imaging or lumbar puncture, their risk factors, and their impact on outcome after allo-SCT were retrospectively analyzed in 888 patients consecutively transplanted 2014-2018 in one institution. Cumulative incidence of non-relapse mortality (NRM) and relapse were compared using a competing risk model.
Results: Cumulative incidence of major CNS complications at one year was 14.77% (95%CI 12.30%-17.24%), at two years 16.40% (95%CI 13.72%-19.07%). Major CNS complications were found in 132 patients: in 36 cases classified as metabolic, 26 as drug-related neurotoxicity (14 attributed to cylosporin A, 4 to antilymphocyte globulin), 11 as cerebrovascular events (ischemic n=8, bleeding n=3), 9 as CNS infections (2 EBV-related, 3 CMV-related, 1 JC-virus-related, 1 HHV6-related, 1 septic embolism, 1 CNS-toxoplasmosis), 9 as malignant (relapse of the underlying disease). Despite the clinical, radiological and laboratory investigations, the cause of CNS symptoms remained unclear for 37 patients (28%). Multivariate analysis demonstrated a statistical association of CNS complication with patient age ($p < .001$). The estimated OS of patients with any CNS complication was significantly lower than of the patients without neurological complications ($p < .001$), and the cumulative incidence of NRM was significantly higher for patients with CNS complication ($p < .001$). Amongst the single categories of CNS complications, a significant negative impact on survival measures can only be demonstrated for metabolic CNS complications and CNS infection (NRM, $p < .0001$ and $p = .0003$, respectively), and for CNS relapse.
Conclusions: Major CNS complications after allo-SCT are a frequent event with a major contribution to morbidity and mortality. Especially the situation of an unclear neurological complication after allo-SCT needs to be clarified by intensive research.

Disclosure: No conflict of interest disclosed.

P733

Outcome of acute myeloid leukemia (AML) patients (pts) with Trisomy 8 (+8) receiving non-myeloablative conditioning allogeneic haematopoietic stem cell transplantation (NMA-HSCT)

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In AML +8 is the most common numerical cytogenetic abnormality & sole +8 is found in about 1/3 of such pts. +8 pts are considered to have intermediate prognosis, but pts consolidated with NMA-HSCT - a conditioning regimen allowing HSCT in older/comorbid pts - have not been investigated.

We analyzed 267 AML pts: 214 pts had normal karyotype (NKT), 53 had +8 (23 with sole +8; 30 with +8 & additional cytogenetic aberrations [+8aCA]) & 24 pts had European LeukemiaNET 2017 intermediate risk excluding +8 (ELN int risk). At diagnosis cytogenetic & immunophenotype analyses & targeted amplicon sequencing was performed for 54 recurrently mutated (mut) genes on the MiSeq platform (Illumina) for pts with material available. Outcome was analyzed in 196 pts transplanted in CR/CRi after NMA-HSCT. Median follow up after HSCT was 4.5 years. Compared to NKT pts, pts with +8 had less *NPM1* (*P*< .01) & more *IDH1/2* (*P*=.04) & *JAK2* (*P*=.02) mut & lower BM CD33 expression (*P*=.03), higher BM expression of CD34+/CD38- cells (*P*=.02) & higher expression of the AML-associated gene *BAALC* located on chromosome 8 (*P*=.02), but not of the *BAALC* embedded microRNA (*miR*)-*3151* (*P*=.24). Compared to NKT pts, pts with sole +8 were older (*P*< .01) & had less *NPM1* (*P*< .01) but more *JAK2* mut (*P*< .01) & lower BM CD33 expression (*P*< .01) & higher BM CD34+/CD38- expression (*P*=.05). Pts with +8aCA had less *NPM1*mut (*P*< .01) & higher *BAALC* expression (*P*=.03), while again *miR-3151* expression was similar (*P*=.42). Compared to ELN int risk, +8 pts had more *FLT3*-TKD (*P*=.03). Compared to ELN int risk pts, pts with sole +8 pts were older (*P*=.04) & had more *JAK2* (*P*=.03) & *RUNX1* mut (*P*=.05). Compared to ELN int risk pts, pts with +8aCA had more *FLT3*-TKD (*P*=.05). There was no different relapse incidence or overall survival comparing NKT *vs* sole +8 *vs* +8aCA (Figure 1A,B) or ELN int risk *vs* sole +8 *vs* +8aCA pts (Figure 1C,D).

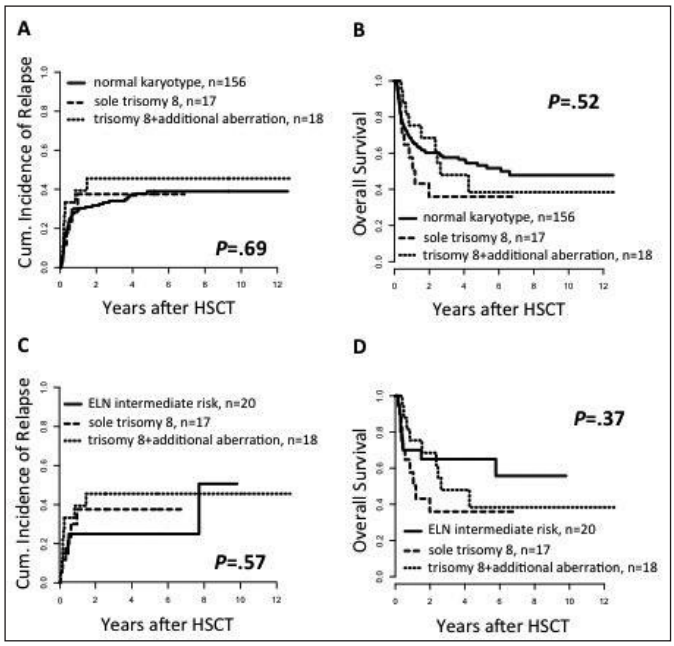

Fig. 1. Outcome analysis comparing (A,B) NKT vs sole +8 vs +8aCA and (C,D) ELN int risk vs sole +8 vs +8aCA

While AML pts with +8 consolidated with NMA-HSCT had comparable outcome to NKT & ELN int risk pts, sole +8 & +8aCA associated with distinct clinical & biological characteristics in AML, leading to potential therapeutic consequences (*e.g* differential CD33 expression for gemtuzumab ozogamicin treatment).

Disclosure: No conflict of interest disclosed.

P734

Cytomegalovirus reactivation kinetics as predictors of survival and relapse after allogeneic cell transplantation for hematologic malignancies

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Introduction: After allogeneic hematopoietic cell transplantation (HCT) for patients with leukemia, human Cytomegalovirus (CMV) reactivation associates with increased non-relapse mortality (NRM) but also with reduced relapse, as shown by numerous studies focusing on the incidence of early CMV reactivation. Little is known on the impact of CMV reactivation kinetics, peak titers and timing. Longitudinal quantitative assessment of reactivation kinetics and virus loads might improve patient-specific clinical outcome associations.

Methods: We retrospectively analyzed CMV reactivation kinetics in 705 consecutive HCT patients with hematologic malignancies treated between 2012 and 2017. CMV titers were monitored weekly by quantitative PCR (qPCR); a minimum of 5 measurements in the first 200 days post-HCT was required; CMV reactivation was defined by a cut-off value of >500 genome copies per ml. Subgroup analyses were performed according to the time of CMV reactivation and CMV viremia peak titers.

Results: CMV time kinetics followed a Gaussian distribution with a median first reactivation at d+33 and peak titers at d+47. Overall survival (OS) was significantly reduced in patients with very early (< d+30) reactivation (17 vs. 59 months, p=0.040) and in patients with CMV titers >100,000 copies/ml (10 vs. 45 months, p< 0.0001). Multivariate analyses confirmed a significantly reduced OS in patients with peak titers >100,000 copies/ml and < day +30 (Hazard ratio (HR) 2.03; 95%Confidence Interval (CI), 1.45-2.86, p< 0.0001 and HR 1.43; 95%CI, 1.10-1.87, p=0.008). NRM was consistently higher (HR 2.59; 95%CI, 1.69-3.97, p< 0.0001) for patients with CMV copies >100,000/ml. Hematologic relapse was only reduced in patients with a peak CMV viremia between 20,000 and 100,000 copies/ml (HR 0.55; 95% CI, 0.32-0.95, p=0.033).

Conclusions: Our data showed that CMV reactivations before +30d or with peak titers of >100,000 copies/ml associated with significantly reduced OS, while CMV reactivations at intermediate titers between 20,000 and 100,000 copies/ml associated with reduced relapse. These findings underline the complexity of CMV reactivations after HCT and support longitudinal evaluation of CMV titers and individualized quantitative kinetics models for risk assessment after HCT to distinguish the advantageous from the detrimental aspects of CMV reactivation.

Disclosure: Saskia Leserer: Employment or Leadership Position: Anstellungsverhältnis: Universität Duisburg-Essen
Amin T. Turki: Employment or Leadership Position: Anstellungsverhältnis: Universität Duisburg-Essen; Advisory Role: JAZZ, CSL Behring; Other Financial Relationships: Reise-Fördermittel: Neovii Biotech

P735

Positioning and effectiveness of donor lymphocyte infusions after allogeneic hematopoietic stem-cell transplantation in adults with acute myeloid leukemia: a single-center nested-cohort study

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Introduction: Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is an effective treatment for acute myeloid leukemia (AML), mediated by graft-versus-leukemia (GvL) immune mechanisms. GvL can be augmented by donor lymphocyte infusions (DLI) to prevent or reverse relapse. Prospective trials of allo-HSCT+DLI efficacy in AML are lack-

ing, and available retrospective studies provide an inconsistent picture, due to variable AML inclusion criteria and frequently combined analyses with myelodysplastic syndrome and/or other leukemias. Thus, the present study focuses on allo-HSCT+DLI use for adult AML in routine clinical practice.

Methods: We carried out a retrospective, nested-cohort analysis based on a prospectively designed and centrally maintained adult AML/allo-HSCT registry, insuring complete follow-up and consistency of data collection and analysis. Descriptive statistics and Kaplan-Meier analysis were used to reconstruct event-driven treatment paths and define outcomes.

Results: Of 423 consecutive allo-HSCT interventions for adult AML at our center, 120 included DLI use (28%), with first dose given in post-HSCT persistent disease (perDLI; n=3), after relapse (relDLI, n=63), or in complete remission (CR) but triggered by molecular or clinical indicators of high individual risk (preDLI; n=54), respectively. In a first-tier nested cohort, with post-HSCT CR and ≥100-day event-free survival without 2° HSCT (EFS) as boundaries, we retained 116 allo-HSCT+DLI interventions (97%) juxtaposed with 231 no-DLI interventions. Within this CR+EFS100 cohort (n=347), distinct relative rates of relapse (rREL) and survival were observed for the second-tier preDLI (2-year EFS: 54%; 5-year rREL: 67%), relDLI (2-year EFS: 23%) and no-DLI cohorts (2-year EFS: 66%; 5-year rREL: 22%), with multivariate analysis identifying major risk factors for mortality. Mapping the time course from allo-HSCT to DLI initiation, relapse, and survival endpoints suggests differences in the biological behaviors underlying the preDLI and relDLI cohorts, beyond an early-detection concept.

Conclusions: Our results, with DLI use in about one-third of allo-HSCT interventions in adult AML, provide realistic estimates for preDLI and relDLI effectiveness and suggest a challenging benchmark for proposed adjuvant DLI concepts. The distinctive clinical timelines of the preDLI and relDLI cohorts deserve additional laboratory exploration.

Disclosure: No conflict of interest disclosed.

P736

Induction of type I interferon signaling before hematopoietic stem cell transplantation reduces allogenicity of recipient dendritic cells

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Background: Recent studies have highlighted the immunoregulatory function of type I interferons (IFNI) during the pathogenesis of graft-versus-host disease (GVHD), a dreaded complication after allogeneic stem cell transplantation (SCT). We demonstrated that selective activation of IFN-I pathways including RIG-I/MAVS and cGAS/STING prior to SCT conditioning chemotherapy can improve the subsequent course of GVHD via protective effects on intestinal epithelial cells and the intestinal barrier. However, whether and how IFN-I modulates immune cell function remains poorly understood.

Methods: We used specific RIG-I agonists (3pRNA) to stimulate IFN-I production in mouse models of (1) conditioning therapy with total body irradiation (TBI) and (2) GVHD. We performed mixed lymphocyte reactions with bone-marrow derived or splenic CD11c$^+$ dendritic cells (DC) co-cultured with allogeneic T cells. DC activation markers were analysed by qPCR. T cell activation was assessed by proliferation and IFN-gamma production.

Results: We found that endogenously produced IFN as well as RIG-I-induced IFN-I do not directly target donor allogeneic T cells. Instead, 3pRNA applied before conditioning therapy reduced the ability of recipient CD11c$^+$ DCs to stimulate proliferation and interferon gamma production of donor T cells (see Figure). Mechanistically, this reduced allogenicity was mediated via IFN-I indirect effects on dendritic cells and was restricted to a scenario where tissue damage occurs.

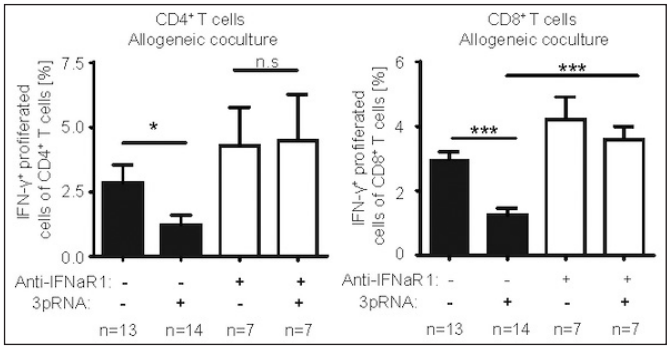

Fig. 1. Induction of IFN-I by RIG-I activation prior to conditioning therapy reduces DC allogenicity

Conclusions: Our findings uncover an IFN-I and context dependent immunosuppressive function of DCs and expand the current understanding regarding cellular targets of IFN-I during GVHD. They underscore the development IFN-I based therapeutic approaches aimed at reducing donor T cell activation after SCT while retaining potent graft versus leukaemia effects.

Disclosure: No conflict of interest disclosed.

P737

Comparison of post-transplantation cyclophosphamide versus anti T-lymphocyte globulin as GvHD prophylaxis in patients with acute lymphoblastic leukemia undergoing allogeneic hematopoietic stem cell transplantation in first complete remission

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Purpose: High risk acute lymphoblastic leukemia (ALL) in first complete hematologic remission (CR1) is best treated using an allogeneic hematopoietic stem cell transplantation (alloSCT). Standard conditioning regimens are myeloablative, based on total body irradiation (TBI), frequently at 12 Gy, combined with cyclophosphamide 120 mg/kg body weight (BW) and sometimes anti T-lymphocyte globulin (ATG). They are associated with a high degree of toxicity, non-relapse mortality and considerable relapse incidence, especially in older patients. Overall survival (OS) after two years ranges between 60% and 76%. Novel approaches, e.g. for the prophylaxis of GvHD, are warranted.

Patients and methods: Between 2013 and 2018, 41 patients with ALL in CR1 were transplanted at one center. TBI 12Gy, cyclophosphamide 120mg/kgBW, ATG 30-90mg/kgBW (ATG cohort) was used for conditioning in 20 patients, and TBI 8-12Gy, fludarabine 120mg/m^2, cyclophosphamide 100mg/kgBW post transplantation (days +3, +4, postCY cohort) in 21 patients.

Results: OS at one year was 77% (postCY cohort) *versus* 80% (ATG cohort, p=.77), disease free survival (DFS) at one year 57% versus 80% (p=.15). Cumulative incidences of NRM and relapse did not differ significantly between the approaches of GvHD prophylaxis. Patients in the postCY cohort were considerably older and received 8 Gy as opposed to 12 Gy in the ATG cohort more frequently. Striking differences in the immune reconstitution were observed: in the postCY cohort, CD4+, CD4+CD45RA+ naïve and CD4+CD45R0+ memory T-cells recovered significantly faster in the postCY cohort.

Conclusion: Conditioning consisting of TBI 8-12 Gy, fludarabine 120mg/m^2 and postCY can be safely administered to an elderly population of patients with high risk ALL in CR1. Efficacy seems to be comparable to a regimen using ATG, and immune reconstitution seems to be enhanced after postCY conditioning compared to ATG. Future trials will have to address the efficacy of this novel approach of GvHD prophylaxis.

Disclosure: No conflict of interest disclosed.

P738

Oxidative stress upon allogeneic hematopoietic stem cell transplantation and its impact on the reconstituting immune system

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Introduction: Therapeutic success of allogeneic hematopoietic stem cell transplantation (allo-HSCT), the only curative treatment option for a range of hematological diseases, relies on the potency of transplanted donor T-cells to eliminate residual malignant cells - termed the Graft-versus-Leukemia (GvL) effect. Oxidative stress, caused by reactive oxygen species (ROS), has a detrimental impact on immune cells and is known to severely affect T-cell biology. In fact, tissue damage during conditioning regimens, activation of the myeloid compartment upon engraftment, and early Graft-versus-Host disease (GvHD) could all lead to oxidative stress. Thus, we hypothesized that oxidative stress is present upon allo-HSCT and could interfere with T-cell function affecting long-term outcome.
Methods: This study comprises an in-depth *ex vivo* analysis of allo-HSCT blood samples. Flow cytometric analysis in conjunction with fluorescence cell barcoding of allo-HSCT patients' (n=50) peripheral blood mononuclear cells (PBMCs), gathered at 6 timepoints post allo (day 30 to day 120), was performed. To this end, markers of oxidative stress (8-OHdG), DNA damage (pH2AX), activation (CD69, CD137), metabolism (GLUT1, HK2), and lymphocyte subsets were scrutinized.
Results: In line with our initial findings of increased levels of oxidized proteins, lipids, and nucleic acids in the patients' sera, we detected elevated ROS-induced DNA damages in the corresponding T-cells. Oxidative stress burden positively correlated with DNA damage, activation, and glucose metabolism in T-cells indicating a link between oxidative stress and T-cell function. Additionally, oxidative stress was positively associated with the proportion of proliferating T- and NK-cells while being negatively related to effector T-cells.
Conclusions: In this study we have shown that presence of oxidative stress upon allo-HSCT is associated with an altered immunophenotype potentially triggering insufficient T-cell effector functions. The observed interrelation between ROS and the ratio of specific lymphocyte subsets suggests oxidative stress as a relevant factor influencing the concurrent immune reconstitution after allo-HSCT. For the near future we aim to identify the underlying mechanisms triggering oxidative stress and to correlate our findings with the patients' clinical course (e.g. infectious complications and disease relapse).
This study is supported by the DFG-TRR221.

Disclosure: No conflict of interest disclosed.

P739

Digital-droplet PCR for quantitative monitoring of IDH1, IDH2 and DNMT3A mutations after allogeneic stem cell transplantation in patients with myelofibrosis

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Introduction: Primary myelofibrosis and post-ET or PV myelofibrosis (MF) are characterized by driver mutations in *JAK2*, *CALR* or *MPL*, and a variable number of other somatic mutations. Driver mutations can be used as minimal residual disease (MRD) marker in the allo-SCT setting. We aimed at evaluating the reliability of digital-droplet PCR (ddPCR) assays for quantification of IDH1, IDH2 and DNMT3A mutations as MRD marker for transplanted MF patients.
Methods: We screened 162 MF patients transplanted between 2013 and 2018 at Hamburg University Medical Center. Blood samples collected pre-allo-SCT were analyzed with a next-generation-sequencing customized panel including the following genes: *DNMT3A*, *IDH1*, *IDH2*, *RUNX1*, *N-RAS*, *K-RAS*, *MPL*, *ASXL1*, *EZH2*, *TET2*, *JAK2*, *CBL*, *SF3B1*, *SRSF2*, *CALR*. We selected 13 patients who harbored one of the following mutations: IDH1R132C, *IDH1*R132H, *IDH2*R140Q, *DNMT3A*R882C, *DNMT3A*R882H, *DNMT3A*R882P. We firstly determined the limit of detection (LOD) of the ddPCR assays (Bio_Rad) for each mutations using 46 healthy donors as controls and progressive dilution of known mutated samples. The follow-up samples from peripheral blood were longitudinally analyzed.
Results: The LOD was 0.05% for *IDH1*R132C, *IDH2*R140Q, *DNMT3A*R882C *and DNMT3A*R882H; 0.1% for *IDH1*R132H *and DNMT3A*R882P. We measured in all the samples:
(I) burden of the known concomitant driver mutation (*JAK2 in 10 cases*, *CALR* in 2 cases; one patient harbored a rare CALR mutation, for which no ddPCR assay was available);
(II) donor chimerism;
(III) burden of the new MRD marker (*IDH1, IDH2, DNMT3A).*
Results of *IDH1-2/DNTMT3A* and *JAK2/CALR* concomitant quantification were concordant in 70/84 cases (83.3%). Six *JAK2*+ and one *CALR*+ samples were negative for *IDH1-2* or *DNTMT3A*. Five *IDH1*+ and two *IDH2*+ samples were negative for the concomitant driver mutation. One patient failed the first allo-SCT and underwent a successful second allo-SCT. Nine patients achieved long-term molecular remission (with JAK2/CALR and IDH/DNMT3A early negativity). We observed 3 cases of molecular relapse that were evident through both ddPCR assays (*JAK2* and *IDH1* in 2 cases, *JAK2* and *IDH2* in one case).
Conclusion: The ddPCR assays for *IDH1*, *IDH2*, and *DNMT3A* are a reliable tool for the molecular follow-up of MF patients, and they can be exploited also for triple-negative patients in order to drive pre-emptive immunotherapeutic approaches in the allo-SCT setting.

Disclosure: No conflict of interest disclosed.

P740

Ruxolitinib for therapy of graft-versus-host disease

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Introduction: Steroid-resistant graft-versus-host disease (GvHD) is a major challenge after allogeneic stem cell transplantation and associated with significant morbidity and mortality. There is no therapeutic standard defined beyond calcineurin inhibitors (CNI) and steroids. Furthermore, some patients may have contraindications against CNI or high-dose steroids. Efficacy of ruxolitinib against GvHD has been described recently.
Methods: Ruxolitinib was used for treatment of acute or chronic GvHD in eight patients. The patients either needed intensification of therapy or had contraindications against the use of CNI or high-dose steroids.
Results: Supplementation of therapy in acute GvHD with severe diarrhea with ruxolitinib was unsuccessful. All these patients died from acute GvHD. Introduction of ruxolitinib into therapy and relapse prophylaxis in other patients was successful in 4/4 cases (CR=3, PR=1). Indications for ruxolitinib were contraindications against CNI due to aHUS in two cases and the need for steroid sparing in two other cases. None of these patients suffered from diarrhea at the initiation of ruxolitinib.
Conclusions: Ruxolitinib was effective for therapy of acute and chronic GvHD in higher lines in patients without severe diarrhea. Ruxolitinib could replace successfully CNI and high-dose steroids. Further investigations are necessary to define the position of ruxolitinib in GvHD-therapy.

Disclosure: No conflict of interest disclosed.

Posterdiskussion

Sonstige Themen I

P741

Communication I: advance care planning (ACP) - attempt of implementation in an oncology department

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Introduction: ACP as an obligatory part of care for patients with advanced cancer requires early discussion of potential treatment limitations, consideration of the patient´s preferences and nomination of an authorized caregiver (1) in order to strengthen patient autonomy. BVP of the German interprofessional association for Advance Care Planning (DiV-BVP e.V..; 2) provides a concept with specifically trained facilitators. In our oncology center, BVP was introduced in parallel to a Bochum wide project for nursing homes and those for disabled by the "Ethikkomitee Bochum e.V." (3).
Methods: Patients with advanced cancers were offered a BVP conversation at least once by the oncologist. Primary endpoint was the completion of an advance directive (AD) according to BVP. Participants, duration and number of conversations were documented. Patient´s preferences were compared with estimated prognosis and in case of incongruencies further analyzed. Additional outcomes: adherence to AD, use of intensive care or tumorspecific therapy in the last two weeks of life.
Results: From January 2017 to April 22, 2019, 143 patients have been offered a BVP conversation; 40 AD were completed; median duration of the first conversation was 60 (20 to 120) min, for the second conversation 30 (10 to 80) min. Discrepancies between patient wishes in the AD and medical prognosis were a common reason for further discussion. Broad acceptance of this conversation process has been observed on both patient´s and caregiver´s side and the treatment team.
Conclusions: Elements of the conversation shed light on patients´ needs that had not been addressed in a formal way before and provide relieve for future care. Standardized documentation provides a chance to inform all persons involved in the care of the individual patient. Due to the fact that discrepancies between patient wishes and medical perspective were frequent a need for a more effective conversation tool to communicate prognosis is suggested.

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Disclosure: No conflict of interest disclosed.

P742

Communication II: "Zukunftsdialog" - a structured communication concept based on "serious illness conversation" for patients with advanced cancer

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Introduction: Patients with advanced cancers demand an early structured, standardized communication about their wishes and goals by their physician, but this is rarely realized. Improving prognostic awareness enhances the use of early palliative care leading to a better outcome[1]. The "Serious illness conversation program" by the Ariadne labs has addressed this issue and has provided a structured conversation protocol for this purpose [2]. We report on the introduction of a German version (ZD) into our oncology department.
Methods: The authors have initiated a German translation of the SIC program after authorization by Ariadne labs. A pilot fourhour workshop was held in November 2018 with hospital oncologists at Bochum and these were asked to offer the ZD to their patients. Appropriate patients had advanced cancers and were to be offered a ZD after a "breaking bad news" conversation by providing key issues and a pre visit letter. Primary endpoint was the documentation of the dialogue. Conversation time, willingness to learn about specific prognosis, recommendations as a result of the conversation were documented.
Results: As of April 22, 2019, 40 patients have been offered a ZD, with 16 completions. A heterogeneous readiness to practice has been observed. The vast majority of patients was willing to learn about their prognosis (15 of 16). Recommendation of palliative care use and providing information about the palliative sedation concept were frequent. A formal way to communicate the results of the dialogue to the key caregivers has yet to be established. Data acquisition is planned until August 31, 2019 and an update will be presented.
Conclusions: ZD provides a useful tool to address patient communication needs from the beginning of their diagnosis. Providing specific wordings for prognostic information is a strength of this tool. Implementation in an oncology department requires more than one workshop.

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Disclosure: No conflict of interest disclosed.

P743

Rinsing blood bags with Ethanol and Tween 20 can wash out plasticizers but no bigger microplastic particles

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Introduction: The global plastic production reached nearly 350 million tonnes in 2017 from which almost 65 tonnes belong to Europe.1 There, 30,000 tonnes of plasticized PVC are used for medical applications every year.2 Blood bags are predominantly made of polyvinyl chloride (PVC) and contain plasticizers like Bis(2-ethylhexyl) phthalate (DEHP). Even though the plasticizers show a positive impact on blood cells, it's generally known that plasticizers get solved in the blood bag solutions and thereby get transferred to patients. The current issue of the plastic pollution on earth raises the question whether microplastics can also be washed out of the PVC blood bags.
Material and methods: To find out whether microplastic particles are released from blood bags, three blood bag systems consisting of four bags were rinsed and incubated with a solution of absolute ethanol and 1% Tween 20. The eluate was vacuum filtered through a 0.2 µm pore size membrane and examined using Fourier transform infrared (FTIR) spectroscopy.
Results: Due to FTIR spectroscopy, DEHP and related plasticizers were identified on the membranes of blood bag eluates. However, the presence of microplastic particles > 25 µm could be excluded.
Conclusion: Although the effects of plasticizers on human health are still not completely enlightened, blood bags seem to be supposedly free from microplastic contamination and therefore, in this regard, safe for the patients. Nevertheless, the plasticizers should not be ignored.

Disclosure: No conflict of interest disclosed.

P744

Combining intervision and balint group work (BGW) for preventing professional burnout (BO) in young oncologists (YO)

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Introduction: The majority of young oncologists (≤ 40 years) experience signs of BO (1). Although the declaration of Geneva demands doctors to attend to their "own health, well-being, and abilities" and in view of the challenge to recruit YO, there are surprisingly few attempts to address this dilemma (1).
Methods: In our department an intervision group was established on a monthly basis. Participation was voluntary and open to all doctors regardless of age and seniority. Based on BGW stressful occupational situations (e.g. treatment of a severely ill patient) were discussed. During intervision methodology was extended, e.g. to modeling.
Results: The majority of the department's YO and some of the senior doctors attended intervision groups regularly and participated enthusiastically. After twelve meetings all of the YO reported that a notable amount of strain was taken off of them. They felt more resilient and satisfied and reported an improved self-esteem. Furthermore positive effects on team-building became obvious, e.g. a higher degree of mutual understanding and more solidarity between team-members. Interestingly, positive effects on team-building were observed beyond the participating colleagues.
Conclusions: By BGW based intervision we were able to establish a means to reduce the risk for BO in YO. These findings are well in line with similar reports (2,3). Our experiences should help young doctors to maintain their work in oncology and offer prospect for more extensive evaluation in order to support the routine application of this concept in oncology.

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Disclosure: No conflict of interest disclosed.

P745

"Well, we have to decide who we can expect to stand this." An empirical-ethics study on Oncologists' reflections concerning communication about chances and limitations of innovative cancer therapies

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Introduction: The involvement of advanced cancer patients in treatment decisions when prognosis is certainly limited is relevant for an authentic decision-making. Against this background two aspects have to be reflected: 1. Biomarker-stratified treatment approaches and immunotherapy successfully improved the outcome of some patient groups. This may increase the uncertainty of prognostication and the right timing for considering limiting tumorspecific therapy. 2. Talking about a limited prognosis with cancer patients is perceived as challenging by oncologists and therefore often avoided. The aim of this empirical study is to investigate oncologists' perceptions with respect to these crucial situations in order to inform the implementation of an ethics policy.
Methods: Guideline-based qualitative interviews were conducted with 24 physicians working at the NCT of Heidelberg University. Transcribed interviews were analyzed according to qualitative content analysis. The empirical data was evaluated in light of the current ethical debate regarding patient involvement in decision-making about therapeutic options.
Results: Almost all interviewed oncologists advocate for open discussions with patients about therapeutic goals and potential therapy limitations. But some fear negative consequences, e.g. with regard to the doctor-patient relationship or compliance of their patients. Particular emphasis is placed on one´s own fear of addressing existential themes, such as death. An interesting finding is that oncologists themselves decide whom they expect to bear how much openness. Additionally, many oncologists refer to the mission of a comprehensive cancer center to develop and to test new cancer therapies. Thus, difficulties may occur, if patients' expectations about the effects of experimental treatments conflict with a realistic therapeutic goal. Overall, the majority of the interviewed oncologists report a need for improvement with regard to the communication of realistic therapy goals.
Conclusions: It is ethically required to put innovative cancer therapies into practice. However, there is a risk that patients' expectations are overly optimistic and therefore it becomes all the more important to discuss treatment goals, which are still achievable. Given the fact that our study shows there is room to improve patient involvement in treatment decisions we aim for an ethics policy to establish the institutionalization of a structured communication concept.

Disclosure: No conflict of interest disclosed.

P746

Older adults with AML: clinical outcome in a large tertiary referral center based on a review of the past two decades

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Introduction: In older patients [pts] with AML, an accumulation of adverse patient- and disease-related factors leads to inferior survival. Data on outcome outside of clinical trials is particularly scarce in this subgroup of pts. Here, we provide clinical/genetic characteristics and long-term survival in a large cohort of AML pts ≥ 60 years [yrs] who were treated at our center, one of the largest tertiary referral centers in Germany, over the past 18 yrs.
Methods: Data were retrieved from the local AML database. 590 pts ≥ 60 yrs with newly diagnosed AML were treated at our center between 2000 and 2017. These pts were characterized based on ECOG score, Charlson comorbidity index [CCI], ELN risk group and type of AML therapy. Survival analysis was performed accordingly using Kaplan-Meier- and Cox regression models.
Results: Median age was 68 yrs (range 60 - 90 yrs) in the entire cohort. Median follow-up was 56.0 months [mo]. Most pts were in good general condition at baseline (median ECOG score = 1, CCI = 1) and had an intermediate / adverse cytogenetic / molecular risk (ELN 2010: 8% favorable, 51% intermediate, 26% adverse, 14% n.a.). 66% of all pts underwent intensive chemotherapy (> 60 yrs: 75%, > 70 yrs: 23%, > 80 yrs: 2%), 26% received palliative chemotherapy (LDAC, HMA) and 9% were eligible for best supportive care [BSC] only. Allogeneic HSCT was performed in 55% of intensively treated pts. Clinical trial enrollment rate was 28%. In the whole cohort, 5- and 10-yr EFS was 12% and 6%; OS was 18% and 9%, respectively. Median OS was 21.6 mo in the intensively treated group as compared to 3.9 mo with palliative chemotherapy and 1.3 mo with BSC. Shorter EFS / OS was significantly associated with an ECOG score > 1, an adverse ELN risk group and baseline serum ferritin [SF] levels ≥ 1000 µg/l. Long-term survival was only observed in intensively treated pts (5-year-OS: > 60 yrs = 26%, > 70 yrs = 20%). In pts > 80 yrs, median OS was 8.3 mo; the longest OS in this subgroup was 12.3 mo.
Conclusions: A substantial proportion of older pts (even > 70-80 yrs) were able to receive intensive chemotherapy, at least under the selection bias of a university medical center. Survival rates are disappointingly low; however, long-term survival was observed with intensive therapy. Furthermore, the negative prognostic impact of high baseline SF that has

recently been described in intensively treated AML pts (Ihlow et al. 2019) was also confirmed in this subgroup of older pts.

Disclosure: No conflict of interest disclosed.

P747

Targeting thymidine-phosphorylase (TP) expressing cells - a possible way to achieve long term disease stabilisation in advanced solid tumours

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Introduction: TP whose activity is identical to the platelet derived endothelial cell growth factor is an enzyme necessary for the conversion of the oral prodrug capecitabine to 5-FU. Additionally, TP expression may be induced by various cytokines such as TNF, IFN, IL-1, and IL-10, and is inhibited by tipiracil which augments the efficiacy of trifluridine. In normal tissues TP preferentially is localised in macrophages and endothelial cells. In malignant situations TP may be found in tumour cells and even more frequently in tumour adjacent stromal cells.
Methods: Based upon an own case who survived gastric cancer with peritoneal metastasis under maintenance therapy with capecitabine for a period of 7.5 years we analysed the literature for similar reports describing long term survival under long term application of capecitabine.
Results: We found several reports mentioning lenghtened survival under long term maintenance capecitabine. A beneficial effect was described in advanced stages of various tumor entities such as esophagogastric junction adenocarcinoma, hepatocellular carcinoma, pancreatic carcinoma, breast cancer and neuroendocrine tumours. The poor prognosis of metastasising gastric cancer has been correlated to the presence of M2 macrophages, to microvessel density, and to TP expression.
Conclusions: By targeting TP it is possible to modify the activity of tumor adjacent and protumoral acting macrophages and endothelial cells. A more detailed analysis of tumor growth supporting non-lymphocytic cells deserves further attention.
The interpretation of studies combining two antiangiogenic substances should take in
consideration a possible concurrence of both drugs with regard to an overlapping target.
Report more of those cases of advanced malignancies whose median overall survival is > 2N.

Disclosure: No conflict of interest disclosed.

P748

A multinational study on diagnostics of Non-Hodgkin lymphomas in Sub-Saharan Africa

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Introduction: Non-Hodgkin Lymphoma (NHL) are the sixth most common cancer type in Sub-Saharan Africa (SSA). Comprehensive diagnostics of NHL may allow for curatively-intended treatment especially in high-grade lymphomas. We aimed to assess NHL subtypes, stage and further diagnostic factors.
Methods: Our observational study included eleven population-based cancer registries in Benin, Congo-Brazzaville, Ethiopia, Ivory Coast, Kenya, Mali, Mozambique, Namibia, Uganda and Zimbabwe. A random sample of 8 to 86 cases diagnosed between 2011 and 2014 was selected and recorded data was amended assessing hospital records.
Results: A total of 516 patients were included. Additional information was traced for 57.6%. 69.0% of NHL diagnoses were confirmed histopathologically, another 16.9% cytologically. For 48.4% NHL subtype was known. The largest share of NHL subtypes known was observed in Windhoek (94.1%), the smallest in Cotonou (0%). Diffuse Large B-Cell Lymphoma, Chronic Lymphocytic Leukemia and Burkitt Lymphoma were the three most common NHL subtypes of 25 identified in total (47,6%, 18,8%, 6,0% respectively). Among NHL subtypes, 57,8% were classified as high-grade B-cell NHL, 31,3% low-grade B-cell NHL and 5,6% T-cell NHL. HIV was found positive for 19.0% of which 84,7% received anti-retroviral treatment, 11,2% of patients were HIV-negative whereas HIV status remained unknown for 69.8%. Stage at diagnosis was advanced for 26.2% and unknown for 64.0%. 23.1% received imaging of any sort. ECOG performance status was 2 or worse for 15.4% and missing for 73.8% of patients.
Conclusions: We found NHL subtype, stage and HIV status unknown for the majority of patients. However, according to NCCN guidelines on NHL diagnostics stratified for SSA, knowledge about these three criteria is crucial for personalized treatment. Investments in comprehensive diagnostics facilities and introduction of a standard immunohistochemistry panel may increase precision of NHL diagnostics and hence the possibility of effective treatment drastically.

Disclosure: No conflict of interest disclosed.

P749

High altitude medicine for medical students in a blended learning concept along the Annapurna trial as basis for the curriculum

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Introduction: The elective course "high altitude medicine" at the University Goettingen, department hematology and oncology is offered for > 10 years. Students of all terms are allowed, therefore previous knowledge is heterogenous. Learning objectives are complex and multidisciplinary. However most pathophysiological changes in high altitude leading to high altitude diseases are exemplary for diseases of blood, heart, kidney and lung. In a lecture students report the content of the current curriculum in groups of 3-4 students after self-study of the subjects thought. Literature is provided on the server for teaching materials.
Methods: To evaluate if a blended learning concept prior to the given lectures is in favor of the established curriculum we developed a concept of blended learning using key feature cases with the Annapurna trekking trail and it`s different altitudinal belts as basis. For each altitudinal belt, videos with field reports of two students and measurement of heart rate, oxygen saturation and breathing rate on the Annapurna trail are available (fig. 1). Goal is to achieve a similar level of knowledge for all students at the beginning of the course.
Results: Learning concept is scheduled with videos and key feature cases on each altitudinal belt. First topic: adaption of heart, lung and kidney to high altitude (physiology and pathophysiology), consequences in case of insufficient adaption to high altitude. Second: mountain sickness with different disease patterns (AMS, HAPE, HACE), symptoms (Anamnesis, Examination, differential diagnosis).Third: treatment of mountain sickness (pharmacokinetic and pharmacology). Each student should solve all key feature cases prior the start of the course.
Conclusions: Since level of students is different and topics are complex this blended learning concept should result in a better preparation for the elective course "high altitude medicine" with a higher learning success. In addition students have in a different way an impart of knowledge with a cross link to other topics and disease patterns in internal medicine.

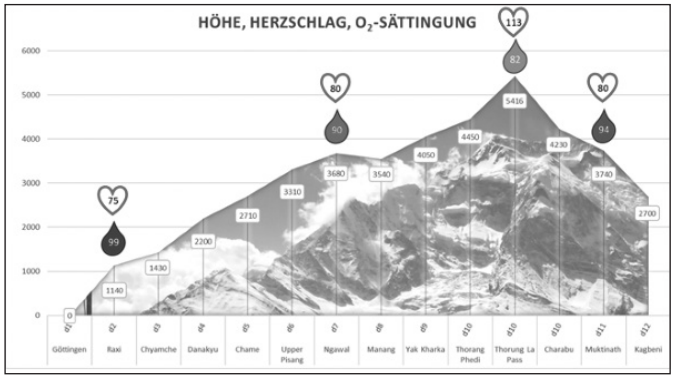

Fig. 1. Altitude, heart rate (heart), and oxygen saturation (red drop)

Disclosure: No conflict of interest disclosed.

P750

Integrating Chinese medicine in Western standard treatment concepts for metastatic colorectal cancer - an international student project

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Introduction: New data support the use of Chinese decoctions (watery extracts of plants) to increase effectiveness of Western standard chemotherapy for metastatic colorectal cancer (mCRC). Most clinicians use Western Medicine (WM) and Chinese Medicine (CM) according to their educational background. At some universities students receive profound teaching of one medical system and fundamentals of another. Will this help them to develop a deeper knowledge and more integrated concepts?
Methods: During a medical exchange program students from the Faculty of Medicine at Rostock University Medical Center and from the School of Chinese Medicine at The Hong Kong University were asked to develop an integrated treatment concept. Mixed groups with six to eight students, not constrained by their daily routine, reviewed selected literature and discussed their findings with experts in WM and CM. Three major topics were selected to reflect the different steps of therapy. The effectiveness of this project-based learning was evaluated with sixty multiple choice questions (MCQ) on the first and at the last day of the meeting.
Results: After five days of cooperative work the students presented their results. During their discussions students from Rostock and Hong Kong had presented and learned the differences and advantages of a more morphologic or functional orientated approach. They noted that with integrated diagnostics the standard procedures of WM will direct the initial phase of therapy. Chinese Diagnoses become more important during the course of the disease. Short term side-effects while on tumor specific treatment may be managed by CM, but potential interactions with standard therapy are not well investigated. Long-term side-effects occurring after tumor specific treatment can be treated by movement, nutrition, acupuncture and decoctions. Priorities of patients and further research on specific advantages could establish integrated concepts. Statistical analysis of the MCQ´s showed a significant improvement of knowledge during the five days, mainly caused by the advanced students from Hong Kong.
Conclusions: After five days of joined learning students increased their measurable knowledge (MCQ) and developed a conclusive concept for an integrative treatment approach. Early project based learning confronting students with different aspects of medicine resulted in new concepts, offering the perspective to evaluate the best of diverse possibilities in future studies.

Disclosure: No conflict of interest disclosed.

Posterdiskussion

Lungenkarzinom

P751

Impact of subsequent post-discontinuation immunotherapy on overall survival in patients with unresectable, stage III NSCLC from PACIFIC

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Introduction: In cancer trials, pts often receive subsequent lines of anticancer Tx following progression, which, in standard ITT analyses, can lead to bias and underestimation of OS Tx effect. In the phase 3 PACIFIC trial of durvalumab vs. placebo in Stage III NSCLC pts without progression after CRT, both primary endpoints PFS and OS were met, significantly improved with durvalumab. However, after discontinuation, many pts received further anticancer Tx (41% and 54% in the durvalumab and placebo groups), including immunotherapies (IMTs), which may have influenced OS. Using the Rank Preserving Structural Failure Time (RPSFT) model, we quantified the specific impact of subsequent IMT on OS in PACIFIC.
Methods: RPSFT modeling is commonly used for analysis of trials with crossover. By assuming a similar effect for Tx in different sequences, RPSFT is capable to pinpoint the most likely effect size based on observed data. Here, we adapted RPSFT to isolate the likely effect of subsequent IMT by assuming similar mortality risk reduction for nivolumab, pembrolizumab, and durvalumab. RPSFT analyses were applied to quantify health outcomes for two hypothetical scenarios: (1) no subsequent IMT was received by pts in either arm, and (2) among placebo pts who received subsequent Tx (54%), all received IMT as first subsequent Tx, and durvalumab pts received no subsequent IMT, to test if delaying IMT was detrimental.
Results: Among pts randomized to durvalumab and placebo, 8% (38/476) and 22% (53/237), respectively, received subsequent IMT. Within the ITT population, the HR for OS with durvalumab vs. placebo was 0.68 (95% CI, 0.53-0.87), with respective median OS not reached (NR) and 28.7 months. For scenario 1, there was minimal change in OS, with an estimated HR of 0.67 (95% CI, 0.52-0.86) and identical median OS estimates. For scenario 2, the estimated HR was 0.79 (95% CI: 0.62-1.00), with median OS NR and 32.2 months, respectively.
Conclusions: After removing the effects of subsequent IMT, the OS benefit with durvalumab was still evident compared with the ITT analysis. In addition, early Tx with durvalumab after CRT appeared to be associated with improved OS compared with starting IMT after progression.

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Maike de Wit: Financing of Scientific Research: AstraZeneca, MSD, Abbvie; Expert Testimony: AstraZeneca, MSD, Pierre fabre; Other Financial Relationships: Astellas, BMS

P752

Top level MET amplification: an unfavourable subgroup in non-small cell lung cancer patients

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Introduction: MET amplification occurs in human tumors, including non-small cell lung cancer (NSCLC). MET inhibitors (tyrosine kinase inhibitors) have demonstrated activity in MET amplified NSCLC, presumably with a gene dose effect. So far, there is no distinct determination of high level MET amplification. Furthermore, there is some ambiguity about MET amplification as a driver mutation with a specific phenotype of the disease.
Methods: 373 patients with NSCLC were consecutively and unselected tested for MET gene copy number (GCN) by FISH. Mean GCN, MET/CEN7 ratio and another FISH parameters were identified and correlated with morphological and molecular pathological characteristics of the tumors.
Results: Based on the variability of obtained data a new top level category of MET amplification was defined (>90th percentile of average GCN; >= 10 MET gene copies per tumor cell). This criterion was fulfilled in 2% of analyzed tumors. These tumors were exclusively poor differentiated adenocarcinomas with a predominant solid subtype and characteristics of pleomorphic carcinomas. Rarely, co-alterations were detected (KRAS mutation or Exon 14 skipping mutation). In this top level group, there were no EGFR mutation or ALK or ROS1 alterations. The most important clinical feature was a significant reduction in overall survival (OS; median OS: 8 months). Worse prognosis was independent from primary stage or kind of therapy.
Conclusions: The new defined top level category of MET amplification in NSCLC defines a specific subgroup of pulmonary adenocarcinoma with adverse prognosis and characteristic morphological features.

Disclosure: No conflict of interest disclosed.

P753

A rare case of large-cell neuroendocrine lung carcinoma sensitive to ALK inhibitors

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Background: Anaplastic lymphoma kinase (ALK) fusions drive 5% of lung adenocarcinomas and confer superior survival due to treatment with tyrosine kinase inhibitors (TKI). In contrast, driver mutations are exceedingly rare in large-cell neuroendocrine lung carcinoma (LCNEC, ca. 3% of NSCLC), for which median survival does not exceed 12 months under chemotherapy.
Case report: We report the unusual case of a 47-year-old female smoker (20 pack-years) patient with metastatic TP53^{wt} LCNEC driven by EML4-ALK V2 (E20;A20), as revealed by RNA and DNA NGS. First-line crizotinib was initiated in 04/17 and resulted in stable disease for six months. Subsequent oligoprogression in the right parotid gland was treated with radiotherapy. Upon multilocular progression two months later (left lung and chest wall, left parotid) without detection of ALK mutation in a repeat tumor biopsy, TKI therapy was empirically switched to alectinib, which resulted in significant tumor shrinkage (partial remission by RECIST). A second oligoprogression in the left breast 10 months later was treated by partial mastectomy. Molecular workup of the surgical specimen revealed an ALK p.V1180L mutation, resistant to both crizotinib and alectinib, but sensitive to ceritinib (PMID: 25228534). Consequently, upon thoracic disease progression 3 months later, alectinib was switched to ceritinib, but no tumor response was noted. Repeat histology and resistance testing two months later revealed a different ALK mutation (p.L1196M), conveying resistance to crizotinib and alectinib, but not to brigatinib (PMID: 27432227, 21502504). Brigatinib was administered, but had to be discontinued 6 weeks later due to disease progression in the brain and thoracic lymph nodes.
Conclusions: This case illustrates that instances of LCNEC with actionable alterations, e.g. ALK fusions, do occur, even in smokers, and can derive significant benefit from targeted therapies. However, TKI sensitivity was generally lower and the disease course more aggressive, including atypical metastatic sites, than in case of ALK$^+$ lung adenocarcinoma, despite presence of the relatively favourable EML4-ALK V2 and wild-type TP53. Moreover, TKI efficacy did not correlate with detection of ALK mutations, since second-line alectinib showed the longest duration of response despite unremarkable ALK sequencing results, while later TKI lines did not confer clinical benefit, despite presence of putatively sensitive ALK mutations based on in vitro results.

Disclosure: Christiane Wiedemann: Financing of Scientific Research: Cellgene Petros Christopoulos: Advisory Role: Boehringer Ingelheim, Roche, Chugai, Novartis; Financing of Scientific Research: Novartis, MSD; Expert Testimony: Novartis, Roche, AstraZeneca, Takeda

P754

Efficacy of Afatinib in the clinical practice - first results of the GIDEON trial: a prospective non-interventional study (NIS) in EGFR mutated NSCLC in Germany

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Background: Afatinib is an irreversible ErbB family blocker, which is approved as monotherapy for the treatment of advanced non-small cell lung cancer (NSCLC) patients with activating EGFR mutations. Here we report the first interim analysis of the NIS GIDEON investigating the effectiveness and tolerability of afatinib as first line treatment in daily clinical routine in Germany.
Methods: EGFR-mutated NSCLC patients were treated with afatinib according to label until progression, death or discontinuation due to patients' or physicians' decision. Effectiveness (objective response rate, ORR; disease control rate, DCR and progression-free survival, PFS) was prospectively assessed by investigators and additional data about tolerability under everyday treatment conditions were documented.
Results: A total of 151 patients were enrolled in the study and were treated with afatinib. EGFR mutations comprised exon 19 deletions (Del19, 56.6%), L858R point mutations (21.9%) and uncommon mutations

(18.5%). Median age was 67 years (IQR 38-89) with 91 Pat. ≥65 years (60.3%). 32% of the patients had brain metastases at study entry. ORR for the total treated population was 73% with a DCR of 90%. ORR was similar according to different subgroups, e.g. mutation type, age and patients with brain metastases. Median PFS at the time of analysis was 12.9 months in the total treated population and 11 months in the population of patients with brain metastases. OS data are not mature yet. The most frequent documented ADRs were diarrhea and rash/acne, with 11.6% of patients discontinued treatment due to ADRs.
Conclusions: Afatinib is a standard therapy for patients with activating EGFR mutations in Germany. The first results of this prospective NIS confirm the robust clinical data for afatinib in clinical routine setting. Patients with brain metastases, which are often underrepresented in clinical trials, do benefit from afatinib as ORR and DCR are comparable with the total treated population. The slightly shorter mPFS is in line with the known negative prognostic impact of brain metastasis.

Trial Registration Number: NCT02047903

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Wolfgang Brückl: Advisory Role: Abbvie, AstraZeneca, BMS, Boehringer Ingelheim, Celgene, Chugai, Lilly, MSD, Pfizer, Roche, Stratifyer; Financing of Scientific Research: Abbvie, Astra Zeneca, BMS, Boehringer Ingelheim, Celgene, Chugai, Lilly, MSD, Pfizer, Roche, Stratifyer

P755

Prevalence of programmed death ligand-1 (PD-L1) by demographic, disease and sample characteristics in unresectable, stage III NSCLC

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Background: PACIFIC (NCT02125461) was a randomised, placebo-controlled, phase 3 trial evaluating the immune checkpoint inhibitor durvalumab in patients with unresectable, Stage III non-small cell lung cancer (NSCLC) who did not have disease progression after concurrent chemoradiotherapy (cCRT). Both primary endpoints of progression-free survival and overall survival were met and significantly improved with durvalumab, with similar safety, versus placebo (Antonia et al, NEJM 2017; 2018). We report exploratory analyses of the prevalence of tumour PD-L1 expression by baseline patient, disease and sample characteristics, and by response to prior treatment, for patients in PACIFIC.
Methods: If available (provision of formalin-fixed paraffin-embedded tumour resection or biopsy samples was optional), archived pre-cCRT tumour tissue was tested retrospectively for PD-L1 tumour cell (TC) expression using the VENTANA PD-L1 (SP263) immunohistochemistry assay and scored at validated cut-offs of ≥25% and ≥1% expression. Overall PD-L1 prevalence (regardless of treatment arm) was summarised by patient subgroups defined by various characteristics, and assessed using a Pearson's chi-squared test for between-group differences.
Results: Of 713 randomized patients, 451 (63.2%) were evaluable for PD-L1 status. Among PD-L1-evaluable patients, 67.2% (303/451) had TC ≥1% and 35.3% (159/451) had TC ≥25% (similar to previous reports in metastatic NSCLC). PD-L1 prevalence by various characteristics at the TC ≥1% cut-off are reported in Table 1.
Conclusions: There were no important differences noted in PD-L1 prevalence between relevant subgroups at the TC ≥1% or TC ≥25% cut-offs (latter data not shown). PD-L1 status was unaffected by sample type or age or biopsy location, suggesting expression is stable from diagnostic biopsies, which supports the use of either primary tumour or lymph node biopsies for PD-L1 testing.
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Maike de Wit: Financing of Scientific Research: AstraZeneca, MSD, Abbvie; Expert Testimony: AstraZeneca, MSD, Pierre fabre; Other Financial Relationships: Astellas, BMS

P756

Complete response to neoadjuvant immunochemotherapy in a patient with non-squamous non-small cell lung cancer

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The advent of checkpoint inhibitors has strongly shaped the therapeutic landscape in the treatment of lung cancer in the recent past. One of the pivotal studies in the last year has been the Keynote-189 clinical trial that revealed superiority of the addition of PD-1 inhibitor pembrolizumab over placebo to pemetrexed and a platinum-based drug regarding overall survival and progression-free survival in the first-line treatment of metastatic non-small cell lung cancer (NSCLC) (Gandhi, 2018 NEJM).
Here, we report the successful treatment with carboplatin, pemetrexed, and pembrolizumab in a 62 year-old female patient an adenocarcinoma of the lung. In October 2018, the patient was diagnosed with non-squamous NSCLC, stage cT4 cN2bulky cM0. No oncogenic driver mutations or fusions in the genes coding for EGFR, ALK, ROS1, or BRAF were identified. Interdisciplinary consultation resulted in advice against both upfront surgical intervention due to T4N2bulky stage and thoracic radiotherapy due to the large radiation field. Based on a high PD-L1 expression (TPS 90%) and the data from the Keynote-189 trial we decided to administer carboplatin, pemetrexed, and pembrolizumab aiming for a remission that would eventually allow resection of the residual tumor. The patient received four cycles without any complications, and tumor assessment with PET-CT in January 2019 revealed complete metabolic response. After a cycle of pembrolizumab monotherapy, a thoracotomy with lobectomy of the inferior lobe, atypical wedge resection of the upper lobe and a systematic lymphadenectomy was performed. Histological analysis revealed no vital tumor tissue and a TNM classification ypT0 pN0 (0/27) pMx L0 V0 Pn R0.
Our case illustrates the high potential of the combined treatment of chemotherapy and checkpoint inhibitors. In order to gain more insight into the molecular premises for such a clinical course, a comprehensive analysis of the patient´s tumor tissue is planned.

Disclosure: Matthias Ulmer: Advisory Role: MSD, Lilly; Financing of Scientific Research: MSD, Lilly; Other Financial Relationships: MSD, Lilly
Inn Chung: No conflict of interest disclosed.

P757

PACIFIC-R: First real-world study of patients with unresectable, stage III NSCLC treated with durvalumab after chemoradiotherapy

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Introduction: Approximately 30% of patients with non-small-cell lung cancer (NSCLC) are diagnosed with Stage III disease, which is often unresectable. Historically, the standard of care (SoC) has been platinum-based chemoradiotherapy (CRT), but outcomes have been poor. Durvalumab is a selective high-affinity, human IgG1 monoclonal antibody that blocks PD-L1 binding to PD-1 and CD80. In the phase 3 PACIFIC trial of durvalumab versus placebo in patients with unresectable, Stage III NSCLC without progression after concurrent CRT (cCRT), both primary endpoints progression-free survival (PFS) and overall survival (OS) were met and significantly improved with durvalumab (HR for PFS, 0.52; 95% CI 0.42-0.65; P < 0.001; HR for OS, 0.68; 99.73% CI 0.47-0.997; P = 0.0025) with similar safety between treatments (Antonia et al, NEJM 2017; 2018). PACIFIC-Real World (PACIFIC-R) will assess if durvalumab treatment after cCRT shows similar efficacy and safety in a large, real-world population.

Methods: Trial design

PACIFIC-R is an international, observational study that will enroll 1200 NSCLC patients who have received durvalumab as part of early access programs (EAPs) between Sept 2017 and Dec 2018. In the EAP, eligible patients are adults with histologically or cytologically documented unresectable, Stage III NSCLC, regardless of tumor PD-L1 expression, who have not progressed after definitive CRT. Pts received durvalumab (10 mg/kg intravenously) every two weeks. Patients will be enrolled in the PACIFIC-R study after discontinuation of the EAP in participating countries. Data will be abstracted from patients' medical records at several time points within the 5 year study period. Primary endpoints are PFS (investigator assessed) and OS. Secondary endpoints include PFS and OS in patient subgroups; time to distant metastases; sites of disease progression; adverse events of special interest leading to treatment interruption, discontinuation or medical intervention; and descriptive analyses of demographic and clinical characteristics of pts treated with durvalumab in a real-world setting. Recruitment for this study is ongoing.

Clinical trial identification NCT03798535.

Funding: AstraZeneca

Disclosure: No conflict of interest disclosed.

P758

Real world molecular testing in patients with EGFR mutation-positive locally advanced or advanced NSCLC in routine practice in Germany - Updated interim results of the clinical registry PANORAMA (NCT02777658)

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Introduction: Epidermal Growth Factor Receptor mutations (EGFRm) are among the most common in patients (pts) with non-small cell lung cancer (NSCLC) and can be targeted with EGFR tyrosine kinase inhibitors (TKIs). Appr. 50% of the pts will acquire resistance by the T790M mutation (T790M). Osimertinib (OSI) is a 3rd generation EGFR-TKI and standard of care (SoC) for pts who developed the acquired resistance by T790M during the prior EGFR-TKI treatments, while other strategies, such as chemotherapy (CT) is used in T790M negative pts. Increasing evidence from both, clinical studies and registry data suggests that only the minority of patients can benefit from sequential TKI treatment with OSI. This analysis therefore aims at shedding light on to this topic.

Methods: PANORAMA is a prospective, clinical registry for pts with EGFR mutation-positive (EGFRm+) locally advanced or metastatic NSCLC, who progressed after prior TKI therapy (cohort 1) or pts diagnosed with *de novo* EGFR T790M (cohort 2). Beside others, routine clinical, molecular testing and patient-reported outcome data are collected. The 2nd interim analysis (cut-off: 1APR2019) will be conducted for the cohort 1. Data were analyzed by descriptive statistics.

Results: The 2nd interim analysis will provide data of 148 evaluable pts: At diagnosis median age was 67.5 yrs (min-max 38.4-84.5 yrs), 49 (33%) pts were male and 98 (66%) were diagnosed with NSCLC Stage IV. 124 pts (84%) were tested for EGFRm at diagnosis, the remaining pts at later time points. At time of progression on/after TKI 74/148 pts (50%) were tested again, overall re-test rate after progression at any time was 76% (113 pts). 107 (95%) out of these 113 re-tested pts were tested forT790M thereof 73 pts (64%) were T790M pos (14 pts not yet documented). 55 (75%) pts who were tested T790M pos after progression (n=73) were treated with OSI. No difference in T790M positivity in the EGFRm subgroups (Ex19Del, L858R) was apparent. Further details on molecular testing will be shown.

Conclusions: The results will help to understand evolving Real World pts management, treatment patterns and associated outcomes among pts with EGFRm locally advanced or advanced NSCLC who have progressed on/after TKI therapy. These data help validating the growing number of data sets suggesting that only a minority of EGFRm NSCLC pts benefit from sequential TKI-treatment with OSI after TKI-progression.

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Disclosure: Christian Schumann: Expert Testimony: AstraZeneca
Frank Griesinger: Advisory Role: AstraZeneca, Boehringer Ingelheim, Novartis, Pfizer, Roche, BMS, MSD, Celgene, Lilly, Takeda, Siemens, Abbvie, Bayer; Financing of Scientific Research: AstraZeneca, Boehringer Ingelheim, Novartis, Pfizer, Roche, BMS, MSD, Celgene, Lilly, Takeda, Siemens, Abbvie, Bayer; Expert Testimony: AstraZeneca, Boehringer Ingelheim, Novartis, Pfizer, Roche, BMS, MSD, Celgene, Lilly, Takeda, Siemens

P759

Feasibility and clinical value of serial circulating tumor DNA testing in metastatic lung adenocarcinoma patients undergoing TKI treatment

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Background: Circulating tumor DNA (ctDNA) has emerged as a promising noninvasive diagnostic tool to guide treatment for patients with non-small cell lung cancer (NSCLC). In this study, we investigate the potential clinical utility of serial ctDNA monitoring in patients with metastatic lung adenocarcinoma undergoing tyrosine-kinase treatment.
Patients and methods: 20 patients with metastatic lung adenocarcinomas undergoing treatment with targeted tyrosine kinase inhibitors (TKI) were included in this single-institution observational cohort study. Plasma samples were obtained prior to treatment (baseline), after 4 weeks, at first radiologic evaluation and at the time of disease progression. ctDNA next-generation sequencing was carried out by Ion Torrent, using the Oncomine Lung cfDNA Assay, which covers 11 genes frequently mutated in NSCLC.
Results: 54 individual plasma samples were obtained from 20 patients (mean 2.7, range 1-4). The median time between first and last ctDNA analysis was 30.5 days (25^{th}-75^{th} percentile: 0-106 days). At baseline, 9 (45%) patients had detectable ctDNA mutations and more than one mutation was detected in 2 out of these 9 patients. TP53 (30%) and EGFR (20%) were the most common mutations detected. At disease progression, samples were collected from 9 patients and of these, 6 patients had detectable mutations, but none of these samples revealed the T790M resistance mutation. Overall, we detected mutations in 50% (27/54) of plasma samples with mutant allele frequencies (MAF) ranging from < 0.1% to 9.3 %. In our cohort, the most common mutations occurred in TP53 (28%) and EGFR (26%). In addition, we detected mutations in KRAS (4%), MAP2K1 (4%), and PIK3CA (4%). Preliminary analysis did not show a significant difference in overall survival (log-rank; P = 0.683) and progression-free survival (log-rank, P =0.849) between patients with detectable and without detectable baseline ctDNA.
Conclusions: In this study, we show the feasibility of mutation detection and potential clinical utility of serial ctDNA analysis in metastatic lung adenocarcinoma patients.

Disclosure: No conflict of interest disclosed.

P760

FIND: a phase II study to evaluate the efficacy of erdafitinib in FGFR-altered squamous NSCLC

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Introduction: Genomic FGFR alterations and their oncogenic driver potential are frequently observed in various cancers. Response rate of above 30% was observed In FGFR mutated or translocated tumor types. Preclinical cell line and patient-derived sqNSCLC xenograft models with FGFR mutations or translocations indicate strong oncogenic activity and potential sensitivity to FGFR inhibitors in patients with sqNSCLC. Approximately 3% of all sqNSCLC patients harbor somatic alterations within FGFR genes. Concerning FGFR mutations, only some of them are shown to be oncogenic drivers *in vitro* and *in vivo* experiments or first in man trials.
Methods: Screening for FGFR mutations/translocations will be performed within the national Network of Genomic Medicine (nNGM) in 15 screening centers in Germany. SqNSCLC patients with activating FGFR genetic alterations will be treated in 9 clinical centers in Germany with the selective FGFR1-4 kinase inhibitor erdafitinib. Archival samples, fresh frozen tumor samples and blood for circulating tumor DNA will be collected before treatment and at time of progression. Patients will be treated until disease progression or unacceptable toxicity.
Results: The study was initiated in April 2019. Until now, one patient with FGFR3 mutation is in screening. The updated analysis will be presented.
Conclusion: FGFR alterations are rare in sqNSCLC patients. To identify these alterations is of clinical importance as treatment options for sqNSCLC are very limited. Screening in large networks such as nNGM is necessary to identify potential patients, who can benefit from FGFR targeted therapy.

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Jürgen Wolf: Advisory Role: Abbvie, Astra Zeneca, Chugai, Ignyta, Roche, Pfizer, MSD, Lilly, Novartis, Boehringer Ingelheim, Bristol Myers Squibb.; Financing of Scientific Research: Abbvie, Astra Zeneca, Chugai, Ignyta, Roche, Pfizer, MSD, Lilly, Novartis, Boehringer Ingelheim, Bristol Myers Squibb.; Expert Testimony: Janssen, Pfizer, Novartis, Bristol Myers Squibb, MSD.; Other Financial Relationships: Travel funding: Abbvie, Astra Zeneca, Chugai, Ignyta, Roche, Pfizer, MSD, Lilly, Novartis, Boehringer Ingelheim, Bristol Myers Squibb.

P761

A prospective, randomized, single blinded multicentre trial to evaluate molecular genetic characterisation of primary diagnosed or relapsed non small cell lung cancer by single or combination of diagnostic procedures - The PROFILER study

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Introduction: Detection of targetable molecular genetic alteration is crucial for individualized treatment of advanced non-small-cell lung cancer (NSCLC). Therefore missing any targetable alteration may has impact on patient's progression free and even overall survival. Although laboratory testing for molecular genetic alterations continuously improve, little is known about how biopsy technique affects the detection rate of different mutations. In a retrospective, single center study the detection rate of EGFR mutations in tissue obtained by bronchoscopic cryobiopsy (BCB) was significantly increased compared to other standard tissue sampling techniques. So we initiated a prospective multicenter randomized single blinded study to evaluate accuracy of molecular genetic characterization of NSCLC patients.
Methods: Key inclusion criteria are suspected lung cancer or suspected relapse of known NSCLC that is bronchoscopically visible. Patients are randomized either to have a BCB or a bronchoscopic forceps biopsy

(BFB). If indicated transbronchial needle of suspect lymph nodes is performed additionally. In each patient preinterventional blood is drawn for liquid biopsy.
As primary endpoint differences of molecular genetic alterations in NSCLC between BCB and BFB is assessed. Secondary endpoints are differences in the combined detection of molecular genetic alterations between BFB and BCB, transbronchial needle aspiration and liquid biopsy.
This trial plans to recruit 540 patients, leading to an evaluable number of 178 NSCLC patients per study cohort (forceps or cryobiopsy). Histopathological and molecular genetic evaluation using next generation sequencing are performed by the affiliated pathological departments using a harmonized workup as defined for cooperation partners in the national network for genomic medicine in lung cancer (Netzwerk Genomische Medizin Lungenkrebs).
Results: We present the design of a prospective multicenter randomized single blinded trial to evaluate the differences in detection rate of various known recurrent molecular genetic alteration by BFB, BCB, endobronchial ultrasound guided needle aspiration and liquid biopsy in NSCLC patients.
This trial was registered at clinicaltrials.gov, initial results are expected in the second quarter of 2021.

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Jürgen Hetzel: Financing of Scientific Research: für Bronchoskopie- Kurse durch Erbe Elektromedizin GmbH; Expert Testimony: Finanzielle Unterstützung dieser IIT durch AstraZeneca und Erve Elektromedizin GmbH

P762

EGFR and HER3 expression in circulating tumor cells and tumor tissue from non-small cell lung cancer patients

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Although clinically relevant, the detection rates of EpCAM positive CTCs in non-small cell lung cancer (NSCLC) are surprisingly low. To find new clinically informative markers for CTC detection in NSCLC, the expression of EGFR and HER3 was first analyzed in NSCLC tissue (n=148). A positiveEGFR and HER3 staining was observed in 52.3% and 82.7% of the primary tumors, and in 62.7% and 91.2%of brain metastases, respectively. Only 3.0% of the brain metastases samples were negative for both HER3 and EGFR proteins, indicating that the majority of metastases express these ERBB proteins, which were therefore chosen for CTC enrichment usingmagnetic cell-separation. Enrichment based on either EGFR or HER3 detected CTCs in 37.8% of thepatients, while the combination of EGFR/HER3 enrichment with the EpCAM-based CellSearch® technique detected a significantly higher number of 66.7% CTC-positive patients (Cohen's kappa = -0.280) which underlines the existence of different CTC subpopulations in NSCLC. The malignant origin of keratin-positive/CD45-negative CTC clusters and single CTCs detected after EGFR/HER3 based enrichment was documented by the detection of NSCLC-associated mutations. In conclusion, EGFR and HER3 expression in metastasized NSCLC patients have considerable value for CTC isolation plus multiple markers can provide a novel liquid biopsy approach.

Disclosure: No conflict of interest disclosed.

P763

Patient-reported outcomes (PROs) with durvalumab by PD-L1 expression in unresectable, stage III NSCLC (PACIFIC)

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Introduction: In the phase 3 PACIFIC study of Stage III NSCLC patients without progression after cCRT, PFS and OS were significantly improved with durvalumab vs. placebo, with no detrimental effect on PROs. We retrospectively investigated the impact of tumour PD-L1 expression on PROs.
Methods: After ≥2 cCRT cycles, patients were randomised (2:1) to durvalumab 10 mg/kg or placebo IV q2w up to 12 mo. If available, optional pre-cCRT tumour tissue was tested for PD-L1 tumour cell (TC) expression using the VENTANA SP263 immunohistochemistry assay and scored at pre-specified (25% or unknown) and post-hoc (1%) cutoffs. PROs were assessed using EORTC QLQ-C30 and -LC13 with changes from BL analysed by a mixed model for repeated measures, HRs for time to deterioration (TTD) by a stratified Cox proportional-hazards model, and ORs for improvement rates by logistic regression.
Results: Of 713 patients, 63% had known PD-L1 status. Similar to the intent-to-treat (ITT) population, most PROs remained stable over time from BL across the PD-L1 subgroups (TC ≥25%, < 25%, ≥1%, < 1%, or unknown), with no clinically meaningful (CM) differences (≥10 points) for durvalumab compared to placebo. However, similar to the ITT population, CM improvements (decreases ≥10 points) from BL to Week 48 were observed for dysphagia and alopecia across most PD-L1 subgroups for both durvalumab (mean changes 8.1 [not CM] – 20.9 and 15.5 – 26.9, respectively) and placebo (mean changes 10.4 – 19.4 and 15.8 – 31.3). Pre-specified and post hoc TTD analyses of PROs by PD-L1 subgroup were generally similar to those of the ITT population, with overlapping HR and 95% CIs. Similarly, PRO improvement rates by PD-L1 subgroup were generally similar to those of the ITT population, with overlapping OR and 95% CIs.
Conclusions: There were no CM differences in PROs between treatment arms across various PD-L1 subgroups. Results were generally consistent with those in the ITT population, suggesting that PD-L1 expression did not influence PROs in this study.

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Posterdiskussion

Translationale Medizin

P764

Evaluation of tumor heterogeneity and therapeutic susceptibility in patient-derived xenograft (PDX) models of gastrointestinal tumors

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Rationally-designed targeted therapies based on distinct molecular fingerprints of indivual tumors are highly promising approaches to improve prognosis in patients with advanced cancer. For the evaluation of these tailored therapies, models are needed, which reflect the individual tumor aspects. This study aimed at establishing cancer xenopatient (PDX/AVATAR) models of gastrointestinal tumors by implanting and propagating samples of the patients' tumors subcutaneously into NSG mice. These PDX were analyzed over several propagation steps with regard to epigenetic alterations. Morevoer xenograft-bearing mice were explored as models for therapeutic intervention by gene knockdown. For this purpose, tumor xenograft tissue was characterized histologically and additional analyses of oncogen expression, proliferation markers, and immunological parameters were carried out by immunohistochemistry and by RT-qPCR. For therapeutic intervention, mice were treated with small interfering RNAs (siRNAs) against target genes of interest. By this means, cancer PDX mouse models were established for several gastrointestinal tumor entities, also allowing biobanking of tumor material. Analyses of expression profiles showed profound inter-patient heterogeneity. Likewise, intratumoral heterogeneity of molecular markers occured. However, for a number of individual tumors remarkably stable expression levels of critical oncogenes were observed over several propagation steps in the mouse. Finally, siRNA-based knockdown approaches showed promising antitumor effects in the mouse. To summarize, murine xenopatient (PDX) models were successfully generated and analyzed. These models will provide deeper tumor-biological insight and may become a platform for treatment prediction and the analysis of molecular effects of targeted therapies.

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P765

Development of pseudomonas exotoxin based Duotoxins for the treatment of hematologic malignancies

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Introduction: Recombinant immunotoxins are fusion proteins composed of an antibody fragment and a fragment of *Pseudomonas* exotoxin A (PE). Paclitaxel, a chemotherapeutic agent and PE-based immunotoxins are highly synergistic against B-cell lymphoma *in vivo*. Aiming to reproduce this synergy in a single molecule, we combined the Paclitaxel analogue DM1 and immunotoxin by lysine-directed conjugation to generate a duotoxin.

Methods: Immunotoxins were genetically modified by site directed mutagenesis using PCR. DM1 was conjugated following manufacturer's instructions. Cytotoxicity of immunotoxin variants and duotoxins was determined by 72 h *in vitro* apoptosis assays against ALL and MCL cell lines. Binding affinity was measured by flow cytometry. *In vivo* efficacy was determined in a systemic JeKo-1 xenograft model.

Results: To prevent DM1-conjugation within PE, a Lysine (K) -free variant was generated by mutating every K (PE-noK). Mutation K590R led to reduced activity, whereas mutation K606R increased activity against selected cell lines. The mutated KDEL motive RDEL was 2.4-fold more cytotoxic than wild-type REDLK and 2.3-fold more cytotoxic than REDL *in vitro* against JeKo-1 cells. In line with *in vitro* data, treatment of mice with K590R decreased immunotoxin efficacy by 0.5-fold whereas K606R increased efficacy by 1.5-fold compared with wild-type PE and KDEL-motive RDEL was 2.3-fold more active than REDLK. Next, the optimized immunotoxin PE-K606R-RDEL was conjugated with DM1 by lysine-conjugation. Conjugation of more than 5 DM1-molecules per immunotoxin molecule decreased activity in a dose dependent manner *in vitro* and *in vivo*. Affinity analysis suggested that conjugation with more than 5 DM1 molecules reduced antibody affinity and therefore likely cytotoxicity. Finally, three bolus doses of optimized duotoxin was 2.7-fold more active than unconjugated immunotoxin PE-K606R-RDEL *in vivo*. We currently determine stability and half-life of optimized duotoxins *in vitro* and *in vivo*.

Conclusions: By combining Paclitaxel-like small molecules and immunotoxins, a novel drug was generated which shows encouraging efficacy *in vivo* justifying further preclinical development.

Disclosure: No conflict of interest disclosed.

P766

Extracellular vesicles as delivery vehicle for small therapeutic RNAs into suspension cells

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Extracellular vesicles (ECVs) represent a heterogeneous group of cell-derived membranous structures containing exosomes (with an approximate size of 30-120 nm) and larger vesicles. Exosomes are generated during multivesicular body formation and secreted to the extracellular space by exocytosis. After secretion, the exosomes can be taken up by neighboring or other specific target cells via endocytosis. Exosomes have been demonstrated to transport different macromolecules, like siRNAs, miRNAs, peptides or proteins between cells, and, since they also present different receptors on their surface, to play an important role in intercellular signaling. In our project, we use modified exosomes, isolated from tumor cell culture, for the delivery of small RNA molecules into tumor cells. These delivery vehicles are especially interesting for the hard-to-transfect cell lines, and could be potentially applied for suspension cells (like SAOS-2) *in vitro*. RNAs include siRNAs for the induction of RNA interference (RNAi), miRNAs for miRNA replacement therapy, or antimiRs as efficient miRNA inhibitors. A purification protocol of exosomes from supernatants of different tumor cell lines was established. Using Nanoparticle Tracking Analysis (NTA, NanoSight, Malvern) and Dynamic Light Scattering (DLS; Zetasizer, Malvern) as high resolution particle-by-particle technologies, particle sizes and particle surface charges (zeta potentials) were measured, as well as particle concentrations and aggregation events of exosomes in liquid suspension. Vesicle sizes and exosome secretion was determined from tissue culture supernatants of different tumor cell lines. For siRNA loading into monodisperse ECV populations, chemical methods and electroporation were explored. In vitro delivery of siRNAs for gene knockdown or antimiRs for miRNA inhibition, each loaded into ECVs, reveals the efficient knockdown of siRNA or of antimiR target genes, as determined in luciferase reporter cell line assays or by RT-qPCR expression level analysis. Furthermore, anti-proliferative effects were observed when targeting tumor-relevant genes. All in all, our data indicate the usability of ECVs as delivery system for otherwise hard-to-deliver drugs like small RNA molecules in SAOS-2 suspension cell line.

Disclosure: No conflict of interest disclosed.

P767

The novel JAK-inhibitor pacritinib exerts fewer immunosuppressive effects on human dendritic cells than Ruxolitinib

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Introduction: Ruxolitinb has been shown to act as an immunosuppressive agent by impairing the phenotype and function of human and murine dendritic cells (DCs), $CD4^+$ and $CD8^+$ T as well as NK cells. In consequence, treatment with ruxolitinib can promote severe opportunistic infections, but has also led to its successful application as immunosuppressant in patients suffering from steroid-refractory graft versus host disease. The novel JAK/FLT3-inhibitor pacritinib decreases constitutional symptoms and spleen size equally effective as ruxolitinib in myelofibrosis (MF) patients, but causes less anemia and thrombozytopenia. However, it is not known whether pacritinib mediates similar suppressive effects on immune cells.
Methods: Human monocyte-derived DCs were incubated with ruxolitinib or pacritinib in different concentrations. Analysis of the activatory status of DCs was performed using flow cytometry. Co-culture experiments with T cells were performed to investigate whether pacritinib suppresses CD8+ T cell function.
Results and conclusions: The application of pacritinib did not block the differentiation of human monocytes into monocyte-derived DCs. Moreover, treatment with pacritinib resulted *in vitro* in almost no reduction of human DC activation upon TLR stimulation, stable CCR7 expression and no impairment of DC migration towards a CCL19 ligand. In contrast, ruxolitinib diminished these parameters significantly. Co-culture experiments revealed a slight suppressive effect of pacritinib on the activation and proliferation of murine $CD4^+$ and $CD8^+$ T cells cultured together with DCs. However, all these effects were detected in concentrations that lie significantly above those used in patients. Taken this into account, we conclude that pacritinib would exert fewer immunosuppressive effects than ruxolitinib *in vivo* in patients. Further studies comparing both compounds *in vivo* need to be performed. These should help to carify whether pacritinib holds the potential to be a good option for MPN patients with fewer immunosuppressive side effects.

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P768

Expression of retroviral elements upon 5-Azacytidine in peripheral blood mononuclear cells of patients with MDS and AML: first in-vivo data

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Introduction: Epigenetic drugs are used for the treatment of several hematologic malignancies, but their pharmacological mechanism remains poorly understood. By genome wide analysis of transcription start sites (TSS), methylation status and chromatin dynamics, we showed for DNA methyltransferase and histone deacetylase inhibitors (DNMTi and HDACi) global reactivation of long terminal repeat elements (LTRs) in vitro (cell line models) and in vivo (neuroblastoma mouse xenograft model). The LTR reactivation is resulting in numerous fusion transcripts that encode novel protein isoforms, which have the potential to influence cell proliferation, seem to be an explanation for the priming effect of epigenetic therapy and might play a role as a potential marker for epigenetic treatment response.
Methods: We investigated the reactivation of LTRs in sequential peripheral blood samples of AML and MDS patients upon epigenetic drug treatment with 5-Azacytidine (DNMT-inhibitor) by qRT-PCR and ddPCR and correlated the expression results with treatment response. Sequential RNA samples from peripheral blood mononuclear cells (PBMCs) of three AML and four MDS patients treated with 5-Azacytidine were analyzed. Consensus primers covering the transcript variants of LTR12C as well as particular primers for specific LTR elements were used.
Results: In AML and MDS patients, we could detect LTR expression in sequential samples from PBMCs over time with 5-Azacytidine treatment. LTR12C expression values measured by qRT-PCR were confirmed by ddPCR and allowed to assess specific LTR elements. Patients with response to 5-Azacytidine showed increased LTR12C expression whereas patients without treatment response had no increase in LTR12C expression. In contrast to the results from our previous NSCLC cell line model, specific LTR elements were only partially expressed in sequential PBMC samples from AML patients treated with 5-Azacytidine.
Conclusions: First in-vivo pilot study, detecting LTR expression in sequential PBMC samples of AML and MDS patients treated with 5-Azacytidine. In this group of patients, treatment response correlated with LTR expression over several treatment cycles with 5-Azacytidine. These are the first results in AML and MDS patients showing expression of LTRs upon epigenetic drug treatment. Larger patient cohorts are necessary to confirm these results by either PCR- or genome wide-analysis of transcription start sites (TSS).

Disclosure: No conflict of interest disclosed.

P769

2-Deoxyglucose induced unfolded protein response enhances efficacy of immunotoxin Moxetumomab pasudotox against lymphoma and leukemia xenografts

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Introduction: B-cell lymphoma commonly show an increase in protein synthesis and glycolysis. The immunotoxin Moxetumomab pasudotox (Moxe) consisting of an anti-CD22 antibody and pseudomonas exotoxin kills tumor cells by arresting protein synthesis and is approved for the treatment of relapsed/refractory hairy cell leukemia. 2-Deoxyglucose (2DG) irreversibly blocks glycolysis and additionally impairs protein glycosylation by competitive inhibition of mannosyltransferase. Without glycosylation, proteins fail to fold properly inducing the unfolded protein response (UPR). Aiming to enhance Moxe activity against CD22 expressing malignancies, we combined Moxe and 2DG.
Methods: Established cell lines and patient-derived B-ALL samples were treated *in vitro* with Moxe and 2DG. Drug synergy was determined mathematically as fold-increase over additivity. Biochemical studies were performed using western blot. *In vivo* enhancement was tested using intravenously injected xenograft models.
Results: *In vitro*, Moxe is highly cytotoxic against malignant B-cell lines, while cytotoxicity of 2DG greatly varies. When combined with 2DG, Moxe cytotoxicity is enhanced 3- to 9-fold against tested cell lines and patient-derived B-ALL of the Burkitt's type. Suggesting an induction of UPR as cause of the strong synergy, mannose abrogated cytotoxicity of 2DG and blocked the enhancement of Moxe. Biochemical studies further supported that 2DG alone and combined with Moxe led to upregulated

CHOP (C/EBP-homologous protein), a central apoptotic protein during UPR. The addition of mannose blocked CHOP upregulation. In line with previous reports, Moxe and 2DG alone reduced MCL1 levels which was additive when combined and not reversed by mannose suggesting that the synergy is not derived from changes in MCL1 levels. Lastly, the combination of Moxe and tunicamycin, a known inducer of UPR, mimicked the synergy of 2DG *in vitro*. In systemic xenografts of JeKo-1 and Ramos, tumor burden in the bone marrow (BM) was not significantly reduced by 2DG or by tunicamycin alone. However, Moxe alone reduced BM infiltration by 5-fold in the JeKo-1 and by 16-fold in the Ramos model which was enhanced by 2DG or tunicamycin up to 3-fold in the JeKo-1 model and achieved MRD-negative BM status in the Ramos model.
Conclusions: The combination of 2DG and Moxe is well tolerated, produces substantial drug synergy, and may be a promising strategy for future clinical testing in patients with high-grade B-cell lymphoma.

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Fabian Müller: Advisory Role: Gutachtertätigkeiten für AstraZeneca; Expert Testimony: Finanzielle Unterstützung für präklinische Untersuchung von Moxetumomab pasudotox.

P770

Inhibition of cancer cell motility by subtoxic concentrations of bosutinib and dasatinib

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Introduction: The prognosis of malignant tumors is to a great extent determined by the ability of cancer cells to form metastases at distant body sites. Interference with the biological processes regulating cellular motility and cell-cell or cell-substrate adherence could provide the basis for novel treatment options complementing the classic cytoreductive approaches. Src- and abl-dependent signaling pathways are critically involved in the regulation of cellular adhesion and motility. Thus, we postulated that the dual src and abl inhibitors bosutinib and dasatinib inhibit the promigratory phenotype of cancer cells.
Methods: To test this hypothesis, we made use of a panel of human cancer cell lines and determined the antiproliferative effect of bosutinib and dasatinib via WST-1 assay and quantitation of apoptosis induction. Furthermore, we evaluated the impact of the inhibitors on cellular motility using in vitro wound healing and transwell migration assays. Additionally, we analysed two dimensional colony spread and spheroid outgrowth.
Results: In most cell lines, bosutinib and led to a pronounced growth inhibition at concentrations > 1 μM. Dasatinib was generally more potent than bosutinib showing antiproliferative effects in most cases already at concentrations > 100 nM. More importantly, bosutinib and dasatinib severly decreased the migratory potential in most investigated cell lines, even in non-toxic concentrations. Of note, their was no clear association between the sensitivity of tumor cells against the antiproliferative and the antimigratory effects of the inhibitors.
Conclusions: Bosutinib and dasatinib show a promising inhibition of cancer cell spread, which is independent of cytotoxicity. Thus, the potential antimetastatic effect of these inhibitors will be further delineated using in vivo models.

Disclosure: No conflict of interest disclosed.

P771

First results from a screening of 300 naturally occurring compounds: 4,6-dibromo-2-(2′,4′-dibromophenoxy)phenol, 3,4,6-tribromo-2-(2′,4′-dibromophenoxy)phenol and 5-epi-Nakijinone Q as substances with the potential for anticancer therapy

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Introduction: A variety of antineoplastic drugs are based on naturally occurring compounds from ecological niches with high evolutionary pressure. Cytotoxic drugs are often modified compounds derived from natural products. But there are targeted therapies rooting on natural compounds as well, e. g. Midostaurin. Marine compounds interfere with signaling pathways relevant for malignant cells such as those involved in cell death and inflammatory processes. These organisms represent a rich, only sparsely exploited source of compounds with a high degree of structural and antineoplastic properties.
Methods: Two cell lines (Jurkat J16 and Ramos) were used in a screening to assess 300 different naturally occurring compounds regarding their antineoplastic activity. The results of the compounds 4,6-dibromo-2-(2′,4′-dibromophenoxy)phenol (P01F03), 3,4,6-tribromo-2-(2′,4′-dibromophenoxy)phenol (P01F08) and 5-epi-Nakijinone Q (P03F03) prompted us to test these compounds in primary human leukemic and healthy hematopoietic cells, using viability, apoptosis and colony forming unit assays.
Results: We found that P01F03 and P01F08 induce apoptosis in the cell lines at IC50 values between 1.61 and 2.95 μM after 72 h. IC50 values of PBMNCs from healthy donors were higher demonstrating that the cytotoxicity in the cell lines reaches 50%, while normal PBMNCs were hardly affected. The colony forming unit assay showed that the hematopoietic progenitor cells were not significantly affected in their growth by P01F08 at a concentration of 3 μM. P01F08 showed a 3.2-fold lower IC50 value in primary leukemic cells (AML), compared to the PBMNCs of healthy donors. We could confirm the antineoplastic effect of 5-epi-Nakijinone Q on the cell lines via induction of apoptosis, but noted a similarly strong cytotoxic effect on healthy PBMNCs.
Conclusions: Based on a large library of naturally occurring compounds with antineoplastic activity we propose a stepwise approach using a variety of different methods to assess the therapeutical potential of candidate compounds. Our results demonstrate sufficient antineoplastic activity for all three compounds without undue toxicity of the two polybrominated diphenyls as far as the normal blood and progenitor cells are concerned. Further studies, concentrating on other types of human leukemia and more elaborate assays such as long-term culture initiating cell assays for determining hematopoietic toxicity may help to pave the way towards clinical application.

Disclosure: No conflict of interest disclosed.

Posterdiskussion

Leukämie

P772

Estimating incidence and prevalence of chronic myeloid leukemia (CML) in the German population using a representative statutory health insurance (SHI) claims dataset

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Introduction: With the introduction of tyrosine kinase inhibitors (TKI) in treatment of CML, life expectancy of patients has reached that of normal population. Real-world data on usage of 1st, 2nd and 3rd generation TKIs are limited as well as information on incidence and prevalence of CML and its therapy outside of clinical trials.
Methods: This observational study was based on the InGef research database, an anonymized representative claims dataset of 4 million patients covered by SHI in Germany. Patients with an ICD-10 code C92.1*,C92.2*,C92.7* or C92.9* in at least two quarters between 1.1.13 and 31.12.14 were included in the incident cohort if they had no corresponding diagnosis in 2012. For the prevalent cohort, diagnoses were assessed in 2012. Furthermore, patients in both cohorts had at least one prescription of a TKI, combined with a relevant ICPM code for diagnostic testing. Patients were followed-up for 3 years in the incident and 5 years in the prevalent cohort. A change in therapy lines was defined by switching TKI within the study period. All analyses were performed descriptively.
Results: 452 and 3,308 patient years in the incident and prevalent cohort were analyzed, respectively. Extrapolated annually incidence for CML was 1,434 and for prevalence was 12,720 patients p.a. in Germany. The median age of the study population was 66 and 65 in the incident and prevalent cohort, respectively and the median Charlson Comorbidity Index (CCI) was 3 in both groups. 65 % of patients in both groups were male. 42% (N=52), 35% (N=44) and 10% (N=12) of the incident patients were treated with imatinib, nilotinib or dasatinib as first line treatment. 21% (N=32) of the incident patients changed to a second and 15% (N=18) to a 3.-line therapy within the next 3 years of follow-up. In the prevalent cohort, around every third patient (N= 216) changed therapy line at least once within a period of 5 years.
Conclusions: This first analyses by health insurance data with strict criteria revealed a 20% higher incidence rate for CML than expected by tumor registries underlying the incompleteness of data. In this real world data cohort, the median age was up to 12 years higher than in clinical studies, however CCI was well comparable to clinical studies. Almost one out of three patients changed to another TKI therapy line within 3 years after diagnosis.Thus, this study confirms the importance of considering age and comorbidities by defining individual CML treatment plans.

Disclosure: Susanne Saußele: Financing of Scientific Research: Bristol-Myers Squibb, Novartis, Incyte, Pfizer; Expert Testimony: Novartis, Bristol-Myers Squibb, Incyte
Tino Schubert: Advisory Role: Incyte; Expert Testimony: Incyte

P773

CML relapse after allogeneic HSCT: survival, treatment efficacy and prognostic factors for outcome

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Introduction: Tyrosine kinase inhibitors (TKI) have fundamentally changed the therapeutic concept in CML leading to excellent outcome. Although allogeneic stem cell transplantation (HSCT) is currently only required for a limited number of patients (pts) post-transplant relapse remains a major challenge.
Patients and methods: Retrospective single center long-term evaluation of overall survival (OS), relapse-free survival (RFS) and the incidence of CML relapse after allo-HSCT. Analysis of OS and leukemia-free survival (LFS) among relapsed transplant recipients compared to non-relapse pts and review for prognostic factors. Data on 488 eligible CML pts transplanted between January 1996 and September 2015 were analyzed. At time of transplant 80% of all pts were in chronic, 12% in accelerated and 8% in blast phase. Cox regression was used to ascertain influencing factors for RFS.
Results: Median follow-up in the cohort was 129 months, 25% (n=120) of all transplant recipients sustained relapse with a median onset of 15 months after HSCT. Cumulative incidences (CI) of relapse were 13%, 23%, 26%, 28% and 30% after 1, 3, 5, 10 and 15 years post-transplant. RFS was assessed 67%, 53% and 47% after 1, 5 and 10 years post-transplant. Multivariate analysis of RFS proved advanced disease stages (> 1. chronic phase) at time of HSCT to be an independent adverse prognostic factor (p=0,005) whereas chronic GvHD showed only significant impact in univariate analysis. Based on landmark analysis, OS could be demonstrated to be significantly higher in transplant recipients w/o relapse (p=0,042). Among relapsed pts OS was significantly worse in hematologic compared to molecular or cytogenetic relapse (p=0,018; p=0,012). In 72% of pts with CML-relapse long-term remission could be induced with a median progression-free survival of 98 months. The sequence of different treatment approaches (e.g. withdrawal of immunosuppression, DLI, IFN, TKI, chemotherapy, re-transplantation) significantly influenced OS in relapsed CML pts.
Conclusion: To achieve favorable RFS in CML, allo-HSCT should be applied in non-advanced disease stages. However, even relapse after HSCT can be effectively treated resulting in long-term survival rates > 80%, in particular when relapse is diagnosed as molecular or cytogenetic CML recurrence.

Disclosure: No conflict of interest disclosed.

P774

Anti-leukemic activity through CDK9 inhibition in T-cell prolymphocytic leukemia

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Introduction: T-cell prolymphocytic leukemia (T-PLL) is an aggressive malignancy characterized by chemotherapy resistance and a median survival of less than two years. Here, we investigated the pharmacological effects of the novel highly specific cyclin-dependent kinase 9 (CDK9) inhibitor LDC526 and its clinically used derivate atuveciclib employing primary T-PLL cells in an ex vivo drug sensitivity testing platform.
Methods: We isolated CD3/CD4 positive tumor cells from peripheral blood samples of T-PLL patients by sort purification and performed drug sensitivity and cell viability assays, microRNA profiling, Western blotting, reverse transcription PCR, microarray based gene expression profiling (GEP), and statistical and bioinformatics analyses including gene ontology (GO) enrichment analysis, hierachical clustering of miRNA expression data, Ingenuity pathway analysis and gene set enrichment analysis (GSEA).
Results: All T-PLL samples were sensitive to CDK9 inhibition at submicromolar concentrations while conventional cytotoxic drugs were found to be largely ineffective. At the cellular level LDC526 inhibited the phosphorylation at serine 2 of the RNA polymerase II C-terminal domain

resulting in decreased de novo RNA transcription. LDC526 induced apoptotic leukemic cell death through down-regulating MYC and MCL1 both at the mRNA and protein level. Microarray based transcriptomic profiling revealed that genes down-modulated in response to CDK9 inhibition were enriched for MYC and JAK-STAT targets. By contrast, CDK9 inhibition increased the expression of the tumor suppressor FBXW7 which may have contributed to the down-modulation of MYC and MCL1 proteins. Finally, the combination of atuvecliclib and the BCL2 inhibitor venetoclax exhibited synergistic anti-leukemic activity, providing the rationale for a novel targeted-agent based treatment of T-PLL.
Conclusions: CDK9 inhibition is a promising novel therapeutic option in T-PLL. Combination with BCL2 inhibition exhibits synergistic anti-leukemic activity in vitro.

Disclosure: No conflict of interest disclosed.

P775

Observational study on CML patients in any phase treated with ponatinib (Iclusig®) at any dose - The Ponderosa Project

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Introduction: The Ponderosa study is a multi-center, prospective and retrospective, non-interventional, observational cohort study of chronic myeloid leukemia (CML) patients in any phase of the disease being treated with ponatinib in Germany and the Czech Republic.
Methods: In July 2015, recruitment was commenced, aiming to give a picture of real-life treatment with ponatinib at various dosages in CML patients. The study will also assess the incidence of adverse events (AEs) and response to treatment as well as for progression free survival (PFS) and overall survival (OS) according to various dosages applied. Enrolled patients are followed for a minimum of 24 months of treatment with ponatinib. Data from 100 patients will be collected during the study in conjunction with routine care visits, usually every 3 months and documented via eCRF from approximately 50 study sites.
Results: As of April 2019, a total of 47 pts (26 male; median age 60; range 21-89 years) were recruited from 24 participating sites in Germany and the Czech Republic. 33 pts were in chronic, 1 in accelerated and 5 in blast phase; phases of 8 pts were not documented. Patients received 1-4 prior TKI therapies (median 2). Median duration of Ponatinib therapy was 16.6 months for patients started therapy with Ponatinib at least one year before data cut. 43 % of the pts started with a dose of 45 mg/d, 33 % received 30 mg/d and 24 % started with 15 mg/d. In 46 % of pts a dose adjustment was registered (2 pts with dose increase). With regard to efficacy, 7 /24 pts (29.2 %) reached MMR (BCR-ABL ≤ 0.1% according to the international scale, IS) at 3 mo and 6 /9 pts (66.7 %) at 18 mo.; 7 pts achieved and maintained the response level MR4 + (BCR-ABL ≤ 0.01% IS) for at least 6 months or until data cut for this interim analysis. Probability of adverse events grade 1-5 during the course of the ponatinib therapy was 59.5 % (86 AEs in 22 pts) with 17 AEs of grade 3-5 (19.8 %). 4 pts progressed to accelerated phase or blast crisis; 2 of them died from BC; 3 pts received allogeneic stem cell transplantation. In total, 2 pts died, both CML related.
Conclusions: This interim analysis shows first data of the real-life treatment with ponatinib in CML patients which have not only been collected from various clinical studies.

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P776

Late relapse of T-Prolymphocytic leukemia after allogeneic hematopoietic stem cell transplantation

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Introduction: T-cell prolymphocytic leukemia (T-PLL) is a mature T-cell leukemia with an inherently mostly aggressive course of disease. Initial treatment with the monoclonal anti-CD52 antibody alemtuzumab induces responses in the majority of patients with T-PLL. In eligible patients, hematological remissions can be consolidated by allogeneic hematopoetic stem cell transplantation (HSCT) in curative intention. However, long-term outcome data for these patients are scarce.
Methods: We here report experience from three T-PLL patients, who received alemtuzumab induction and consolidative allogeneic stem cell transplantation, leading to MRD-negative complete remissions.
Results: All patients reported here entered conditioning therapy at complete remission (CR) after alemtuzumab therapy. Donor chimerism (DC) was monitored regularly. In 2/3 patients donor lymphocyte infusions were required at decreasing DC early after transplantation, and led to complete remissions in all cases. However, at the time of last follow-up, none of the patients were alive, due to relapsed disease in all cases. Relapses occurred at months +12, +64 and +84. Cytogenetics revealed identical clonal alterations at initial diagnosis and relapse after HSCT in all patients, without evidence of clonal evolution. Furthermore, clinical relapses compromised similar disease sites diagnosed at first manifestation and were accompanied by rapidly progressive extranodal T-PLL involvement. The disease was refractory to cytostatic therapy (purine analogs, bendamustine) and alemtuzumab-retreatment in all cases.
Conclusions: We here report long-term follow up on patients with T-PLL treated with HSCT in CR. Alemtuzumab induction and consolidative allogeneic stem cell transplantation led to prolonged disease-free survival in these patients. However, disease relapses and eventually fatal outcome occurred late, suggesting long-term persistence of minimal residual disease after allogeneic stem cell transplantation in T-PLL patients.

Disclosure: No conflict of interest disclosed.

P777

LMO2 activation by deacetylation is indispensable for hematopoiesis and T-ALL leukemogenesis

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LMO2 (hematopoietic transcription factor LIM domain only 2), a member of the TAL1 transcriptional complex, plays an essential role during early hematopoiesis and is frequently activated in T cell acute lymphoblastic leukemia (T-ALL) patients. Here, we demonstrated that LMO2 is activated by deacetylation on lysine 74 and 78 via the nicotinamide phosphoribosyltransferase (NAMPT)/sirtuin 2 (SIRT2) pathway. LMO2 deacetylation enables LMO2 to interact with LDB1 and activate the TAL1 complex. NAMPT/SIRT2-mediated activation of LMO2 by deacetylation is essential for hematopoietic differentiation of induced pluripotent stem (iPS) cells and blood formation in zebrafish embryos. In T-ALL, deacetylated LMO2 induces expression of TAL1 complex target genes HHEX, NKX3.1 as well as LMO2 autoregulation. Consistent with this, inhibition of NAMPT or SIRT2 suppressed the *in vitro* growth and *in vivo* engraftment of T-ALL cells via diminished LMO2 deacetylation. This new molecular mechanism may provide new therapeutic possibilities in T-ALL and may contribute to the development of new methods *for in vitro* generation of blood cells.

Disclosure: No conflict of interest disclosed.

P778

Strand displacement synthesis activity of reverse transcriptases impacts on qPCR results in BCR-ABL1 monitoring of patients with CML

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Introduction: DNA-/RNA-dependent DNA polymerases (reverse transcriptases, RT) are essential tools in RNA-/cDNA-based gene expression analyses and in qPCR-based routine *BCR-ABL1* transcript quantification for monitoring minimal residual disease in chronic myeloid leukemia (CML). Strand displacement (SD) synthesis activity is a characteristic feature of natural RTs as it is essential for polymerization of highly structured retroviral RNA during cDNA second strand synthesis in vivo. Commercially available cDNA first strand kits with recombinant MoMuLV-RT derivatives are not free of SD synthesis activity.
Methods: We have comparatively tested our lab "gold standard", six commercially available cDNA first strand kits and several RT/PCR "one-in-all" reaction systems on a standardized dilution of K562 total RNA. Furthermore, the influence of the priming method (specific vs. random) was analyzed. Using TaqMan qPCR the absolute numbers of *BCR-ABL1* and *GUSB* transcripts were estimated and the corresponding *BCR-ABL1* lab quotients (BCR-ABL1/GUSB*100 [%]) were calculated.
Results: The majority of tested cDNA first strand kits revealed comparable results with *BCR-ABL1* quotients ranging between 235 and 384 when random hexamer oligonucleotides were used for cDNA synthesis priming indicating a 2.3 to 3.8fold excess of *BCR-ABL1* over *GUSB* transcripts in the K562 transcriptome. However, *BCR-ABL1* quotients diminished to 102 to 150 (1.0 to 1.5fold) when single target-specific primers were used. The observed changes were mainly due to diminished *BCR-ABL1* transcript numbers. The testing of RT/PCR "one-in-all" reaction systems confirmed the authenticity of specific priming results. The priming-dependent changes in *BCR-ABL1* quotients positively correlated with the length of the mRNA stretch located 3' to the PCR target regions.
Conclusions: The combination of multiple random priming events together with SD synthesis activity of RTs can result in undesired amplification of *BCR-ABL1* targets during cDNA synthesis. Only specific priming is able to suppress SD synthesis activity as there is only one single priming event per molecule possible. Employment of recombinant RTs with SD synthesis activity, often advertised as "high fidelity" RTs, can introduce a bias masking the real number of targets and making data compensation by the proper conversion factor according to the international standard (IS) crucial.

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P779

Signaling lymphocytic activation molecule family receptors negatively regulate B cell receptor signaling in chronic lymphocytic leukemia

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Objectives: Chronic Lymphocytic Leukemia (CLL) is the most common hematological disease in the western countries and despite novel therapeutic concepts it is still considered incurable. Deregulated signaling networks and pathological immune control are a hallmark of CLL and a new generation of drugs targeting these pathways is entering clinical practice. However, resistance remains a serious problem and identification of novel targets is needed to improve the prognosis of (especially young and high-risk) patients.
Methods: Propagation of B cell receptor (BCR) signaling and other CLL-related pathways depends on a network of regulatory proteins that bind phosphorylated tyrosine residues via Src Homology 2 (SH2) domains. We performed far western blotting based SH2 profiling in two clinically well-characterized CLL cohorts to assess the pathological signaling network in this disease and to identify key regulators as therapeutic targets. Functional characterization of potential target proteins was carried out using the well-established CLL cell lines MEC-1 and JVM3. We created a model system in which we lentivirally overexpressed candidate proteins or knocked them out using CRISPR/Cas9. We subjected the different cell lines to proliferation assays and assessed BCR signaling capacity by Ca^{2+}-flux measurements.
Results: The experiments pointed to a population of patients with high SLAM family (SLAMF) receptor related signaling that showed an indolent clinical course. Overexpression of SLAMF1 and 7 in the CLL cell lines MEC-1 and JVM3 resulted in reduced proliferation and lower basal Ca^{2+} mobilization as well as mitigated responses to anti-IgM stimulation. The SLAMF receptor signature was closely associated with a mutated immunoglobulin status further supporting the notion that SLAMF receptor signaling negatively regulates the B cell receptor signaling axis in CLL. We could also show that the SLAMF overexpressing cells were less sensitive towards BCR directed inhibition using Ibrutinib.
Conclusions: Our data indicate that SLAMF receptor signaling negatively impacts the BCR signaling axis in CLL and might determine treatment response to BCR inhibiting compounds. This may pave the way for the identification of new therapeutic targets in this disease and improve rationally guided choice of treatment.

Disclosure: No conflict of interest disclosed.

P780

Functional role of Bruton´s tyrosine kinase inhibitor therapy in the tumor microenvironment of B-cell malignancies

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Introduction: Inhibition of Bruton's tyrosine kinase (BTK) is an established therapeutic approach in B-cell malignancy. Combinations with monoclonal antibodies have been applied in various approaches. However, the value of combinatorial use Ibrutinib remains to be clarified both clinically and on a mechanistic level. The clinical relevance of off-target signaling similarly remains to be clarified in the light of more specific second generation BTK inhibitors. Since Ibrutinib reveals only limited effect *in vitro* despite its high clinical efficiency the mechanisms of therapeutic response have to be addressed in the context of tumor microenvironment.
Methods: To address Antibody-Dependent Cellular Phagocytosis (ADCP) J774A.1 macrophages in co-culture with MYC/Bcl2 Double-hit-lymphoma (hMB) cells or primary chronic lymphocytic leukemia (CLL) patient cells were used and treated with combinations using BTK inhibitors and monoclonal CD20, CD52 and CD38 antibodies. PamStation analysis was carried out for kinase activity assessment. In vivo treatment was performed in the hMB humanized Double-Hit lymphoma model.
Results: Our data suggest that the Bruton's tyrosine kinase (BTK)inhibitor Ibrutinib increases the antibody dependent phagocytosis of malignant B cells by Rituximab, Alemtuzumab and Obinutuzumab. Moreover, we used the hMB humanized mouse model of Double-Hit B cell lymphoma and could observe prolonged survival of combination treatment of alemtuzumab and ibrutinib as compared to alemtuzumab monotherapy.
Synergy of Ibrutinib with monoclonal antibodies is partially mediated by secretory responses from target cells activating macrophages. Additionally, ibrutinib directly activates macrophage activity. Interestingly, this activation is also present in macrophages derived from $BTK^{-/-}$ mice and

not seen with more specific second generation BTK-inhibitors. In order to identify ibrutinib targets we performed PAM station analysis identifying numerous phosphopeptide sites significantly reduced by ibrutinib treatment indicating targeting of not only BTK but also ALK, ARG, TEC, BMX, ITK, ABL, SYK and AXL-Kinase activity.
Conclusions: Ibrutinib positively affects tumor clearance by macrophages in the context of antibody therapies. These synergistic effects are not exclusively mediated by BTK-inhibition but also suggest relevant off-target effects. Here we have identified novel potential off-target effects of ibrutinib that might explain therapeutic effects.

Disclosure: Verena Barbarino: No conflict of interest disclosed.
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P781

Drug cytokine interaction map in chronic lymphocytic leukemia

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Introduction: Microenvironment signals modify pathway activities, including those targeted by drugs, and thereby can modulate drug response. We aim to generate a system-level understanding of how the microenvironment and the individual genetic and molecular make-up of chronic lymphocytic leukemia (CLL) interact and modify drug response using a high throughput functional drug ~ stimulation screening approach.
Methods: We established and conducted a high-throughput combinatorial screen using 18 soluble stimuli mimicking the tumor microenvironment combined with 15 drugs from chemotherapies to targeted inhibitors. Peripheral blood mononuclear cells from 192 CLL patients as well as 23 lymphoma cell lines were treated for 48h and the viability was determined based on ATP levels. In total we screened 304 conditions per sample.
Results: CLL showed heterogenous responses to different stimuli, e.g. interleukin-4 exhibited a strong protective effect against spontaneous apoptosis, whereas transforming growth factor-β induced apoptosis in the same samples. In addition we defined subgroups with distinct responses to stimuli of the microenvironment and systematically investigated how genetic alterations determine the dependence of CLL cells on external stimuli.
To model interactions of soluble factors of the microenvironment and drug-induced apoptosis we use the following linear model: Viability ~ $effect_{drug}$ + $effect_{stimulation}$ + $effect_{drug}$:$effect_{stimulation}$. This allows us to model separately the effect of stimuli on spontaneous apoptosis in-vitro and the interference of stimuli with specific drug responses. We systematically identify stimuli signatures which confer resistance to B-cell receptor (BCR) inhibitors in CLL. We further validate the biological importance of these stimuli in 100 CLL lymph node biopsies and normal controls by assessing their specific pathway activity by Immunohistochemistry. Based on these discoveries we rationally combine BCR inhibitors and stimuli specific pathway inhibitors to overcome microenvironment mediated resistance.
Conclusions: Targeted treatments against cytokine pathways could further improve response to BCR inhibitors in CLL and lymphoma.

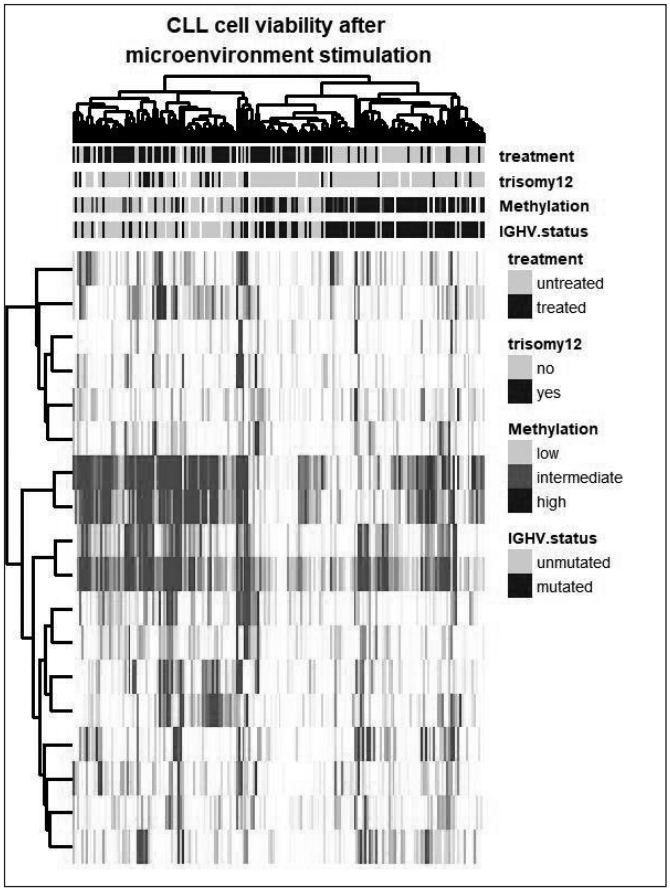

Fig. 1. Heatmap of microenvironment response, red signifies high viability, blue low viability

Disclosure: No conflict of interest disclosed.

P782

CLL/NHL - patient registry OncoReg (Rituximab original vs. biosimilar)

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Introduction: Rituximab is a biotechnologically produced chimeric anti-CD20 monoclonal antibody that is used as a drug in cancer immunotherapy, primarily for the treatment of malignant lymphomas. Since May 2017, the first biosimilar Truxima has been available for the treatment of chronic lymphocytic leukemia (CLL) and non-Hodgkin´s lymphoma (NHL).
Methods: Data on the therapy of CLL (ICD-10 C91.1) and NHL (ICD10 C82-C88) were analysed within the national scientific progress registry ONCOReg of the Project team of Internal Oncology (PIO). The registry contains the progress documentation of a total of 35,713 patients with 100,604 therapies from 373 practices, among them 1,944 haematological diseases from 76 practices nationwide.
Results: This analysis examines patients who started therapy in June 2017 and who had been treated with a therapy containing rituximab. Out of

286 registered patients, 174 are documented and evaluable. 93 (53.4%) patients received a biosimilar, of which 82 (88.2%) received Truxima. 1 patient received a biosimilar and MabThera. 76 (43.7%) patients had chronic lymphocytic leukemia, 98 (56.3%) had non-Hodgkin´s lymphoma. The median age at the start of therapy was 72 (26-92) years, the general condition 1 (0-2) according to ECOG, 64.9% men; 35.1% women. Therapy: 123 (70.7%) patients received a first-line therapy, 125 (71.8%) patients received a combination therapy of bendamustine/rituximab. A median of 6 cycles was administered. The median dose of rituximab is 2,250 mg/m². 42 (24.1%) patients continue to receive rituximab as maintenance therapy. Concomitant medication per patient: 26.4% G-CSF; 14.9% blood substitute; 21.3% antibiotic; 13.8% analgesic. The dose was reduced for 39 (22.4%) patients, the therapy was postponed for 79 (45.4%). 30 (17.2%) patients had to be hospitalised. Response: 28.2% CR; 59.2% PR; 5.7% NC; 2.3% PD; 4.6% not assessable Heme side effects grade 3/4 per patient: 25.9% neutropenia; 23.6% leukopenia; 8.1% thrombopenia; 7.5% anemia. Non-heme side effects grade 1-4 per patient (< 20%): 32.8% nausea; 29.9% infection; 28.7% fatigue; 22.4% pain.
Conclusions: More than 50% of patients receive a biosimilar in clinical routine. Objective response rates and side effects are comparable to the original.

Further data will be presented.

Disclosure: No conflict of interest disclosed.

P783
Effectiveness, safety, and adherence to ramp-up monitoring in CLL patients treated with venetoclax under real-life conditions - data from the observational study VeRVe

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Introduction: In clinical trials, treatment of chronic lymphocytic leukaemia (CLL) with venetoclax (Ven) has shown promising efficacy and good tolerability. To mitigate the risk of tumor lysis syndrome (TLS), Ven is started with a gradual dose increase over 5 weeks. Real-world data on Ven usage are limited. Therefore, we conduct a non-interventional observational study assessing effectiveness, safety, and quality of life in patients treated with Ven in Austria, Germany, and Switzerland. This interim report focuses on the ramp-up phase.
Methods: Adult patients with CLL requiring therapy treated with Ven according to local label are eligible for the study. Patients' visits are scheduled at the physician's discretion and according to clinical practice. Study documentation is possible at baseline, weekly during ramp-up, monthly until the end of 6 months and 3-monthly afterwards up to a maximum of 2 years. Response assessment according to IwCLL criteria can be documented at the end of ramp-up, after 3, 12, and 24 months.
Results: The study started in November 2017. On January 21, 2019, 43 patients were enrolled, 36 had received at least one dose of Ven (= safety population), and 21 had completed ramp-up (effectiveness population). Median age was 77 a, 62.5% of patients were male, 56% had at least one comorbidity, most commonly cardiovascular (30%), 42% received comedication. 95% of patients were pre-treated with a median of 2 (range 1-8) lines of therapy, i.e., chemo-immuno-therapy (77%) and therapy with B-cell receptor inhibitors (68%). Del(17p), *TP53* mutation, and presence of unmutated *IGHV* had been diagnosed in 49%, 41%, and 8%, respectively (excl. missing data: 53%, 52%, 18%). The median duration of ramp-up was 35 d (range 33-177), 72% and 33% of patients had ≥1 AE and SAE. Adherence to laboratory monitoring according to label during the first two dose steps ranged from 89% (i.e. 20 mg dose, 24h value) to 60% (i.e. 50 mg dose, 6-8h value). Prevention of hyperuricemia with allopurinol was given to 21% of patients. 4 and 2 patients experienced laboratory and clinical TLS, respectively. At the end of ramp-up (median 35d), 14% of patients had a complete remission, 48% a partial remission and 38% stable disease.
Conclusions: Under real-world conditions, Ven is mainly prescribed to pre-treated CLL-patients. Events of TLS observed may be attributed to less-than-perfect adherence to ramp-up lab monitoring and low usage of anti-hyperuricamic agents.

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Johannes Hülsenbeck: Employment or Leadership Position: AbbVie; Stock Ownership: AbbVie

P784
Functional relevance of IRAK 4 for the pathogenesis of ZAP-70 positive and negative CLL

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Introduction: Chronic lymphocytic leukemia (CLL) is the most common leukemia in the Western world. The disease is characterized by an accumulation of immunologically incompetent B cells and shows a strong variability in the clinical course. Based on cytogenetic and molecular genetic alterations, patients with CLL can be divided into different risk groups, whereby the expression of the kinase ZAP-70 is a surrogate marker for a more aggressive disease course. A key aspect in the pathogenesis of CLL is the B cell receptor (BCR) signaling pathway. As we showed in our recent publication (Wagner et al Blood 2016), the activity of this pathway in the progressive patient group is strongly influenced by the innate immunity responses. BCR activation in ZAP-70 positive CLL cells occurs through the integration of Toll Like Receptor 9 (TLR9) -mediated signals into the BCR signaling cascade. Cells of ZAP-70 negative CLL are also signal competent in the context of TLR9 stimulation, but the integration of the mediated signal and the resulting BCR activation does not occur in that subpopulation. The molecular causes of this divergence are unknown and central to our current research.
Methods: We studied the molecular and functional consequences of IRAK 4 inhibition in freshly isolated cells from CLL patient samples with different ZAP-70 status. We investigated whether the different molecular processes "apoptosis" and "proliferation" in the corresponding subgroups of patients are related with the functions of IRAK 4.
Results: We found significant functional differences in the apoptotic behavior of ZAP-70 positive and negative patients, based on the catalytic activity of interleukin-1 receptor-associated kinase 4 (IRAK 4), a key enzyme of innate immunity.
Conclusions: The interaction of IRAK 4 and ZAP-70 in CLL is important for the integration of TLR9 signals into the BCR signaling cascade. These events may be causally related to the adverse clinical prognosis of ZAP-70 positive CLL patients, so the results of these investigations could open up a new perspective in the molecular understanding of the respective patient groups and be of therapeutic interest.

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P785

Overall survival among patients diagnosed with B-chronic lymphocytic leukemia with 17p deletion status (del(17p))

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Introduction: The B-chronic lymphocytic leukemia (B-CLL) is the prototype of B-cell chronic lymphatic malignancies and one of the most common leukemia in adults. So far, various prognostic markers of B-CLL have been validated and are routinely used in clinical practice. The aim of the study was to investigate the prognostic role of chromosome 17p deletion (del(17p)) among patients with B-CLL.
Methods: The study enrolled 197 patiens (104 males, age 71± 11 years; 93 feemales; age 68±9 years) with B-CLL. The tumor lymphocytes samples were collected from peripheral blood. Tumor DNA was extracted using QIAamp Blood DNA and Oragene DNA kits respectively, according to the manufacturer´s directions. FISH cytogenetics were assessed by the official clinical cytogenetics laboratory. The cutoff for 17p deletion was 10% cells positive. Overall survival (OS) was estimated using the Kaplan-Meier method.
Results: From total number of 197 subjects, 48 (24.36%) (31 male (64.58%) and 17 feemales (35.41%) had del(17p) and 149 (75.63%) subjects were without this mutation. The OS among subjects with del(17p) was 35 months versus 58 months in subjects without del(17p) ($p< 0.001$).
Conclusions: Our study indicates that 17p deletion status is associated with shorter OS. These results have direct impact on clinical prognosis and outcome as well as for future therapy of B-CLL.

Disclosure: No conflict of interest disclosed.

Fortbildung

Update: Prophylaxe und Therapie der tumorassoziierten venösen Thromboembolie

V789

Primary VTE prophylaxis in patients with cancer: YES? But in whom?

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In patients with cancer, venous thromboembolism (VTE), a composite of deep vein thrombosis and pulmonary embolism, significantly contributes to morbidity and mortality. Epidemiological data indicates that, dependent on the clinical setting, up to 20 % of patients with solid tumors or hematological malignancies will develop VTE over the course of their treatment. Pharmacological VTE prophylaxis with low-molecular-weight heparin (LMWH) is established in surgical cancer patients. LMWH prophylaxis should be commenced 2-12 hours preoperatively and continued for at least 7-10 days at the highest prophylactic dosage used to prevent VTE. Extended LMWH prophylaxis over 4 weeks is indicated in high-risk procedures (e.g. major abdominal or pelvic surgery). Although not supported by robust clinical trial data, pharmacological VTE prophylaxis, preferably with LMWH or fondaparinux, is also indicated in non-surgical cancer patients hospitalized for an acute medical illness. Studies on heterogeneous cancer patients with locally advanced or metastatic malignancies receiving ambulatory chemotherapy have indicated that LMWH prophylaxis over 3-6 months is safe and efficacious, but absolute risk reductions of only about 2 % (with numbers needed to treat of up to 50) have prevented implementation of routine LMWH prophylaxis in this setting. Two recent placebo-controlled studies involving cancer outpatients with an intermediate-to-high risk of VTE, as defined by a Khorana score of ≥ 2, indicate that prophylactic dosages of rivaroxaban (CASSINI trial) or apixaban (AVERT trial) are efficacious and reasonably safe in preventing VTE in this setting, with absolute risk reductions of 4-6 %. However, neither of the two direct oral factor Xa inhibitors is currently approved for VTE prophylaxis outside elective hip or knee replacement surgery. Pharmacological VTE prophylaxis with LMWH, albeit at a therapeutic (FRGAEM trial) or half-therapeutic dosage (CONKO-004 trial), is also highly efficacious in patients with locally advanced or metastatic pancreatic cancer, but does not reduce all-cause mortality. While patients with multiple myeloma should receive pharmacological VTE prophylaxis during treatment with thalidomide or lenalidomide in combination with chemotherapy/corticosteroids (either with LMWH or with acetylsalicylic acid or low-dose vitamin K antagonists), prophylactic anticoagulation is not routinely indicated in patients with central venous catheters.

Disclosure: Florian Langer: Advisory Role: Bayer, Bristol-Myers Squibb, LEO, Pfizer; Financing of Scientific Research: Bayer, Bristol-Myers Squibb, LEO, Pfizer

V791

Drug Interactions with NOAC/DOAC during Treatment of Hematologic or Oncologic Malignancies

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Patients with an active cancer diagnosis have a several fold-increased risk to develop a venous thromboembolism (VTE) compared to the general population. Therefore indications for anticoagulation during treatment for a malignancy are common. In the past, low molecular weight heparins have in general been preferred as anticoagulation in cancer patients due to their higher effectiveness in reducing recurrent VTE compared to vitamin K antagonists (VKA). Most recently new oral anticoagulants (NOAC) have been studied for anticoagulation in cancer patients. NOACs offer an attractive option for anticoagulation with the ease of an oral medication without the need for laboratory monitoring. Drug interactions of chemotherapeutic agents via the CYP3A4 enzyme or P-glycoprotein transporter can represent a major challenge of treating patients on NOACs. Significant interactions can alter the level of NOACs and predispose to bleeding or a higher thrombotic risk. This presentation will focus on basic pharmacology of currently approved NOACS and challenges encountered during cancer treatment.

Disclosure: No conflict of interest disclosed.

Wissenschaftliches Symposium

Biologie hämatopoetischer Stammzellen

V792

Mechanisms of HSC quiescence

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Introduction: Hematopoietic stem cells (HSCs) hold the unique potential to generate multipotent progenitors which can differentiate into lin-

eage-committed populations and subsequently into mature blood cells. Our laboratory and others (Wilson et al., Cell 2008; Foudi et al., Nat. Biotechnol. 2009; Takizawa et al., JEM 2011; Qiu et al., Stem Cell Reports 2014) have applied long-term labeling strategies to identify a subpopulation of label-retaining cells within most refined HSCs. These highly quiescent cells, termed dormant HSCs (dHSCs), divide only five times per lifetime of a healthy mouse, but harbor the highest long-term reconstitution potential within the hematopoietic system (Wilson et al., 2008). The rest of HSCs -although still quiescent- are named active HSCs (aHSCs).
Methods: Single-cell and bulk RNA-seq, low input metabolomics, in vivo mouse models.
Results: Recently, we established the molecular fingerprint of HSC dormancy (Cabezas-Wallscheid et al., Cell 2017). We found that stem cell dormancy is defined by a low biosynthetic state (low transcription, translation) which gets gradually up-regulated upon commitment.Further, we found that retinoic acid (RA) signaling is highly expressed in dormant HSCs. Intriguingly, multipotent progenitors are negatively enriched for RA metabolism suggesting a specific role of this in regulating the most potent stem cells (Cabezas-Wallscheid et al., Cell Stem Cell 2014). We performed proof-of principle experiments and showed that RA/vitamin A plays an important role for the *in vivo* regulation of stem cell dormancy.
Conclusions: HSC dormancy is regulated by dietary vitamin A.

Disclosure: No conflict of interest disclosed.

Wissenschaftliches Symposium

Bio Banking

V799

Practical experiences

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Biobanking in hematologic diagnoses is mandatory. With respect to stained smears, paraffin embedded tumors (FFPE) or trephine biopsis this is state of the art since decades. It is also mandatory from the reimbursement and quality control point of view.
Today cell pellets from cytogenetics, hybridized FISH slides and especially cell pellets for molecular investigations, including DNA, RNA and viable cells play an important role for diagnostic approaches in hematology. Thus, the respective processes, storage capacities and workflows need to be installed.
First, several pre-analytics steps from drawing the blood or bone marrow at the site of the patient, sending the material to the respective laboratory and label everything accordingly is a critical procedure with many mistakes that happen. Let's assume that the material drawn from the patients blood or bone marrow is correct (EDTA or Heparin or trephine biopsy in respective buffer) and let's assume that everything is correctly labeled and transport time is as short as possible (between 1-2 days best), what can be done in the respective laboratories?
It is proposed to label all further steps in the respective laboratory by barcoding and install readers for scanning systems at all places with machines, microscopes, robots or personnel, implementing a complete tracking system for all samples. This is routine in any kind of clinical chemistry laboratory and needs to be implemented into all workflows for hematological samples as well. Further, so called "human ID" can be added to any kind of molecular workflow to be sequenced in parallel to the respective genes of interest. This helps to define patients sample at first appearance and the information can be used for tracking the respective follow-up samples.
Materials need different storage at temperatures such as +4° C, -20° C, -80° C or even -160-180° C. All these storage options need to be installed and controlled, the best way to organise these procedures in parallel is a completely automated algorithm including the option of more or less hands on time of technical personnel for bringing material into freezers or taking material out of freezers for further investigations. In infrastructure such as an "Internet of things, IoT" is now possible for biobanking in medicine.

Disclosure: Torsten Haferlach: Employment or Leadership Position: MLL Münchner Leukämie Labor

V800

Hospital-integrated biobanking as a service: the interdisciplinary bank of biomaterials and data Würzburg hosting the tissue-bank of the CCC Mainfranken (CCCM)

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Background: Funded by the Federal Ministry of Education and Research (BMBF), in 2011/2012 the interdisciplinary bank of biomaterials and data Würzburg (ibdw) was set up as a fully centralized faculty-wide operating clinical biobank that also includes the fresh frozen CCCM tumor tissue-bank. The ibdw collects solid (tissues, biopsies) and liquid (blood, serum, urine etc.) biological materials (BM) from patients across the Medical Campus Würzburg both based on a «broad consent» but also supports clinical (IIT-)studies & projects. The central mission of the ibdw is to foster medical research, particularly cancer research, for the benefit of patients/public health.
Methods: This mission is achieved by a strictly quality controlled collection and storage of human BM (since 2016 the ibdw is certified according to DIN ISO 9001:2015), the structured acquisition of BM-related clinical core data, and by means of the Clinical Data Warehouse (SAP HANA-MRI, which is also linked to the CCCM-cancer registry). Since its implementation, the ibdw is registered in the German Biobank Directory and participates in the German Biobank Node. Since 2017 the ibdw receives BMBF-funding as a key player of the German Biobank Alliance (GBA).
Results: Since 2014 n=3.400 prospectively collected and n=400 pre-existing fresh frozen tissue samples were stored in the central CCCM tissue-bank (as of 04/2019). In addition, previously scattered tissue collections are gradually integrated into the central CCCM tissue-bank. With regard to liquid human BM, more than n=100.000 prospective (broad consent) and n=120.000 study-specific as well as n=130.000 pre-existing (CHFC-initiated studies and the population-based franconian STAAB-study) whole blood, serum and EDTA-plasma samples as well as urine and saliva are stored in the fully automated central ibdw repositories.
Conclusions: As a main pillar of GBA the ibdw participates as ELSI work package leader in the coordination and harmonization of all national biobank-activities, comprising -amongst others- harmonization of data-acquisition and -exchange (to achieve biobank-interoperability), standardization of quality-criteria (ring-trials), and the development of a joint national strategy regarding ELSI-matters, including public visibility and stakeholder-involvement. Thereby the ibdw and the CCCM tissue-bank offer an ideal interdisciplinary platform for future national, European (BBMRI) and global networking in medical including cancer research.

Disclosure: Jörg Geiger: No conflict of interest disclosed.
Roland Jahns: Advisory Role: Gutachter Lebenswiss., Bundeswirtschaftsministerium; Expert Testimony: BMBF (FKZ 01EY1712) und IZKF Würzburg (FKZ Z-9)

Wissenschaftliches Symposium

Gastro-Ösophageale Tumore: Therapie der Zukunft

V808

Immunotherapy for esophagogastric cancer

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Despite the use of palliative chemotherapy outcome of patients with metastatic esophagogastric cancer remains poor with a median survival of less than one year. After failure of platinum- and taxane-based treatment only few salvage treatment options exist. In the recent years several targeted agents could not demonstrate an increase in survival in comparison to cytotoxic treatment alone, currently a molecularly-defined targeted therapy is only available for Her-2 positive tumors.

In early phase I and phase II trials immunotherapy in forms of checkpoint blockade (PD-1 or PD-L1 inhibitors) has shown clinically relevant activity in patients with refractory esophagogastric cancers with responses seen in 10-20% of patients. However, in recent phase III trials superiority of checkpoint blockade in comparison to salvage chemotherapy as second- or third-line treatment could not be demonstrated in patients with gastric or gastroesophageal-junction adenocarcinoma. In 2019 results of phase III trials exploring the efficacy of checkpoint blockade alone and in combination with chemotherapy in the first-line setting are expected.

In summary checkpoint inhibition as a monotherapy shows efficacy in patients with esophagogastric cancer, however response rates are low in pretreated unselected cohorts.

As a consequence predictive biomarkers beyond PD-L1 expression are required for a better therapy selection. In adenocarcinoma, molecularly-defined subgroups such as MSI-H tumors or EBV- associated tumors are associated with a high clinical activity of checkpoint inhibitors, paving the path towards a molecularly-tailored therapy.

Disclosure: Georg Martin Haag: Advisory Role: Bristol-Myers Squibb, MSD Sharp & Dohme (Inst), EsoCap; Financing of Scientific Research: Pfizer, Servier; Expert Testimony: Nordic Pharma (Inst); Taiho Pharmaceutical (Inst); Other Financial Relationships: Travel Support: Ipsen; Bristol-Myers Squibb; Lilly

V809

Potential future of immunotherapy in esophagogastric cancers

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Introduction: Immunotherapeutic antibodies targeting the programmed death 1 (PD-1) and programmed death ligand 1 (PD-L1) emerged as new treatment options for advanced gastric and gastroesophageal junction cancers (GC/GEJC).

Methods: We screened the most recent publications and abstracts for IO mono- or combination therapies.

Results: Monotherapy with anti-PD-1/PD-L1 antibodies, including pembrolizumab, nivolumab or avelumab showed objective response rates (ORRs 9-30%) across GC/GEJC populations, possibly higher in PD-L1+ tumors. Safety compares favorably with chemotherapy, with grade ≥3 treatment-related adverse events (TRAE) occurring mostly < 15%. Immune-related adverse events (irAEs) may affect gastrointestinal, skin, pulmonary, endocrine, neurologic, hepatic and renal tissues. Quite higher TRAEs rates and reduced QoL are seen in CPI-chemotherapy combinations. In a phase 3 trial, nivolumab increased overall survival vs placebo in an Asian third+later line population, leading to approval in Japan and Switzerland. Based on a large phase 2, pembrolizumab was approved in US for third-line PD-L1+ tumor patients (≥1% cutoff), by higher ORR (16% vs 6% for PD-L1-). PD-L1+ was based on combined positive score (CPS) including PD-L1 expression in tumor cells, lymphocytes, and macrophages.

After the press releases and presentations at ASCO 2019 with pembrolizumab or nivolumab vs. chemotherapy in first- and second-line of advanced esophageal adeno- and squamous cancers (KN181, Attraction3 and KN062, patient selection according to PD-L1+ will be included as important endpoint in many ongoing trials, for various CPI-based strategies, including monotherapy or combinations, in first- and later-line, and switch-maintenance settings, and results are awaited. Chemo-free IO regimens in first line might be another option for highly selected metastatic patients with low tumor burden and good prognostic markers, such as CPS10, MSI and EBV positivity.

Conclusions: Innovative combinations with other IO agents, PARP inhibitors, targeted agents and stem cell blocker, such as DKN-01 or oncolytic viruses may additionally increase the immune responses and prolong PFS or OS in these patients.

Disclosure: Markus Moehler: Employment or Leadership Position: Leiter der gastroenterologisch-onkologischen Ambulanz, Uniklinik Mainz; Advisory Role: Lilly, Onyx, Roche, BMS, MSD, Amgen, MerckSerono, Pfizer, Taiho, Servier; Financing of Scientific Research: Falk, Nordic, Amgen, mci, Lilly, MSD, Pfizer, BMS, Amgen, MerckSerono, Taiho, SErvier, ESMO, ASCO; Expert Testimony: Merck, Amgen, BMS, Taiho, Roche, MSD, AIO, EORTC, Transgene

V810

Promising targeted therapy options

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New treatment options are clearly warranted to improve outcome in patients with advanced gastric cancer. The combination of trifluridine/tipiracil (TAS-102) is a new oral anticancer drug with activity in gastrointestinal cancer. TAS-102 consists of a thymidine-based nucleoside analogue, trifluridine and the thymidine-phosphorylase inhibitor tipiracil. TAS-102 showed significant clinical activity in heavily pretreated patients with advanced gastric cancer. In the TAGS-study, a double-blind, placebo-controlled phase 3 study with 507 patients, the median overall survival (primary endpoint of the study) was significantly increased with 5,7 months in the TAS-102 group compared to 3,6 months in the placebo group (HR 0,69, two-sided p=0,00058). No baseline patient characteristics or disease factors were identified to be predictive for overall survival. The therapy with TAS-102 was well tolerated. Based on the results of the TAGS-study TAS-102 is a new treatment option for patients with heavily pretreated advanced gastric cancer. Apatinib is a small-molecule tyrosine kinase inhibitor that selectively inhibits the VEGFR-2 tyrosine kinase. Apatinib showed promising efficacy and safety in the third-line or more therapy in chemotherapy-refractory advanced gastric cancer. Data from a recent published phase 3 study showed that treatment with apatinib significantly improved overall survival compared with BSC/placebo (6,5 versus 4,7 months for placebo, HR 0,709, p=0,0156). The recent results from a large phase 3 trial with andecaliximab, a monoclonal antibody that inhibits matrix-metalloproteinase-9 (MMP-9), failed to replicate the positive data from a previous study of andecaliximab in combination with chemotherapy in untreated HER2-negative gastric or gastroesophageal junction adenocarcinoma. However, a sensitivity analysis has revealed that andecaliximab may be beneficial in older patients. Zolbetuximab is a chimeric monoclonal antibody directed against CLDN18.2-positive gastric cancer cells through immune effector mechanisms. Zolbetuximab combined with chemotherapy (EOX) showed for advanced CLDN18.2-positive/HER2-negative gastric and gastroesophageal junction cancer significant clinical activity in the first-line therapy. The combination of zolbetuximab and EOX was generally well tolerated. Randomized clinical studies with zolbetuximab are ongoing.

Data on new targeted therapy options (excluding immunotherapy) will be discussed.

Disclosure: No conflict of interest disclosed.

Fortbildung

Kompetenznetz Akute und Chronische Leukämien

V811

Age-related clonal hematopoiesis

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Age-related changes in haematopoiesis have been known for some time. Using the new high-throughput sequencing technologies it has been shown that age-related, reduced genetic diversity can be found both at the stem cell level and in B- and T-cells. This reduced diversity is most likely due to somatic mutations and/or changes in the microenvironmental niche.

Age-related clonal hematopoiesis (ARCH) was initially defined by detection of somatic mutations in the blood or bone marrow in healthy individuals. It was shown that the incidence increases with age and so far no clinical significance was found. Recently, the term ARCH has been more clearly defined as the expansion of hematopoietic stem cell and progenitor cell clones with specific, disruptive and recurrent genetic variants in individuals without a clear diagnosis of hematologic malignancies. The list of recurrent variants is still rapidly evolving, however, it is important to define this list in order to achieve a consistent use of the term. ARCH must be distinguished from other clonal haematopoiesis. Clonal hematopoiesis of indeterminate potential (CHIP) is the presence of somatic mutations in genes typically mutated in myeloid neoplasia in blood or bone marrow cells in the absence of signs of hematological neoplasia. Furthermore, the respective mutation load must be ≥2%. In clonal cytopenia of undetermined significance (CCUS) one or more unexplained cytopenia are present. However, the diagnostic criteria for MDS are not fulfilled. However, as in CHIP, somatic mutations are found in genes associated with myeloid neoplasias with a mutation load of ≥2%. Clonal hematopoiesis with oncogenic potential (CHOP) is the presence of disease-associated or disease-specific mutations without a disease being diagnosed.

The incidence of ARCH, CHIP, CCUS, CHOP, MDS and AML increases with age. While, for example, CHIP is very rare in persons under 40 years of age, about 10% of persons under 70 years of age have CHIP. Individuals with CHIP have been shown to have an 11 to 13-fold increased risk of developing hematological neoplasia, but the overall transformation rate is relatively low at 0.5-1% per year.

A continuous transition between ARCH, CHIP, CCUS, CHOP, MDS and AML can be assumed, whereby the complexity of the genetic changes increases. The first models are available, which determine probabilities for progression on the basis of mutated genes and mutation loads.

Disclosure: Claudia Haferlach: Stock Ownership: MLL - Münchner Leukämie Labor

Freier Vortrag

Chronische myeloproliferative Neoplasien II

V816

Genomic landscape and molecular risk in patients with DIPSS Low- and Intermediate-1 risk primary myelofibrosis (PMF)

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Introduction: The Dynamic International Prognostic Scoring System (DIPSS) stratifies primary myelofibrosis (PMF) patients (pts) by prognosis into low-, intermediate-1 (int1), intermediate-2, or high-risk categories. Independent of the DIPSS category, PMF pts carrying mutations (muts) in the High Molecular Risk (HMR) genes ASXL1, SRSF2, EZH2 and/or IDH1/2 incur a higher risk of death or leukemic transformation. Here, our aim was to assess the genomic landscape in DIPSS low- and int1- risk PMF pts and to explore disease progression in pts with HMR mut (HMR^{mut}).

Methods: The coding regions of 42 genes associated with myeloid neoplasms were sequenced by Next Generation Sequencing (NGS) (HaloPlex HS, Agilent/MiSeq, Illumina®) in 78 pts with low- and int1-risk PMF, mainly taken from the GSG-MPN Bioregistry (NCT03125707)

Results: 182 muts were found in 74/78 pts (95%). The classical MPN driver muts were distributed as previously described: 64% $JAK2^{V617F}$, 5% MPL (W515, n=3; Y591, n=1), and 26% CALR mut; 8% pts were triple-negative. 59% of the pts carried non-driver muts in TET2 (13%), DNMT3A (6%) or FLT3, KMT2A, KRAS, CBL, and ZRSR2 (2% each). In total, 32 HMR^{mut} were found in 20/78 (26%) pts, occurring more frequently in the int1 (39%) than in the low-risk (14%) group (p=.019). These encompassed ASXL1 in 19% (15/78), SRSF2 in 9% (7/78), EZH2 and IDH2 in 4% each (3/78), and IDH1 in 1% (1/78) of pts. 9/78 pts (12%) displayed 2 different HMR^{mut}, of these 8/9 co-occurred with ASXL1. Pts with HMR^{mut} showed more co-mutations than HMR wildtype (HMR^{wt}) pts (median 4 vs 2; p< .0001). Moreover, HMR^{mut} were significantly associated with the $JAK2^{V617F}$ driver mutation (p=.03) but not with any other mutational pattern.

Clinical outcomes were analyzed in 47/78 pts with a median follow-up (FU) of 3.5 years in HMR^{mut} and 6.5 years in HMR^{wt} pts. Despite the shorter FU, a larger proportion of HMR^{mut} pts 5/13 (38%) than HMR^{wt} pts 4/34 (12%) progressed to a higher DIPSS category (n=8) or incurred a leukemic transformation (n=1) [p=.09].

Conclusions: Using targeted NGS we identified HMR mutations in 26% of 78 DIPSS low- and int-1 risk PMF pts. As HMR^{mut} define a higher risk for disease exacerbation independent of the DIPPS category, these data underscore the clinical importance of HMR marker screening. However, prospective studies with longer FU-time are required to demonstrate the prognostic impact of HMR^{mut}, thereby possibly providing a rationale for earlier therapeutic intervention.

Disclosure: No conflict of interest disclosed.

V817

Ruxolitinib plus pomalidomide in myelofibrosis with anemia: results from the MPNSG-0212 combination trial (NCT01644110)

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As pomalidomide (POM) improved cytopenia in 14% (POM 0.5 mg QD) and 29% (POM 2.0 mg QD) of myelofibrosis (MF) patients (pts) in our previous MPNSG-0109 trial, we sought to investigate the drug in combination with ruxolitinib (RUX) in MF with anemia.

MPNSG-0212 is a multicenter phase-Ib/II trial with a target population of 90 pts. Pts 1-40 (cohort 1 [co1]) are treated with RUX 10 mg BID plus POM 0.5 mg QD, while pts 41-90 (cohort 2 [co2]) receive RUX 10 mg BID plus POM 0.5 -> 1 -> 2 mg QD. Primary endpoints are safety and anemia response after 12 28-day-cycles. Main inclusion criterion is MF with anemia (Hb < 10 g/dL and/or red blood cell transfusion dependency [RBC-TD]).

Data from 59 pts were available: Median age 72 yrs (range 49-84), prior RUX treatment in 22%, median Hb level 8.5 g/dL (range 5.4-11.7), RBC-TD in 27%, median spleen size 17.8 cm (range 12.6-36), 93% intermediate-2 (64%) or high-risk (29%) according to DIPSS, and ≥1 HMR mutation (ASXL1, SRSF2, EZH2, and/or IDH1/2) in 55%.

Median treatment time was 12 cycles (range 2-59) in co1 and 11 cycles (range 1-16) in co2. Most common AE (°I/II) were anemia (34% of pts) and fatigue (29%) in the first weeks of treatment as well as musculoskeletal cramps (25%). Most common serious AE were pneumonia (12%), leukemic transformation (10%), and worsening of general condition (7%).

In co1, 18/40 pts (45%) continued treatment beyond cycle 12 because of objective anemia response (7/40, 18%: Hb increase ≥2 g/dL, n=5, PR and RBC-TI n=1 each) or clinical benefit (11/40, 28%) defined as: Hb increase ≥1 g/dL and/or doubling of RBC transfusion intervals (n=4) or improvement of fatigue and/or overall quality of life >25% according to MPN-SAF (n=7).

Most notably, 16 pts of co1 (40%) were on treatment for more than 24 cycles, and mean Hb increased continuously from 8.7 g/dl to 9.8 g/dL at end of cycle 18 and sustained thereafter at 9.7 g/dL until end of cycle 30.

In co2, 16/19 pts (84%) were still on treatment at the time of the analysis; 10/19 pts (52%) have not yet reached cycle 12. Increase of the POM dose to 1 mg QD after 3 cycles and 2 mg QD after 6 cycles was feasible in 94% and 69% of pts, respectively.

Combination treatment of RUX and POM was safe and feasible in pts with poor-risk MF and resulted in an objective anemia response rate of 18% in co1, while 40% of pts showed a long-lasting stabilization of their disease with sustained improvement of Hb and quality of life.

Disclosure: No conflict of interest disclosed.

V818

Blockade of the TNFR1 and TNFR2 pathways in a JAK2-V617F positive mouse model as a potential therapy to control chronic inflammation in MPN

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Introduction: Myeloproliferative neoplasms (MPN) are characterized by expansion of myeloid cells, splenomegaly and development of thrombosis. Recent studies show that MPN-induced chronic inflammation promotes disease development and increases symptom burden. In the Vav1-Cre x $JAK2^{+/V617F}$ knock-in ($JAK2^{VF+}$) MPN mouse model, we studied the role of the TNF receptor (TNFR) 1 and 2 pathways as potential therapeutic targets to control chronic inflammation.

Methods: $JAK2^{VF+}$ mice received i.p. either αTNFR1 (H398; 20 mg/kg), αTNFR2 (TR75-54.7; 5 mg/kg) antibodies (Ab) or specific IgG controls 3 x per week (αTNFR1) or 2 x per week (αTNFR2) for 3 weeks. The total blood count was analyzed weekly during treatment. At the end of treatment; cell composition of blood, bone marrow and spleen were analyzed by flow cytometry. Serum concentrations of cytokines in blood were measured by a bead-based multiplex assay. In addition, to study the role of TNFR1 and TNFR2 signaling in disease development, the $JAK2^{VF+}$ model was crossed with TNFR1 or TNFR2 KO mice. At the age of 12 weeks mice were analyzed as at end of Ab treatment.

Results: At the age of 12 weeks, $TNFR1^{-/-}$ and $TNFR2^{-/-}$ x $JAK2^{VF+}$ mice showed similar disease development as $TNFR^{WT}$ x $JAK2^{VF+}$ mice indicating minor importance of single cytokine pathways, as TNFR1 or TNFR2, in MPN development.

In contrary, upon αTNFR1 Ab treatment, the mean hematocrit (HCT) was significantly reduced after 3 weeks of treatment from 72.5% to 60% ($p = 0.0152$) as compared to a 2.0% increase observed in the control group. There was no difference in RBC, WBC or PLT number between αTNFR1 Ab and control group during treatment. Interestingly, analysis of pro-inflammatory cytokine levels in the serum displayed a major decrease in TNF, IL-1β or IL-6 and others in H398 treated mice as compared to controls (15-50%).

αTNFR2 Ab treatment reduced HCT from 79.0% to 67.8%, but the IgG group also had a decrease (75.5% to 71.0%; $p = 0.1$). RBC and PLT stayed stable during Ab treatment, whereas WBC slightly decreased during α-TNFR2 treatment. There was almost no change in cytokine levels in comparison of αTNFR2 treated and control mice.

Conclusions: Our mouse study revealed an involvement of the TNFR1 rather than the TNFR2 pathway in chronic inflammation. αTNFR1 Ab treatment downregulated HCT and levels of pro-inflammatory cytokines. Therefore, TNFR1 blockade may have therapeutic potential, in particular in combination with JAK1/2 inhibition.

Disclosure: Peter Müller: No conflict of interest disclosed.
Thomas Fischer: Honoraria: submitted a patent application related to compounds for the treatment of JAK2-V617F–associated chronic myeloproliferative neoplasia (European Patent Office application MKEY)

V819

Molecular determinants of fibrotic progression in myeloproliferative neoplasms (MPN)

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Introduction: Unlike in BCR-ABL positive chronic myeloid leukemia, in BCR-ABL negative myeloproliferative neoplasms (MPN), comprising polycythemia vera (PV), essential thrombocythemia and prefibrotic primary myelofibrosis (pPMF) blastic or fibrotic progression do occur only

in a minority of cases. Molecular aberrations associated with development of fibrosis in BCR-ABL negative MPN could help to identify the subgroup of patients at risk.
Methods: Follow-up bone marrow biopsies from PV (n= 36) without progression (median follow-up 4.25 years, range 1.0 to 11.5 years) and with progression (n=28; median follow-up 6.25 years, range 1.0 to 17.0 years) were retrospectively analysed by next generation sequencing (NGS) using a panel of 23 genes. Similarly, sequential biopsies from 71 pPMF cases with progression from fibrosis grade 0 to grade 2/3 within a median interval between first and second biopsy of 2.5 years were compared to stable PMF cases without fibrotic progression within a follow-up period of at least 4 years (n=23). In addition, tumor mutational burden (TMB) was determined.
Results: In PV IDH1/2 and splice factor gene mutations (26%) were demonstrable exclusively in cases with fibrotic progression. Only in the progressive but not the stable PV cohort, two or more mutations besides JAK2V617F were found (35%). With regard to TMB progressive and stable pPMF did not differ although a set of 25 selected genes exhibited significantly more mutations in progressive cases (p=0.0218). MPN-specific driver mutations (JAK2, CALR type 1 and 2, MPL) were not predicitive with regard to type of mutation and allelic burden. In PV and pPMF alterations of TET2, DNMT3A and ASXL1 genes, also occurring in CHIP (clonal hematopoiesis of indetermined potential) were encountered in both groups with a tendency to be increased in the fibrosis cohort. By contrast, in pPMF like in PV, EZH2 (5%), IDH mutations (4%) and splice factor gene mutations (SRSF2, U2AF1; 21%) were restricted to cases with fibrotic progression. Clonal evolution with novel mutations of TP53, KRAS, EZH2, RUNX1 in follow-up biopsies occurred in 34% of pPMF cases.
Conclusions: A set of non-CHIP mutations usually associated with myelodysplastic syndromes can be found already at presentation in a subgroup of MPN cases and convey an increased risk of fibrotic progression in PV and pPMF.

Disclosure: Stephan Bartels: No conflict of interest disclosed.
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V820

Epidemiologic aspects of advanced systemic mastocytosis in Germany

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Within the 'German Registry on Disorders of Eosinophilia and Mast Cells', we analyzed epidemiologic characteristics of 140 patients (pts) with advanced systemic mastocytosis (advSM) referred to our reference center of the European Competence Network on Mastocytosis (ECNM) between 2009 and 2018. The median age was 68 years (range 26-86) with a male predominance of 2:1. Overall survival (OS) was inferior in male pts (2.6 vs. 4.2 years, p=0.02). A mutation in *KIT* D816 and an elevated serum tryptase were present in 97% and 95% of pts, respectively. Initial work-up in 28/140 (20%) patients, who were primarily diagnosed with various subtypes of myeloid neoplasms (e.g. CMML or MDS/MPNu), failed to identify the association to SM for median 24 months (range 1-86). On the contrary, 23/140 (16%) pts progressed from indolent SM (ISM) to advSM after median 32 months (range 1-165). The high median *KIT* D816V allele burden of 39% (range 0-76) in peripheral blood (PB) in all but one ISM pts clearly suggests primary multilineage involvement, as known adverse prognostic marker in ISM, or missing of a yet undiagnosed SM with associated hematologic neoplasm (SM-AHN). OS of pts progressing from ISM to advSM was significantly better than in primary advSM (OS not reached vs. 3.1 years, p=0.015). In the 'Metropolitan Region Rhein-Neckar' with 2.4 million inhabitants, we estimated an incidence of 2 per year and a prevalence of 4.6 per million inhabitants. Our data was confirmed by an independent German ECNM center (University Hospital RWTH Aachen) with comparable results. Based on this data, we calculated a yet significantly underestimated prevalence of at least 380 advSM patients for all of Germany (82 million inhabitants). We therefore conclude that i) incidence and prevalence of advSM are significantly higher than assumed, ii) advSM (usually SM without AHN or AHN without SM) is missed or incorrectly diagnosed in up to 30% of pts, iii) all ISM patients should be screened for the *KIT* D816V mutation burden in PB, iv) all patients with chronic myeloid neoplasms should be screened for tryptase and positive cases for the *KIT* D816V mutation burden in PB and dense mast cell infiltrates in BM and v) establishment of reference centers, registries and clinical trials have clearly improved awareness, diagnosis and treatment of patients with advSM.

Disclosure: No conflict of interest disclosed.

V821

Telomere shortening in Philadelphia chromosome negative myeloproliferative neoplasms

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Introduction: Telomeres are repetitive sequences at the end of chromosomes and shorten with each cell division, thereby reflecting the replicative history of an individual somatic cell. In chronic myeloid leukemia, a correlation between accelerated telomere shortening and clonal dominance in the hematopoietic stem cell compartment has been demonstrated and found to be linked to disease stage/progression. Data on the role of telomere biology for disease progression in classical Philadelphia negative (Ph-neg) myeloproliferative neoplasms (MPN) such as Essential Thrombocythemia (ET), Polycythemia vera (PV) and Myelofibrosis (MF) are more controversial and the relevance of telomere length (TL) in distinct leukocyte subsets as marker for prognosis, disease progression or clonal evolution in the different clinical or genetic subgroups of classical Ph-neg MPN has not been studied systematically so far.
Methods: 73 MPN patients (median age men: 56y [20-80]; women: 61y [21-87]) with classical Ph-neg MPN (ET (n=27, 37%), PV (n=19, 26%) and MF (N=27, 37%, 23 primary MF, 4 post-PV/ET-M) and 354 controls were analyzed. TL in viable peripheral blood cells (lymphocytes and granulocytes) was performed by flow FISH. Genotype and allele burden was assessed by using panel-based next generation sequencing (NGS). JAK2 positive patients were 37% in the ET group, 100% in the PV group and 60% in the MF group. CALR mutations were present in 13 ET samples (35%) and 7 MF samples (19%).
Results: TL of granulocytes was significantly shortened in the MPN cohort as compared to controls, amounting to -0.4kb in ET (p=0.036), -0.78 kb in PV (p=0.004), and -1.04kb in MF (p< 0.001). In addition, mean TL differed significantly between ET and MF (p=0.0438), whereas no significant difference was found between ET and PV or PV and MF. A significant inverse correlation of JAK2 allele burden and TL was detected in our cohort (R=-0.53548; p=0.00076). CALR positive samples showed significant shorter telomeres than CALR negative samples both in ET (p=0.00528) and in MF (p=0.00854).
Conclusions: We demonstrate significantly shortened TL in MPN overall and a negative correlation with JAK2 allelic burden. In addition, CALR positive mutational status was correlated with telomere shortening. A statistically significant difference in TL was found when comparing ET and MF samples pointing to a role of accelerated telomere shortening for disease progression or defining more complex stages in MPN.

Disclosure: Martin Kirschner: Advisory Role: Roche
Tim H. Brümmendorf: Advisory Role: Pfizer, Novartis, Takeda, Janssen, Merck (no personal honoraria); Expert Testimony: Pfizer, Novartis, RepeatDx

Freier Vortrag

Multiples Myelom II

V822

Biomodulatory therapy approach with lenalidomide in combination with pioglitazone, dexamethasone, and metronomic low-dose chemotherapy with treosulfan in patients with relapsed/refractory multiple myeloma > second-line

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Background: Nowadays, therapy for relapsed or refractory multiple myeloma (rrMM) usually consists of multi-targeted combination regimens for achieving complete remission. In this context, resistance resembles a therapeutic challenge that may be overcome by novel biomodulatory therapies communicatively reprogramming dysregulated cellular and intercellular homeostasis in neoplasia.
Methods: The present, prospective phase II, one-arm, one-stage multi-center, open label trial, following phase I, focused on reprogramming myeloma and adjacent stroma cells in order to control rrMM beyond > 2nd-line treatment and following lenalidomide resistance in prior line. Adults with rrMM were eligible for receiving continuously, oral, daily dexamethasone 1mg, pioglitazone 45mg, low-dose treosulfan as metronomic chemotherapy (250mg bid) and lenalidomide 15mg, respectively, until disease progression.
Results: Thirty-nine patients (mean time since diagnosis, 5.7 years; 66.7% with age > 60 years) had received a median of 5.5 (range 2 to 10) prior treatments. 89.5% of the patients were refractory to last therapy (all IMiD resistant), and 48.7% had received autologous stem-cell transplants. The overall response rate (CR, VGPR) was 17.9%. Eighteen patients (46.2%) had partial response or better; ten patients (25.6%) had stable disease. The disease control rate (DCR) was 71.8%. Time-to-progression was not significantly different between IMiD refractory patients and those relapsing following prior IMiD therapy or between high-risk versus non-high-risk cytogenetics. The median progression-free survival (PFS) and overall survival was 5.6 months (95% confidence interval [CI], 3.8 to 8.5) and 17.6 months (95% [CI], 14.9 to 39.2), respectively. The major AE (NCI-CTCAE grade) with grade ≥ 3 and relation to study drugs was hematologic toxicity (N = 31, 67.4%). Due to scheduled dose reductions, this was associated with only 7 (15.2%) grade ≥ 3 infections.
Conclusions: The favorable safety profile, encouraging efficacy and equivalent median PFS between biomodulatory and modern targeted therapy in a historic comparison reveal a proof of concept of combined biomodulatory therapy in patients with heavily pretreated and IMiD-resistant rrMM, which should be further evaluated. (Funded by Celgene; ClinicalTrials.gov number NCT001010243).

Disclosure: No conflict of interest disclosed.

V823

Single-tube 10-fluorochrome next generation flow cytometry (NGF) analysis for efficient evaluation of aberrant (aPC) vs normal plasma cells (nPC) and MRD in multiple myeloma (MM) patients (pts)

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Introduction: MM is characterized by the accumulation of bone marrow (BM) aPC. With the usage of novel agents in anti-MM treatment, much deeper treatment responses and prolonged progression free and overall-survival can be achieved. NGF allows the detection of residual aPC after therapy with high sensitivity. The incorporation of readily available, standardized MRD tools into clinical trials (CTs) and clinical practice is essential to allow improved decisions on timing of stem cell transplantation (SCT), need for consolidation, duration of maintenance and early relapse detection.
Methods: We systematically validated a single-tube, novel 10color panel using the antigens CD38, CD138, CD19, CD45, CD27, CD56, CD28, CD81, CD117 and CD200 in 9 different MM cell lines (MMCLs) and 124 BM, peripheral blood (PB), and leukapheresis (LA) samples from 94 different MM pts and 13 healthy individuals (HI). For high sensitivity, $3x10^6$ viable nucleated cells were analyzed on a Fortessa. NGF validation included fluorescence-minus-one (FMO) and spike-in-controls. Spike-in controls were performed using dilution assays to recover defined numbers of MMCL cells in the PB of HI. Here we assessed BM and PB samples of HI, MM pts at initial diagnosis (ID) or at progression (PD), after standard therapy (ST) and SCT. The study was performed with written consent and approval from the ethics committee.
Results: We established an easy-to-adapt gating strategy to identify aPC vs nPC in MM pts. Through the use of dilution assays, we determined a MRD sensitivity of 10^{-5} and stable recovery of MMCL for >3 hours. The 10color antigen expression levels in 9 MMCL (RPMI8226; U266; IM-9; MM1.S; MM1.R; L363; Karpas620; NCI-H929; OPM-2) were confirmed as reported. Expectedly, our panel showed significant decrease of aPC between symptomatic MM vs SMM/MGUS pts (p=0.009). Moreover, nPC were significantly increased in MGUS/SMM compared with MM samples ($p< 0.05$). Our MRD negativity rate (< 0.001%) in BM samples under ST- or SCT-treatment is currently 26%, with a median time of 45 days from treatment to first MRD evaluation.
Conclusion: The EuroFlow Consortium has established a two 8color tube MRD assay. Despite its successful use in CTs other highly sensitive and validated panels, such as this one, also provide efficient, flexible and reliable MRD assessment. Our 10color panel allows the sensitive detection of aPC vs nPC in MM and precursor diseases and can now be implemented into routine diagnostics.

Disclosure: Veronika Christine Riebl: No conflict of interest disclosed.
Monika Engelhardt: Advisory Role: Amgen, Janssen, Celgene, Novartis, Takeda; Financing of Scientific Research: Reiseunterstützung Amgen, Celgene, Janssen; Expert Testimony: educational grants Amgen, Janssen, Novartis, Celgene

V824

The transcriptome of pomalidomide-resistant multiple myeloma

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Introduction: While the molecular target of pomalidomide and other immunomodulators has been identified, the mechanisms underlying therapeutic resistance remain incompletely understood. The uniformly emerging resistance to therapy over time in the absence of identifiable cereblon pathway mutations in the majority of patients raises questions about alternative mechanisms including aberrant gene expression.
Methods: We performed gene expression profiling using an Affymetrix GeneChip Human Genome U133 Plus 2.0 microarray on CD138$^+$ bone marrow mononuclear cells of 30 patients with relapsed multiple myeloma prior to initiating treatment with pomalidomide. We categorized patients based on their IMWG response as non-responders (SD, n=15) and responders (VGPR+, n=15). We compared overall survival, gene expression patterns, and involved cellular pathways between the two groups.
Results: Pomalidomide resistance was associated with an increase in mortality (median overall survival 1.6 versus 6.4 years, p = 0.009). There were 1077 differentially regulated genes (q < 0.05) between responders and non-responders. Unsupervised hierarchical clustering of the 192 most significant genes (q < 0.01) demonstrated distinct patterns of gene expression in pomalidomide-resistant disease. Gene ontology analysis of these 192 genes revealed protein synthesis as one of the most enriched biological processes. Differentially expressed genes involved key protein degradation pathways (CUL family members, USP13, DTL), epigenetic modifiers (NSD2, NAP1L3, HMGN5), and transcription factors (HEY1, ZBTB8A, MLLT11).

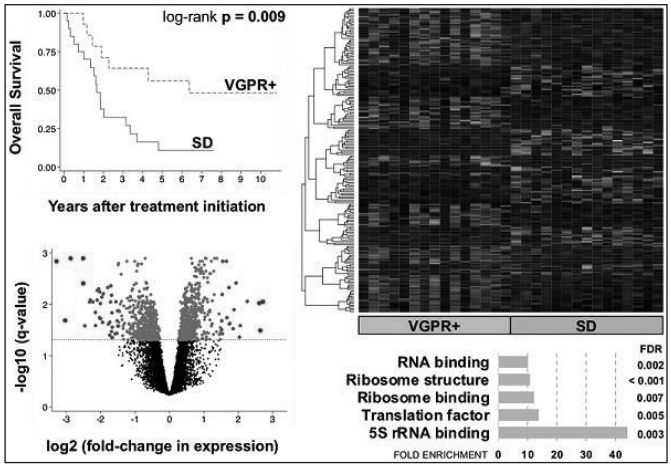

Fig. 1. Clinical significance, transcriptomic changes, and biological processes in pomalidomide resistance

Conclusions: Overall survival of patients with pomalidomide-resistant relapsed multiple myeloma remains poor. Pomalidomide resistance was associated with differential gene expression in several potentially targetable cellular pathways, beyond the known drug target cereblon. Elucidating the exact molecular mechanisms underlying immunomodulator resistance is of considerable interest for biomarker development and the identification of novel therapeutic targets and warrants further exploration.

Disclosure: Moritz Binder: No conflict of interest disclosed.
Shaji K Kumar: Expert Testimony: AbbVie, Celgene, Janssen, KITE

V825

Heterogeneity of serum free light chain determination - implications on diagnostic and therapeutic monitoring of multiple myeloma

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Introduction: Determination of serum free light chains (FLC) is established as standard for diagnosis and monitoring of multiple myeloma (MM). In 2014, the revised IMWG criteria implemented the serum free light chain ratio (involved FLC/non-involved FLC) > 100 as a biomarker defining MM requiring treatment. This recommendation was based on a single assay method (Freelite), which relies on polyclonal antisera. Additionally, the monoclonal N-Latex FLC assay and more recently, the polyclonal Sebia FLC assay are available and approved for determination of FLC. The aim of this trial was to compare the three different assays for correlation and potential implication for diagnostic and clinical use.
Methods: Blood samples from patients with MM in a single center were collected at the beginning of the study and after a maximum of six follow-up visits. Total of 187 samples from 47 patients were examined. Determination of FLC (κ, λ and κ/λ ratio) was conducted. N Latex reagents (Siemens Healthineers, Germany) and Freelite reagents (The Binding Site (TBS), United Kingdom) were used on a Siemens BN II nephelometer. Sebia FLC (Sebia, France), was performed manually. Statistical analyses included Passing-Bablok regression analyses, Spearman rank correlation, Bland-Altman plots and Cohens Kappa coefficient.
Results: Comparison of N Latex and Freelite assay shows higher total values for Freelite kappa and lambda compared to N Latex, which lead in higher FLC ratios. Comparison of Sebia FLC to N Latex and Freelite shows similar results for Sebia FLC and N Latex with markedly lower values compared to Freelite. Using Freelite to determine the iFLC/niFLC ratio, 18 of 47 patients exhibited a ratio >100. With N Latex and Sebia FLC just 10 and 9 patients respectively were quantified as FLC ratio >100. Using the recently proposed modified thresholds for N Latex (> 30) or Sebia FLC (> 16), comparable results to the Freelite assay were achieved.
Conclusions: This is the first report on comparing three different assays to determine serum free light chain values. Our data show that the assays should not be used interchangeably to monitor patients. Absolute values differ as well as the FLC ratio, which shows high discrepancy between the different assays. In light of these results, modification of the diagnostic threshold for the definition of MM requiring treatment is recommended.

Disclosure: Aneta Schieferdecker: No conflict of interest disclosed.
Katja Christina Weisel: Advisory Role: Amgen, Adaptive Biotech, Bristol Myers Squibb, Celgene, Janssen, Juno, Sanofi, Takeda; Financing of Scientific Research: Amgen, Celgene, Bristol Myers Squibb, Janssen,Takeda; Expert Testimony: Amgen, Celgene, Sanofi, Janssen

V826

A multi-OMIC screening approach for DUB-based tumor vulnerabilities identifies OTUD6B as a new oncogene in multiple myeloma

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Introduction: Multiple myeloma (MM) is a cancer of plasma cells in the bone marrow and represents the second most common haematological malignancy. Despite recent therapeutic advances, this disease is incurable necessitating the identification of new druggable vulnerabilities. High

response rates to proteasomal inhibition implicate that aberrant functions of the ubiquitin proteasome system play a pivotal role in the pathophysiology of MM.
Methods: A pooled CRISPR/Cas9 based genetic screen was performed to identify MM relevant members of deubiquitinases (DUBs). Relevance of identified candidates for MM growth was confirmed by proliferation and cell cycle analyses in knockout and knockdown settings. Two mass spectrometry-based proteome wide screening approaches were performed in order to identify substrates. Binding and deubiquitylation of a substrate candidate were confirmed by immunoprecipitation and *in vivo* ubiquitylation assays, respectively. DUB activity assays and cycloheximide experiments were conducted in different cell cycle stages. mRNA levels of various proteins were analysed by qPCR in MM cell lines and patient derived samples.
Results: In search for new potential oncogenes, we performed a CRISPR/Cas9 screen of DUBs in MM cells and found OTUD6B as an essential gene for MM cell proliferation. Furthermore, we could show that the antiproliferative effect of OTUD6B loss is caused by a cell cycle arrest at G1/S transition, at which OTUD6B activity was found to peak. By combining affinity and non-affinity-based mass spectrometric screens, we identified LIN28B as potential substrate of OTUD6B. LIN28B has been previously described as oncogene, which stabilizes various other oncogenes like RAS and MYC by decreasing let-7 miRNAs. We could show that LIN28B specifically binds to OTUD6B in a phosphorylation-dependent manner and that OTUD6B removes K48-linked polyubiquitin from LIN28B *in vivo*. In line with these findings, we found that knockdown of OTUD6B prevents proteolytic degradation of LIN28B in G1/S synchronized cells. In accordance with these results, loss of OTUD6B led to a strong reduction of MYC mRNA in various MM cell lines and qPCR analysis of 89 patient samples revealed a significant correlation between OTUD6B and MYC mRNA level.
Conclusions: We identified a novel role of OTUD6B in MYC stabilization via the LIN28B/let-7 axis in MM cells and specify OTUD6B as a potential therapeutic target in this disease.

Disclosure: Carmen Richter: No conflict of interest disclosed.
Florian Bassermann: Advisory Role: Beratertätigkeit für BMS, Janssen, und Amgen; Expert Testimony: Forschungsförderung durch Celgene

V827

The role of metabolic factor SIRT3 in bone marrow stroma in MM patients

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Introduction: SIRT3 (Sirtuins-3) is the main mitochondrial deacetylase, which controls the activity of many metabolic enzymes in the mitochondria. SIRT3 deacetylates mitochondrial proteins that act in the oxidation of fatty acids, glutamine metabolism, and the production of mitochondrial Reactive Oxygen Species (ROS). Moreover, SIRT3 is involved in regulation of cancer metabolism.
Methods: Bone marrow mesenchymal stromal cells (BMSCs) from multiple myeloma (MM) patients (MM-BMSCs, n=35) and healthy individuals (HD-BMSCs, n=4) were isolated using adhesion method and co-cultured with KMS12-PE cell line. Expression of SIRT3 was estimated using RT-qPCR and western blotting. HD-BMSCs were transfected to transient knock-down of SIRT3 using siRNAs. In addition, each cell type was investigated after the addition of drugs to the cell culture. Using our in vitro model, we studied a monoclonal antibody (elotuzumab) and an immunomodulatory drug (lenalidomide).
Results: Significant lower expression of SIRT3 was detected in MM-BMMSC as compared with HD-BMSC ($p< 0.001$). The data were reproduced at the protein level. In addition, was shown that MM-BMSCS show significant increasing of mitochondrial mass compared to HD-BMSC ($p=0.0149$). These changes were not detected in MGUS-BMMSC, suggesting an association with disease progression. To explore the influence of MM cells on SIRT3 expression in BMSC, co-culturing with KMS12-PE cells and transwell experiments were performed. We found a 4-fold upregulation of SIRT3 expression in MM-BMSC when co-cultured with KMS12-PE MM cells. The absence of changes in transwell cultures confirmed the need for cell-cell contact between BMSC and MM cells. Moreover, co-cultivation reduced amount of ROS in both cells system. Inhibition of SIRT3 in HD-BMSC using siRNA induced increased senescence and a higher level of ROS. Furthermore, knockdown of SIRT3 led to the accumulation of HD-BMSC in S phase of the cell cycle. Co-cultivation of MM-BMSCs and MM cells with monoclonal antibody (elozuzumab), and immunmodulator (lenalidomid) have changed expression of SIRT3 in both type of cells.
Conclusions: The interaction between MM cells and MM-BMSC is a complex mechanism that relies on multiple interacting signaling pathways. The analysis of the metabolic exchange in BMSC may provide further insight into the molecular interplay between MM cells and BMSCs and aid identifying signaling-molecules as therapeutic targets or combination partners in therapy.

Disclosure: No conflict of interest disclosed.

Freier Vortrag

Allogene Stammzelltransplantation II

V828

Randomized, multi-center, phase II trial of Clofarabine / Ara-C (ClAraC) or of FLAMSA treatment in high risk AML or advanced MDS scheduled for allogeneic SCT

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Background: High-risk leukemia is associated with poor prognosis and inferior outcome. In elderly or comorbid patients allogeneic SCT with myeloablativ conditioning regimen as the most effective treatment option is not available. Sequential regimen combining cytoreductive therapy with RIC has shown high antileukemic activity for high-risk patients with acceptable toxicity profile. This study is based on the observation that antileukemic effects have been described previously for the nucleoside analogue clofarabine.
Methods: This trial was designed as an investigator-initiated prospective, multicenter, open-label, two-arm, parallel-group phase II study comparing ClAraC to FLAMSA regimen. FLAMSA regimen consists of Fludarabine, Amsacrine and Cytarabine. ClAraC regimen consists of Clofarabine and Cytarabine. Both cytoreductive therapies were combined with Bu/Cy. As GvHD-prophylaxis ATG, CsA and MMF were used.
Results: Between 2011 and 2017, 62 patients were recruited, 2 patients did not meet the in-/exclusion criteria. A total of 60 were randomized with 30 patients each in the ClAraC and FLAMSA group. Mean time to event was 656.6 ± 84.6 days for FLAMSA and 565.6 ± 49.2 days for ClAraC, respectively ($p=0.177$, figure 1). In total 38 of the adverse events were serious with fatal outcome of 3 patients in the ClAraC and 4 patients in the FLAMSA group. Cardiac toxicity was observed in 26 patients in the ClAraC treatment arm, whereas 27 patients were affected in the FLAMSA treatment arm ($p=0.730$). Overall survival for ClAraC was numerically, but not statistically inferior to FLAMSA ($p=0.134$). A part of 16/30 (53.3%) patients died until the end of the study in the ClAraC treatment arm, whereas only 12/30 (40.0%) died in the FLAMSA treatment arm ($p=0.134$).
Conclusions: This study did compare two different conditioning regimens for allogeneic stem cell recipients with high risk AML/MDS. 62 patients

have been included and 60 were randomized. The treatment arms were well-balanced at study baseline for relevant covariates. Superiority of the ClAraC treatment regimen over the FLAMSA regimen could not be demonstrated. Consistently hazard ratios for event free survival, overall survival and relapse-free survival were in favor of the control group with FLAMSA treatment. No differences were found regarding cardiac toxicity, rate of engraftment, or chimerism.

Clinical Trial Registry: EudraCT-No. 2010-021944-17

Disclosure: No conflict of interest disclosed.

V829

Microbial-derived metabolites drive protective type-I interferon responses in models of gut epithelial damage and limit graft-versus-host disease

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Background: Graft-versus-host disease (GVHD) is a dreaded complication after stem-cell transplantation (SCT). Standard treatment relies on immunosuppressants but is associated with an increased risk of infection and relapse. Up 50% of patients develop steroid-refractory GVHD, with dismal impact on SCT outcomes.
Recently, we reported that induction of type-I interferon (IFN-I) signalling or activation of IFN-I inducing pathways such as cGAS/STING or RIGI/MAVS can promote gut barrier integrity and limit GVHD. However, the endogenous ligands that drive this "protective" IFN-I response are still poorly defined. New data in mice and humans suggest that microbial-derived metabolites such as small-chain fatty acids or indoles can decrease GHVD mortality. Here, we describe a IFN-I inducing metabolite that improves outcomes in mouse models of gut epithelial damage and acute GVHD.
Methods: To investigate which cell types mediate protection and how, we generated intestinal organoids and bone marrow-derived antigen presenting cells (APC) of WT or genetically deficient mice ($STING^{-/-}$, $IFN\alpha R^{-/-}$) under steady state conditions versus chemotherapy, total body irradiation and after allogeneic SCT in the presence or absence of bacterial metabolites. Analysis was performed by microscopy, immunoblotting, qPCR, ELISA and flow cytometry. Outcomes of gut injured mice were assessed by clinical scoring, flow cytometry and histopathology.
Results: Metabolite treatment promoted regeneration of intestinal organoids as assayed by organoid numbers as well as proliferation. These effects were dependent on IFN-I and STING signalling. In addition, we found activated pro-inflammatory NFκB signalling and decreased apoptosis as evidenced by reduced caspase-3 cleavage. In APCs, IFN-I responses were enhanced in the presence of metabolites including increased IFN-β production and upregulation of IFN stimulated genes. Metabolite-treated mice showed improved recovery of intestinal stem cells following gut injury and increased survival in acute GVHD.
Conclusions: Our findings uncover a mechanism by which microbial metabolites amplify IFN-I signals, limit gut damage and thereby prevent allo-activation and GVHD. Perhaps the poor prognosis of GVHD patients exhibiting a loss of microbiota diversity can be explained in part by an absence of "protective" metabolites able to amplify IFN signalling. We are currently studying whether metabolite levels correlate with severity and outcome of GVHD in humans.

Disclosure: No conflict of interest disclosed.

V830

Prognostic factors for survival after allogeneic transplantation in acute lymphoblastic leukemia (ALL)

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Introduction: ALL is a heterogeneous disease and treatment guidelines are still evolving. Allogeneic stem cell transplantation (allo-SCT) offers a potentially curative option and is recommended in first relapse and for high-risk patients (pts) in first complete remission (CR). Survival after allo-SCT could be substantially improved due to better risk stratification, patient selection and adapted treatment protocols leading to reduced non-relapse mortality (NRM). Prognostic factors for survival after allo-SCT still need to be defined: pheno-/genotype, pts´ age, conditioning regimens and remission status prior to allo-SCT are under discussion.
Methods: We analyzed the outcome of 180 consecutive ALL pts who received allo-SCT at the Freiburg University Medical Center between 1995 and 2018 with regard to treatment response, survival, adverse reactions, and performed subgroup analyses.
Results: The median age in our cohort was 37 years (ys), 19% were older than 55 ys. 27% were diagnosed with Philadelphia (Ph)-positive ALL, 24% with T-ALL. 36% were treated with relapsed/refractory disease. 48% of allo-SCTs were conducted with a HLA-matched, 19% with a HLA-mismatched unrelated and 33% with a related donor. In 61% the conditioning regimen included total body irradiation (TBI). In 48% no minimal residual disease (MRD) was detected prior to allo-SCT, 20% were transplanted in MRD-positive CR. With a median follow up of 10 ys, we observed a median overall survival (OS) of 23 months and progression free survival (PFS) of 11 months. The 10ys-OS was 33%, the 10ys-PFS 31%. The overall response rate was 86%, with MRD-negativity in 78%. The NRM was 31%. Acute graft-versus-host disease (GvHD) III-IV° occurred in 17%, severe chronic GvHD in 9%.
Survival was significantly better in patients reaching MRD-negative CR before allo-SCT (10ys-OS 48% vs. 19%) and in those receiving TBI (10ys-OS 40% vs. 19%). There was no significant difference in sur vival between pts younger or older than 55 ys and between pts diagnosed with T-, Ph-positive or -negative B-ALL.
Conclusions: With a very long follow-up and high rate of MRD-assessment, we observed a high response rate and a low rate of severe GvHD. Our data confirm that allo-SCT enables long-term survival in high-risk ALL, suggest that, in certain subgroups, survival may be best in pts transplanted in CR and receiving TBI for conditioning, including the relevant observation that allo-SCT can be performed in carefully selected elderly pts.

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V832

Treatment of refractory relapse after allogeneic hematopoietic stem cell transplantation (aHSCT) with venetoclax, hypomethylating agents and DLI

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Introduction: Relapse is the most common cause of death after aHSCT. Early studies on the combination of venetoclax and the hypomethylating agents (HMA) azacitidine (AZA) or decitabine (DAC) have shown promising efficacy in elderly patients with AML. We here present clinical data collected retrospectively on 11 patients (pts) who were treated with a HMA/venetoclax combination therapy (HMAClax) after failing AZA ± lenalidomide ± DLI for relapse of a myeloid malignancy after aHSCT.
Results: Diagnoses were 9 AML (4 primary, 5 emerging from MDS, CMML or OMF), 1 MDS and 1 CMML. Median age was 60.3 years (30.8-71.3). Eight pts had relapsed after 1st aHSCT, 3 had 2 preceding aHSCTs. Median time to relapse was 3.3 months (ms, range 1.9-40.2). In 10 patients relapse had been refractory to AZA ± DLI, ± lenalidomide). Median time from relapse to HMAClax was 7.1 ms (0.7-62). Three pts had molecular and 8 had hematologic relapses. Two pts received venetoclax with AZA and 8 with DAC, 1 was switched from AZAClax to DAClax because of rising MRD after 6 cycles. Three pts received DLI. Median number of cy-cles was 2 (1-13) and cycle duration was 35 days (27-84). Median veneto-clax dose per cycle was 3.7g (0.8-17.8, corrected for treatment with azoles, ciprofloxacin or clarithromycin). In total 29 cycles were given, 1 pt had non-fatal tumor lysis syndrome. All pts suffered from grade 3/4 neutro-penia and 10 from grade 3/4 thrombocytopenia. Hospital admission for grade 3/4 infections was necessary in 13 cycles. Twelve cycles were started neutropenic while pts had grade 3/4 neutropenia as a result of the under-lying malignancy. Overall response rate was 64% (7/11), in detail 1 CR MRD-, 2 CRi, 1 PR, 1 MLFS and 2 WT1 responses. Three pts progressed and 1 was stable. Time to best response was 1.1ms (0.9-1.8), response du-ration was 0.9ms (0.2-5.6). Four pts lost best response after 1ms (0.7-3.4) and 3 were censored at last follow up. On April 10th 2019, median follow up was 3.2 ms (1-14.8), 5 pts had died and 6 were alive. Three were con-tinuing HMAClax. One pt developed cGvHD and 1 underwent second aHSCT. Estimated overall survival was 11.1 ms (CI 3.0-19.1).
Conclusions: Venetoclax plus AZA or DAC is an effective, but also highly hematotoxic therapy for refractory relapse after aHSCT. Responses oc-curred fast, but since duration of response was short in this heavily pre-treated patient population HMAClax may better be started earlier follow-ing relapse after aHSCT.

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V833

Relative contribution of naive and memory T cells to alloreactivity in hematopoietic stem cell transplantation

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Introduction: Graft versus host disease (GvHD) is a major impediment to the cure of blood disorders by hematopoietic stem cell transplantation (HSCT). GvHD is mediated by alloreactive T cells recognizing histocompatibility antigen mismatches between patient and donor. Naïve T cells are thought to be mainly responsible for alloreactivity in healthy people, except for multiparous women who could harbor memory T cells against paternal histocompatibility antigens. Accordingly, clinical trials using naïve T cell depleted allografts are being conducted with the aim to reduce GvHD after human leukocyte antigen (HLA)-matched HSCT. We hypothesized that this strategy will be efficient in HLA-identical sibling HSCT, where minor histocompatibility antigens (mHAg) presented by self-HLA are the only targets of T cell alloreactivity, but less so in HLA-matched unrelated HSCT, where HLA-DPB1 mismatches (mmDPB1) are frequent and recognized through molecular mimicry which can be mediated by both naïve and memory T cells.
Methods: T cell alloreactivity to mHAg and to mmDPB1 was modelled by quantitative mixed lymphocyte reactions, using as stimulators irradiated HeLa cells transfected with individual HLA-DP antigens autologous (mHAg) or allogeneic (mmDPB1) to the responder, against purified naïve (CD45RA+) or memory (CD45RA-) CD4+ T cells from healthy individuals. After 14 days of culture, T cells were restimulated overnight and the response was quantified by cell surface staining for the activation marker CD137.
Results: In 36 independent T cell cultures from 8 different individuals, the overall levels of alloreactivity against mHAg were significantly lower than those against mmDPB1 (mean 47.8% vs 19.1%, $p< 0.0001$). Consistent with current concepts, alloreactivity to mHAg was significantly higher in the naïve than in the memory subset (mean 34.1% vs 14.1%, $p=0.03$), in particular in females under 40 years of age. In contrast, alloreactivity against mmDPB1 was evenly distributed between the naïve and the memory subset (mean 47.7% vs 48.0%, $p=0.97$), independently from the age, sex or cytomegalovirus serostatus of the responder.
Conclusions: Our data provide the first direct experimental evidence that alloreactivity against mmDP1 is stronger than against mHAg, and importantly that it is mediated equally by naïve and memory T cells. This should be taken into account in clinical trials aimed at improving the outcome of unrelated HSCT by selective depletion of naïve T cells.

Disclosure: No conflict of interest disclosed.

Freier Vortrag

Versorgungsforschung II

V834

Impact of emergency department admissions on length of in-hospital stays and allocation of hospital resources at an urban tertiary cancer care clinic. A single centre analysis

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Introduction: Emergency departments (EDs) have become a major source of admissions to hospitals. Patients admitted via EDs to internal medical wards are more likely to be older and suffer from multimorbidity. The need to organise ambulatory nursing and social services (ANSS) additionally prolongs length of in-hospital stays (LOS) of these patients. It is unclear, whether it will be feasible in the long term to take care of these patients within specialised departments such as cancer wards where human and structural resources are scarce due to the well-known increase in incidence and prevalence of relevant diseases. The goal of this project was to evaluate patient characteristics, LOS and allocation of hospital resources for patients admitted via the ED to our department.
Methods: Overall, 811 consecutive admissions to our department (106 beds) between 10/2018 and 01/2019 were included in this prospective analysis. We performed a more in-depth review for 108 patients admitted during a three-week timespan for which we evaluated the need for specialist consultations, advanced radiological studies and ANSS.
Results: Out of 811 admissions, 241 (29.7 %) patients were admitted via the ED. The majority of these patients (62 %) had no malignant diagnosis. However, patients admitted via the ED had significantly higher LOS (median: 9 days vs. 4 days, $P < 0.001$), were older (mean: 75.4y vs. 64.5y, $P < 0.001$) and required more specialist consultations and radiologic studies (mean: 2.2 vs. 0.19, $P < 0.001$). At discharge, one third of all patients admitted via the ED needed the implementation of ANSS in comparison to 2 % of cancer patients with a scheduled admission.
Conclusions: LOS, the need for advanced imaging studies, specialist consultations and ANSS were significantly longer and higher for patients admitted via the ED compared to admissions via our outpatient department or scheduled admissions for application of chemotherapy or supportive measures. Hence, a high number of admissions of non-oncology patients via the ED, as observed at our centre, consumes a large percentage of structural and human resources. This may be harmful as the field of oncology and haematology is getting increasingly complex and requires specialist treatment. It may be warranted to limit admissions to cancer wards to those patients who are in need of specialised oncologic services in order to guarantee a high quality of service for these patients that can then be delivered more efficiently.

Disclosure: No conflict of interest disclosed.

V835

BluStar.NRW - a project for typing refugees and migrants as potential blood and stem cell donors

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19.3 million of Germany´s population, so just under a quarter of residents, have a migration background. The majority of these has roots in regions where the population has a distribution pattern of blood group and HLA-antigens that differs considerably from the predominant one in the German population. Sufficient supply of these individuals with red blood cell (RBC) and platelet concentrates (TC) will continue to be a major challenge in the future, as blood donors with compatible blood group antigens are dramatically underrepresented in the local donor pools.
Many migrants suffer from severe hematological disorders such as β-thalassemia or sickle cell disease and will not only need compatible blood transfusions, but an allogeneic stem cell transplantation in the foreseeable future. As healthy family donors often are not available, at present suitable stem cell donors with a similar genetic background can only be found in international donor registries.
This project was initiated to recruit new donors with a migration background for blood donation and to increase the number of blood stem cell donors among this group.
Methods: Serological extended blood group phenotyping was performed and included AB0, Rh (CcDEe), Kk, Fy(ab), Jk(ab), Lu(ab), M, N, S, s. HLA typing for HLA-A, -B, -C, -DR, -DQ, and -DP was performed by Next Generation Sequencing. Rare and very rare alleles were defined according to the Allele Frequency Database (www.allelefrequencies.net). RBC genotyping using Next Generation Sequencing is currently being established and will include additional antigens with the most frequent distribution pattern differences between migrant and resident populations.
So far, more than 8800 blood donors with a migration background have been recruited for a blood donation in this project. Amongst this group, over 1000 blood donors from more than 20 non-European countries enrolled as potential stem cell donors.
An initial evaluation of the data revealed a very similar distribution of blood groups compared to the current blood donor population in North Rhine-Westphalia. Of 600 migrant donors, ten Fy(a-b-) donors were identified (1.6%). Amongst 509 HLA-typed potential stem cell donors, we found 28 (5,5%) with rare and very rare alleles.
The technological development of blood group determination by NGS will significantly improve the supply for all blood transfusion recipients.

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V836

Shared decision making (SDM) in routine care treatment of breast cancer patients - a survey of patients following surgery

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Introduction: The aim of shared decision making (SDM) is a treatment decision in which patients are meaningfully involved. Many preference-sensitive decisions have to be made in breast cancer treatment and little is known about the implementation of SDM. We therefore investigated the process of SDM in routine care treatment.
Methods: All breast cancer patients who underwent surgery in 4 German breast centers between 07/2016-07/2018 were invited to take part. The experienced decision-making process was assessed using the German version of the 9-item SDM questionnaire (PEF-FB-9). Furthermore, satisfaction with care with focus on patient participation was assessed using the ZAPA questionnaire. PEF-FB-9 and ZAPA items were summed up and transformed into a total score ranging from 0 to 100. The higher the total score the higher the experienced degree of participation and satisfaction,

respectively. Participants were asked to separately rate decision-making consultations with their inpatient hospital doctors, outpatient gynecologists, outpatient oncologists and primary care providers (PCP). In addition, satisfaction with decision, participation preferences as well as other items for the complete decision process were queried.
Results: Of 1,068 approached patients, 563 with a median age of 62 (31-92) filled in the survey (response rate: 53%). 81% had breast conserving surgery, 19% mastectomy. Consultations were assessed most often for hospital doctors (n=484). Gynecologists (n=270), oncologists (n=174) and PCP (n=64) were evaluated less often. Hospital doctors (mean (M): 75, standard deviation (SD): 22) and oncologists (M: 74, SD: 22) achieved the highest PEF-FB-9 scores indicating the highest degree of SDM. Gynecologists and PCP were rated almost as good with mean scores of 71 (SD: 23) and 69 (SD: 28), respectively. The mean score for all groups of doctors was 74 (SD: 21), less than 4% of patients reported SDM scores < 25. The values for satisfaction with decision were distributed as follows: PCP (M: 90, SD: 16), hospital doctors (M: 89, SD: 16), oncologists (M: 89, SD: 17), gynecologists (M: 85, SD: 22).
Conclusions: Overall, patients reported to have experienced SDM in many situations where treatment decisions were necessary. Patients were quite satisfied with the quality of information and their participation in medical decisions. However, we do not know whether non-respondents might have had different experiences regarding their treatment decision-making.

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V837

Development of a telemedical software for the organization of oncological councils and tumor conferences within the project "Tumornetzwerk Sachsen"

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Introduction: Cancer patient's diagnosis, therapy and follow up strategies need to be discussed within interdisciplinary tumor conferences. The development of the software "eTumorkonsil" for telemedical consultation of oncological patients will allow physicians of various disciplines and medical facilities to network digitally wherever located. This will improve the medical care of cancer patients, also for patients in structurally weak areas.
Methods: The application "eTumorkonsil" is going to be developed on an established telemedicine platform and will allow physicians to share oncological councils using electronical (e-) councils or to take part in e-tumor conferences, two possible functions within the software. Furthermore, all clinical information will be made available directly to a digital patient record. The user of the application, defined by a login, may request second opinions on oncological issues and discuss patients digitally using a high quality phone and video conferencing system. The program is web based and therefore capable of running independent and free of any connection into operating systems.
Results: Uniform processes ensure a fast procedure of the digital councils without media disruption. The transmitted patient data is encrypted in agreement with the data protection requirements. The application is user friendly, so that the preparation and follow-up as well as the execution of the tumor conference are logically organized. Therapy recommendations are provided on the platform by standardized digital paths within 24 hours.
Conclusions: In the Free State of Saxony physicians who are responsible for outpatient and inpatient treatment are able to be networked with the telemedical application "eTumorkonsil" in a multidirectional way. Hereby it is possible to optimize the care of cancer patients, especially in structurally weak regions, by connecting them to certified cancer centers. „eTumorkonsil" offers an innovative and time-efficient support in oncological care for everyday medical practice and stand for a continuous quality assurance in the context of patient care.

Disclosure: No conflict of interest disclosed.

V838

Prolonged time to treatment initiation in advanced pancreatic cancer patients does not affect treatment outcome - a retrospective cohort study controlled for lead time bias and waiting time paradox

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Background: A prolonged time to treatment initiation correlates with an adverse prognosis in different cancer types including resectable pancreatic cancer (PC). Only limited evidence on the correlation between time to treatment initiation and prognosis in advanced PC exists.
Methods: Consecutive PC patients (n = 368) who were diagnosed or treated at our high-volume comprehensive cancer center were included in a prospectively maintained database. We retrospectively analyzed time from first imaging showing advanced PC to initiation of palliative first-line chemotherapy (TTI). Lead time bias and waiting time paradox were addressed by land mark analysis and correlation of tumor burden with TTI.
Results: 298 patients met the pre-specified in- and exclusion criteria of our study. Reasons for exclusion were: no palliative chemotherapy (n = 36), other histology than ductal adenocarcinoma (n = 12), insufficient data quality (n = 6), no imaging study prior to initiation of palliative chemotherapy (n = 2), surgery in palliative intent (n = 1) or second malignancy (n = 1). For the 298 included patients, median TTI was 29 days (range: 1 to 147 days). Most common reasons for prolonged TTI (>21 days) were referral from an external treatment center (39%) and a second biopsy (31%). A TTI above the median-, 75th or 90th percentile (47 or 60 days, respectively) had no impact on overall survival. Similar results were observed using a landmark analysis for the different time points mentioned above. No correlation between levels of carbohydrate antigen 19-9 (CA 19-9) at time of treatment initiation and TTI was observed.
Conclusions: After controlling for lead time bias and waiting time paradox, no correlation between prolonged TTI and prognosis in advanced PC was observed.

Disclosure: No conflict of interest disclosed.

V839

Appreciation of physicians in their role as supervisor: evaluation of the employees

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Introduction: Less turnover and job satisfaction of non-physician staff has been correlated with better outcomes for patients (Szecsenyi 2011). Continuous employment can be enhanced by a good relationship with the management and social support, defined through communication, cooperativeness and appreciation as well as aspects like group cohesiveness and good working atmosphere (Gloede 2014). Therefore, WINHO conducted a survey regarding the perception of the employees in oncology practices about the social support. Results from two surveys carried out in 2018 and 2019 are presented and compared.
Methods: Both surveys are based on the same questionnaire which was developed by the Institute for Medical Sociology, Health Services Research and Rehabilitation Science of the University of Cologne (Pfaff 2004). The

questionnaire consisted of 18 modules (132 items in total) about working conditions, job satisfaction, work situation, workload and other items; 4-point Likert scales were used. Non-physician staff as practice nurses and medical assistants from 40 oncology practices (80 physicians) in 2019 and 33 practices (87 physicians) in 2018 from the WINHO network (N=440 physicians) participated in the anonymous survey conducted by mail.
Results: In total, 856 non-physician staff completed the study. Regarding social support from the management the results, scale 0 (negative) - 100 (positive), are the following: conversational atmosphere (2019: 77.89%, 2018: 77.27%), assistance in difficult work situations (2019: 79.63%, 2018: 77.80%), praise and appreciation for work effort (2019: 72.87 %, 2018: 70.77%), group cohesiveness (2019: 68.18, 2018: 67.54), good working atmosphere (2019: 62.89, 2018: 60.37) and good communication (2019: 57.50, 2018: 55.67). Only regarding assistance in difficult work situations, the differences between 2019 and 2018 are significant (p=0.34). More results will be shown on the congress.
Discussion: In 2019, better outcomes were reached in all categories.The sample may not be representative for all oncology practices in Germany because only the practices are involved that are connected with the institute. Some physicians work with the results in order to improve the job situation. They were recommended to focus on their social support, especially appreciation of good work efforts, or team building actions in order to achieve less shortage of employees.

Disclosure: No conflict of interest disclosed.

Freier Vortrag

Zelltherapie

V840

Third-generation CAR T cell therapy targeting relapsed or refractory CD19+ lymphoid disease (HD-CAR-1)

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Background: Chimeric antigen receptor transduced T cells (CARTs) have demonstrated significant efficacy in patients with lymphoid malignancies including relapsed or refractory (r/r) B-lineage acute lymphoblastic leukemia (ALL) or r/r B-cell non-Hodgkin's lymphoma (NHL). Here, we report on results of the first investigator-initiated trial (IIT) CART trial in Germany. HD-CAR-1 (EudraCT 2016-004808-60; NCT03676504) is a phase I/II trial initiated 09/18 with in-house leukapheresis and CART manufacturing at the University Hospital Heidelberg.
Methods: Adult and pediatric patients with r/r ALL and patients with r/r chronic lymphocytic leukemia (CLL) or NHL including diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL) or mantle cell lymphoma (MCL) are treated with autologous T lymphocytes transduced with anti-CD19 3rd-generation CAR retroviral vector (RV-SFG.CD19. CD28.4-1BBzeta). The main purpose of HD-CAR-1 is to evaluate safety and feasibility of escalating CART doses (1-20×10^6 transduced cells/m^2) after lymphodepletion with fludarabine and cyclophosphamide. Patients are monitored for cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS) and/or other toxicities. In vivo function, survival and anti-tumor efficacy of CARTs are assessed.
Results: To date, 7 patients (2 ALL, 5 NHL) have been enrolled and subjected to leukapheresis. High numbers of transduced CARTs were harvested (70-123x10^6 CARTs). Transduction efficiency ranged between 33%-66%. No production failure occurred. CART products were sterile and free from mycoplasms and endotoxins. 6 patients have received the CART product. 4 patients (1 ALL, 3 NHL) are evaluable for response at day +90 after receiving 1x10^6 CARTs/m^2 (dose level 1). Of note, no signs of CRS or ICANS > grade 2 have been observed. Response to treatment was observed in all treated patients.
Conclusions: For HD-CAR-1, GMP-conform leukapheresis and CART manufacturing was effective for all enrolled patients so far. All evaluable patients responded to treatment despite low number of CARTs (by 2 logs lower than the currently commercially available CD19-directed CART products) administered. CARTs displayed an exquisite safety profile. In HD-CAR-1, CART administration, patient monitoring and follow-up are performed in-house providing autarky from production sites outside the University Hospital Heidelberg, altogether proving that academic CART IITs are feasible in Germany.

Disclosure: No conflict of interest disclosed.

V841

CRISPR/Cas9 mediated gene editing of ELANE enables neutrophilic maturation of primary HSPCs and iPSCs of severe congenital neutropenia patients

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Severe congenital neutropenia (CN) is a monogenic bone marrow failure syndrome characterized by an absolute neutrophil count below 500/ul. Autosomal-dominant *ELANE* mutations are the common cause of CN. ca. 15 % do not respond to G-CSF therapy at doses up to 50 µg/kg/day and ca. 15% of G-CSF treated patients developed MDS or AML.
"Maturation arrest," the failure of the marrow myeloid progenitors to form mature neutrophils, is a consistent feature of *ELANE* associated congenital neutropenia and because mutant neutrophil elastase is the cause of this abnormality, we hypothesized that *ELANE* associated neutropenia could be treated and "maturation arrest" corrected by CRISPR/Cas9-sgRNA ribonucleoprotein (RNP)-mediated *ELANE* editing. We therefore develop a platform for CRISPR/Cas9 RNP-mediated gene correction or knockout of *ELANE* in induced pluripotent stem cells (iPSC) and primary HSPCs of CN patients. We observed that granulocytic differentiation of *ELANE* knock out iPSC and HSPCs was comparable to that of healthy individuals. Reactive oxygen species production, chemotaxis and phagocytic function of the *ELANE* knock out neutrophils also were normal. Simultaneously, CRISPR/Cas9 mediated correction of *ELANE* mutations in CN patients derived iPSCs also enables neutrophilic maturation. By applying an in vitro embryoid body (EB)-based iPSC differentiation that allows generation of hematopoietic cells and mature myeloid cells for approximately 30 days, we detected a marked increase in the percentage of $CD15^+CD16^+CD45^+$ granulocytes in *ELANE* mutations corrected CN-iPSCs cell culture, as compared to CN-iPSCs. The generation of granulocytes from *ELANE* corrected CN-iPSCs was comparable to iPSC generated from a healthy donor control. Moreover, using whole transcriptome analysis that was performed on myeloid committed early progenitors generated from our iPSC hematopoietic differentiation method, we identified key signaling pathways regulated by mutated *ELANE* in CN HSPCs.
In summary, we established CRISPR/Cas9 based gene-modification platform for CN patient`s HSPCs and iPSCs that can be also applied for the treatment of patients with other inherited monogenic bone marrow failure syndromes.

Disclosure: No conflict of interest disclosed.

V842

SLAMF7 CAR-T cells for immunotherapy of multiple myeloma: 'real-world' experience of GMP-manufacturing using virus-free Sleeping Beauty gene-transfer

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Introduction: We are pursuing the development of immunotherapy for multiple myeloma (MM) with chimeric antigen receptor -T cells (CAR-T) specific for the SLAMF7 antigen, and are in preparations for a phase I/IIa clinical trial in the CARAMBA project. We have shown that SLAMF7 CAR-T recognize and eliminate MM in pre-clinical models (Gogishvili, Blood 2017), and have set out to scale-up and validate a GMP-compliant manufacturing process for SLAMF7 CAR-T using *Sleeping Beauty* (SB) gene-transfer.
Methods: CAR gene-transfer into CD8 and CD4 T cells was performed by nucleofecting mRNA encoding hyperactive SB100X transposase and a minicircle DNA transposon encoding the SLAMF7 CAR *in cis* with an EGFRt marker. Training, scale-up and validation runs were performed with T cells from >20 healthy donors and MM patients. SLAMF7 CAR-T products were qualified by in-process and release testing, comprising analyses of phenotype, transposon copy number and genomic insertion profile and potency.
Results: Training and scale-up runs were completed and optimal conditions for CD3/CD28-activation, subsequent nucleofection and expansion in gas-permeable culture flasks established. Three validation runs were passed and allowed obtaining therapeutic doses of SLAMF7 CAR-T cells. The average gene transfer rates were 51.9% in CD4 and 71.4% in CD8 T cells. SLAMF7 CAR-T exhibited an effector phenotype and were SLAMF7$^{-/low}$, consistent with deletion of SLAMF7$^{+/high}$ T cells due to fratricide. SLAMF7 CAR-T products were formulated at 1:1 CD8:CD4 ratio and conferred complete elimination of MM1.S myeloma xenografts in mice. In a subset of mice, we observed myeloma relapse in extramedullary lesions, which was controlled by (memory) SLAMF7 CAR-T that re-expanded and re-induced remission. Genome analyses revealed average transposon copy numbers between 6 and 12, and showed that transpositions had occurred with an overall random insertion profile, characteristic for SB. The absence pf SB transposase in the infusion product was confirmed by Western blotting.
Conclusion: We present 'real-word' data on the manufacture of clinical-grade SLAMF7 CAR-T prepared by SB gene-transfer. This approach provides CAR-T products with excellent characteristics in safety and potency, and has favourable practical and socioeconomic attributes. A phase I/IIa clinical trial with SLAMF7 CAR-T in MM is being initiated and is the first in the EU to take advantage of SB as virus-free tool in T-cell engineering.

Disclosure: No conflict of interest disclosed.

V843

Regulation of immunological checkpoints in human mesenchymal stromal cells

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Introduction: Graft-versus-Host Disease (GvHD) remains the major fatal complication after allogeneic hematopoietic stem cell transplantation. Mesenchymal stromal cells (MSCs) are an emerging population for cellular therapy of steroid-refractory GvHD. MSCs have a broad immunoregulatory potential as demonstrated in numerous studies *in vitro* as well as *in vivo* and clinical trials of the adoptive transfer of MSCs show low/no toxicity. The response rates against GvHD, however, are discordant and overall efficacy of MSC-based therapies remains not satisfactory. Thus, deciphering the immunoregulatory mechanisms of MSCs is pivotal.
Methods: We investigated expression of the immune checkpoint molecule programmed death ligand 1 (PD-L1) in MSCs isolated from bone marrow aspirates of 10 healthy donors on protein and mRNA level in response to pro-inflammatory stimuli (=licensing) and the link to various bioenergetic pathways. Additionally, analysis of stress-responsive pathways such as endoplasmic reticulum (ER) stress, autophagy, and proteasomal degradation was performed.
Results: Licensing of MSCs led to a marked increase of PD-L1 mRNA and surface protein levels. The glucose analogue 2-deoxyglucose (2-DG) abrogated this upregulation but no other glycolysis inhibitor had this effect. We therefore proposed that the modulation of PD-L1 after 2-DG treatment is mediated by its off-target effect on N-glycosylation. This hypothesis was confirmed by experiments showing that an excess of mannose can rescue PD-L1 levels whereas the inhibition of N-glycosylation caused similar effects as 2-DG. We did not see differences in PD-L1 levels after addition of inhibitors of autophagy, ER stress or proteasomal degradation. Furthermore, total (intracellular) levels of PD-L1 were partly sustained in 2-DG treated MSCs, thus we hypothesize a translocation defect.
Conclusions: To unlock the clinical potential of MSCs, a profound understanding of their immunoregulatory mechanisms is crucial. Therefore, we analysed the regulation of PD-L1. We ascertained that the complex network controlling PD-L1 in an inflammatory environment involves post-translational modifications, namely N-glycosylation. In our future work, we aim at increasing our knowledge regarding PD-L1 regulation to foster immunoregulatory functions of MSCs, for example via the generation of specific PD-L1^{high} subsets with increased immunosuppressive activity.
This study is supported by the German Research Foundation (DFG)-SFB TRR221.

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V844

Sustained disease control and correlative analyses in tisagenlecleucel treated relapsed/refractory diffuse large B-Cell lymphoma patients (r/r DLBCL)

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Background: Tisagenlecleucel (anti-CD19 CAR-T cell therapy) has demonstrated durable responses and a manageable safety profile in adult patients (pts) with r/r DLBCL. We report a 24-mo clinical update and correlative analyses between cytokine release syndrome (CRS)/neurological events (NE) and inflammatory and lab analyte markers of pts in the JULIET trial.

Methods: JULIET (NCT02445248) is a single-arm, pivotal, phase 2 trial of tisagenlecleucel in adult pts with r/r DLBCL. Eligible patients were ≥18 years with r/r DLBCL, had received ≥2 lines of therapy, including rituximab and an anthracycline, and were ineligible for or had failed autologous stem cell transplant. The primary endpoint was overall response rate (ORR: complete response [CR] + partial response).

Results: As of 11 December 2018, 115 pts were infused. Median age was 56 years (range, 22-76 years); 23% were aged ≥65 years. At study entry, 77% of infused patients had stage III/IV disease and 17% had double/triple hit disease. ORR remained 54% (95% CI: 43, 64), CR rate was 40%, and median duration of response was not reached (NR; 95% CI: 10.0, -) at a median follow-up of almost 24 mo. Median overall survival for all 115 pts was 10.3 mo (NR for pts in CR). Severe (grade 3/4) CRS and NE occurred in 23% and 11%, respectively; no grade 5 CRS/NE occurred. Majority of any grade and severe NE were observed in pts with severe CRS. A trend of higher C-reactive protein, ferritin, interferon-γ (IFNG), interleukin (IL) 2, IL6, and IL10 levels within 1 mo of infusion was observed in pts with severe CRS; similar trends, but to a lesser degree, were observed with severe NE. Cytokines peaked on days 6-9; there was early increase of IL2, IL6 and IFNG levels in pts with severe CRS in the first 2 days post-infusion. As CRS progressed, hepatic and kidney dysfunction-related analytes trended towards an increase, peaking 2 weeks post-infusion in pts with severe CRS.

Conclusions: With almost 24 mo follow-up, tisagenlecleucel continued to demonstrate durable efficacy. Efficacy was consistent in all predefined subgroups, including elderly patients, patients with r/r disease, and other clinical or biological subgroups expected to have a worse prognosis with available treatments. Severe NE appeared to correlate with severe CRS. Trends in peak levels of several markers were especially noted with severe CRS.

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Stephen Schuster: Advisory Role: Novartis; Honoraria: Novartis; Financing of Scientific Research: Celgene, Genentech, Merck, Pharamcyclics, Novartis, Nordic Nanovactor,Acerta, Pfizer, Gilead; Expert Testimony: Celgene, Genentech, Merck, Pharamcyclics, Novartis, Nordic Nanovactor,Acerta, Pfizer, Gilead

V845

Optimization of quantitative real-time polymerase chain reaction (qPCR)-based assessment of vector copy number as safety release criterion for clinical grade CAR T cell products

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Background: Chimeric antigen receptor T cells (CART) treatment is strictly regulated given that CARTs are considered gene therapy medicinal products (GTMP) and genetically modified organisms (GMO). Appropriate methods assessing chimeric antigen receptor (CAR) transgene/vector copy numbers (VCN) in CART products are mandatory. Here, we report on a single copy gene-based (SCG) duplex (DP) PCR (SCG-DP-PCR) to determine the VCN in CART products and in patient samples after CART administration. SCG-DP-PCR was validated and compared to the absolute copy number qPCR (ACN) approach within the framework of a clinical CART trial treating patients with good manufacturing practice (GMP)-grade CARTs (HD-CAR-1).

Methods: For ACN, primers and probe targeting the CAR vector RV-SFG.CD19.CD28.4-1BBzeta were designed and standard curves established (dilutions of SFG.CAR plasmid). Amplification was performed as singleplex (SP) PCR (SP-CAR) (method A). On the same qPCR plate, duplex (DP) qPCR reactions were carried out: besides components comprised within method A, experimental setup contained the haploid human genome as well as primers and probe targeting ribonuclease (RNAse) P as human SCG. Amplifications of SFG.CAR plasmid (DP-CAR) and RNAseP gene (DP-RNAseP) were performed simultaneously (SCG-DP-PCR; method B) for standard curves as well as DNA samples extracted from CARTs of three healthy donors (HD).

Results: For method validation, linear regression of the PCR signal to the reference standard curve was performed and efficiency and linearity of qPCR reactions of method A (SP-CAR) and method B (DP-CAR, DP-RNAseP) compared. Correlation coefficient (R^2) of above 0.98 and efficiencies of 100% ± 10% were achieved. Subsequently, VCNs of HD target samples applying method A and B were compared. Efficiencies of 103.5 ± 7.1% (SP-CAR PCR) 104.2% ± 2.1% (DP-CAR) and 99.3 ± 1.6% (DP-RNAse PCR) were achieved. Applying SCG-DP-PCR using the formula for relative VCN assessment ($2^{-\Delta Ct\ (DP\text{-}CAR\ -\ DP\text{-}RNAseP)}$) on samples of HD, a difference of 0.8 ± 0.2 VCNs was observed when compared to method A.

Conclusion: In terms of efficiency and linearity, qPCR reactions were comparable. Due to relation to a SCG, SCG-DP-PCR represents an exact and robust method of VCN assessment to fulfil regulatory safety release

criteria of CART products. Applying SCG-DP-PCR, no standard curve is required, hence significantly economizing required material as well as time.

Disclosure: No conflict of interest disclosed.

Wissenschaftliches Symposium

Big Data und Digitale Medizin

V852

Precision Medicine - Where are we?

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The advent of second generation sequencing technologies facilitated multi-platform omic approaches, which are nowadays supplemented by functional data obtained from genome-wide Crispr/Cas9 screens and large scale pharmacology screens. This development in preclinical laboratories will pave the way to the clinics. However, we are not quite there yet. This presentation will therefore highlight current obstacles in the translation and provide future opportunities.

Disclosure: No conflict of interest disclosed.

Wissenschaftliches Symposium

Erfolge und Herausforderungen in der Präzisionsonkologie – Klinische Implementierung

V861

Precision medicine for hematologic malignancies

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Precision hematology attempts to identify individual tailored treatments based on patient specific tumor vulnerabilities. For most hematologic disease entities such as acute leukemia, lymphoma or myeloma we group patients based on morphologic-, immunophenotypic- or single genomic features, which have been used to discriminate groups of patients with good or poor survival. Conventional treatments are often intensified for patients with a poor prognosis, but such an approach still neglects individual tumor specific vulnerabilities. This "group-based" approach has led to an improvement of treatment strategies for selected hematologic disease entities on a population level. However, to determine the individual patient's tumor vulnerabilities and risk profiles remains the big challenge of precision oncology. Genomics has been studied as the main work horse to do this task, but so far only a limited number of examples such as FLT3-inhibition in FLT3 mutated acute myeloid leukemia or BRAF inhibition in hairy cell leukemia ended up as established genomic biomarkers in clinical use. Unfortunately most patients with hematologic malignancies who receive genomic testing do not benefit from a genomic precision medicine strategy, because most genetic variants have not been linked to drug vulnerabilities. Moreover, additional layers of complexity, such the proteome or methylome might explain the variance of response to individual drugs even better than genomics. High throughput functional assays which could integrate across all these layers might represent a promising alternative to overcome this challenge. The recent development to measure multiple omics data types in parallel along with the improvement of mathematical models to integrate these different layers of complexity bear the chance to significantly improve precision medicine strategies for hematologic malignancies in the near future. I will review these developments with a specific focus on hematological malignancies and present some examples which illustrate how these developments could be implemented in the clinical routine.

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Wissenschaftliches Symposium

Sarkome: Kontroversen

V864

How much molecular diagnostics is required in sarcomas?

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According to current concepts, soft tissue tumors comprise more than 80 different entities. Concomitantly with the increasing knowledge on the genetic background of these tumors several molecularly targeted therapeutic approaches were successfully introduced into clinical care, e.g. in gastrointestinal stromal tumors, dermatofibrosarcoma protuberans, and, very recently, soft tissue neoplasias with NTRK-rearrangements. The crucial importance of correct molecular classification of such lesions is evident, and often the key diagnostic marker at the same time is the therapeutic target in these tumors. The role of molecular characterization is equally important in the group of round cell sarcomas which comprise, beyond classic Ewing sarcoma, the recently defined entities of sarcomas with CIC- or BCOR rearrangement. Though treatment of these tumors is uniform to date, it is important to recognize these entities as they differ biologically and prognostically from Ewing sarcoma. However, molecular diagnostics may also be associated with major therapeutic differences in sarcomas with (occasionally occurring) round cell phenotype, e.g. in myxoid/round cell liposarcoma or synovial sarcoma, in which molecularly informed classification is essential due to grey zones in morphology. Finally, even in pleomorphic sarcomas molecular stratification is of clinical relevance, since a subgroup of these lesions carries MDM2 amplifications and thus biologically corresponds to dedifferentiated liposarcoma. Referring to these and other examples, the role and limitations of molecular diagnostics in the classification of mesenchymal tumors will be discussed.

Disclosure: No conflict of interest disclosed.

V865

Which therapies for which molecular subtypes?

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Introduction: For a long time, cytotoxic agents such as Doxorubicin and Ifosfamide were the mainstream systemic therapy for all soft tissue sarcoma (STS) patients. However, STS is not a homogenous entity but represents an umbrella term for a diverse group of more than 70 different histological subtypes, each with distinct underlying biology, natural history and response to treatments. These days, investigations of sarcoma genomics have provided insights into pathogenesis, and molecular targeted therapy development has brought about a new era of drug treatments for STS. This progress has resulted in an increasingly subtype-dependent management of STS, replacing the former "one-size-fits-all" approach.
Methods: This presentation aims to provide an overview of subtype-specific systemic therapy options for STS. Recent approaches towards a personalised treatment of various tumours of soft-tissue are reviewed.
Results: The accuracy of the histological and molecular diagnosis has shown to be crucial for the optimal treatment of STS patients. Besides from doxorubicin-based regimens, novel chemotherapy agents, eribulin and trabectedin, have demonstrated efficacy in liposarcomas (LPS) and

leiomyosarcomas (LMS), highlighting the role of histology-directed therapy for these malignancies. Further understanding of the complex genomic landscape of STS and the importance of STS subtype-directed therapy has led to development of several small molecule inhibitors for specific STS histologies. Agents targeting vascular endothelial growth factors (VEGF), platelet-derived growth factors (PDGF), and cyclin-dependent kinases (CDK) 4 and 6 have all demonstrated some activity in numerous STS subtypes. Similar to the selective efficacy of cytotoxic agents and small molecule inhibitors, immunotherapy, which has revolutionised management of various cancers, has also shown activity in selected STS subtypes.
Conclusion: Taken together, these novel therapies underline the importance of histology-driven therapy and of a greater understanding of the genomic complexities of STS. Given their variable genomic structure, histology-directed approaches should be regarded as the future of treatment for STS patients.

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Wissenschaftliches Symposium

CML

V868

Molecular defined clones in CML

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In the last decade a large number of somatic mutations affecting multiple pathways have been identified in myeloid malignancies with varying frequencies and combinations that overlap the different disease entities. The essential role of BCR-ABL1 for the pathogenesis of CML has been confirmed by the therapeutic success of selective BCR-ABL1 tyrosine kinase inhibitors (TKI). Recently, using next-generation sequencing (NGS) approaches, we and others identified frequent mutations additionally to the BCR-ABL1 fusion gene in CML patients affecting the genes ASXL1, DNMT3A, EZH2, RUNX1, TET2, TP53, U2AF1, and ZRSR2. These mutations may be involved in the pathogenesis, clonal evolution, and progression of CML. The aim of this session is to review publications that reported mutated cancer-associated genes in CML patients at various disease phases. Genomic studies have the potential to lay the foundation for improved diagnostic risk classification according to clinical and genomic risk, and to enable more precise early identification of TKI resistance.

Disclosure: No conflict of interest disclosed.

Wissenschaftliches Symposium

Geriatrische Onkologie: Inflamm-Aging

V872

Inflammasomes in atherosclerosis - An unbiased approach to link metaflammaging with disease progression

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Introduction: Aging is the major risk factor for atherosclerosis. Although aging implicates advanced age, socioeconomic disadvantages and modern life styles already target the young. "Western diet" (WD) provides strong danger signals, which are common in inflammatory diseases, and their appearance is sensed by inflammasomes. Inflammasomes have been linked to sterile inflammatory processes, such as atherogenesis, and a better understanding of early mechanisms may provide the big picture of the aging process.
Methods: Ldlr$^{-/-}$ mice were fed a high fat (42%), high cholesterol (0.21%) diet for 8 weeks and plaque size, cytokines, lipids, liver pathology, portal vein metabolome, etc., were assessed. Analyses also included co-housing studies with antibiotics treatment. An unbiased analysis of >500 mice and >1,100 features influencing atherogenesis was done, using artificial intelligence and machine learning.
Results: We identified the Nlrp6 inflammasome with athero-protective functions. Ldlr/Nlrp6$^{-/-}$ mice were highly susceptible to atherosclerosis. In addition, Ldlr/Nlrp6$^{/}$ show a dominant microbial configuration, which was transferable to Ldlr$^{-/-}$ recipient mice; however, the observed phenotype was not transferable. Surprisingly, we also observed a high variability in plaque sizes of Ldlr$^{/}$ controls, which was independent of the housing conditions. To exploit variabilities of phenotypes that dissect (non)-genetic factors, we used gradient boosting regressions and random forest classifications to predict the individual feature importance for atherosclerosis. Besides inflammasomes, we were able to identify lipids, bacterial species and metabolites that highly influence pro- and antiatherogenic disease progression.
Conclusions: Using machine learning and computational analyses of reasonable cohorts, we were able to identify factors, which are highly predictive for atherosclerosis. Inflammasomes have a highly predictive power, pointing out inflammasomes as attractive but challenging target for drug design and development. We identified metabolites, which have the strongest predictive power; and there is also evidence in human cohorts. It needs to be determined, if and how those factors are linked to disease progression in young and aged organisms, which might contribute to the understanding of the creeping process of "metaflammaging".

Disclosure: No conflict of interest disclosed.

Freier Vortrag

Hepatobiläres Karzinom

V889

Subsequent anticancer medication following first-line Lenvatinib: a post hoc responder analysis from the phase 3 REFLECT study in unresectable hepatocellular carcinoma

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Introduction: Lenvatinib (LEN) was shown to be noninferior to sorafenib (SOR) for overall survival (OS) in REFLECT (median OS [mOS], 13.6 vs 12.3 months [mo]; HR 0.92; 95% CI 0.79-1.06). LEN was superior vs SOR for secondary endpoints including objective response rate (ORR) per mRECIST: 24.1% vs 9.2% by investigator and 40.6% vs 12.4% by independent review (Kudo M et al. *Lancet* 2018). We report a post hoc responder analysis of patients who received first-line LEN in REFLECT and subsequent anticancer medication during survival follow up.

Methods: In REFLECT, patients with unresectable hepatocellular carcinoma were randomized 1:1 to receive first-line LEN or SOR. Objective response was defined as complete or partial response by mRECIST per investigator. Patients with disease progression and who discontinued treatment were followed for survival every 12 weeks; subsequent anticancer medication during survival follow-up were recorded until time of death. Data cutoff: Nov 13, 2016. mOS was calculated using Kaplan-Meier estimates with 2-sided 95% CIs.
Results: In REFLECT, one-third of the overall study population (156/478 patients randomized to LEN and 184/476 to SOR) received subsequent anticancer medication, most commonly SOR (25% in LEN arm). ECOG performance status and laboratory assessments, including liver function tests, were comparable between arms prior to subsequent treatments. Among these patients, mOS was 21 vs 17 mo and ORR was 27.6% vs 8.7% for LEN vs SOR arms, respectively. In a subset analysis of LEN responders who received any subsequent anticancer medication (n=43), mOS was 26 mo (95% CI 18.5-34.6). For SOR responders who received any subsequent anticancer medication (n=16), mOS was 22 mo (95% CI, 14.6-NE). For LEN responders who subsequently received SOR (n=35), mOS was 26 mo (95% CI 18.2-34.6).
Conclusions: In REFLECT, one-third of patients randomized to first-line LEN received subsequent anticancer medication, including SOR, with a mOS of 21 mo. In this exploratory post hoc analysis of patients who responded to LEN and received any subsequent anticancer medication or SOR, mOS was 26 mo.

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V890

Quality-adjusted life years accrued with cabozantinib in patients with advanced hepatocellular carcinoma (aHCC) in the CELESTIAL trial

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Introduction: In patients previously treated for aHCC, cabozantinib (cabo) led to longer overall survival and progression-free survival vs placebo (pbo) in the randomized, phase 3 CELESTIAL trial (NCT01908426; N=707). CELESTIAL was stopped early for benefit at the second interim analysis. This post hoc analysis estimated the incremental quality-adjusted life years (QALYs) accrued in CELESTIAL.
Methods: Health utility was elicited at each study visit using the EQ-5D-5L quality of life questionnaire. (completed by 82-100% of patients overall). UK crosswalk tariffs were applied for health states. Cumulative QALYs by patient were calculated by linear interpolation; for patients who were censored (31% of patients; including 9% within 100 days of randomization), the last observed utility value was carried forward to study end. The difference in restricted mean QALYs was calculated using generalized linear models, accounting for baseline utility, and with 0.06-0.08 QALYs considered the minimal important difference.
Results: At day 50 after randomization (acute treatment phase), cabo was associated with a small reduction in mean total QALYs vs pbo (difference −0.003; 95% CI −0.005 to −0.002; p≤0.001; n=601 [cabo, n=389; pbo, n=212]). At day 100, there was a numerical benefit in mean total QALYs for cabo (difference +0.007; 95% CI −0.001 to 0.015; p=0.103; n=627 [cabo, n=410; pbo, n=217]), and at day 150 the difference was +0.032 QALYs (95% CI 0.017 to 0.047; p≤0.001; n=629 [cabo, n=412; pbo, n=217]) in favor of cabo. Over the entire follow-up, patients randomized to cabo accrued a mean of +0.092 (95% CI 0.016 to 0.169; p=0.018; n=700 [cabo, n=465; pbo, n=235]) additional QALYs compared with those receiving pbo. Using alternative Devlin weights for health states, the mean accrued QALYs with cabo was +0.115 vs pbo (95% CI 0.032 to 0.198; p=0.007).
Conclusions: Cabo was associated with an initial, small reduction in health utility. However, with continued treatment, health utility increased and at the end of the study there was a clinically and statistically significant benefit in mean QALYs in favor of cabo.

Disclosure: No conflict of interest disclosed.

V891

Integrated population pharmacokinetic (PopPK) modeling of cabozantinib (C) in patients (pts) with various cancer types including advanced hepatocellular carcinoma (HCC)

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Introduction: C significantly improved overall survival and progression-free survival vs placebo in pts with previously treated advanced HCC in the phase 3 CELESTIAL trial (NCT01908426). In a previous single dose PK study, increased C exposure was observed in pts with mild or moderate hepatic impairment compared with healthy volunteers (HV) (Nguyen, J Clin Pharmacol. 2016). An integrated PopPK model was recently developed to characterize C concentration data from HV and pts with various cancer types, including renal cell carcinoma, castration-resistant prostate cancer, and medullary thyroid cancer (MTC) (Lacy, Cancer Chemother Pharmacol. 2018). Here the model has been updated to include data for pts with advanced HCC from CELESTIAL and a previous phase 2 trial.
Methods: The updated PopPK model was developed using nonlinear mixed effects modeling methodology (NONMEM v7.3) and incorporated data from 10 clinical studies with 9510 measurable C concentrations from 2023 subjects, including 489 pts with advanced HCC. Eligible pts with HCC had Child-Pugh A liver function. Covariates that were evaluated included age, gender, race, body weight, cancer type, and liver dysfunction as defined by the National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG).
Results: A 2-compartment model with first-order elimination and dual first- and zero-order absorption processes adequately described the observed C concentration data. Similar to the previous model, the MTC population was the only cancer type to have a notable difference in C PK, with an ~90% increase in apparent clearance (CL/F) compared to HV and pts with other cancer types including HCC. For a White male subject, CL/F was estimated as 2.48 L/hr and apparent volume of the central compartment (Vc/F) as 212 L. Inter-individual variability was estimated as 46% for CL/F and 67% for Vc/F. Other demographic covariates were predicted to have a small to moderate impact on C CL/F. Liver dysfunction, as defined by NCI-ODWG criteria, had no discernable effect on C CL/F.
Conclusions: C exposure at an equivalent daily dose is predicted to be similar in pts with several cancer types including advanced HCC with mild liver dysfunction.

Disclosure: No conflict of interest disclosed.

V892

Neoadjuvant chemotherapy with Gemcitabine plus Cisplatin followed by radical liver resection versus immediate radical liver resection alone in incidentally detected gallbladder carcinoma after simple cholecystectomy or in front of radical resection of BTC - a phase III study

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Background: Currently, complete surgical resection represents the only potentially curative treatment option for Biliary Tract Cancer (BTC) including Gallbladder Cancer (GBC). Even after curative resection, 5-year OS is only 20-40%. Gallbladder carcinoma is relatively rare, but still the fifth most common neoplasm of the digestive tract and even the most frequent cancer of the biliary system. Gallbladder carcinoma is suspected preoperatively in only 30% of all pts, while the majority of cases are discovered incidentally by the pathologist after cholecystectomy for a benign indication. For improving curative rates in BTC and GBC, early systemic therapy combined with radical resection seems to be a promising approach. The earliest moment to apply chemotherapy would be in front of radical surgery. The encouraging results of neoadjuvant/perioperative concepts in other malignancies provide an additional rationale to use this treatment in the early phase of GBC management and even ICC/ECC. Especially because data regarding pure adjuvant chemotherapy in BTC`s are conflicting.
Methods: This is a multicenter, randomized, controlled, open-label phase III study including pts with pT2-3 incidentally discovered GBCs after simple cholecystectomy in front of radical liver resection and pts with resectable/ borderline resectable cholangiocarcinomas (ICC/ ECC) scheduled to receive perioperative chemotherapy (Gemcitabine + Cisplatin 3 cycles pre- and post-surgery) or surgery alone followed by a therapy of investigator's choice. Primary endpoint is OS; secondary endpoints are PFS, R0-resection rate, toxicity, perioperative morbidity, mortality and QoL. A total of N=333 patients with GBC or BTC will be included.
In addition the talk will focus the treatment options in curative BTC patients.
ClinicalTrials.gov ID: NCT03673072; EudraCT number: 2017-004444-38

Disclosure: No conflict of interest disclosed.

V893

Safety and efficacy of 12 mg/d lenvatinib (LEN) in patients with unresectable hepatocellular carcinoma (uHCC) and bodyweight (bw) >80 kg in REFLECT

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Introduction: LEN is a multikinase inhibitor of VEGFR 1-3, FGFR 1-4, PDGFRα, RET, and KIT. In a phase 3 trial (REFLECT), LEN demonstrated a treatment effect on overall survival (OS) by statistical confirmation of noninferiority vs sorafenib for first-line treatment of uHCC. Dosing by bw was implemented in REFLECT based on a phase 2 study of LEN in uHCC and PK modeling showing an exposure-response relationship with higher LEN AUC and lower bw resulting in earlier drug withdrawal or dose reduction. Cutoff values established were LEN 8 mg/d for bw < 60 kg and 12 mg/d for bw ≥60 kg. This post hoc analysis of REFLECT assessed safety and efficacy of LEN in patients with bw >80 kg.
Methods: Details of REFLECT methodology are previously published. For this analysis, patients were stratified by baseline bw: < 60 kg, ≥60 to ≤80 kg, and >80 kg. Safety and efficacy outcomes by bw group were generated.
Results: Baseline demographics among the groups were similar, except that patients with bw >80 kg were more likely to be white, from western regions, and have higher body mass indexes. For bw < 60 kg, bw ≥60 to ≤80 kg, and >80 kg: the median treatment durations (months) were 5.59, 6.29, and 6.54, respectively; mean LEN relative dose intensities were 87%, 86%, and 93%, respectively. Key safety and efficacy data are reported in the **Table**. Adjusted by treatment duration, AE rates (episodes/patient-year) were similar across bw groups. No adjustments were made for comorbidities by bw groups.
Table: Summary of Efficacy and AEs of Interest by bw

Tab. 1. Summary of Efficacy and AEs of Interest by bw

	BW <60 kg (n=153)	BW ≥60 to ≤80 kg (n=234)	BW > 80 kg (n=89)
Median OS, months	13.4	13.6	14.9
Median PFS, months	7.4	7.3	9.2
ORR (mRECIST by investigator), %	22	24	28
Hypertension, n (%)	66 (43)	97 (42)	38 (43)
Fatigue, n (%)	43 (28)	69 (30)	29 (33)
Palmar-plantar erythrodysesthesia, n (%)	37 (24)	65 (28)	26 (29)
Proteinuria, n (%)	38 (25)	59 (25)	20 (23)
Diarrhea, n (%)	54 (35)	91 (39)	39 (44)

Conclusions: In this post hoc analysis including patients of bw >80 kg receiving LEN 12 mg/d, efficacy and safety were similar to results in REFLECT. These results are consistent with the approved dose of 8 mg/d (bw < 60 kg) and 12 mg/d (bw ≥60 kg) of LEN in uHCC.

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TR Jeffry Evans: Employment or Leadership Position: co-editor of the clinical subjects section of the British Journal of Cancer; Advisory Role: Celgene, Karus Therapeutics, Baxalta, TC Biopharm, Immunova; Financing of Scientific Research: honoraria from Eisai for advisory boards and speaker's bureau (payable to his institution); support from Eisai for sponsored clinical trials (payable to the institution); honoraria for advisory boards and speaker's bureau from Bristol-Myers Squibb, Bayer, GlaxoSmithKline, Roche/Genentech (all payable to his institution); honoraria for advisory boards from Celgene, Karus Therapeutics, Baxalta, TC Biopharm, Immunova (all payable to his institution); Expert Testimony: support for sponsored clinical trials (payable to the institution) from Bristol-Myers Squibb, GlaxoSmithKIine, Roche / Genentech, Celgene, TC Biopharm, Merck, Novartis, e-Therapeutics, Vertex, Verastem, Daiichi, AstraZeneca, Basilea, Immunocore, Chugai; Other Financial Relationships: Bristol-Myers Squibb, Roche/Genentech, Bayer, Merck, Eisai

V894

Association of adverse events (AEs) with efficiacy outcomes for Cabozantinib (C) in patients (pts) with advanced hepatocellular carcinoma (aHCC) in the phase 3 CELESTIAL trial

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Introduction: Class-specific AEs occurring with tyrosine kinase inhibitors havs been sssoclated with improved efficacy outcomes in several tumor types including aHCC. In the phase 3 CELESTIAL trial (NCT01908426), C, an inhibitor of VEGFR, MET, and AXL, improved overall survival (OS) and progression-free survival (PfS) vs placebo (P) in pts with previously treated aHCC. Here, we retrospectively evaluate the associatlon of palmar-plantar erythrodysaesthesia (PPE) and hypertension (HTN) with OS and PFS for C in the CELESTIAL trial.
Methods: 707 pts with aHCC were randomized 2: 1 to receive 60 mg C or P once daily. Eligible pts had Child-Puqh score A, ECOG PS ≤1, must have received prior sorafenib and could have received up to two prior regimens of systemic therapy for HCC. OS and PFS with C were evaluated for pts with any grade PPE or ≥ grade 3HTN within the first 8weeks of study treatment.
Results: Overall, 374 (80%) pts in the C arm and 179 (76) pts in the P arm completed ≥ 8 weeks of treatment. In the first 8 weeks, 188 (40%) of C-treated pts developed any grade PPE vs 11 (5%) of P-treated pts and 61 (13%) of C-treated pts developed grade ≥3 HTN vs 3 (1%) of P-treated pts. Median OS with C was 14.4 mo for pts with any grade PPE vs 3.4 mo for pts without PPE (HR 0.59, 95% CI 0.47-0.74). and median PFS with C was 6.5 mo vs 3.7 mo, respectively (HR 0.63,95% CI 0.51-0.78). Median OS with C was 16.1 mo for pts with grade ≥3 HTN vs 9.5 mo for pts without grade ≥3 HTN (HR 0.56, 95 CI 0.39-0.80), and median PFS with C was 7.4 mo vs 4.4 mo, respectively (HR 0.59, 95% CI 0.43-0.82). Some imbalances in baseline characteristics were present. Pts with PPE had better ECOG PS (60% vs 47% ECOG 0), better liver function (48% vs 34% ALBl grade 1), and less macrovascular invasion (24% vs 30%) than those without. Likewise, pts with grade ≥3 HTN had better ECOG PS (61% vs 51% ECOG 0), better liver function (56% vs 37% ALBI grade 1), and less macrovascular invasion (20% vs 29%) than those without.
Conclusions: The development of PPE or grade ≥3 HTN with C was associated with prolonged OS and PFS in pts with previously treated aHCC although some imbalances in baseline characteristics between comparator qroups were present.

Disclosure: No conflict of interest disclosed.

Freier Vortrag

Sonstige Hämatologie

V895

Interim analysis results from the prospective, non-interventional study of ruxolitinib in patients with polycythemia vera (PAVE): safety results were consistent with previous findings

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Introduction: In the clinical trial setting, ruxolitinib, a JAK1/2 inhibitor (JAKi 1/2), demonstrated efficacy in terms of hematocrit control, spleen volume reduction, and improved symptoms and quality of life in polycythemia vera (PV) patients, resistant/intolerant to hydroxyurea. Here, we present interim analysis data from a non-interventional study in patients with PV who received ruxolitinib in daily clinical practice in selected centers across Germany.
Methods: Patients were monitored for safety, efficacy, and symptom scores for up to 36 months.
Results: Of the 365 patients (135 JAKi-naive, 230 JAKi-pretreated; data cut-off date, 19 Feb 2019), 48 completed the study, 230 were ongoing, and 87 dropped out.
Adverse events (AEs) were reported in 259 (71.0%) patients, with anemia (20.0%), thrombocytosis (6.8%), fatigue (6.8%), and dizziness (5.8%) being the most frequent. One case of second primary malignancy was reported that was deemed as unrelated to the study treatment. No aggressive B-cell lymphoma incidences were seen. Infections/infestations were reported in 77 (21.1%) patients, including nasopharyngitis (4.4%), herpes zoster (3.0%), and urinary tract infection (2.7%). Serious AEs were reported in 98 (26.8%) patients, with pneumonia (1.6%), anemia (1.4%), and atrial fibrillation (1.4%) being some of the most common.
At baseline, the median (range) spleen size was 11 cm (0 to 30) in JAKi-naive patients and 10 cm (0 to 20.4) in JAKi-pretreated patients, which changed by −2 cm (−13 to 2) and 0 cm (−13.9 to 9), respectively, at the last post-baseline follow-up. The median (range) hematocrit levels changed from baseline to last post-baseline visit by −5.3% (−27.5% to 48.1%) in JAKi-naive and −1.5% (−17.5% to 16.0) in JAKi-pretreated patients.
Myeloproliferative neoplasm symptom assessment form derived total symptom scores (MPN-SAF TSS) have improved in the JAKi-naive patients, whereas JAKi-pretreated patients who benefited from prior ruxolitinib therapy maintained their scores; the median (range) MPN-SAF TSS scores were 28.5 (10.0 to 83.0) and 24.0 (6.0 to 65.0) at baseline, and 20.0 (8.0 to 61.0) and 24.5 (10.0 to 73.0) at the last post-baseline visit, respectively.

Conclusion: The safety profile of ruxolitinib in daily clinical practice was consistent with the previous findings, with anemia and diverse infections being the most frequent AEs. Ruxolitinib treatment showed a positive effect on symptom burden, spleen size and hematocrit levels.

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V896

Case series: Treatment of post-transplant lymphoproliferative disorders (PTLD) with single-agent Brentuximab Vedotin

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Introduction: Patients after solid organ or hematopoietic stem cell transplantation are at an increased risk of developing post-transplant lymphoproliferative disorders due to intense immunosuppression. Typically, therapy consists of reducing immunosuppression in the first place. Chemotherapy-based induction is particularly difficult in this setting, since an exceedingly high lethality has been reported for the upfront use of CHOP-based regimens. Hence, PTLD protocols were developed that initiated treatment more subtly with several courses of the anti-CD20 antibody Rituximab as a single agent preceding CHOP, or even entirely omitted chemotherapy in Rituximab-only responders. The surface receptor protein CD30, often associated with EBV infection, is detectable in the vast majority of PTLD cases, correlates with better prognosis in retrospective analyses, and is the target of the antibody drug conjugate Brentuximab Vedotin (BV), which is approved under certain conditions for classical Hodgkin's lymphoma (cHL) and anaplastic large cell lymphoma (ALCL). As we reported in a single case of T-cell PTLD before, the monomethyl auristatin E-conjugated BV offers the opportunity to start induction therapy without conventional chemotherapy in PTLD histologies not suitable for anti-CD20 mono-therapy. Only a few cases have been documented so far.
Methods: We present a series of five patients with CD30+ PTLD subjected to chemo-free BV induction therapy between 2013 and 2019. A retrospective chart review was performed and the clinical and histological data were collected.
Results/Conclusion: We treated five patients with PTLD, two cases of ALCL (one ALK+, one ALK-) after heart transplantation, one cHL, a B-cell malignancy not expressing CD20, after renal transplantation, a CD20+ and CD30+ diffuse large B-cell lymphoma (DLBCL) after allogenic blood stem cell transplantation, and a peripheral T-cell lymphoma (NOS) after renal transplantation (two of the five cases EBV+ in the lymphoma, three positive in the blood), either with single-agent BV, or - in 3 patients - with a chemo-free BV/Rituximab combination. In all five patients, a regression (PR or CR) of the lymphoma manifestations was achieved. In one case, single-agent BV was not sufficient to lastingly control the disease, with need of systemic chemotherapy after six cycles of BV.
At the meeting, we will present a focused literature review and in-depth clinical data of the case series.

Disclosure: No conflict of interest disclosed.

V897

Autologous stem cell transplantation in non-Hodgkin lymphoma: a retrospective single-center analysis

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Introduction: Patients with high-risk or relapsed non-Hodgkin lymphoma (NHL) are characterized by poor prognosis. High-dose chemotherapy followed by autologous stem cell transplantation (ASCT) can induce durable remissions in these patients and is potentially curative. In this single-center study we analyzed outcome after ASCT in different lymphoma entities and influencing factors on outcome.
Methods: We retrospectively analyzed data from 264 patients with NHL who received ASCT between 2007 and 2017 at the University Hospital Münster. Kaplan-Meier method was used for analyzing overall survival (OS) and progression-free survival (PFS) from day 0 of ASCT.
Results: Median age at ASCT was 60 years (18-79). 95 (36%) patients were diagnosed with diffuse large B-cell lymphomas (DLBCL) including 85 primary DLBCLs and 10 transformed NHLs, 39 (15%) patients with T-NHL, 28 (10%) with primary central nervous system lymphomas (PCNSL), 52 (20%) with mantle cell lymphomas (MCL) and 50 (19%) with indolent NHL (iNHL). Median follow-up of surviving patients was 4.2 years (2.3 mo.-11.9 years).
Non-hematologic adverse events grade 3 or higher occurred in 224 (85%) of all patients, with infections (66%) and mucositis (44%) as most frequent events. Cumulative incidence of death not related to relapse or progression was 6% (15/264) at day 100 and 15% (40/264) 3 years after ASCT, with infections as most common cause. Overall response rate (complete or partial remission) after ASCT was 86%. Median PFS of all patients was 29 months (95%CI:18-40) and median OS 70 months (95%CI:33-108). NHL subgroup analyses revealed a median PFS of 21 months (95%CI:6-36) for DLBCL, 21 months (95%CI:18-40) for T-NHL, 25 months (95%CI:0-60) for iNHL, 41 months (95%CI:22-61) for MCL and was not reached for PCNSL. Median PFS for patients over 60 years was 35 months (95%CI:16-54) compared to 26 months (95%CI:14-39) for patients under the age of 60 (p=0.761). Patients with complete remission before ASCT showed a median PFS of 71 months (95%CI:30-112) compared to 22 months (95%CI:5-39) for patients achieving partial remission (p=0,15) and 10 months (95%CI:0-28) for patients with refractory/progressive disease (p< 0,001), respectively.
Conclusions: High-dose chemotherapy followed by ASCT remains an effective approach for patients with high-risk or relapsed lymphoma. Lymphoma entity and age showed no significant impact on the outcome after ASCT, whereas remission status before ASCT correlated with survival outcome.

Disclosure: No conflict of interest disclosed.

V898

Subcutaneous Crovalimab (SKY59) for PNH: COMPOSER long term follow-up

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Crovalimab is a SMART* [Fukuzawa et al., SciRep 2017] anti-C5antibody to allow for infrequent, small volume SC dosing. Patients included in P2 and P3 of COMPOSER (Röth et al., Blood 2018 132:535) were rolled over into an open label extension (OLE) at week 20 for continued treatment.
In the OLE patients stayed on the same treatment schedule they were already using in part 2 or 3.
25 of 26 patients chose to roll over to the OLE. Data of the 15 patients (8 from part 2 and 7 from part 3) with > 20 weeks in the OLE are reported here. The median total duration on treatment with crovalimab including the OLE was 68 weeks; 77 weeks for patients from P2 and 57 weeks for patients from P3. All 8 patients from P2 were on 170mg QW SC (volume: 1ml); from P3, 2 were on 170mg QW, 3 were on 340mg Q2W (2ml) and 2 were on 680mg Q4W (2x2ml), all SC. Crovalimab plasma levels in all patients were above 150 µg/mL at all times.
Markers of complement activation and intravascular hemolysis (CH50, LDH) remained at stable low values with no signs of loss of response throughout the observation period. No BTH events were reported in the OLES. No additional doses or dose intensification of crovalimab were given. Hemoglobin levels remained stable with extended treatment duration.
Accumulation of C5 at the OLE was limited (mean 225 µg/mL), a significant reduction when compared to baseline C5 of eculizumab treated patients 295 µg/mL (205 - 354 µg/mL) at entry in part3 of COMPOSER.
OLE treatment with crovalimab which was self-administered in most patients was well tolerated: no injection site AEs were observed. 4 non-related SAEs in 3 patients were reported (coronary stenosis, atrial fibrillation, abdominal pain and choledocholithiasis). No AEs resulted in withdrawal from the study or death.
Crovalimab administered SC in a small volume is very well tolerated, has a good benefit/risk ratio and is efficacious in long term treatment of naïve and eculizumab-treated patients with PNH in all dosing regimens tested. Updated data will be presented at the meeting.

* Sequential Monoclonal Antibody Recycling Technology

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V899

Hematopoietic lineages are characterized by specific solute carrier co-expression patterns

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Introduction: During differentiation of hematopoietic stem cells to myeloid and lymphoid effector cells, the gene expression changes profoundly, reflecting the distinct metabolic and functional needs of the respective cell types. Solute carriers (SLCs), the largest group of membrane transporters, are responsible for the exchange of nutrients, metabolites or ions between cells and their environment and play a central role in cellular homeostasis and metabolism. It is hence conceivable that SLC expression patterns are characteristic for specific hematopoietic effector cells or malignant cells, however systematic analyses have been missing so far.
Methods: Based on published ATACseq and single-cell RNAseq datasets, we analyzed the expression of SLCs across different hematopoietic and leukemic cell types.
Results: We found highly specific SLC co-expression patterns, which evolve during hematopoietic differentiation, reflecting the metabolic and functional needs of the cells. Erythrocytes for instance, do not only exclusively express the anion exchanger SLC4A1 (Band 3), but demonstrate also particularly high expression of the glucose transporter SLC2A1, reflecting their glycolytic metabolism. Within the hematopoietic system, the SLC expression patterns were specific enough to define hematopoietic lineages and discriminate between leukemic and healthy cells, qualifying them as novel markers of lineage and disease. They are moreover of relevance for the druggability of cells by chemotherapeutic agents and other small molecule compounds entering the cell via SLCs. Sensitivity to metabolic drugs or specific SLC inhibitors should likewise depend on SLC expression. Cellular SLC expression repertoires could hence form the basis of specific targeting of hematopoietic cell types in the context of cancer, immune-modulation or infection.
Conclusion: Altogether, these results characterize the SLC co-expression patterns as highly specific for the various cells of the hematopoietic system, reflecting their metabolic needs and suggesting important further implications such as different drug sensitivities.

Disclosure: No conflict of interest disclosed.

V900

Development of an interdisciplinary diagnostic program accompanying the introduction of CAR-T therapy in Switzerland

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Introduction: Swissmedics approved 01/2018 Kymriah® (Novartis) for CAR-T therapy for patients < 26 yrs with R/R B-ALL and for adults with DLBCL after ≥2 therapy lines. Since 01/2019, the first two adults received Kymriah® in Switzerland. We aimed at improving risk prediction for developing cytokine release syndrome (CRS) in CAR-T cell recipients.
Methods: Supported by an interdisciplinary diagnostic board, we established digital droplet (dd)PCR for CAR-T cell specific TCR measurement from peripheral blood (PB), and established evaluation of the immunologic environment and IL-6 measurement.
Results: The first patient (25y) had *BCR-ABL1*+ B-ALL in MRD-negative CR2 following salvage chemotherapy with ponatinib 5 years after allogeneic transplant. After lymphocyte apheresis (11/2018), cyclophosphamide/fludarabine lymphocyte depletion, and Kymriah® infusion (01/2019), the clinical course was largely uneventful, in particular without CRS or encephalopathy. IL-6 levels were nearly normal. ddPCR without lymphocyte enrichment revealed Kymriah®-specific TCR in PB at day +8 following Kymriah® infusion, increasing to 15'330 copies CTL019/µg DNA

(day +14), and decreasing rapidly below detection level after day +23. Transient viral infections occurred in weeks 5 and 11 despite continued immunoglobulin substitution.
The second patient (71y) with relapsed secondary DLBCL following CLL was in PR4 following four therapy lines including ASCT. $CD3^+$ counts in the first lymphocyte graft (03/2019) were with 6.79×10^9 above the requirement for Kymriah®, but CAR-T cell generation was insufficient. Ultimately, repetition of lymphocyte apheresis (03/2019) allowed sufficient Kymriah® CAR-T cell production. Four days after Kymriah® application (in 04/2019), the patient developed CRS grade 1 with fever preceded by increase of IL-6 to 35 pg/mL (maximum 555 pg/mL at day +5). Three doses of tocilizumab resulted in clearance of CRS symptoms and decrease of IL-6. By ddPCR, 97 copies of CTL019/µg DNA were detectable in PB at day +3, with a maximum of 2,071 at day +9, and steadily decreasing after day +11.
Conclusions: These preliminary results suggest that residual lymphoma/leukemia burden and early increase of Kymriah®-specific TCR in PB and of IL-6 serum levels may identify patients at increased risk of CRS. We will continue this diagnostic program in subsequent CAR-T recipients to optimize in- and outpatient management.

Disclosure: No conflict of interest disclosed.

Freier Vortrag

Immuntherapie II

V901

Glycolytic insufficiency and mitochondrial dysregulation impair immune-function of tumor infiltrating CD8 T cells

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Introduction: CD8 T cells infiltrate tumors, but factors that regulate T cell anti-tumor activity are not sufficiently explored. T cells are highly metabolically active and metabolic impairment of tumor-infiltrating T cells might lead to immune dysfunction, cancer progression and resistance to cancer immune therapies.
Methods: We studied human tumor infiltrating lymphocytes (TIL) from melanoma and renal cell carcinoma (RCC) patients and used murine melanoma models. TIL phenotype was assessed using mass cytometry (CyTOF) and flow cytometry. CD8 TIL expression of key metabolic enzymes was assessed and glucose uptake, glycolysis, mitochondrial respiration, morphology and reactive oxygen species (ROS) production was studied in resting and stimulated CD8 TIL. In a mouse melanoma model, immune checkpoint blockade was performed and metabolism of CD8 TIL was assessed. Metabolic intermediates or chemical compounds were provided to rescue metabolic defects and to improve CD8 TIL function.
Results: CD8 TIL from melanoma and RCC patients presented an effector-memory-like phenotype and showed impaired in vitro activation and proliferation. Metabolic studies revealed only minor impairments in glucose uptake, however glycolysis was down-regulated. This correlated with decreased GAPDH expression (RCC TIL) and enolase 1 expression (melanoma TIL). CD8 TIL that responded to immune checkpoint blockade showed increased enolase 1 activity. In line, bypassing enolase 1 by providing pyruvate rescued CD8 activation. Glycolytic defects might have been compensated by increased mitochondrial activity, as CD8 TIL showed increase mitochondrial mass and polarization. However, mitochondrial ROS production was increased in TIL and pharmacological ROS scavenging rescued CD8 TIL activation.
Conclusions: Tumor infiltrating CD8 T cells were metabolically impaired but metabolic modulation improved in vitro T cell immune function. Strategies to restore metabolic function of CD8 TIL may improve the anti-tumor immune response.

References: Siska PJ, et al. JCI Insight. 2017 Jun 15;2(12), Gemta L, et al. Science Immunology. 2019 Jan 25;4(31)

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V902

A human CD22 transgenic, myc-driven lymphoma model to test effects of targeted therapies on lymphoma immune microenvironment in immunecompetent mice

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Background: Next to lymphoma cells, the lymphoma immune microenvironment (LIM) consists of various cell types which interact via cell-cell contacts and cytokines thereby establishing lymphoma growth, immune cell inhibition, and drug resistance. Myeloid cells are increasingly recognized for their immune suppressive role in LIM and suspected to limit activity of CAR-T cells or. Despite importance of LIM, preclinical studies in mice have been performed in models lacking a functional immune system.
Objectives: To study the effects of targeted therapies on LIM we developed an immune competent murine lymphoma model transgenic to human CD22.
Methods: A chimeric CD22 consisting of human extracellular and murine intracellular CD22 (h/mCD22) was introduced in BL6 mice and cross-bred with $BL6^{\lambda\text{-myc}}$. Spontaneously developing murine lymphoma were characterized, viably frozen, and serially transplanted. The LIM of allografts was characterized by flow cytometry. Tumor-bearing mice were treated with Moxetumomab pasudotox, a CD22-targeted immunotoxin and lymphoma burden measured by flow cytometry.
Results: $BL6^{h/mCD22\ x\ \lambda\text{-myc}}$ spontaneously developed a monomorphic population of h/mCD22+ murine B-cells in lymphoid organs. Stable engraftment of three distinct lymphoma was established after subcutaneous (SC) or intravenous injection. SC established lymphoma were infiltrated by less than 1% immune cells while systemically established lymphoma were infiltrated by 30% myeloid and by 1% T cells in the bone marrow (BM) and by 10% myeloid and by 30% T cells in the spleen. Thus, only the systemic model mimicked myc-driven lymphoma in men closely. To test function of h/mCD22, lymphoma-bearing mice were treated with Moxetumomab. Moxetumomab reduced BM lymphoma infiltration by 20 to 100-fold and spleen infiltration by 5 to 20-fold in the three lymphoma models. Effects on LIM were analyzed after treatment with doxorubicin which is known to activate myeloid cells *in vivo*. Doxorubicin increased CD11b+ myeloid cells in spleen by 1.5-fold compared to untreated controls. These CD11b+ cells were dominated by Ly6G+ granulocytic cells.
Conclusions: Primary murine, h/mCD22+ lymphoma can be serially transplanted in syngeneic mice and LIM similar to men is established in lymphoid organs. Lymphoma respond well to CD22-targeted therapy and doxorubicin induces expected immunologic changes. The model provides

a novel and unique platform to test human CD22 targeted therapies in immune competent mice.

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Fabian Müller: Advisory Role: Beratungstätigkeiten für AstraZeneka; Expert Testimony: Unterstützung zur präklinischen Testung von Moxetumomab pasudotox

V903

Tumor cell-intrinsic activity of the RNA receptor RIG-I promotes checkpoint inhibitor-mediated anticancer immunity

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Introduction: Durable clinical responses to immune checkpoint inhibitors are limited to a minority of patients, and the molecular pathways that modulate their efficacy remain incompletely defined.
Methods: In preclinical models, we used CRISPR/Cas9-mediated somatic mutagenesis to generate tumor cells lines that lack innate immune nucleic acid receptors or downstream signaling molecules (RIG-I, STING, IRF3/7). Together with available genetically deficient mouse models, we hereby addressed the importance of nucleic acid receptor signaling in both tumor and host cells for the efficacy of immune checkpoint inhibitors. Furthermore, we retrospectively analyzed genome-wide transcriptional programs in primary melanoma patient tumor samples at diagnosis and during checkpoint inhibitor treatment for the transcriptional activity of these pathways and possible association with treatment outcome.
Results: We here demonstrate that immunotherapy with anti-CTLA-4 and its combination with anti-PD-1 rely on tumor cell-intrinsic activation of the cytosolic RNA receptor RIG-I. Mechanistically, tumor cell-intrinsic RIG-I signaling induced caspase-3-mediated tumor cell death, cross-presentation of tumor-associated antigen by $CD103^+$ dendritic cells, subsequent expansion of tumor antigen-specific $CD8^+$ T cells, and their accumulation within the tumor tissue. Consistently, therapeutic targeting of RIG-I with 5'phosphorylated-RNA in both tumor and non-malignant host cells potently augmented the efficacy of CTLA-4 and PD-1 checkpoint blockade in several preclinical cancer models. In humans, transcriptome analysis of primary melanoma samples revealed a strong association between high expression of *DDX58* (the gene encoding RIG-I), T cell receptor and antigen presentation pathway activity and prolonged overall survival. Moreover, in melanoma patients treated with anti-CTLA-4 checkpoint blockade, high RIG-I transcriptional activity significantly associated with durable clinical responses.
Conclusions: We identify aberrant tumor cell-intrinsic RIG-I signaling in mice and humans as a crucial mechanism underlying cancer resistance to immune checkpoint inhibition and establish high tumoral RIG-I expression as a potential biomarker for its efficacy. Our data predict that clinical RIG-I targeting in patients may increase response rates of checkpoint inhibitor-based immunotherapy and reduce inter-individual variability of treatment outcome.

Disclosure: No conflict of interest disclosed.

V904

Development of a novel, highly effective trifold immunotherapeutic approach using autologous humanized PDX models and genetically-engineered mouse models of cancer

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Less than 10% of all cancer patients respond to immune-checkpoint-inhibitors and less than 30% to any form of immunotherapy. Therefore, novel approaches are needed and ought to be developed rationally using appropriate model systems.
Here, we develop a combination immunotherapy of intratumorally delivered TLR agonists, aPD1-checkpoint-blockade and a multicellular therapy of innate and adaptive effectors.
Using TCGA-data, we found that combined infiltration of activated NK-cells, γδT-cells and non-regulatory αβT-cells confers a uniform survival benefit across cancers. Thus, we adapted protocols to selectively expand NK-like-, γδT- and tumor-specific αβT-cells in vitro from human PBMCs or mouse splenocytes. We found that NK-like-, γδT- and tumor-specific αβT-cells act synergistically in combination to kill lung-, breast-, and lymphoid cancer cells and exhibit increased cytotoxic activity when exposed to aPD1-antibodies in vitro.
Next, we performed in vivo experiments in humanized NSG-mice carrying lung- (H441, H1975), breast- (JimT1), and lymphoid (KMH2) cancers, in a syngeneic melanoma model (B16F10) and in a difficult to treat K-ras / p53 driven (KP), autochthonous genetically-engineered mouse model of lung cancer as well as autologous humanized PDX lung cancer models. We sequentially combined intratumoral TLR agonist therapy targeting TLR-3, TLR-7 and TLR-9, a combined adoptive cellular therapy of NK-like-, γδT- and tumor-specific αβT-cells and aPD1 immune checkpoint blockade. Strikingly, we were able to show that all 3 elements were needed in order to effectively eradicate or at least reduce tumor growth in all models.
Using immunohistochemistry analyses and flow cytometry, we found that combination treatment leads to a notable increase in tumor-infiltrating γδT-cells and marked increases in CD4+ and CD8+ T-cells as well as NK-cells across models. Employing multiplex cytokine arrays we identified a pattern of increased cytokine levels of MIP-1a, IL-5, IL-4, IL-9 and IL-15 associated with both reduced tumor growth and combination immunotherapy.
In conclusion, we were able to develop a novel, highly effective, trifold immunotherapy combination treatment regimen with broad efficacy across cancer entities and model systems that is completely agnostic of the precise target antigen and thus translationally highly relevant. Merely requiring a tumor biopsy and peripheral blood, our study has high translational relevance.

Disclosure: No conflict of interest disclosed.

V905

Identification of a neoantigen targeted by tumor-infiltrating lymphocytes in a patient with Her2+ breast cancer

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Introduction: The number of tumor infiltrating lymphocytes (TILs) positively correlates with survival in patients with HER2+ Breast Cancer (BC). However, the targets of those TILs remain unknown. Neoantigens, which arise in the process of tumorigenesis, appear as promising targets. They can elicit high avidity, tumor-specific T-cell responses. Thus, this study aims to determine whether these TILs are directed against neoantigens.
Methods: TILs were expanded from BC biopsies by unspecific stimulation. For the identification of potential neoantigens tumor specific mutations were identified by comparing whole genome sequencing data from tumor and autologous blood cells as reference. All non-synonymous mutations and in-frame indels were analyzed for RNA expression of the respective genes as well as confirmation of the mutations, and binding analysis of the mutated peptides to patient's HLA molecules was performed. Potential neoantigens were loaded as peptides onto autologous antigen presenting cells (APCs) and cocultured with TILs. IFN-y producing T-cells were clonally expanded and tested for peptide specificity.
Results: In a patient with HER2+ BC we identified three CD4+ T-cell clones from the biopsy at the timepoint of diagnosis and one from the resected tumor tissue after neoadjuvant chemotherapy. All T-cell clones recognized the same neoantigen derived from RBMX protein without showing any reactivity against the wildtype counterpart. Based on CDR3 sequencing of the T-cell receptor, we could demonstrate that all T-cell clones represent individual clones. Interestingly, the same neoepitope was presented in two different HLA-restriction molecules. Three of the clones recognized the epitope in HLA-DPB1*0401 and one in HLA-DPB1*0201. Furthermore, we showed direct presentation of the neoantigen on RBMX transduced MCF7 cells after IFN-y induced upregulation of MHC-II as well as indirect presentation on APCs loaded with cell lysates generated from RBMX transduced MCF7 cells. This indicates that inflammation may lead to direct neoantigen presentation on BC cells, and that indirect presentation on surrounding APCs in the context of destroyed tumor cells is also possible.
Conclusions: We show the feasibility to identify individual neoantigen specific T-cell responses in BC patients, which in future may contribute to the development of targeted patient-specific therapies.

Disclosure: No conflict of interest disclosed.

V906

Identifying the mutational signature of spontaneously developing MLH1$^{-/-}$ tumors - a comparative analysis in a preclinical model

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Introduction: MLH1 knock out mice represent a preclinical model that resembles features of the human counterpart. These mice develop mismatch repair deficient (MMR-D) neoplasias spontaneously. The tumor spectrum is complex, with a high prevalence of early Non-Hodgkin T cell lymphomas (NHL), lymphoid skin lesions as well as later developing epithelial tumors of the gastrointestinal tract (GIT).
Methods: Using whole-exome sequencing on MLH1$^{-/-}$ primary tumors (2x GIT, 1x splenic NHL, 1x skin lymphoma) as well as GIT-derived cell lines (n=2), we aimed at identification of the underlying molecular mechanisms. We focused on (I) shared and (II) mutually exclusive mutations and described the processes of ongoing mutational events in tumor-derived cultures.
Results: MLH1$^{-/-}$ tumors show high tumor mutational burden with 3/4 primary tumor samples even being ultra-hypermutated (> 100 mut/MB). Missense mutations were more frequent than nonsense mutations, and base changes were mainly due to transitions (C>T; A>G). The resulting mutational landscape was heterogeneous and in accordance with the human counterpart, MLH1$^{-/-}$ tumors frequently harbor mutations in PIK3CA, EGFR, BRAF, KRAS, and ERBB3. Of note, only a few shared mutations were detectable among different tumor entities (ARID1A and IDH2). Mutations in tumor suppressor genes SMAD4 and POLE were mutually exclusive in lymphomas, most likely contributing to a more aggressive in vivo phenotype. Comparing the mutational profile of selected primary tumors and their corresponding cell line upon in vitro culture revealed continuous increased numbers of somatic gene mutations. The same was true for coding microsatellite mutations in selected MMR-D target genes, showing a gradual increase during in vitro passage. With respect to this latter type of mutations, partial overlap was detectable, yet recognizing shared antigens. The two most promising candidates are AKT3, a RAC-gamma serine/threonine-protein kinase with relevance in maintenance of cellular homeostasis and the endonuclease ERCC5 (Excision Repair 5), involved in DNA excision repair.
Conclusions: The present study is the first reporting results of a comparison between different spontaneously developing tumors as models for MMR-D driven tumorigenesis. Additionally to identifying ARID1A as potential causative mutation hotspot, this comprehensive characterization of the mutational landscape may be a good starting point to predict antigens for vaccination approaches.

Disclosure: No conflict of interest disclosed.

Freier Vortrag

AYA

V907

Health status of AYA cancer survivors compared to age-matched controls

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Introduction: It is an undisputed fact that cancer patients in young adulthood (AYA) often have to live with additional health burden after completion of the invasive medical therapies. However, there is little reliable data available on the incidence of different diseases for AYA survivors and compared to young adults without cancer.
Methods: Young patients (aged 18-39 years at time of diagnosis) with malignant cancer sites of all sorts were surveyed using the disease list of the short version of the Work Ability Index (contains 14 overall disease patterns, e.g. cardiovascular diseases, or respiratory diseases, psychological impairments). The response format for recording the current diseases included: own diagnosis; reliable diagnosis made by the doctor; does not exist. For the comparison group (CG), data from Leipzig citizens in young adulthood without cancer were used. The first step in the analysis was to determine group differences.
Results: Data of 438 AYA (mean time since diagnosis: 50 months) and 406 Leipzig citizens were available. Every fifth AYA (20.1%; N=88) and three of five of the CG (59.9%; N=243) reported no reliable diagnosis of a disease (except cancer for AYA). On average, AYA reported 2.12 reliable diagnoses of diseases (range 0-9; SD=1.99) compared to 0.55 diseases (range 0-5; SD=.90) in the CG ($p < .001$). For all 14 disease patterns, AYA reported a significantly more frequent reliable diagnosis compared to the CG (effect size Cramer´s v between 0.15 and 0.39). Medium effect sizes were found for hormonal and metabolic diseases (AYA: 30.6% vs. CG: 1.8%; Cramer´s V=0.39) and allergies (AYA: 30.9% vs. CG: 5.1%; Cramer´s V=0.33). When including both response formats (own diagnosis and reliable diagnosis), we found group differences for six of the 14 disease patterns (diseases of the musculoskeletal system, diseases of the digestive system, diseases of the urogenital tract, psychological impairments, skin diseases, and hormonal and metabolic diseases), whereby AYA reported more diseases than the CG.
Conclusions: The clearly increased number of diseases in the group of AYA survivors compared to peers indicates the necessity of establishing fixed and fundable aftercare concepts far beyond the 5 years. Furthermore, a good interdisciplinary cooperation between the different specialist disciplines is necessary in view of the frequent multimorbidities of AYA cancer survivors. An after-care consultation should ensure this pilot function.

Disclosure: No conflict of interest disclosed.

V908

Improvement of psychosocial support for adolescents and young adults (AYA): experiences in a specialised psychosocial support service for patients between the age of 18 and 50 years

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Introduction: Only 9% of cancer patients affirmed that they received psycho-oncological support in hospitals and only 3% reported that they received help from cancer counselling centres. The diagnosis puts them in complex situations that do need individual care and experience of the therapist. In practice it was evident, that the responsible therapist played a significant role. We can reach the patients by offering services of low threshold, professional competence and personal accompaniment. Through the current medical care structures this cannot be guaranteed.
Methods: The pilot project "Diagnose Krebs - Mitten im Leben" tries to assess the entire living environment of a patient. The decision on the kind of support is up to the patient. Social assistance, psycho-oncological support and emotional support are offered by one therapist only. The therapist is a contact person for the patient, the family and friends, irrespective of treatment in the in- or out-patient-setting. Uncomplicated relationships for example by asking social questions shows the basis of building up trust, through this emotional topics can be talked about with ease. By having one therapist the patient must not repeat to talk about painful moments over and over or live through them again.
Results: With this system we were able to support 90% of 321 cancer patients between age 18-50 years in 2018. The therapist-motivated outreach enabled support to the patient, independent of gender, social or migration-background, in which social topics are key before starting emotional and psycho-oncologic topics. By having low thresholds and dedicated staff members we could assist significantly more patients and the documentation burden was also reduced significantly.
Conclusions: Patients in the age of 18-50 years can be supported by combining psycho-oncological and social support with one therapist. By building up trust and having a reference person, it is possible for most of the clients to talk about emotional topics that are difficult and painful. To change the medical care structure in this way will is challenging but could be a way to significantly improve the social, psycho-oncological and emotional care.

Disclosure: No conflict of interest disclosed.

V909

Emotional and social support for AYA: peer support of healthy young adults for young patients at the haematological monitoring ward

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Introduction: The particular problems of AYA (Adolescent Young Adults) have - been pointed out many times. From the AYA´s point of view, social problems are - the centre of attention besides the life-threatening disease. These are often not sufficiently observed by medical personnel. AYA depends on support of their loved ones emotionally, physically, practically and financially. However, partners and friends are often overwhelmed by the burden of the disease and sometimes retreat. At the same time, many AYA isolate themselves from their social surrounding during the disease. In order to support AYA diagnosed with an acute life - threatening oncological or haematological disease this peer support was established at the Robert Bosch Hospital (RBK) in Stuttgart. Since 2016, eight peers at the RBK have socialized with 32 AYA. The period of support was sometimes only a few days, but often several months. The feedback from the AYA in regard to the peer support was very positive. 21 AYA died while receiving peer support.
Methods: A qualitative study was conducted in cooperation with the Protestant University of Applied Sciences Ludwigsburg. Six problem-centred interviews were conducted with the AYA after receiving peer support. The interview focused on the question "who was emotionally and socially enriching and what was their impact on you?". Peer support was not explicitly mentioned in the survey in order to exclude supposedly socially desirable answers.
Results: The support of the peers was ranked by AYA as very helpful. The following topics were explored in relation to peer support: 1: Motivation, self-efficiency and empowerment are strengthened. 2. Activation of the patient and reduction of helplessness. 3. AYA felt that their personality was more the focus and not their role as a patient. 4. Peers often offered practical support to AYA regarding basic necessities. 5. Peer support enabled a positive interaction with the outside world. 6. Peer support established an equal level of understanding and relationship despite the disease.

Conclusions: Peer support for AYA is an important complement to typical psycho-oncological interventions. It provides significant emotional and social support, especially for patients who do not have access to traditional psycho-oncological interventions or staff. Since we consider this work area to be very valuable, we are in the process of training a second group of five new volunteers as Peer Support.

Disclosure: No conflict of interest disclosed.

V910

Financial and social impact of cancer in adolescents and young adults (AYA)

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Introduction: 16,000 AYA cancer patients from 15 to 39 years are diagnosed per year in Germany. More than 80% of them can be cured but the disease and its treatment can lead to serious financial and social consequences.
Methods: Publications on the financial situation, employment, and return to work in AYAs with cancer were analyzed. Data were reviewed and put into the context of epidemiological and medical data. Furthermore questions asked in the portal "Young and Cancer" operated by the German Foundation for Young Adults with Cancer are discussed.
Results: Publications show a drastic reduction of the quality of life after cancer due to financial impairments. Reduced or absent employment is an important cause. AYA patients are heterogeneous in diagnoses, social situations and in different age groups. Publications are often poorly differentiated in these respects due to small numbers and unspecified selections. The effects of national social security systems, legal regulations, development of economy and labor market are often not considered. In Germany financial burdens arise in the early course of cancer by out of the pocket payments and co-payments as well as by gaps in the financial security in special groups such as students. Employment after cancer is reduced but exact and differentiated data are missing for Germany. Cancer-related fatigue is a major obstacle for full return to work but does not receive sufficient scientific attention. Long-term survivors experience discrimination trying to become public officers or getting housing mortgages and health insurances. Patients' questions focus on rehabilitation, stepwise reintegration into work, and disability. They demonstrate the need for easy to access and continuous support.
Conclusions: In Germany the data base on social and financial consequences of cancer in AYA needs to be improved. The differentiated data needed can only be achieved by a population-based approach - an essential task of the public data infrastructure. Data from cancer registries, social security, and health insurances have to be connected with data on economic development and working market. Relief from out of the pocket payments and co-payments is needed. Further steps include improvements of social security in some groups and steps against discrimination of long-term survivors. Innovative programs for the treatment of cancer-related fatigue and age- and social group-specific rehabilitation are also necessary fields of action.

Disclosure: Mathias Freund: Immaterial Conflict of Interests: Vorsitzender des Kuratoriums der Deutschen Stiftung für junge Erwachsene mit Krebs
Ulf Seifart: Employment or Leadership Position: Angestellter Arzt in eine Fachklinik der Deutschen Rentenversicherung

V911

The burden of psychosocial distress after cancer treatment in adolescents and young adults

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Introduction: Adolescents and young adults (AYA) may suffer from various psychosocial sequelae after cancer treatment. Aiming to explore unmet needs and psychosocial distress, we performed a survey among all AYA-survivors treated for a haematological malignancy at our center since January 2010.
Methods: 85 AYA were invited to join the survey; at median of 36 (2-86) months after completion of hematological therapy. A set of standardized screening instruments for psychosocial stressors (PhQ-S), symptoms of depression (PHQ-9), generalized anxiety (GAD7), fear of progression (PAF-KF) and a self-designed questionnaire were sent to the patients.
Results: 47 (27 female) patients (55.3%) completed and returned the questionnaires. Median age was 35 (20-45) years. 21.3% of the participants reported on increased psychosocial stressors (cut-off score of 10 points, PHQ-S) and 25.5% were identified with moderate or severe depression symptoms (PHQ-9). In addition, 14.9% of the participants suffered from moderate or severe anxiety symptoms (GAD-7). The majority of AYA were sometimes (38.3%) or often (21.2%) stressed by fear of progression of their disease (PAF12). Strain was also caused by psychosocial issues emerge from daily life topics. Patients rated the difficulties for the re-entry into employment with a median score of three on a one to five graded Likert-type scale. Problems with the sexuality in a classification of at least moderate severity were reported by 44.7% of the AYA. Furthermore, the participants struggled with excessive demands of everyday life in an increased frequency. The relevance of this topic is also emphasised by significant correlations to the PHQ-9 ($p < 0.001$) and GAD-7 tests ($p< 0.001$). Psycho-oncological support offered during the therapy was used by 34% of the patients and granted as helpful (median score: 4 [2-5], n=16). Females were found with a higher rate of occupying the offer (25% of the male population vs 40.7% of the female population, $p = 0.355$). Whereas 31.9% of all AYA reported that any psycho-oncological support has not been offered.
Conclusions: AYA have a high disposition for psychosocial distress after cancer treatment and reported on excessive demands in everyday life and resumption of work. Regarding those issues' psycho-oncological and social support are valuable resources and need to become an inherent part in the aftercare of AYA patients.

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Posterdiskussion

AML II

P917

Hematopoietic stem cell mobilization with plerixafor is safe and effective in poorly mobilizing acute myeloid leukemia patients

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Introduction: Autologous stem cell transplantation (ASCT) represents an option for consolidation in patients (pts) in first remission (CR1) of favorable/intermediate-risk acute myeloid leukemia (AML). However, up to 20% of AML pts in CR1 fail to mobilize sufficient peripheral blood stem cells (PBSC). The CXCR4 antagonist plerixafor is approved for myeloma/lymphoma pts with CD34+ mobilization failure. We investigated the safety and effectiveness of adding rescue plerixafor in AML pts, who otherwise would have failed stem cell mobilization.
Methods: We studied five pts with therapy-naïve *de novo* AML, who received two cycles of induction chemotherapy at the University Hospital Bern. All pts achieved MRD-negative CR1 during induction and were planned for consolidation with high dose chemotherapy (HDCT)/ASCT based on their ELN risk assessment. All five pts failed to mobilize at least 10 circulating CD34+ cells per µL despite continued G-CSF stimulation following 2nd induction (cytarabine/daunorubicin) and were considered mobilization failure. In these pts, a single dose of 24 µg plerixafor was applied intravenously. Stem cell collection was started four hours after plerixafor administration independently of the CD34+ count. All patients including apheresis samples underwent comprehensive MRD assessment by qPCR, Sanger and NGS during follow-up.
Results: PBSC collection after plerixafor was successful in all pts enabling them for subsequent busulfan/melphalan HDCT and ASCT. Median circulating peripheral CD34+ cells increased from 3.8 (range 1.6-6.0) before plerixafor to 24.9 CD34+ cells/µL (3.0-46.8) at start of PBSC collection. A median of 4.05×10^6 CD34+ cells/kg was collected ($2.05\text{-}6.29\times10^6$/kg). All autografts were molecularly MRD-negative, and vitality was excellent (97-99%). Median neutrophil recovery >0.5 G/L occurred at day +12. Platelet recovery >20 G/L was prolonged (median 45 days versus 16 days in G-CSF-only mobilized AML pts in a previous series). Possibly, delayed platelet recovery in plerixafor mobilized AML pts reflects the background of primary mobilization failure and a poor stem cell pool in these particular pts. At the time of this report, all five pts were alive in CR1 after a median follow-up of 14 months.
Conclusions: Our data suggest that plerixafor added to G-CSF stimulation is effective and safe in AML pts in CR1 with imminent stem cell mobilization failure, and prospective studies are warranted to further evaluate this approach.

Disclosure: No conflict of interest disclosed.

P918

Cooperative effects of a DNMT inhibitor and all-trans retinoic acid in an AML cell line model lacking PML-RARA

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Introduction: All-*trans* retinoic acid (RA) has powerful activity in APL; its efficacy in non-APL AML is still unclear. In a randomized phase II study (DECIDER trial, NCT00867672) the addition of RA to decitabine (DAC) in newly diagnosed non-fit older AML patients led to a clinically meaningful extension of survival. We hypothesize that *in vitro*, the add-on of RA to DAC results in cooperative transcriptome changes, which may at least in part explain the clinical result.
Materials and methods: U937 cells were treated with daily pulses of 200 nM DAC, 1 µM RA was administered after 48 hours (hr). Cells were harvested after 72 and 120 hr of treatment. Proliferation, apoptosis and the ability to form colonies were assessed. Transcriptomes were acquired by RNA-Seq, Methylomes were generated using Infinium Human Methylation 450K BeadChip arrays.
Results: In suspension culture, RA alone had no effect on the proliferation of U937 cells, while DAC reduced proliferation by 74 % and DAC+RA by 81 %. The Colony Formation Assay also showed no effect for RA but a reduction of colony formation of 85 % for DAC, and by 96 % for DAC+RA. The RNA-Seq-analysis revealed DAC+ATRA to significantly induce/downregulate 2848 and 1173 transcripts (DAC alone: 2538 and 620 transcripts), respectively. 29.6 % of all DAC+RA-altered transcripts were uniquely regulated by combination treatment. GO analysis of upregulated genes revealed a significant enrichment for immune system and cellular decay. 55.5 % of transcripts already up- or downregulated by DAC or RA alone were further enhanced by DAC+RA. Among those, the RA receptors *RARA, RARB* and the RA response element (RARE)-containing tumor suppressor *HIC-1* were induced 8.6-, 8.3- and 179.8-fold, respectively. In order to further investigate this add-on effect of RA on DAC-induced transcriptome changes, DNA methylation was analyzed (72 and 120 hr). As expected, DAC significantly reduced CpG methylation in gene bodies and promoters, without further demethylation upon RA add-on.
Conclusions: In U937 cells, the combination of DAC with RA resulted in enhanced growth inhibition and reduced colony formation compared to DAC alone. Transcriptome analyses revealed a high number of uniquely regulated transcripts and an enhancement of regulation by the drug combination. The enrichment for genes involved in immune response, such as interferon-response genes, further encourages the combination of DNMTi-based therapies with immunotherapeutic agents.

Disclosure: No conflict of interest disclosed.

P919

Immunophenotypic characterization of T cells in Acute Myeloid Leukemia

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Background: Acute myeloid leukemia (AML) is the most common acute leukemia in adults. Survival rates of AML patients have only slowly improved in the past 40 years. Although induction chemotherapy induces complete remission in up to 80% of patients, a high percentage of patients

still relapses, most likely due to various immune escape mechanisms. It is pivotal to identify relevant immune checkpoints, especially coinhibitory receptor ligand interactions of tumor cells with specific immune effector cells to design future targeted therapeutic concepts that will harness the immune system and will be able to overcome immune escape.
Methods: We performed 16-color, multiparameter flow cytometry (MFC) on PB mononuclear cells (PBMCs) and AML blasts of 14 patients with newly diagnosed AML and 9 PBMCs of healthy donors (HDs) with focus on CD8+ and CD4+ T effector cells and Tregs, looking at the activation, differentiation, and exhaustion (PD-1,TIGIT) status as well as at the expression of purinergic signaling molecules (CD39, CD73).
Results: There was an increased frequency of PD1+ CD8+ (AML vs HD: 11.2% vs 3.9%; *p*=0.08) and CD4+T cells (AML vs HD: 11.1% vs 2.3%; *p*=0.05) and an increased frequency of TIGIT+ CD8+ T cells (AML vs HD: 43.45% vs 21%; *p*=0.00) in PBMCs of patients with AML. When comparing co-expression of TIGIT and PD1 on T cells of AML patients and of HDs, we did not find any difference in the frequency of TIGIT+ PD1+ CD8+ effector T cells (cells 20.8% vs 15.2%; p=0.2). Of note, while the frequency of Tregs in AML was comparable with HDs. Tregs highly expressed PD1 (24.4% vs 11.7%; *p*=0.05), TIGIT (68% vs 43.9%; *p*=0.01) and CD39 (67.9% vs 39.2%; *p*=0.01). Moreover, a subset of 50% (7/14) AML samples showed a high expression of CD39 on the surface of AML blasts (median 52.9%, minimum 2.39%, maximum 98.2%).
Conclusion: Based on these data, we are currently carrying out functional assays to evaluate the role of TIGIT and CD39 in order to their potential as therapeutic targets with regards to the boosting of antileukemic immune responses.
We are also investigating the role of TIGIT and CD39 in AML by analyzing the fraction of tumor specific (WT1 specific) T cells.

Disclosure: No conflict of interest disclosed.

P920

Novel circulating tumor DNA (ctDNA) based ddPCR drop-off assays for improved Minimal Residual Disease (MRD) monitoring in Acute Myeloid Leukemia (AML)

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Background: Most AML patients achieve remission after induction therapy, but relapse
rates are high. MRD assessment is important for early relapse detection. MRD monitoring by bone marrow (BM) aspiration is more sensitive than analyses of peripheral blood (pB), yet it is invasive. Moreover, both fail to detect extramedullary disease (EMD). CtDNA analyses may address these limitations.
Methods: Plasma samples were collected using Streck tubes. CtDNA was isolated using the QIAampCNA Kit and quantified by Agilent 2100 Bioanalyzer High Sensitivity DNA Kit. Mutations in *IDH2* and *NPM1* were detected using custom drop-off ddPCR assays (BioRad QX200 ddPCR System). All assays achieved >99.9% sensitivity. All patients provided written informed consent. The LMU medical faculty ethical committee approved the study.
Results: Data from illustrative AML patients are shown.
In patient 1 (Panel A), who received enasidenib, we identified an *IDH2* p.R172K mutation and compared serial samples of the patient (ctDNA, pB and BM). We observed that ctDNA analysis was more sensitive than pB gDNA analysis. Variant Allele Frequency (VAF) of *IDH2* in ctDNA and BM correlated closely, suggesting applicability in monitoring AML.
Patient 2 (Panel B) received induction therapy. We identified a *NPM1* Type A mutation. Despite pB blast clearance by d4, plasma ctDNA levels remained elevated and the mutation remained detectable in ctDNA until d15. These data suggest that ctDNA in AML originates from BM and may mirror response kinetics. Total ctDNA concentration, but not *NPM1* VAF, increased concurrently with Leukocyte regeneration, implicating ctDNA concentration as marker for cell turnover.
Patient 3 (Panel C) presented with myelosarcoma. An *IDH2* p.R140Q mutation was detected in EMD tissue, but not the BM. This mutation was detectable in ctDNA. Hence, ctDNA allows monitoring of patients with EMD.
Conclusions: DdPCR-based ctDNA analysis allows minimally-invasive AML monitoring. Our results indicate that ctDNA analyses may be more sensitive than gDNA analyses from pB and may capture EMD. We are currently investigating the prognostic value of response kinetics under treatment. Patient recruitment is ongoing.

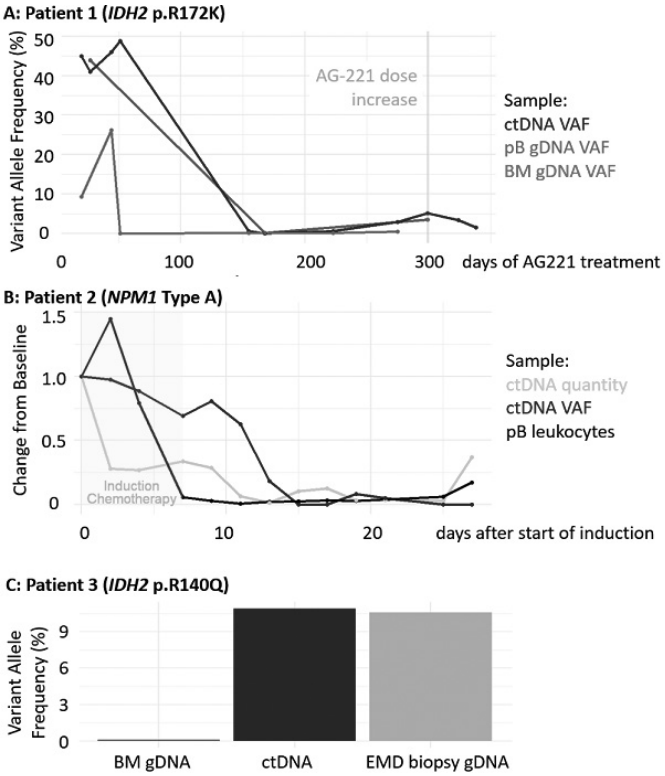

Fig. 1. A: Patient treated with enasidenib B: Patient treated with 7+3 C: Patient with isolated myelosarcoma

Disclosure: No conflict of interest disclosed.

P921

Characteristics of patients with acute myeloid leukaemia (AML) diagnosed in regular care. Data from the regular care AML-MDS-registry in Germany

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Introduction: The regular care MDS-registry started in July 2009. Since September 2014 the enrollment was expanded by patients (pts) with AML and was continued till December 2016. This is the first evaluation of AML pts diagnosed in regular care and documented in the MDS-AML-registry with the aim to describe their characteristics.
Methods: Pts could be included into the registry if the diagnosis was confirmed by bone marrow biopsy and if they had given their written informed consent. Baseline parameters at the time of diagnosis and the clinical course were quarterly documented in an online database (IoStudy by Iomedico) by 90 centers all over Germany.

Results: Within 90 months of recruitment 2,505 pts were included in the registry. 2,487 (99.3%) pts were evaluable with documented baseline characteristics. 187 (7.5%) pts were included with the diagnosis of de-novo AML and 2,300 (92.5%) pts with MDS. 5 of 2,300 (0.2%) pts, who were included with MDS with excess of blasts in transformation, were relabeled as de-novo AML for this analysis. 96 of 2,300 (4.2%) MDS pts progressed into AML (MDS-AML). The characteristics of these 288 AML pts are given in the table.

Conclusions: In the regular care AML-MDS-registry were predominantly documented pts older than 70 years. The mean time of observation from AML-diagnosis till last data input or death was 15 months in de-novo AML and longer than two years in pts with MDS-AML. Most of the pts were treated with HMA.

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	De-novo AML	MDS-AML	All
N %	192 (66.6%)	96 (33.3%)	288 (100%)
Female/male N	91/101	41/55	132/156
%	47.4/52.6	42.7/57.3	45.8/54.2
Age mean (SD)	78.47 (8.57)	77.43 (7.23)	78.13 (8.15)
median	80	78.5	79.5
min-max	46 – 96	56 – 91	46 – 96
>70 y (N, %)	166 (86.5%)	83 (86.5%)	249 (86.5%)
Time of observation*			
Mean (month, SD)	15,06 (14.61)	25.59 (14.40)	18.57 (15.34)
Median (month, min-max)	9.27 (0 – 89.13)	22.42 (3.43 – 76.5)	14.44 (0 – 89.13)
Cytogenetics**	100 (52.1%)	75 (78.1%)	175 (60.8%)
Therapy***	182 (94.8%)	82 (85.4%)	264 (91.7%)
CT	12 (6.3%)	3 (3.1%)	15 (5.2%)
Allo-SCT	7 (3.6%)	8 (8.3%)	15 (5.2%)
CT+HMA	32 (16.7%)	18 (18.8%)	50 (17.4%)
HMA	129 (67.2%)	52 (54.2%)	181 (62.8%)
Other	2 (1.0%)	1 (1.0%)	3 (1.0%)
ni	10 (5.2%)	14 (14.6%)	24 (8.3%)
Status at data cut N (%)			
- Ongoing observation	64 (33.3%)	17 (17.7%)	81 (28.1%)
- Lost to follow up	17 (8.9%)	8 (8.3%)	25 (8.7%)
- Deceased	111 (57.8%)	71 (74.0%)	182 (63.2%)

* Time from AML-diagnosis till the last documentation or death of the pts. **results available
*** Specific AML-therapy among these: CT= Chemotherapy (AraC, Antracykline, Hydroxyurea and other); allo-SCT= allogenetic stem cell transplantation including induction CT; HMA= hypomethylating agents; ni= no information

Fig. 1. Characteristics of AML pts in regular care

Disclosure: Tilman Steinmetz: Employment or Leadership Position: Anstellungsverhältnis: MZ-Zentrum für Hämatologie und Onkologie Köln Am Sachsenring, Geschäftsführer: 1. X-Med GmbH, 2. MV-Zentrum für Hämatologie und Onkologie Köln, Ärztlicher Leiter: MV-Zentrum für Hämatologie und Onkologie Köln Am Sachsenring; Advisory Role: Accord Healthcare, Amgen, Ariad, BMS, Boehringer, Celgene, Hexal-Sandoz, Novartis; Janssen-Cilag, Omnicare, Oncopeptides, Otsuka, Pfizer, Sanofi, Shire, TAD; Stock Ownership: Keine (evtl. kleine Anteile in Fonds?); Financing of Scientific Research: KV-No, Privatpatienten; Expert Testimony: Accord Healthcare, Amgen, Celgene, Novartis; Other Financial Relationships: Reisekosten: Alexion, Amgen, Bayer, BMS, Boehringer, Celgene, Jansen-Cilag, Novartis, Omnicare, Sanofi; Immaterial Conflict of Interests: DGHO, ESMO, DGPM, BNHO, NIONo
Stephan Schmitz: Employment or Leadership Position: Anstellungsverhältnis: MZ-Zentrum für Hämatologie und Onkologie Köln Am Sachsenring, Geschäftsführer: 1. X-Med GmbH, 2. MV-Zentrum für Hämatologie und Onkologie Köln,; Advisory Role: Diverse Adboards; Financing of Scientific Research: KV-No, Privatpatienten; Expert Testimony: Accord Healthcare, Amgen, Celgene, Novartis,; Immaterial Conflict of Interests: DGHO, ESMO, BNHO, NIONo

P922

The expression of DNMT3A and some cooperating genes in AML patients

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Introduction: DNA methylation and histone modifications are a key epigenetic modification involved in regulating gene expression. Recently, it was shown that both processes function cooperatively. In this study, we analyzed expression level of five genes that linked together in epigenetic regulations: *DNMT3A* (DNA methyltransferase 3A), *DNMT3B* (DNA methyltransferase 3B), *PRMT5* (arginine methyltranferase that catalyzes dimethylation of arginine residues), *COPRS* (coordinator of *PRMT5*), and *GFI1* (Growth Factor Independent 1, that is one of the targets of PRMT5).

Methods: Using RT-qPCR, we analyzed gene expression in 151 AML patients and 15 healthy individuals. Mutation status in all AML patients was evaliated using NGS. Statistical analysis was performed using the GraphPad Prism 7.0 and SPSS 17.0 statistical software.

Results: Expression levels of all genes except *COPRS* were significantly higher in the AML patients compared with those of healthy controls (log2). *DNMT3A* expression was shown an inverse correlation with *DNMT3B and PRMT5*, and direct correlation with *CORPS* and *GFI1*. Age was not associated with the level of *DNMT3A* expression, regardless of the mutation. However, the *GFI1B* expression level revealed a significant difference in terms of age 60 as a threshold. Expressions of all studied genes were significantly lower in the AML patients with *DNMT3A* mutations compared with patients without mutations.

Gene mutations profiling in different cytogenetic risk subgroup from AML patients illustrated the distinct distributions. The mostly gene mutations were distributed in the intermediate subgroup. Besides, *DNMT3A* gene expression level in cytogenetic stratification subgroup indicated high difference between unfavorable and intermediate subgroup (p=0.04).

Finally, we found a negative effect of high *DNMT3A* expression levels on the outcome of AML, especially in the context of relapse rate (p=0.009).

Conclusions: We can conclude that AML patients are characterized by upregulation of *DNMT3A* expression and some partners in epigenetic regulation, such as *DNMT3B*, *PRMT5,* and *GFI1*. However, in the AML patients with *DNMT3A* mutation, lower expression of these genes was observed. This could be caused by the "loss of function" mutation. Moreover, our data demonstrate that not only mutations in *DNMT3A* but also its expression level correlate with outcome of AML. This data could help to understand pathogenesis of AML and can be used to introduce new therapeutic strategies.

Disclosure: No conflict of interest disclosed.

P923

Mitochondrial mass is increased in residual acute myeloid leukemia cells under treatment with cytarabine

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Introduction: Resistance to cytarabine (Ara-C) in acute myeloid leukemia (AML) is characterized by maintenance of the mitochondrial membrane potential (MMP) associated with high oxidative phosphorylation activity. Additionally, some evidence suggests a gain in mitochondrial mass as determined by mitotracker staining in surviving AML cells under treatment with Ara-C. Here we apply complementary techniques to quantify mitochondrial mass in AML cells exposed to Ara-C in order to corroborate these previous observations.

Methods: We treated Ara-C -sensitive and Ara-C-resistant HL-60 single cell clones with Ara-C and determined mitochondrial mass using staining of mitochondria with mitotracker deep red and flow cytometry or fluores-

cence microscopy. Moreover, we analyzed the ratio of mitochondrial and nuclear DNA using quantitative PCR.
Results: Flow cytometry showed an increase in mitotracker intensity in sensitive HL-60(S) cells treated with 1μM of Ara-C, but not with 10μM, while no shifts were detected in Ara-C resistant HL-60(R) cells. There were no differences in mitotracker intensity between untreated HL-60(S) and (R) cells, although HL-60(R) cells displayed a stronger signal with tetramethyl rhodamine esther, indicative for higher MMP. Immunofluorescence microscopy revealed an elevated number of mitochondria in HL-60(S) cells exposed to Ara-C compared to untreated cells. Relative mitochondrial DNA copy number was also higher in HL-60(S) cells treated with 1 μM Ara-C than in untreated controls, but did not increase in HL-60(R) cells under Ara-C treatment.
Conclusions: Together, our results confirm that mitochondrial mass is increased in residual AML cells under chemotherapeutic stress induced by Ara-C treatment. The particular mechanism underlying this finding remains to be elucidated.

Disclosure: No conflict of interest disclosed.

P924

Treatment of acute myeloid leukemia with arsenic trioxide plus granulocyte colony-stimulating factor inhibits leukemia cell growth through induction of aquaglyceroporin 9 expression

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Despite enormous improvements in cancer cell therapy, especially in targeted therapy strategies over the last decades, acute myeloid leukemia (AML) is still a life-threatening disease for children and adults. Due to the strong heterogeneity among its various forms, AML treatment is overall difficult. Even less than 10% of elderly patients can be cured. In our study the combination of arsenic trioxide (ATO) and granulocyte-colony stimulating factor (G-CSF) is considered as a potential new pharmacological therapeutic approach for AML. Based on micro array data, we found that G-CSF significantly induces the mRNA expression of the main ATO transporter aquaglyceroporin 9 (AQP9) in hematopoietic CD33-positive cells of healthy individuals and AML cell lines. Using this AQP9 upregulating effect of G-CSF and an accompanying increased ATO sensitivity for AML cells, we observed cell growth inhibition and elevated apoptosis of AML cells *in vitro* and in xenograft mouse model *in vivo*. We further detected increased ATO levels inside the ATO-G-CSF-treated cells due to increased AQP9 protein expression levels rendering AQP9 to be a promising candidate biomarker for predicting the efficacy of ATO treatment. In addition to it, combinatorial ATO-G-CSF treatment also showed an enhanced differentiation capacity of AML cells raising the question whether and to what extent AQP9 is involved in granulocytic maturation.

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P925

Risk factors for induction failure of standard chemotherapy with anthracycline and cytarabine in acute myeloid leukemia patient

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Induction therapy (IT) with anthracycline and cytarabine (DA) is, despite the new era with targeted therapies as FLT3- or IDH-1/2- inhibitors, still the backbone of AML-treatment worldwide. In this retrospective study we investigated risk factors for primary induction failure (IF) in 109 AML-pts, who were consecutively treated between 2013 and 2018 at our institution.
We evaluated in all pts at diagnosis CMV igG status, LDH-value, platelet counts, peripheral blood (PB) and bone marrow (BM) blast count, Sorror comorbidity score (range 0-6), age (< 70 yrs or >), cytogenetic risk factors according to the ELN classification (favourable [n=15], intermediate [n=56], or high risk [n=38]), detection of biclonal AML by flow cytometry, and extramedullary manifestation of AML. Study objective was to identify risk factors for IF after DA therapy and the rate of OS in pts with IF.
In 43 (39%) of 109 pts (56 male) an IF was observed after DA. 38 of these pts received a salvage therapy with idarubicin and fludarabine (n=30) or allotransplant (n=8), whereas 5 pts received only best supportive care. Consolidation therapies were in 6 pts high dose cytarabine and in 68 pts allotransplant. By flow cytometry detectable biclonal AML was found in 9,3% cases, and extramedullary manifestation of AML was reported in 7,8% of pts. Only age >70-yrs (p=0.04, OR 2.5), cytogenetic adverse risk classification (p=0.006; OR 3.21), Sorror score of $\geq$2, (p=0.019, OR 2.72), and >40% blasts in BM (p=0.01; OR 3.64), had influence on the occurrence of IF after DA. All other factors had no influence statistically for the occurrence of IF. PFS and OS did not differ statistically between responders and non-responders of IT when an allotransplant subsequently was performed. Pts with IF and w/o transplant had a worse prognosis (2-yr OS 19% $\pm$ 17% vs 87% $\pm$ 8%, p< 0.0001). Further reduced 2-yr OS was found for pts >70 yrs (2-yr OS 57% vs 71%, p< 0.046). Multivariate analysis identified only transplant (HR 0.37; [95% CI 0.19-0.76], p=0.007) and blast counts >40% in BM (HR 2.24, [95% CI 1.07 - 4.68], p= 0.032) as independent risk factors for OS.
Conclusions: In our study we identified age >70 yrs, adverse cytogenetic risk classification according to ELN, Sorror score of >2 and blast count > 40% in BM as risk factors for IF after DA chemotherapy. Only allotransplant and blast count >40% in BM were independent risk factors for OS outcome regardless of the occurrence of IF.

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P926

Patient-derived AML- and ALL- xenograft models for translational research

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Acute leukemias are a class of heterogeneous hematological malignancies, which are characterised by a rapid increase of functionally immature blood cells. The most patients have a poor prognosis with the currently used standards of care (SoC) therapy. Advancing progress in molecular profiling of leukemias enables the identification of new potential drivers for leukemia, with some of them being potential therapeutic targets. Further target validation and drug development is highly dependent on predictive preclinical models representing the different leukemia subtypes. We established new patient derived xenografts (PDX) of acute myeloid leukemia (AML) and acute lymphoid leukemia (ALL) for drug development and evaluation of new treatment approaches.
AML-and ALL-xenografts were derived from bone marrow aspirates or peripheral blood samples of primary or relapsed AML or ALL patients. Enriched leukemia cells were transplanted either intravenously and/or subcutaneously into immunodeficient mice. Systemic development of leukemia was monitored by regular flow cytometric analysis of blood samples. Mice were sacrificed when signs of disease were obvious and single cell suspensions of spleens or tumor fragments were transplanted to new recipient mice. After at least three serial transplantations, chemosensitivity to SoC drugs was evaluated and gene expression as well as mutations were analysed.

More than 20 PDX models from different AML- and ALL- subtypes have been successfully established and characterized. The majority of the established xenografts are growing as solid tumors and some grow systemically. All PDX models revealed a highly individual response to SoC drugs. Correlation analyses with mutations and gene expression are ongoing.
The newly established PDX models of AML and ALL provide an exceptional platform for the identification and validation of new targets and allow the preclinical testing of new compounds and combinations within translational research projects.
In order to cover the complex heterogeneity of acute leukemias, further establishment of PDX models is in progress.

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P927

Short term culture of primary AML MNCs under growth factor starvation reveals functional heterogeneity of potential prognostic relevance

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Introduction: Most diagnostic and prognostic approaches in the treatment of acute myeloid leukemia (AML) address the entire bone marrow cell population whereas the success of therapy depends largely on the fate of leukemia initiating cells (LICs). Culture conditions that enrich for progenitor populations and enable measurement of their response to therapy in vitro may therefore provide a functional test of prognostic relevance.
The aims of this work were to identify short term culture conditions supporting the ex-vivo survival of progenitors from bone marrow samples of AML patients, examine the inter-patient response variability and ultimately test for associations between culture read-outs and prognosis of patients in the RAS AZIC trial (OSHO#083).
Methods: Mononuclear cells from 57 pretreatment AML bone marrow samples from patients included in the RAS-AZIC study were cultured over 4 days in a medium based on Iscove´s Modified Dulbecco´s Media (IMDM) in the absence of serum and hematopoietic growth factors, with selective addition of the mTOR inhibitor Rapamycin and GSK-3 inhibitor Chiron (*Bhavanasi, Dheeraj et al. Blood cancer journal, 2017;7(12):636.)*.
Based on preliminary tests, samples were analyzed using nine different culture conditions including standard (0,32 osmol/l) and low (0,15 osmol/l) osmolarity in the presence or absence of 5-azacytidine (5-AZA). FACS analysis was carried out on days 0 and 4 to assess cell counts, viability and expression of the LIC markers CD34, CD38 and CD123.
Results: Preliminary analysis revealed a wide functional variability between patient samples. Specifically,low osmolarity increased the $CD34^+CD38^-CD123^+$ compartment by at least 20% during short term culture in 26 samples (32 in the presence of Chiron and Rapamycin) and decreased it by at least 20% in 6 samples (5 with Chiron and Rapamycin). The in vitro response to 5-AZA was also highly variable between AMLs, the addition of 10 ng/ml AZA to cultures containing Chiron and Rapamycin resulting in changes in the $CD34^+CD38^-CD123^+$ compartment of ≥ 20% in 17 samples, with 10 increases and 7 decreases.
Conclusions: The short-term culture of AML bone marrow mononuclear cells under growth factor starvation reveals a high degree of functional heterogeneity between patients. Culture readouts are currently being compared to clinical responses within the RAS-AZIC trial to determine the potential relevance to prognosis and treatment stratification.

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P928

Transformation of essential thrombocythemia into a TP53 mutated acute megakaryoblastic leukemia: a very rare case report

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Introduction: The clinical course of essential thrombocythemia (ET) is relatively benign and transformation into acute myeloblastic leukemia (AML) is rare. Life-threatening thromboembolic episodes are possible consequences of marked thrombocytosis and require cytoreductive treatment. There are several cytoreductive therapies available such as hydroxyurea (HU) or pipobroman (PI). However, there are cytogenetic reports of deletion of chromosome 17 in HU-treated patients and monosomy 7q in PI-treated patients, indicating a risk of therapy-induced transformation of ET. We report a very rare case of transformed ET into an acute megakaryoblastic leukemia (AML M7 by the French-American-British classification) with a complex karyotype with deletion of 5q, 7q and 17p, after treatment with HU and PI.
Results: In June 2018, a 33-year-old man with a long history of ET presented with a thrombosis of the V. tibialis posterior, anemia and neutropenia but normal thrombocyte values at our hospital. His past medical history showed many complications with incidents of thrombosis due to a difficult-to-manage very high thrombocyte count with the consequence of different treatment regimens including HU and finally PI, which led to stable thrombocyte values around 600G/l. Due to the blood value changes, bone marrow puncture was performed and revealed typical morphological and immunophenotyping findings of AML M7. Cytogenetic analysis showed a complex karyotype with deletion of 5q, 7q and 17p and NGS analysis confirmed a TP53 mutation. This distinct karyotype linked the chromosomal aberrations to the patients´ cytoreductive treatment, rather than to the natural history of the disease. Chromosome 17p or TP53 mutation has not yet been reported in combination with the morphology of megakaryoblastic leukemia. After induction chemotherapy complete morphological and cytogenetic remission was achieved. Unfortunately, AML relapsed 2 months after allogeneic stem cell transplantation and the patient died 2 months later despite palliative therapy.
Conclusions: An increased risk for disease transformation after cytoreductive therapy remains an uncertainty in patients with ET. An intermediate cytogenetic assessment in younger patients with difficult-to-control thrombocytosis under cytoreductive therapy seems to be recommendable to possibly initiate an allogeneic stem cell transplantation in case of detected complex cytogenetic aberrations at an early stage before the development of an AML.

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P929

Inflammatory pseudotumor (IPT) of the liver in an 79-year-old patient with acute myeloid leukemia (AML), prostate cancer and colorectal cancer

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Introduction: Inflammatory pseudotumor (IPT) of the liver is a rare benign tumor, characterized by a prominent inflammatory infiltration as the predominant cellular component.
Case presentation: We report the case of an 79-year-old man, who was diagnosed with an acute myeloid leukemia (AML) arising from a myelodysplastic syndrome (MDS) after therapy for prostate cancer and colorectal cancer. The colorectal cancer was diagnosed in 2011 and treated adjuvant with 12 cycles of the FOLFOX regimen. The prostate cancer which was diagnosed with distant metastases (bone metastases) in 2015 was treat-

ed with androgen deprivation therapy. In September 2018 we started the treatment of AML with demethylating chemotherapy (decitabine 20 mg/m2 d1-5 intravenously in monthly intervals) because of deteriorating peripheral blood cell values. In March 2019 the patient was incidentally diagnosed with an unknown heterogenous mass in the computed tomography and magnetic resonance imaging of the liver. Alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9) levels were not elevated. We performed a computed tomography (CT)-guided biopsy of the liver lesion in order to exclude a malignant process including e.g. metastases of the colorectal cancer and prostate cancer, however histopathological analysis of the biopsy revealed an inflammatory pseudotumor of the liver.
Conclusions: Although the etiology and pathology of an inflammatory pseudotumor are unknown, the disease is usually a benign process. In this case report, we review the existing literature and evaluate the percutaneous liver biopsy to identify the pathology of the liver lesion. In such cases a hepatic resection, usually recommended as treatment of choice, can be avoided.

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P930

Characterization of the deubiquitinase USP48 as a potential oncogene in acute myeloid leukemia (AML)

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Introduction: Acute myeloid leukemia (AML) is a malignant blood cancer with poor prognosis. It is characterized by clonal myeloid cell proliferation in the bone marrow and blood. While cytogenetics and mutational gene aberrations are well described in AML, little is known about the impact of post-translational modifications (PTM) on the pathogenesis, maintenance and therapy of this disease. Ubiquitylation comprises the covalent modification of proteins with the small protein ubiquitin, which is attached by E3-ligases and detached by Deubiquitylases (DUBs).
Methods: To identify PTMs, we conducted a clustered regularly interspaced short palindromic repeats (CRISPR)-Cas screening using a custom-made library focusing on PTMs of the ubiquitin-proteasome system. Furthermore, we performed affinity purification-based techniques as well as yeast two-hybrid screening for interaction partner and ubiquitylation substrate identification.
Results: CRISPR-Cas based drop-out screening identified the deubiquitinase USP48 as a potential oncogene in AML. USP48 is a largely uncharacterized DUB with nuclear localization and the capability of cleaving both K48- and K63-type of ubiquitin chains. Validation experiments established USP48 as a gene required for survival in common AML cell line models. Furthermore, our proteome-wide screens for biologically relevant USP48 substrates and respective deubiquitylation experiments yielded several candidates that are currently being investigated in the context of AML biology.
Conclusions: Due to the poor prognosis of AML there is a dire need for the identification of novel therapeutic mechanisms. Within the ubiquitin proteasome system, DUBs are promising new vulnerabilities, given their active enzymatic sites, which can be targeted in a specific manner. Our results specify USP48 as a promising new oncogene and vulnerability in AML, whose further investigation is warranted.

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P931

Prognostic impact of post-transplant detectable minimal measurable in acute myeloid leukaemia patients

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Presence of measurable residual disease (MRD) prior to allo-SCT has been shown to be predictive for survival in patients in CR of AML. In this study we analyzed the impact of MRD in such patients measured by 8-color multiparameter flow cytometry (MFC) focusing on MRD persistence on day +100 post-transplant. A number of 68 AML patients (male, n=43) with median age of 57 years (range 24-77) in hematological CR at allo-SCT were enrolled in this study. The bone marrow samples pre-transplant and on day +100 post-transplant were analyzed using an extended monoclonal antibody panel and different to normal method. Prior to allo-SCT, 29 patients (43%) were MRD negative, whereas 39 (57%) were MRD positive. We demonstrated negative independent impact of MRD positivity prior to allo-SCT on overall mortality (HR 5.2, p=0.01), relapse (HR 6.9, p=0.009), and failure to DFS (HR 4.3, p=0.008), but not on NRM (HR 1.2, p=0.83). We also observed an independent impact of poor risk cytogenetics at diagnosis for failure to DFS (HR 2.7, p=0.03) and for relapse (HR 5.2, p=0.01).
At the day +100 (n=43), 12 (28%) patients were MRD positive and 31 (72%) MRD negative. The adjusted hazard ratios of MRD positive vs. MRD negative at day +100 were 6.3 (p=0.03) for overall mortality, 3.2 (p=0.059) for relapse, and 4.1 (p=0.026) for failure for DFS, respectively. Patients who experienced MRD clearance on day +100 had comparable survival outcomes as that of MRD negative patients (1y OS 84% vs. 100%, p=0.13; 1y DFS: 73% vs. 93%, p=0.13). After adjustment for various covariates, the hazard ratios of MRD persistence on day +100 for overall mortality, relapse and failure for DFS were 14.6 (p=0.003), 4.2 (p=0.02), and 6.9 (p=0.004), respectively. The median time to relapse in patients who survived 100 days after allo-SCT was 146 days (range, 34-385). In a landmark analysis at day +100 1 year OS and DFS were significantly worse for patients with MRD positivity at both time points comparing to patients with other remission status (OS: 40% vs 94%, p=0.001; DFS: 38% vs 84%, p=0.004). We confirm the pre-transplant MRD status as an independent factor for OS, DFS and relapse in patients with AML in CR. Further, we propose day +100 to detect patients with MRD persistence, who may be candidates for post-transplant therapeutic intervention (e.g. tapering of immunosuppression or administration of donor lymphocyte) to reduce the relapse rate and improve survival outcomes.

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Posterdiskussion

Sonstige Themen II

P932

Early-onset auto-inflammatory disease associated with a novel heterozygous mutation in TNFAIP3 (A20)

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Background: The *tumor necrosis factor-alpha-induced protein 3* (*TNFAIP3*; *A20*) gene negatively regulates NF-κB, a key signaling pathway in innate and adaptive immune response and a pivotal mediator of inflammatory diseases. Recently, heterozygous germline loss-of-function muta-

tions in *TNFAIP3* have been identified to lead to Beçhet-like inflammatory disease termed haploinsufficiency of A20 (HA20).

Case report: A 21-year old Caucasian woman was presented to our clinic with pre-diagnosed periodic fever syndrome. Since the age of 12 she suffered from recurrent fever, myalgia, arthralgia, urticaria, abdominal pain, headaches and intermittent mucosal aphthae. Additionally, periodically occurring neutropenia and a COOMBS negative hemolytic anemia was observed. Mutational analysis for different periodic fever syndromes revealed a heterogenetic mutation in the *MEFV* gene for familial Mediterranean Fever. Despite lacking familiar background, treatment with colchicine was initiated with minimal improvement. Therapy was switched to Anakinra and stopped by the patient itself, who was then lost to follow-up for 3 years. She was readmitted due to fever and neutropenia. Malignancy, aplastic anemia, PNH rheumatologic or infectious disease were excluded again. Detection of anti-neutrophil and anti-TPO antibodies indicated an auto-inflammatory process. A restart of colchicine did not improve symptoms. Treatment with high dose steroids, immunoglobulins and mycophenolate failed.

Using whole exome sequencing of peripheral blood DNA we found a yet unreported heterozygous c.1631dupC mutation in the *TNFAIP3*/*A20* gene resulting in a frameshift and downstream premature stop codon (p.A545fs*127). Located within the TNFAIP3/A20 zinc finger domain, this germline mutation resembles *TNFAIP3* variants we recently identified in a cohort of 51 ABC-DLBCL patients as well as loss-of-function mutations described for a Beçhet-like inflammatory disease mediated by unrestricted NF-κB signaling. Quantification of TNF-α plasma levels showed massive upregulation as compared to healthy controls indicative of constitutive NF-κB activation.

Conclusions: Our data suggests that novel heterozygous c.1631dupC *TNFAIP3* mutation as loss-of-function leading to unrestricted NF-κB signaling which causes the persistent auto-inflammatory phenotype. Given the importance of *TNFAIP3* somatic mutations as drivers in B cell lymphomas, especially ABC-DLBCLs, the patient may have an increased risk to develop this malignancy

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P933

Evaluation of a clinical tool for early detection of infection and sepsis in patients after high-dose chemotherapy

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Introduction: Patients after high-dose chemotherapy (HD) and autologous haematopoietic stem cell transplantation (autoHSCT) are at high risk for infection and sepsis. Timely treatment with empiric antibiotics (EA) is crucial but the best point of time is unclear. A clinical tool for early sepsis recognition by ward nurses is associated with improved clinical outcome in patients with sepsis (Torsvik et al, Crit Care 2016). We evaluated the utility and effectiveness a of clinical tool for early detection and initiation (EDI) of treatment with EA in patients in aplasia after HD. This tool was systematically applied by trained ward nurses and consists of vital parameter changes (heart rate, hypotension, respiration rate, level of consciousness, O_2-saturation, temperature) combined with clinical signs and symptoms frequently associated with infections and sepsis after HD.

Methods: Prospective cohort study of patients treated 09/2016-12/2018 with application of EDI in addition to conventional criteria for febrile neutropenia (FN); historical comparison with 01/2012-08/2016 when EA was triggered by conventional criteria for FN only.

Results: 174 patients (median age 58.3 years) treated with HD and autoHSCT 2012-2018 at a single institution with a total of 186 periods of aplasia were included. EDI was systematically applied in 86 periods of aplasia 09/2016-12/2018: Treatment with EA was initiated in 67.5% (56/83) of cases due to EDI-criteria, in 22.8% (19/83) because of conventional criteria for FN. A clinical diagnosis of infection and specific treatment occurred in 4.8% (4/83) independent of EDI- or FN-criteria; no EA were administered in absence of FN and EDI-criteria in 4.8% (4/83), respectively. Further data in table 1.

Tab. 1. Demographic and clinical data, Median (95% Confidence interval)

	Before EDI 01/2012 - 08/2016 N=103	After start of EDI 09/2016 - 12/2018 N=83	P-value
Type of HD-Treatment	Melphalan: 78.6% (81/103) BEAM: 16.5% (17/103) Others (GC): 4.8% (5/103)	Melphalan: 66.3% (55/83) BEAM: 16.7% (14/83) Others (AM-L,GC): 16.7% (14/83)	
Duration of aplasia (days)	7.0 (6.6 - 7.4)	7.0 (6.5 - 7.2)	0.57
Duration of i.v. antibiotic treatment (days)	9 (8.6 - 10.7)	7 (6.9 - 9.0)	0.025
30-day mortality	2.7% (3/103)	0% (0/83)	0.25
Rate of ICU-admission	6.8% (7/103)	2.4% (2/83)	0.2
Duration of ICU stay per aplasia (days)	0.48 (0.09 - 0.89)	0.17 (-0.07 - 0.41)	0.17

Conclusions: A clinical tool for early detection of infection and sepsis, systematically applied by trained ward nurses, is feasible and useful for triggering EA treatment of patients in aplasia after HD and autoHSCT. It does not result in longer administration of i.v.-antibiotics. Clinical outcome parameters trend favourably; it appears save and could reduce the burden on healthcare resources.

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P934

10-chanel flow cytometry enables bone marrow overview in a single tube: a single center experience

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Immunophenotyping by flow cytometry is indispensable for the diagnosis of hematologic diseases. The development of multi-laser flow cytometers with >= 10 channels allows the reduction of so called "backbone" antibodies at the one side and an extended depth of diagnostic parameters on the other side.

In order to optimize sample processing and cost effectiveness, we established a screening tube for immunophenotypic evaluation of bone marrow samples lacking a clear suspected diagnosis.

Here we present our 1-tube-panel, used for more than a year in routine immunophenotyping as a screening and orientation tube in bone marrow specimens: CD71-FITC/ HLA-DR-PE/ CD19-ECD/ CD13-PC5.5/ CD34-PC7/ CD5-APC/ CD56-A-700/ CD117-A-750/ CD38-PB/ CD45-KrO.

This panel allowes the quantification of the following parameters: nucleated erythroid cells (CD71++/CD45-), CD34+ stem-/progenitor cells/"-blasts", mast cell forms (CD117++/CD34-), maturation of granulocytopoiesis (CD45, CD38, CD13, CD71, CD117), eosinophilia, basophilia, monocytic cells (CD45/SSC/HLA-DR/CD5-/CD19-/CD34-), T cells (CD5+/CD19-) and T cell activation (HLA-DR, CD38), NK cells (CD56+/CD5-/CD13-), B cells (CD19+; CD5+/CD19+, B cell maturation (CD-45dim, CD38++, CD34+/-), plasma cells (CD38+++/CD45-/dim/CD19-/dim; aberrant CD56 expression for screening of neoplastic plasma cells).

It should be pointed out that this tube is used for screening for different kinds of hematologic disorders. It allows by systematic estimation of different bone marrow cell populations a better comparison of flow cytometric quantification in more or less contaminated specimens with cytomorphological results from bone marrow aspirates For special indications,

like lymphoma, leukemia or MRD-diagnostics, of course, additional tubes are necessary.
We here show examples of different hematologic disorders and discuss the informational content of our analysis. This multi-parameter-message of different cell lines allows systematic detection of phenotypic heterogeneities. Interestingly upon this screening strategy we observed for instance aberrant CD56 coexpression within the neutrophilic development. However, the biologic relevance of this finding needs to be determined.

Disclosure: No conflict of interest disclosed.

P935

Diagnosis of an indolent malignant Nnon-Hodgkin lymphoma (NHL) in a patient with paroxysmal nocturnal hemoglobinuria (PNH) under long-term treatment with Eculizumab

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Introduction: Paroxysmal nocturnal hemoglobinuria is a rare hematological disorder, frequently associated with aplastic anemia or myelodysplastic syndrome (MDS). In this report we present a patient with PNH who developed malignant NHL, while being treated with eculizumab.
Case presentation: A 74-year old male patient known in our hematology department since September 1990 because of PNH was successfully treated with eculizumab since 2010. Blood count and hemolysis parameters were normal, except for a positive direct Coombs test. In 2013 he experienced a hemolytic crisis, due to a urinary tract infection with coagulase-negative staphylococci. During routine follow-up in 2019 bone marrow cytology smears showed a hyperplastic erythropoiesis due to chronic hemolytic anemia. The histological evaluation, however, found a clonal population belonging to a B-cell NHL of follicular subtype, without any suppression of the hematopoiesis. The lymphoid cells were positive for CD79a, CD20, BCL2, partially for CD23 and negative for CD5, CD10, cyclin D1, BCL6 and CD3. The further staging examination with computed tomography, gastroscopy and colonoscopy did not reveal any other manifestation of malignant lymphoma.
Conclusions: Other authors have also described the development of NHL under treatment of PNH with eculizumab, suggesting that PNH clones may lead not only to myeloid tumors such as MDS or acute myeloid leukemia, but also to lymphoid malignancies. The precise role of eculizumab in this case however remains unclear.

Disclosure: No conflict of interest disclosed.

P936

Hemophagocytic syndrome in aggressive NK-cell leukemia: case report and discussion

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A 39 year old male patient presented with signs and symptoms fulfilling the criteria of hemophagocytic syndrome. Treatment had to be started before an underlying aggressive NK-cell leukemia was diagnosed: We describe and discuss diagnostic findings - including a p53 mutation - and the course of the disease.

Disclosure: No conflict of interest disclosed.

P937

Ibrutinib - two rare complications of an oral treatment

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Introduction: Ibrutinib is a tyrosine kinase inhibitor approved 11/13 by FDA for the treatment of mantle cell lymphoma and 2/14 for the treatment of CLL. Meanwhile Ibrutinib is used successfully in the therapy of low malignant B-cell lymphoma. As side effects especially grade 3 and 4 neutropenia (16%), diarrhea (4%), occurrence of atrial fibrillation (3%) and increased risk of bleeding are to be mentioned. However, it comes to the occurrence of unexpected side effects. Two of them will be presented as case study.
Results:
Case 1: Posterior reversible encephalopathy syndrome
Patient: D.J., 75 years
7/18: diagnosis of B-CLL, stage Binet A
10/18: Inclusion in CLL-12 trial (Ibrutinib vs Placebo) of the German CLL Study Group
05.02.19: slight vision deterioration
18.02.19:
in the morning: increasing vision deterioration
13:00: serious deterioration, cardiovascular system problems, RR: 142/64 mmHg
14:00: increasing confusion syndrome
14:30: general practitioner initiated admission in neurological department
Admission into hospital: restless patient, requests were neglected, eyes not opened, increased sensitivity to pain, no paresis, no meningismus
Examination: CT, MRI cranial, cerebrospinal fluid unobstrusive
18.02.19: increasingly delirious, not oriented
IMP stopped
19.02.19: patient slowly recovers, retrograde amnesia, RR: 221/82 mmHg
27.02.19: neurologically normal, on spec encephalopathy
05.03.19: IMP unblinding: Ibrutinib
Conclusions: Visual deterioration is described as side effect of Ibrutinib. Whereas, the occurrence of delirious state syndrome, which corresponds to the clinical symptom of an encephalopathy, is unknown. Similar side effects are known to Cyclosporin. Continuous monitoring of patients regarding the occurrence of neurological symptoms is recommended.
Case 2: Cardiomyopathy
Patient: B.G., 71 years
11/11: Diagnosis of mantle cell lymphoma stage IV
11/11 - 3/12: 6 cycles R-CHOP
06/12: starting maintenance with rituximab
12/12: starting Ibrutinib
22.01.18: dilative cardiomyopathy, Ibrutinib stopped
23.01.-30.01.18: stay on intensive care unit due to cardiac decompensation with pulmonary oedema
11.05.18: pumping function normal
Conclusions: Whereas, atrial fibrillation is a known side effect of Ibrutinib, a cardiomyopathy is not common. As consequence, a continuous echocardiogram control during Ibrutinib therapy is recommended.

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P938

Invasive fusariosis in a patient undergoing double induction chemotherapy for FLT3-ITD positive acute myeloid leukemia

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Invasive fungal infections (IFI) are a major cause of morbidity and mortality in neutropenic patients treated with intensive chemotherapy for acute myeloid leukemia (AML). Invasive fusariosis is rare but associated with high mortality. Here we report a case of a neutropenic AML patient with invasive fusariosis successfully treated with voriconazole and liposomal amphotericin B.

A 65 years old male patient was diagnosed with de novo *FLT3-ITD* positive AML. He received "7+3" double induction chemotherapy with additional midostaurin. Antifungal prophylaxis was initiated with micafungin. A CT scan on day 17 of the second induction cycle due to an increase of the c-reactive protein (CRP) and fever showed discrete subpleural infiltrates of the right middle and lower lobe. Antibiotic treatment with meropenem was started and complemented with vancomycin. On day 21 the patient developed multiple disseminated cutaneous, palmar and plantar lesions (figure 1) with central necrosis suggestive of septic emboli. On the same day, microscopic evaluation of the peripheral blood was suggestive of a candidemia and treatment with caspofungin (CASP) was initiated. Since further microbiological workup was highly suspicious of filamentous fungi, we started treatment with voriconazole (VOR) in addition to CASP. After the final characterization of the fungi as *Fusarium oxysporum* without presence of *Candida spp.*we continued treatment with VOR only. Due to a progressive hyponatriaemia which was assumed to be VOR induced, antifungal treatment was continued with liposomal amphotericin B (AMB). The patient was free of fever from day 27 onwards and CRP continuously decreased early after initiation of antifungal therapy.

Invasive fusariosis is a serious acute complication with high mortality rates in intensively treated, neutropenic patients with AML and should be consequently treated. Careful examination of neutropenic patients with potential infectious complications can provide helpful information and should be regularly done.

Fig. 1.

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Antibiotic switch in hematological patients with persistent or recurrent fever after second-line antibiotic treatment: a retrospective, monocentric review of 169 cases

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Introduction: Fever after intensive chemotherapy (ctx) may be a sign of infection which can be life-threatening, especially in neutropenia. An antibiotic switch can be indicated but may be unnecessary in some cases. Broad-spectrum antibiotics like tigecycline (TGC) are used in some centers to treat infections unresponsive to initial treatment. This study aims to review the treatment strategies in patients (pts) with persistent or recurrent (p/r) fever.

Methods: Cases with p/r fever after intensive ctx and clinically/microbiologically documented infections (CDI/MDI) or fever of unknown origin (FUO) were retrospectively reviewed. P/r fever was defined as fever after 3 days of 2nd-line antibiotic treatment. Pts were divided into 3 groups: Switch to TGC as 3rd-line (TGC-group), switch to any other antibiotic (Other-group) or watch and wait (W&W-group). Response rates and 30-day mortality were evaluated. Response was defined as defervescence for ≥7 days.

Results: 169 cases (median age 59 years, 55% men) treated in our department from 09/2004 to 12/2017 were reviewed. All pts were treated for hematological malignancies (mostly acute myeloid leukemia, 60.9%) with intensive ctx. 141 pts (83.4%) were neutropenic. Piperacillin/tazobactam (PIP/TAZ) (71,6%) or ceftazidime (CEF) (27,2%) were used in 1st-line. 167 pts (98.8%) had received meropenem as 2nd-line. 142 pts (84.0%) were switched to 3rd-line. 77 pts (45.6%) were switched to TGC in combination with an antipseudomonal antibiotic (mostly CEF, 94.8%). 65 pts (38.5%) were switched to any other antibiotic (CEF or PIP/TAZ in 43.0%) or an antibiotic was added to 2nd-line (e.g. vancomycin in 30.7%). In 27 pts (15.9%) no antibiotic switch was made. CDI, MDI and FUO rates were comparable between the 3 groups. There was no significant difference in response rates (TGC, Other, W&W: 71.4% *vs.* 60.0% *vs.* 81.5%; p=0.10) or in 30-day mortality rates (TGC, Other, W&W: 7.8% *vs.* 7.7% *vs.* 3.7%; p=0.75) between the 3 groups. The use of broad-spectrum antibiotics in our department was average or higher compared to the German ADKA-if-DGI Anti-infective Surveillance. For example, the use of broad-spectrum penicillins from 2014-2015 was in median 14.7-21.1 recommended daily doses (RDD). In the German comparison the interquartile range was 11.9-17.4 RDD.

Conclusions: In our experience, TGC does not increase the rate of defervescence in hematological pts with p/r fever. Also in some cases no antibiotic switch may be necessary at all.

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P940

Patients with hematological malignancies suffering from hepatitis E infections - a systematic review of case reports and observational studies

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Introduction: Hepatitis E-Infection(HEV-I) is an emerging infectious disease in Europe. Initially described in solid-organ transplant recipient, all kinds of immunosuppressed patients are at risk. This normally self-limiting disease can progress to chronic hepatitis. Experience with HEV-I in hematological patients is very limited.
Methods: We conducted a systematic review of case reports and observational studies dealing with HEV-I in hematological patients, searching PubMed from 1995 to 2019. All cases have been evaluated by two independent researchers.
Results: Our search revealed 93 cases with hematological malignancies and HEV-I. Mean age was 48.7yrs (4-81yrs), 32.6% were female. Mostly underlying disease were B-cell neoplasms (ALL(13), CLL(12), NHL(8), MM(6), MCL(5)) and myeloid leukemias (AML/APL(14)) from whom only 7% had not received chemotherapy before HEV-I. 81% had elevated liver enzymes as only sign of HEV-I, 5% showed GI- symptoms, 5% fever. Screening for non-HEV hepatitis was performed prior therapy initiation and remained negative in all cases. Transmission via transfusion was comprehensible in 10% of cases. In 32 patients therapy was started, monitoring HEV-I until start of therapy lasted 2.3m(1-12m), therapy-duration was 4.8m(1-12m) with a median dosage of 800mg/d ribavirin(rib). 60.6% cleared HEV successfully, 42.1% of whom were treated with either rib(n=22) or interferon(n=2). In untreated patients, HEV-I was cleared in 3.2m(1-5.7m). 12 patients relapsed or did not clear HEV after initiation of ribavirin, from whom nearly all had lymphoid malignancies(n=11). Level of liver enzymes did not predict relapse of HEV-I (ALT p=0.92;AST p=0.99) as well as viral copy number(p=0.10). 28 patients died, mostly due to malignant disease or infectious complications other then HEV. Death of only two patients can potentially attributed to HEV-I(one patient died on cirrhosis, the other one on liver and renal failure).
Conclusions: This is the largest sample collection of patients with HEV-I and hematological diseases. Even in this immunosuppressed cohort HEV-I can be self-limiting. Clearance of HEV-I lasted about 3.2m, confirming suggested time-to-treatment in current guidelines. Even though, treatment is common with a median dosage of 800mg/d rib. In our cohort 13% of patients relapsed, most of them suffering from lymphoid malignancies. Neither liver enzymes nor viral load predicted relapse of HEV-I.

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P941

AsperGenius® PCR combined with galactomannan determination and MucorGenius® PCR analysis used for detection of fungal DNA in clinical samples of immunocompromised patients

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Introduction: Invasive aspergillosis (IA) and mucormycosis are emerging and life-threatening infectious diseases in immunocompromised patients. As the diagnosis of both diseases is rarely based on positive culture in this group of patients, molecular analysis of clinical samples is crucial.
Methods: Two realtime PCR methods were evaluated in clinical samples of immunocompromised patients mainly suffering from hematological malignancies. The diagnostic performance of the AsperGenius® assay (PathoNostics BV, Maastricht, The Netherlands) for *Aspergillus* DNA was determined by investigating 90 BAL samples of 4 proven, 58 probable and 28 noIA patients. In altogether 53 BAL samples of 1 proven, 31 probable and 21 noIA patients the system was evaluated in combination with galactomannan (GM) analysis.
Furthermore 16 clinical samples of patients with various diagnostic results for invasive *Mucorales* infections (13 BALs (6 probable, 5 possible, 2 no invasive fungal infection (IFI)) and 3 biopsies (proven IFI)) were examined for *Mucorales* DNA using the MucorGenius® system (PathoNostics BV).
Results: The detected diagnostic values of the AsperGenius and GM assays in BAL samples are shown in Table 1.

Tab. 1. Diagnostic performance of AsperGenius and GM determination

Test/ combination	Sensitivity	Specificity	PPV	NPV	DOR (CI: 95%)
AsperGenius® diagnostic assay (n=90)	55% (34/62)	93% (26/28)	94% (34/36)	48% (26/54)	16 (3.4-72.4)
AsperGenius® diagnostic assay (n=53)	31% (10/32)	91% (19/21)	83% (10/12)	46% (19/41)	4.3 (0.9-22.2)
GM ≥0.5	50% (16/32)	100% (21/21)	100% (16/16)	57% (21/37)	43 (2.4-770.4)
AsperGenius® diagnostic assay OR GM ≥0.5	59% (19/32)	91% (19/21)	91% (19/21)	59% (19/32)	13.9 (2.8-70.1)
GM ≥1.0	38% (12/32)	100% (21/21)	100% (12/12)	51% (21/41)	26.2 (1.5-472.1)
AsperGenius® diagnostic assay OR GM ≥1.0	47% (15/32)	91% (19/21)	88% (15/17)	53% (19/36)	8.4 (1.7-42.1)

Table 1. Evaluation of the AsperGenius alone and in combination with GM in BAL samples. PPV/NPV, positive/negative predictive value; DOR, diagnostic odds ratio; CI, confidence interval. In 2 out of 3 proven and 2 out of 6 probable IFI samples *Mucorales* DNA was detected by the MucorGenius. No DNA was found in the remaining 5 possible and 2 noIFI samples.
Conclusions: Our analyses revealed a slight improvement in sensitivity of the AsperGenius PCR performance in BAL samples in combina-

tion with GM determination (if GM cut-off ≥0.5). Investigations of a larger sample size using the MucorGenius PCR are work in progress. In summary, we consider the early molecular detection of fungal DNA to be of high clinical relevance in patients with hematological malignancies.

Disclosure: No conflict of interest disclosed.

P942

Prophylaxis of chemotherapy-induced neutropenia and febrile neutropenia with long-acting G-CSF in patients treated with chemotherapy in Germany: results of the epidemiological cross-sectional survey "G-CSF Day"

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Introduction: Chemotherapy-induced neutropenia (CIN) and febrile neutropenia (FN) are major reasons of therapy modifications, morbidity and mortality in patients (pts) following chemotherapy (CTx). Clinical practice guidelines recommend prophylaxis of CIN/FN with granulocyte-colony stimulating factor (G-CSF); starting 24-72 hours after CTx to ensure efficacy. Correct use of G-CSF can be burdensome due to additional clinic visits or need to self-inject (which is error prone). The cross-sectional survey "G-CSF Day" examined real-world treatment patterns and resource utilization of long-acting (LA) G-CSF in CTx treated pts in clinical practice in Germany.
Methods: This retrospective, multicenter survey was performed on medical records of adult cancer pts who had received LA G-CSF following CTx within 6 weeks prior to documentation. The LimeSurvey software was used for online documentation by site personnel. Data were analyzed descriptively.
Results: From January to April 2018, 325 pts treated with LA G-CSF were included from 31 sites in Germany. Baseline characteristics: median age 64 years (range 28-90), 69.2% female, 38.8% breast cancer, 21.5% NHL, 17.5% lung cancer, 22.2% other cancer. LA G-CSF was administered in CTx cycles 1 (26.2%), 2 (20.6%), 3 (14.8) and >3 in 38.5%. The majority of pts (66.8%) did not receive LA G-CSF at the site. LA G-CSF use at site followed guideline in 52.8% and 37.0% did not (missing: 10.2%). Distance between patient's home and site was < 5 km (23.4%), 5-20 km (51.7%), 20-45 km (20.6%) and < 45 km (4.3 %). Interestingly, for 32.4% of pts receiving LA G-CSF at the site, the distance was < 5 km.
LA G-CSF was usually administered by a doctor´s assistant in 71.9%, a nurse in 21.9% or a doctor in 6.3% of sites (n=32 sites; 1 site included no pts). The mean time spent for LA G-CSF administration at the site was 14.4±11.4 minutes. In 59.4%, 21.9% and 18.8% of sites, information on self-injection was provided by a doctor´s assistant, a nurse or a doctor. To this end, they informed the patient verbally in 90.6%. 9.4% of sites used written information only.
Conclusions: Two thirds of pts did not receive LA G-CSF at the site and for these pts application details are unknown. Journey to and stay at the site are time-consuming and even at the site LA G-CSF is often not administered as per guidelines. Hence, there is a major gap in medical care which may impact on effectiveness. Improvement in LA G-CSF application and timing is still necessary.

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P943

Prospective evaluation of oral and dental hygiene in patients (pts) with chemotherapy-induced, long-term neutropenia

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Introduction: Recommendations about oral-dental hygiene in pts with neutropenia are based on limited data. Regular dental brushing is usually recommended despite the risk of associated bacteremia. We evaluated prospectively the oral-dental hygiene measures and associated complications in pts with neutropenia.
Methods: Pts with an expected duration of neutropenia >=10 days were enrolled and asked to record their daily oral-dental hygiene measures through a standardized diary. Pts were encouraged to brush their teeth 3x daily and perform oral rinses with disinfectants (PVP-iodine or chlorhexidine plus amphotericin B solution) for up to 6x daily. For all pts, detailed oral-dental examinations were scheduled prior, during and after neutropenia. Clinical and laboratory data were retrieved from medical records.
Results: Overall, 50 pts (median age: 53 years, range 21-78; male 33, female 17) were enrolled. Underlying conditions were acute leukemia 12, multiple myeloma 17, lymphoma 17, and testicular cancer 4. High-dose chemotherapy (HDC) with autologous hematopoietic stem cell transplantation (autoHSCT) was given to 38 pts. In 34 pts, the median duration of neutropenia was 9 days (range 3-64). The remaining 16 pts had insufficient neutrophil count data; in these pts, the median duration of leucopenia (< 1.5/nL) was 11 days (range 6-22). Systemic antibacterial prophylaxis was given to 48 pts (quinolone 41, cotrimoxazole 4, other 3). In 34 pts with available, completed diaries, the average number of daily tooth brushings during neutropenia was 1.65 (range 0.1-3.23). 33 pts performed regular oral rinsing (daily average 2.85, range 0.29-5.5). None of the pts required oro-surgical intervention (eg, tooth extraction). Mucositis was recorded in 37 pts (minor 4, moderate 14, severe 19). Of these, 31 had received HDCT with autoHSCT. 34 pts systemic therapies for a variety of infections (fever of unknown origin 14, bacteremia 7, other 13).
Conclusions: The adherence with our local oral-dental hygiene recommendations was poor in the majority of pts. Despite the frequent use of mechanical dental hygiene, we did not observe severe complications requiring oro-surgical interventions. Mucositis was associated with HDC/autoHSCT, which was expected. The data quality was limited with only 68% pts completing their diaries. App-based, electronic data capture is under development, which might improve compliance and data quality.

Disclosure: No conflict of interest disclosed.

P944

Administration of pegfilgrastim prophylaxis via pre-filled syringe (Neulasta®) or on-body injector (OBI): interim results on patient preference and health economics from the CONVENIENCE study

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Introduction: The effectiveness of granulocyte colony-stimulating factors (G-CSFs) like pegfilgrastim depends on the optimal timing of administration, recommended ≥24 h after chemotherapy (CTx) according to SmPC and guidelines. Return visits to the medical office for pegfilgrastim administration, however, may be burdensome and cause additional expenditure of time and costs for both, patients and medical staff. Logistic issues may result in suboptimal timing of pegfilgrastim administration, thus causing an increased risk for patients to develop severe or febrile neutropenia.
The pegfilgrastim On-body injector (OBI) is a small injector automatically delivering a subcutaneous pegfilgrastim dose 27 h later without need of return visit to the medical office. Thus, this alternative application form has the potential to optimize pegfilgrastim prophylaxis by improving administration time point as well as saving time and costs for patients and medical offices. The CONVENIENCE study aims to evaluate patient's preference and health economics for pegfilgrastim administration via OBI compared to injection via pre-filled syringe (PS).
Methods: In this randomized, multicenter, cross-over study (funded by AMGEN GmbH) 400 patients with early breast cancer receiving 2 or 3 weekly anthracycline/cyclophosphamide or 3 weekly taxane-based CTx or patients with non-Hodgkin lymphoma receiving 1st-line R-CHOP-14 or-21 will be enrolled at 50 sites in Germany. Patients are observed for 4 CTx cycles supported with pegfilgrastim OBI or PS in an alternating sequence with 1:1 randomization of the application form to start with. Patient's preference and influence of pegfilgrastim administration on daily life and cost factors will be evaluated using patient surveys.
Results: Here we present interim results on the first 200 patients randomized between 06/2018 and 01/2019. Data on patient characteristics (e.g. age, distance from medical office to patient's home), time interval between CTx and pegfilgrastim administration, patient's preference before and after study including reasons for decision and influence of the different application forms on daily life (daily routine, social life, time restriction) will be presented.
Conclusions: The pegfilgrastim OBI is a novel G-CSF application form aiming to optimize G-CSF prophylaxis in terms of effectiveness and convenience for patients and medical offices. The CONVENIENCE study evaluates the implementation of this new device in routine clinical practice.

Disclosure: Michael Metz: Advisory Role: AMGEN GmbH
Karin Potthoff: No conflict of interest disclosed.

P945

Nutrition therapy in oncological patients in outpatient setting - a retrospective analysis of oncology UnterEms

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Introduction: The nutritional status of a tumor patient influences not only the quality of life, but also the results of the therapy. Not only the starting point is decisive, but also the development during the therapy. Data on the use of nutrition therapy in outpatients are very sparse (S3-guideline of the German Society for Nutrition Therapy DGEM).
Methods: In the period from 09/15-05/19 all cancer patients of Oncology UnterEms with indication for chemotherapy for malnutrition were screened (weight loss of > 5% in the past three months). Patients with malnutrition were subjected to a standardized nutritional assessment (consumption protocol, MNA-LF, BIA, upper arm/ calf circumference measurement, hand strength measurement) and subsequently received as needed nutritional fortification (NF) or enteral nutrition (EN) or parenteral nutrition (PEN) according actual guidlines. All patients agreed to the evaluation of the data.
Results: 342 patients received nutrition therapy - 118 NF, 89 EN, 135 PEN (Table 1). Of the 342 patients, 4 refused further care after the initial nutritional consultation.

Tab. 1. Nutrition groups

NF	EN	PEN
118	89	135

Table 2 shows the distribution of PEN patients according to diagnoses, average duration of PEN therapy and termination at the request of patients. (Ø=mean value)

Tab. 2. Parenteral nutrition

	No. (%)	Mean value PEN duration (min.-max.) in days	Termination by patients (PEN duration in days)
Lung cancer	16 (12)	41 (5-149)	0
Breast cancer	11 (8)	65 (8-260)	2 (16; 30)
Esophageal-+/ Stomach cancer	36 (27)	101 (7-518)	3 (8; 28; 31)
Pancreas cancer	9 (7)	45 (1-140)	1 (18)
Colorectal cancer	22 (16)	66 (1-284)	0
Other	41 (30)	/	/

Discussion: Through a structured nutrition therapy it is possible to carry out an individual nutrition therapy with high acceptance in an ambulatory setting. The data of NF, EN, body fat mass development, development of phase angles as measures of cell density and membrane integrity (cell health) and the effectiveness of nutritional therapy will be presented at the congress.

Disclosure: No conflict of interest disclosed.

P946

Exploring the T-cell-receptor redirected CD3+ natural killer cell line NK92 for adoptive immunotherapy to acute myeloid leukemia

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Introduction: Adoptive cellular therapy (ACT) with chimeric antigen receptor (CAR) or T cell receptor (TCR) redirected T cells has revolutionized treatment of B cell lymphomas, and shows great promise for solid tumors. While CARs only detect fully expressed targets, TCRs also recognize peptides of tumor neoantigens. However, TCR-redirected ACT is currently limited by TCR-mispairing and restrained to autologous T cells with variable "fitness" depending on general condition and age of the patient. The FDA approved natural killer (NK) cell line NK92 elicits lytic activity comparable to T cells and does not cause GVH-disease. Since NK cell redirection is currently limited to CARs, NK92 cells engineered to express a CD3/TCR complex might evolve as an attractive, standardized source for off-the-shelf ACT. Thus, in this study we examined the antileukemic immunity of NK92 CD3+/CD3+CD8+variants redirected to acute myeloid leukemia (AML) by expression of different AML-reactive TCRs.
Methods: NK92CD3+cells (provided by Dr. C. Wölfel, III. Dept. of Med.) were further engineered to express human CD8. After viral gene transfer of 3 different optimized TCRs obtained from AML-specific CD8+CTL clones and enrichment >90% of NK92CD3+TCR+ and NK92CD3+CD8+TCR+ cells (referred to as NK92TCR+) were obtained. Expression profiling *of* checkpoint molecules (e.g. CD80/86, PD1/PDL1, NKG2A, TIM3, TIGIT) and HLA-E was performed by FACS. IFN-γ release and cytotoxicity of NK92TCR+ to primary AML blasts was tested *in vitro* and *in vivo* using a patient-derived AML-xenograft (PDX) NSG mouse model.
Results: Upon coculture with different primary AML samples and corresponding EBV-LCL blasts used as controls NK92TCR+ cells elicited strong TCR dependent IFN-γ release and cytolytic activity to AML samples. CD8 coexpression slightly increased reactivity as measured by IFN-γ release. Interestingly, as NK92TCR+-mediated anti leukemic responses revealed to be inhibited to some AML samples we found high expression of HLA-E on these AML blasts and of NGK2A on NK92TCR+ cells. However, blocking experiments did not ameliorate reactivity, and further studies are ongoing to address this point. Moreover, first adoptive transfer studies of NK92TCR+ cells into a NSG-AML PDX model indicated tumor reduction, and more studies are in progress.
Conclusions: NK92TCR+cells successfully elicit TCR-mediated antitumor immunity to AML. TCR-redirected NK92 cells might thus represent a promising tool for 'off-the-shelf' ACT.

Disclosure: No conflict of interest disclosed.

Posterdiskussion

Der spezielle Fall

P947

Checkpoint inhibition and re-challenging in thymoma: report of a 60-year old female patient with intensively treated advanced thymoma

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Introduction: Thymic epithelial tumors are rare neoplasms of the anterior mediastinum. Treatment recommendations consist of surgery, radiation, and chemotherapy, particularly for advanced stages.

Material and methods: Report on a 60-year old female patient suffering from a locally advanced thymoma WHO B2 with high proliferation rate (Ki-67: 80%). Condition dependent dyspnea was the main symptom. Infiltrating left lung and mediastinum precluded primary resection.
Results: She received 6 neo-adjuvant cycles of ADOC regimen. After completion of chemotherapy, a partial remission (PR) was achieved and surgery was planned. Unfortunately, within 6 weeks progression of at least 30% with a subtotal compression of the left pulmonary arteria and the left atrium was observed. Re-biopsy showed a lymphocyte rich thymoma B1/B2 (9:1). The high amount of lymphocytes was interpreted as a sign of resistance to chemotherapy. Therefore and based on a positive octreotide PET scan treatment with octreotide LAR plus prednisone was initiated. After 3 months, no response was seen necessitating 3rd-line treatment. Due to high PD-L1-expression off-label treatment with Nivolmab 3 mg/kg KG was started. Already after the first infusion patient suffered from a severe immune related hyperthyreodism requiring treatment (CTCAE grade 3). Nevertheless, nivolumab could be continued leading to a 2nd PR with >30% reduction after 6 applications. After a total of 11 courses a tumor progression was observed. Subsequent 6 cycles carboplatin/paclitaxel resulted in 3rd PR lasting 4 months. Since at this time NGS based targeted resequencing revealed a *KIT*^{M541L} mutation, we initiated imatinib treatment that lasted in stable disease for 6 months. In March 2019 again a progress was measured and clinical symptoms as at the beginning of the disease in 2016. Considering high-level PD-L1 expression and data on chemotherapy sensitizing for immunotherapy, encouraging therapeutic opportunity for checkpoint inhibition re-challenging was suggested and off-label therapy with PD-L1 inhibitor atezolizumab (1200 mg abs. q3w) started. A remarkable improvement of clinical symptoms was observed after first infusion. Next staging examination is planned for June 2019.
Conclusion: Especially advanced stages therapy of thymic tumors remains challenging. Checkpoint inhibition seems to be a therapeutic option. Further studies on immune oncologic treatment in this rare entity are warranted.

Disclosure: No conflict of interest disclosed.

P948

A rare case of BCR-ABL1 positive AML - Driver mutation as a bystander

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Introduction: The 2016 revision of the WHO classification of myeloid neoplasms and acute leukemia was the first to recognize BCR-ABL1 positive AML. However, it remains a provisional entity, due to its rarity and difficulties in distinguishing it from CML in blast crisis.
Here we present a case of BCR-ABL1 positive AML, which not only demonstrates the distinctive features of this disease, but also illustrates that in contrast to CML the BCR-ABL1 mutation acts as a bystander rather than a driver mutation.
Case: In January 2019, a 64-year-old woman presented to our emergency department with sternal pain. Initial diagnostics excluded a cardiovascular or pulmonary disorder but demonstrated leukocytosis and presence of myeloid precursor cells including blasts. Workup for CML was initiated. In the meantime, the patient deteriorated rapidly, while WBC and LDH doubled.
Bone marrow histology showed focal accumulation of blasts consistent with CML blast phase or AML. Referral pathological analysis suggested AML evolved from a prior CML. Following clinicopathological features together with the clinical course of rapid deterioration however prompted us to prefer a de novo BCR-ABL1 positive AML diagnosis: lack of splenomegaly, lack of basophilia, rapidly progressive anemia, presence of complex-aberrant karyotype, limited BCR-ABL1 expression (94%). The patient's prior history was also not suggestive for CML.
Consequentially we initiated induction therapy with CPX-351, which was well tolerated expect for infectious complications. Upon hematological regeneration, the peripheral blood again exhibited a continuous left-shift

consistent with pretherapeutic results. Bone marrow biopsy revealed a marked discrepancy between cytological and molecular response: Microscopy showed refractory disease without CML characteristics, i.e. a nearly complete replacement of hematopoiesis by blasts. BCR-ABL1 transcripts however, were reduced by 2/3 (to 37.2%). These findings supported our initial assessment that BCR-ABL1 was indeed a bystander rather than a driver mutation. Thus, BCR-ABL1 targeted therapy was not attempted. The patient was ultimately referred to palliative care and died soon after.
Conclusion: This cases demonstrates that while BCR-ABL1 might determine the phenotype, it is not chiefly responsible for proliferation in BCR-ABL1 positive AML. More research is needed to elucidate the optimal approach to diagnosis and therapy sequence.

Disclosure: No conflict of interest disclosed.

P949

Extramedullary findings of clonal hematopoiesis of indeterminate potential (CHIP) in an otherwise healthy patient

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Introduction: Extramedullary hematopoesis (EH) is defined as hematopoesis (HP) occurring in organs or body parts outside of the bone marrow. EH is a rare condition most commonly seen in therapy naïve patients with severe thalassaemia (TH) or primary myelofibrosis (PMF). CHIP is defined as acquisition of malignancy related mutations in HP-cells without the outbreak of a defined hematologic disease. In population studies it is associated with an increased risk of a subsequent myeloid or lymphoid disease. Here we present an otherwise healthy patient with EH with CHIP-like features.
Patient: The 67-years old caucasian male patient presented with no history of hematological diseases. He had previous history of arterial hypertonia, hyperuricemia and nicotine addiction with 3-5 cigarettes per day.
The chest X-ray showed multiple mediastinal opacities (Figure 1) and CT-scan showed a right paravertebral mass with inhomogeneous internal structure and a diameter of 5 cm as well as a bulky mass left 12x4.8x4.7cm. The complete blood cell counts and lab chemistry including haemoglobin electrophoresis were normal. The histology of a surgically obtained sample of the thoracic mass showed adipose tissue with presence of normal HP without myelodysplastic changes or excess of blasts. All three cell lines were present and regularly differentiated, showing a typical CD-pattern (MPO,CD71,CD42b,CD71,CD117,CD3,CD20,CD23). Next generation sequencing analysis revealed an *ASXL1* mutation (c.1774C>T; p.Q592*, VAF 30%, stop gain) implicating extramedullary clonal hematopoiesis while mutation analysis for *BRAF*,*CALR*,*CBL*,*CSF3R*,*DNMT3A*,*EZH2*,-*FLT3*,*IDH1/2*,IDH2,*JAK2*,*KIT*,*KRAS*,*NPM1*,*NRAS*,*RUNX1*,*SETBP1SRSF2*,*TET2*,*TP 53*,*U2AF1*,*MPL* were negative. Bone marrow biopsy showed regular cellularity with all three cell lines without signs of fibrosis. The PCR showed negativity for *JAK2* V617F, *CALR* or *MPL*.
The patient is without signs of hematological disease one year after the diagnosis of EH.
Discussion: In our research we found sporadic cases of EH, mostly in patients with TH or PMF. Our patient showed no signs of hematologic disease. In case of progression surgery is a potential treatment possibility.

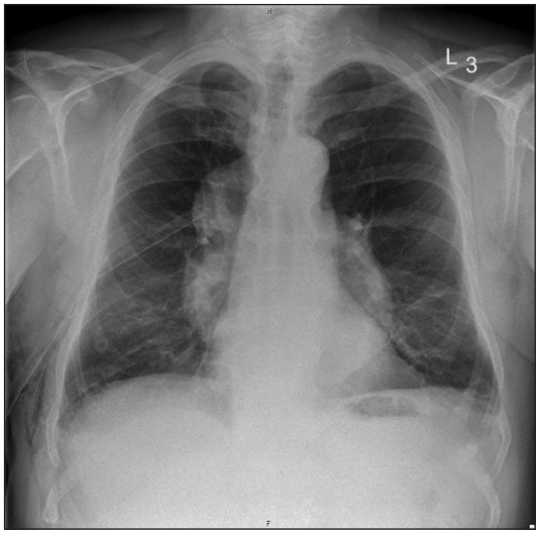

Fig. 1.

Disclosure: No conflict of interest disclosed.

P950

Simultaneous development of characteristic agranulocytosis leads to unmasking of fulminant metamizole-induced hepatotoxicity

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Introduction: Although introduced to the market nearly one hundred years ago, metamizole still is extensively used due to its favorable analgesic and spasmolytic properties. While agranulocytosis is an, albeit rare, well-known side effect of metamizole, liver failure is even more seldom and therefore often remains unconsidered. Here, we present a unique case where simultaneous development of characteristic agranulocytosis led to unmasking of fulminant metamizole-induced hepatotoxicity.
Case report: A 22-year-old female patient presented with headache, nausea, vomiting and subsequent weight loss over the last weeks. She reported about uneventful journeys to Australia eleven months ago and to Hong Kong and Vietnam seven months ago and denied any unusual contact to animals or lentic water. Except from her oral contraception, she explicitly denied intake of any other medication. Her physical exam revealed jaundice as well as maculopapular rash of both arms and lower legs. Ultrasound was unremarkable apart from moderate hepatomegaly. Laboratory tests confirmed liver failure and furthermore showed an isolated leukopenia (granulopenia, as a matter of fact) while extensive microbiological and virological tests remained negative. Ultrasound-guided needle biopsy of the liver revealed picture of drug- or substance-induced acute allergic hepatitis. Due to further decrease of leukocytes we furthermore performed a bone marrow biopsy showing the classical picture of metamizole-induced agranulocytosis. Immediately performed in-depth interview of the patient indeed revealed that she had taken a total of 10 g metamizole over the two months before due to headache. We could therefore confirm the diagnosis of metamizole-induced myelo- and hepatotoxicity with concomitant rash (which is also characteristic for metamizole). Subsequently initiated stim-

ulation with G-CSF led to full recovery of leukocytes and application of steroids to rapid decrease of liver parameters. Follow-up after four months showed the patient in good condition and liver function tests as well as blood count were normal.

Conclusions: Although metamizole-induced hepatotoxicity is a very rare condition, it should be kept in mind due to its sometimes life-threatening course. Diagnosis can be challenging especially if anamnesis and written record are without any hints for prior intake of metamizole. In our case, pathologic demonstration of characteristic metamizole-induced agranulocytosis led to proper diagnosis.

Disclosure: No conflict of interest disclosed.

P951

Immune thrombocytopenia after therapy with cladribine in a patient with advanced systemic mastocytosis

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Introduction: In patients with aggressive systemic mastocytosis (ASM) cladribine is often used as a second line off-label therapy, especially after failure of midostaurin. We report on a patient with ASM treated with cladribine who developed an immune thrombocytopenia (ITP) during the 5th cycle, a complication rarely described in this setting.

Case report: A 70 year old female patient suffered from an untreated ASM with ascites and massive weight loss when first referred to our center in July 2017. Despite a 15% mast cell bone marrow infiltration she did not show any signs of cytopenia at that time. She was treated with midostaurin; however, despite broad antiemetic support she experienced severe nausea and vomiting, leading to a switch of therapy to cladribine [0,14mg/kg body weight (bw) for 5d] in June 2018. She tolerated the treatment very well and showed rapid clinical improvement. On day 4 of cycle 5 her platelets unexpectedly dropped to 11.000/µl, hence therapy was stopped immediately. Within the following days, platelet counts decreased further to 1.000/µl and she developed multiple ecchymoses and petechiae. Because of suspected ITP therapy with prednisone (1mg/kg bw) was started at once. Laboratory results provided evidence of antibodies type IgG against platelet membrane glycoprotein IIb/IIIa, demonstrating ITP most likely due to therapy with cladribine. Following no significant increase in platelet counts after one week of prednisone, we switched to dexamethasone (0,6mg/kg bw for 4d). Additionally she received immunoglobulins (0,5mg/kg bw) for 4 days. Platelets went up quickly to 42.000/µl (Fig.1), she was discharged and therapy with dexamethasone was continued for six cycles in three week intervals. The platelets increased to a normal range and remained stable until now.

Conclusions: ITP after therapy with cladribine is a rarely described complication, mostly known in patients with CLL. A possible mechanism could be the inhibitory effect on regulatory T cells, which are important for the maintenance of peripheral tolerance. ITP after cladribine is a possible side effect that should be kept in mind, especially as lethal bleeding complications may occur.

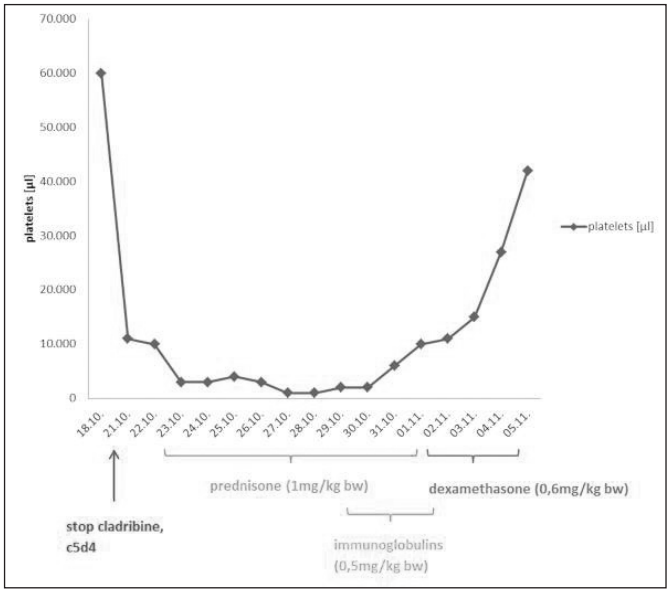

Fig. 1. Development platelets and therapeutic steps

Disclosure: No conflict of interest disclosed.

P952

Mantle cell lymphoma and meningeal relapse: intrathecal chemotherapy and systemic treatment

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Introduction: Despite several first-line treatment options, patients with mantle cell lymphoma often suffer from relapse preferentially localised in lymphnodes, bone marrow or intestinal Infiltration. Meningeal relapse is rarely documented; treatment options may include high-dose methotrexate, spinal irradiation or allogeneic stem cell transplantation. We present combined systemic and intrathecal cytotoxic therapy in a 77 year old male patient with second relapse of mantle cell lymphoma.

Methods: The patient came to admission to our emergency department after suicide attack he had committed due to abdominal pain and paraplegia of his legs. MRI showed intraspinal lymphoma manifestation next to thoracal vertebra 11 and 12 with myelon infiltration and spinal compression. Diagnosis of mantle cell lymphoma had been made 22 months, first cutaneous relapse 5 months earlier, respectively. The patient had been treated with bendamustine and rituximab elsewhere.

After both psychiatric and surgical intervention we started therapy with temsirolimus, rituximab and steroids combined with intrathecal triple therapy (MTX, cytosinarabinoside, dexamethasone; 8 i.th. applications; treatment twice a week Nov 30th, 2018 until Febr 15th, 2019). Due to bone marrow toxicity (granulocytopenia IV, thrombocytopenia IV) i.th. applications could not be offered every second day as we had planned initially, but dosage of temsirolimus had to be adjusted starting with 120 mg iv to 75 mg iv, 6 courses.

Results: The patient received a very good partial remission, flow cytometry of cerebrospinal fluid showed no more residual lymphoma cells. Paraplegia dissolved, the patient improved by pain and paresis. Therefore, we switched to ibrutinib 280 mg daily po and local irradiation of the former lymphoma site (40 Gy, April 8, 2019 until May 8, 2019). MRI findings are enclosed.

Conclusions: Even in elderly disabled patients intrathecal combined with systemic chemotherapy seems to be a helpful alternative compared to high dose methotrexate, ablative regimens or total spinal axis irradiation. As spinal location of relapse is rare, only a few data could be found in literature, and registry data may be useful.

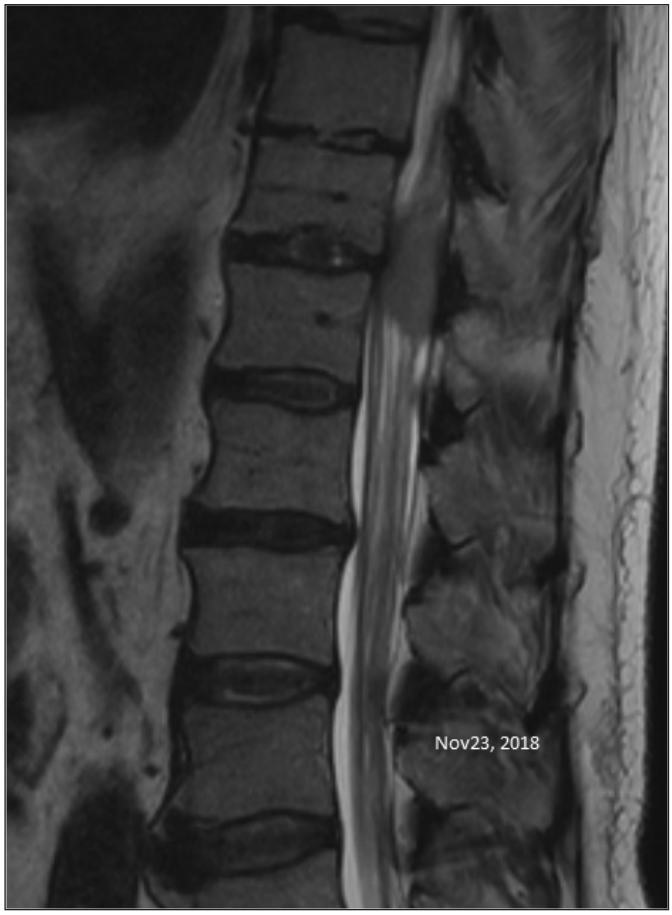

Fig. 1. MRI at diagnosis

Disclosure: No conflict of interest disclosed.

P953

Reactive hemophagocytosis syndrome in a patient with fever, night sweats, shivering and concomitant pancytopenia and signs of inflammation

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Introduction: Reactive hemophagocytosis syndrome or hemophagocytic lymphohistiocytosis (HLH) is a potentially lethal syndrome of excessive inflammation and tissue destruction caused by a deregulated immune system. Activated macrophages and lymphocytes lead to increased inflammatory cytokines with systemic inflammatory symptoms.

Diagnosis of HLH is made by the 2004 published diagnostic criteria (HLH-2004 trial): Heterozygosity of one of determined genes or 5 of the following 8 findings:

fever ≥38.5°C, splenomegaly, cytopenia, hypertriglyceridemia, hemophagocytosis in bone marrow, spleen, lymph node or liver, low or absent NK cell activity, ferritin >500ng/mL and elevated soluble IL2 receptor.

In our case, a 65-year-old male presented with deterioration of his general condition, fever, night sweats, weight loss and shivering starting a few weeks ago. Blood tests showed pancytopenia, elevated CRP, LDH and increased liver enzymes. Ferritin was up to 10'000mg/L and the soluble IL 2 receptor 6900U/ml. Triglyceride-levels were lightly elevated (2.9mol/l).

Methods: Clinical examination showed no evidence for infection except for a urinary tract infection caused by E. coli. CT scan of brain and whole body showed only hepatosplenomegaly without any lesions or lymph node enlargement.

Apart from an undergone hepatitis C infection, no other underlying viral or bacterial infection, rheumatologic, autoimmune disorder or venereal disease could be detected.

Results: Activated bone marrow with no signs of infiltration due to malignant lymphoma was found. PET-CT was showing diffuse, massive FDG-uptake in liver, spleen and in not enlarged celiac, mediastinal and cervical lymph nodes. Liver and bone marrow biopsy showed no evidence of hemophagocytosis, but infiltration with Sternberg-Reed-cells leading to diagnosis of a classical Hodgkin's disease.

Conclusions: In conclusion, our patient presented with a HLH triggered by a classical Hodgkin Lymphoma stage IV B (Ann Arbor), positive for EBV.

A compounding factor for the diagnosis was the fact that neither solid tumour nor enlarged lymph nodes were seen in the CT scan. Hemophagocytosis could be detected neither in liver nor bone marrow. Genetic analysis was not performed. But showing 6 out of 8 criteria for HLH L, we presume that our patient was affected by HLH triggered by an EBV-positive Hodgkin Lymphoma.

Disclosure: No conflict of interest disclosed.

P954

Amyloidoma - a rare cause of gastrointestinal bleeding

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Background: Gastrointestinal bleeding is a common clinical symptom and stomach cancer among it's common causes. In patients with anticoagulation this may even be the first symptom of a yet undetected malignancy. However, even with a macroscopically typical presentation unexpected diagnoses may be encountered. Here we present the case of a gastric amyloidoma and discuss its clinical course and treatment options with particular respect to anticoagulation.

Case-report: An 81-year-old male was admitted for GI bleeding. He had a vitamin K antagonist for atrial fibrillation. His Hgb was 5.6 mmol/l, INR 3.1 Endoscopy revealed a 4 cm tumor in the gastric fundus which bled significantly after biopsy. However, the histologic examination found no malignant cells but amyloid. Bone marrow biopsy: 10% plasma cells, no amyloid, serum: monoclonal IgG lambda, no lytic bone lesions, no rectal amyloid. After bleeding had stopped the patient declined surgery and was discharged home. In 10/18 he was readmitted but at that time the

gastric lesion was significantly smaller (2.5 cm) with intact mucosa and no signs of bleeding. The decision was made to continue with watch&wait. In 11/18, the patient developed a third bleed and the stomach was completely removed. Pathology showed multiple erosions and amyloid deposits throughout the entire gastric mucosa.

Conclusion: Amyloidosis is characterized by extracellular accumulation of fibrillar proteins in organs and tissues. GI involvement is not uncommon but localized, tumor-like amyloidal deposits (amyloidoma) is an unusual and rare manifestation. Clinical symptoms of GI amyloidomas stretch from asymptomatic to gastric outlet obstruction, perforation, and severe bleeding. Because of its rarity there are no specific therapeutic strategy for localized gastric amyloidosis. In asymptomatic or mildly symptomatic patients watch and wait may be an option. In our patient need for anticoagulation was a strong argument for surgical removal of the stomach but subsequent shrinking drove the patient to favor a watch&wait strategy until bleeding recurred and gastrectomy could not be postponed any more. We do not argue that every patient with amyloidoma of the GI tract and need of anticoagulation should undergo surgery but rather suggest an individualized approach based on both severity of bleeding, associated other symptoms and individual capacity of the patient to undergo this surgery and cope with its consequences.

Disclosure: No conflict of interest disclosed.

P955

Hodgkin lymphoma arising in a patient with chronic lymphocytic leukemia (Richter syndrome)

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Introduction: Richter syndrome (RS) defines the development of an aggressive lymphoma in the setting of chronic lymphocytic leukemia Two distinct variants of RS are recognized, diffuse large B-cell lymphoma and Hodgkin lymphoma

Methods: We report about a 56-year-old patient who was diagnosed by B-CLL in October 2014. Stage II after Rai, B after Binet.Immunophenotypically: CD5, CD23 positive, ZAP 70 negative.Cytogenetics: Trisomy 12. IgVH status: mutated

He had palpable cervical lymphadenopathy. Clinically there were no B symptoms and the ECOG status was 0.There was also no haemopoietic insufficiency.We chose the watch and wait regimen.

In 2016, then with further progress with multiple lymphadenopathy and splenomegaly the indication for therapy was done. He received 6 cycles according to the R-FC protocol reaching partial remission. In Progress a year later he received Ibrutinib with no response , even with Obinutzumab/Chlorambucil we saw improvement of abdominal lymphoma but progress cervical. We decided on lymph node biopsy.

Results: Histology of lymph node biopsy showed the diagnosis of an EBV negative classical Hodgkin While a significant CD30 staining of the blasts, the Hodgkin/Reed-Sternberg cells are CD20 negative. In a low percentage of 10-15% small lymphocytes, which correspond to the CLL .

He was treated with 4 cycle of the ABVD regimen with regression of lymph node cervical. At the end of therapy, atypical pneumonia and bleomycin induced pulmonary fibrosis were complicating the course of therapy. PET / CT still showed PET positive lymphnode at the neck, so we aim for a Radiation.

Conclusion: Hodgkin like Richter Syndrom is very rare. Only 0.4-0.7% of CLL patient transformed into a M. Hodgkin.Prognostically is Hodgkin transformation better than DLBCL, but worse than de novo Hodgkin. There exists two types with different pattern of Richter transformation of CLL. Our Patient showed type II with typical CHL morphology showing HRS cells segregated from CLL.

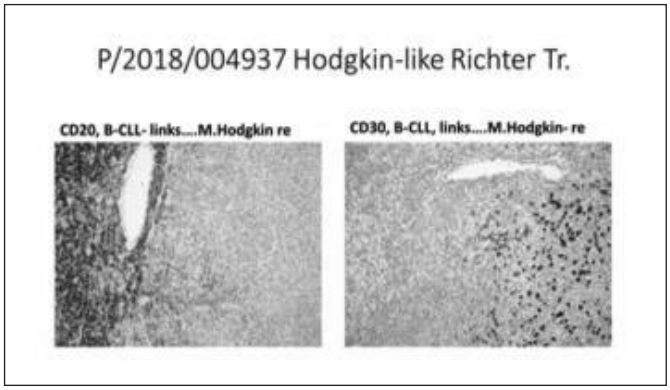

Fig. 1. CLL/HL

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Hartmut Merz: No conflict of interest disclosed.

P956

Case report: multiple intestinal metastases at time of primary diagnose of a Cutaneous Melanoma

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A 58 year old man turned into the emergency room because of pain and increasing circumference of the belly. By sonography an omental cake and ascites were diagnosed. He neither reported weight loss, dysphagia, nausea or vomiting nor irregularities of bowel movement. In the physical examination the only clinical finding was a melanoma-like lesion on his back. We caused further imaging diagnostics which detected advanced peritoneal tumour masses, two pulmonary metastases and cerebral metastases, but no primarius. We decided to complete the diagnostis by endoscopy of stomach and bowel, where multiple small black spots were found. A polyp of the colon was resected. Furthermore a needle biopsy of the omental cake was cased. The histopathological examination showed manifestations of a cutaneous melanoma in the omental cake as well es in the colon adenoma. Our literatur investigation revealed, that to 60% of patients with melanoma are found to have intestinal metastases at autopsy. Frequent sites of invasion are the small bowel, the colon and anorectum.

Disclosure: No conflict of interest disclosed.

Posterdiskussion

Supportive Angebote

P957

Supportive care needs of advanced cancer patients entering specialist palliative care

Oechsle K.[1], *Schulz H.*[2], *Goldbach S.*[3], *Hollburg W.*[3], *Rommel A.*[3], *Müller M.*[4], *Kirsch D.*[5], *Kopplin-Förtsch K.*[6], *Messerer J.*[1], *Schulz-Kindermann F.*[2], *Bokemeyer C.*[1], *Ullrich A.*[1]

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Introduction: Addressing supportive care needs is a core component of specialist palliative care (SPC). Early assessment enables SPC teams to

prevent or at least reduce problems by allocation of resources to problems most urgent. This multicenter study aimed to investigate the problems and unmet needs for professional support among cancer patients (pts) at initiation of in- and outpatient palliative care.
Methods: Within 12 months, 386 cancer pts (52% male, median age 71, 67% outpatient SPC) entering an urban SPC network consecutively completed the "Problems and Needs in Palliative Care questionnaire - short version" (PNPC-sv). We used seven domains of the PNPC-sv, addressing 22 problems (physical symptoms omitted). Univariate statistics (Chi-square tests) were used to investigate the relationship of gender, age (median split: < 71 vs. ≥ 71) and SPC setting with specific problems.
Results: Pts experienced in mean 11.6 problems (SD 4.7; range, 0-22) and reported need for more professional support for 5.4 problems (SD 5.8; range, 0-21). The number of problems was strongly correlated with the number of need for more professional support (Pearson's r=.756, p< .001). Male pts experienced more problems in finding someone to talk to and showing emotions, but less in giving tasks out of hands (p=0.002 to 0.044). Younger pts reported less problems in body care/dressing/toileting, but more problems in experiencing loss of control as well as various social, psychological and financial issues (p< 0.001 to 0.036). With regard to SPC setting, outpatients experienced more problems in daily activities, their relationship to life companions, talking about the disease with life companions, acceptance of the disease, loss of income and insufficient information (p=0.007 to 0.040). The proportion of pts requiring more professional support for at least 1 problem was 55% for daily activities, 53% for autonomy, 42% for spiritual issues, 40% for psychological issues, 36% for social issues, 31% for need of information and 20% for financial problems.
Conclusions: Many pts experienced problems and unmet needs of which oncologists may partly be unaware. Compared to the extent of problems, more professional support was required less often, indicating the relevancy of assessing both aspects. Fewer differences than expected were found for gender, but findings indicate that age- and setting-specific assessment might be useful for tailoring care.

Disclosure: No conflict of interest disclosed.

P958

Unlimited health care? - factors for successful intercultural access to hospice and palliative care from a provider's perspective

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Introduction: An ever-increasing number of migrants adds growing relevance to the subject of intercultural competence in public health. Accordingly, those involved in hospice and palliative care strive to improve intercultural competence in order to reach all patient groups. However, the lack of research makes it difficult to identify successful strategies for advancing intercultural competence.
Methods: Qualitative research design, 4 focus groups comprising hospice and palliative care providers in 4 German cities, 5 subject-specific individual interviews, qualitative content analysis (Mayring method) to identify factors hindering or helping successful intercultural competence-building.
Results: Research revealed that care providers do not share a uniform understanding of intercultural competence. Predominantly, it implies personal and institutional openness, which exceeds religious and cultural aspects. Helpful factors included the guiding idea of culture-sensitive openness represented throughout a given facility and exemplified, among other things, by the composition of teams. Networks and cooperations were perceived as particularly helpful. Referring to external offers (e.g. translating and interpreting services) and gatekeepers into specific (regional) communities will facilitate working with people from a migration background and may overcome access barriers.
Hindering factors identified by care providers included a lack of cultural sensitivity on the provider side, and a lack of knowledge about availability of care, proper procedures as well as the meaning of palliative and hospice care on the recipient side.
Conclusions: There is consensus that striving for intercultural competence is both relevant and required. Persons with a migration background would benefit from a clearly targeted publicity campaign addressing the lack of information about available care. In addition, teaching culture-sensitive skills ought to be integrated into the education and training of care providers from the earliest stages.
Promoting the establishment, expansion and use of (regional) networks may facilitate providing care for migrants. Further research into the factors of intercultural competence ought to challenge the concept of "culture". The migration background is just one, even though an important one, in the care providers´ point of view.

Disclosure: No conflict of interest disclosed.

P959

Data analysis of the routine documentation from 6818 patients in the specialized outpatients palliative care in North Rhine regarding the cancer diagnosis

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Introduction: In recent times, German legislation has given terminally ill patients the right to receive a specialized outpatient palliativ care (SAPV), a multi-professional palliative care model which is aimed at prevention of hospital admission and enabling patients to die at home despite severe symptoms and a high need for care. Complex symptom clusters and special supply requirement have been designated as a condition for access. This raises the question which diagnoses characterize this patients, besides other criterias.
Methods: VSTN e.V. represents the majority of SAPV teams in the North Rhine region. These teams are responsible for over 5 million inhabitants. Data were collected during daily care in 2017 by 14 Teams from 6816 treated patients. We present first preliminary data on malignant diagnoses in SAPV.
Results: On average, the multimorbid patients in this outpatient program had 4.7 main diagnoses. Only 17% had only one main diagnosis. This was a neoplasia in 3/4 of those cases. 77.6 % of all patients had a neoplasia according ICD 10 Chapter II as main diagnosis and 22.4 % not. Although 5.1 % had a neoplasia, this was not classified as main diagnosis. The most frequent diagnoses were lung, colorectal, breast, pancreas and prostate cancer. A comparison with the cancer deaths from the annual report 2017 of the North Rhine-Westphalia cancer registry shows that carcinomas of the lung, breast and pancreas and in particular prostate carcinoma are overrepresented, while the hematological neoplasias multiple myeloma, NHL and leukaemias are clearly underrepresented in SAPV treatment.

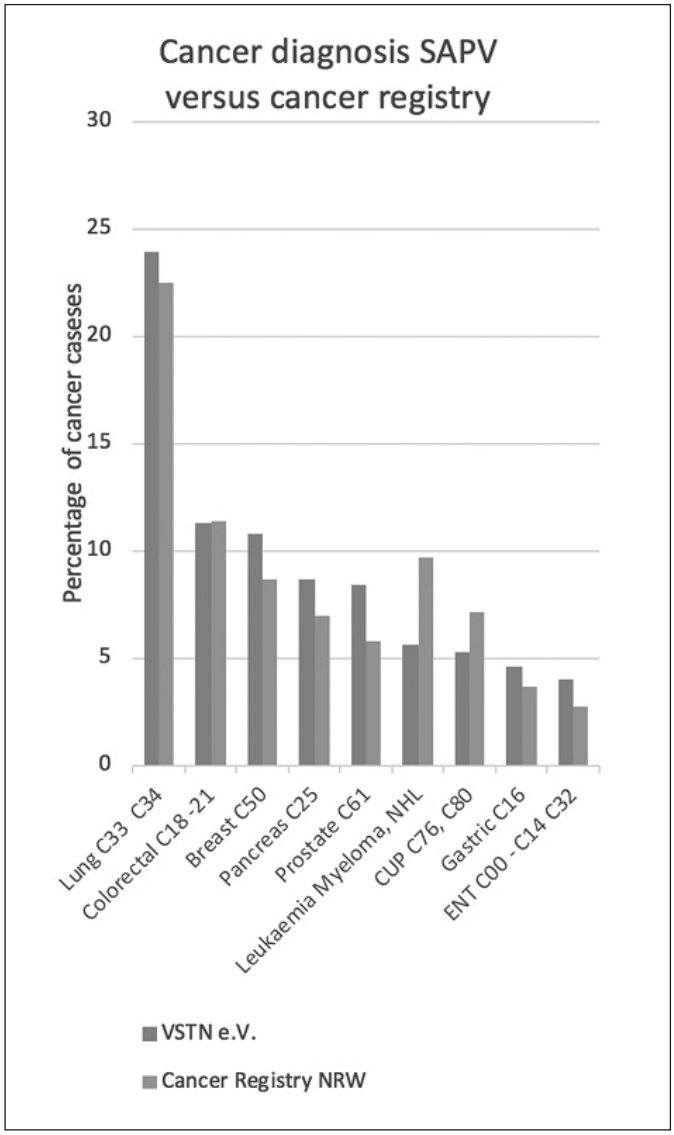

Fig. 1. Cancer diagnosis from routine documentation in SAPV

Conclusions: Also the feared heavy burden of symptoms of e.g. dyspnoea in bronchial carcinoma and exulcerating wounds in breast carcinoma etc. can be sufficiently controlled in the outpatient situation of SAPV, so that SAPV is administered overproportionally in these diagnoses. Surprisingly patients with prostate cancer are also treated disproportionately often in SAPV, while haematological systemic diseases are clearly underrepresented. Further investigations are necessary to clarify the background.

Disclosure: No conflict of interest disclosed.

P960

The understanding of death in relation to cultural and religious differences of refugees seeking asylum in Germany

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Introduction: In Germany the number of people seeking refuge since 2015 exceeded a million characterized by different ages, both sexes and various geographic origins. Our aim was to explore different points concerning the general view on death, the anticipation towards the own death, expected rituals while dying and for accompanying parties among asylum seekers in Germany.
Methods: A cross-sectional study was enrolled from May 2016 to May 2017 in Germany with 193 participants. Participants were asked 50 objective questions from a multilingual questionnaire (Arabic, English and German) designed solely for this study including several personal questions as well as descriptive questions. The interviews took place in Rostock and Bremerhaven, Germany by an interviewing party of two Rostock based medical students (native Arabic and German and highly fluent English speaking).
Results: Of the 193 participants 181 refugees (94 %) had made experiences with death and dying in various situations. Of all participants 185 belonged to the Islam, of which 92 (50 %) believed that death was the beginning of a new life. The way of dealing with death is heterogeneous. The majority of refugees has had thoughts about their own dying (128; 66 %), 105 could imagine dying in hospital. Of all 101(52,3 %) would accept professional help in process of dying. 135 (70 %) of all have rituals that would be important to them in the dying process.
Conclusions: Refugees have a heterogeneous imagination of what happens after death. The expectations about accompanying the process of dying in a professional manner are values individually. Certain rituals appear to be important to refugees in dying process. As professionals we will be confronted with different needs accompanying refugees in palliative and hospice care.

Disclosure: No conflict of interest disclosed.

P961

Effective symptom relief through specialized palliative care intervention in patients with advanced renal cell carcinoma: comprehensive measurement using the palliative care base assessment

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Introduction: Due to modern therapies, survival in advanced renal cell carcinoma (RCC) has been significantly prolonged. Nevertheless, patients with advanced disease often suffer from severe symptoms. There is increasing evidence that the early integration of palliative care into anti-cancer treatment may improve quality of life and even prolong survival[1]. Therefore, the WHO, as well as ASCO and NCCN recommend offering palliative care not only in end stage disease, but also to patients with complex symptoms independent of the entity. To our knowledge, there is no published data on the role of palliative care in RCC patients.
Methods: We performed a retrospective analysis of patients with symptomatic advanced RCC admitted to the palliative care unit at our institution between 2011 and 2017. We assessed the symptom burden at admission, throughout the palliative care intervention, and upon discharge. The assessment consisted of the palliative care base assessment (PBA) (including the MIDOS symptom score, the distress thermometer, and standardized numeric symptom rating scales) as well as daily documentation of relevant symptoms.

Results: Overall, we evaluated 110 hospitalizations of 58 RCC patients. Main causes for admission were pain and dyspnea, the most frequent patient reported symptoms were weakness, fatigue/exhaustion and dyspnea. Palliative care interventions led to a significant reduction of the median MIDOS symptom score (13 to 9) and the median numeric pain rating scale in our patient population (1.5 to 0). Additionally, there was a significant reduction in ratings of the distress thermometer (6 to 3.5), and the performance status improved from a median ECOG of 3 to 2. The majority of patients (69%) could be discharged home.
Conclusions: Our analysis shows that the integration of specialized palliative care interventions is effective in patients with advanced RCC and measurably reduced the symptom burden in our patient population. Palliative care does not equate end-of-life care, but should rather be integrated early and throughout the disease course to alleviate symptom burden at any time point.

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[1] Jennifer S. Temel u. a., „Early Palliative Care for Patients with Metastatic Non-Small-Cell Lung Cancer", *The New England Journal of Medicine* 363, Nr. 8 (19. August 2010): 733-42, doi:10.1056/NEJMoa1000678.

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P962

Supply situation of patients with malignant haematological disease in hospices in Lower Bavaria

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Introduction: The proportion of patients with malignant haematological disease takes only a fraction of the palliative supply structure compared to solid tumors. Thus a German work group proved that the malignant haematological disease amount of SAPV (Specialised Palliative out-patient Care) takes only 2%. A retrospective study evaluated the supply situation of patients with malignant haematological disease in Lower Bavarian hospices. An ethics approval was not necessary according to ethics committee Munich.
Methods: Patient data from hospice Vilsbiburg (HV) (Landshut district) and hospice Niederalteich (HN) (Deggendorf disctrict) were analyzed. Both districts have a similar population and demographic structure. The HV dwellers are supplied by primary physicians and an oncologist with an additional designation for palliative medicine and the HN dwellers are supplied by primary physicians.
The HV is part of an ESMO-Center. The investigation period took 40 months in both hospices. The recorded data referred to the number of inhabitants, the number of all admitted patients due to a primary disease as well as number of patients with a haematological disease treated with tumor specific therapies.
Results: Data of 706 dwellers were analyzed (HV: n = 336, HN: n= 370). The total number of patients with malignant disease was 646 (HV: n = 313, HN: n = 333). Overall 33 of them had a malignant haematological disease. 31 dwellers from HV and two from HN. Three dwellers from HV with a malignant haematological disease received a tumor specific therapy, in HN none.
Conclusions: Patients with malignant haematological disease are even in hospices underrepresented. The study revealed distinct differences between the two Lower Bavarian hospices: HV: 10%, HN: 1%. The dwellers received partly tumor specific therapies that were not life-prolonging but improved quality of life. The present discrepancy could be explained by the fact that the HV is part of an ESMO center and the continuous supply of an oncologist and physician in palliative care. Thus, the assistance of oncologists in hospices and the involvement of hospices in oncological/palliative medical care networks seems to be meaningful with regards to the improvement of the supply of patients with malignant haematological disease.

Disclosure: No conflict of interest disclosed.

P963

Chemotherapy induced polyneuropathy - Purdue Pegboard for diagnostic and control of functional deficits during oncological rehabilitation

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Introduction: Polyneuropathy is a common side effect of neurotoxic chemotherapy in breast cancer patients. Aim of this study was the evaluation of the Purdue Pegboard test in diagnostics of polyneuropathy induced functional deficits.
Methods: 89 patients (mean age 66,4 y) suffering on chemotherapy induced polyneuropathy manual dexterity and bimanual coordination were examined using Purdue Pegboard test at the beginning and at the end of a three-week inpatient rehabilitation.
Results: For the dominant [mean score 12.3 (SD 2.6) to 13.4 (SD 2.5); effect size d=0.6] and non-dominant side [mean score 12.0 (SD 2.5) to 12.6 (SD 2.7); effect size d=0.4], the functionality during rehabilitation was significantly improved ($p < 0.001$). The two-handed test [mean score 9.9 (SD 2.6) to 10.3 (SD 2.3); effect size d=0.2] showed a significant difference only ($p = 0.05$). With the assembly test [mean score 22.7 (SD 7.8) to 23.5 (SD 8.2); effect size d=0.2], no significant difference was found ($p = 0.154$).
Conclusions: Purdue Pegboard test is a useful diagnostic tool in evaluation and control of functional deficits due to polyneuropathy.

Disclosure: No conflict of interest disclosed.

P964

Handgrip strength for diagnostic and control of functional deficits during oncological rehabilitation - comparison with normative reference values

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Introduction: Improving physical performance is one of the important expectations on oncological rehabilitation. Aim of this study was the evaluation of the handgrip strength with a hand dynamometer for diagnostic during oncological rehabilitation. A comparison with normative reference values was performed.
Methods: 109 patients (mean age 66.8 y) were examined performing a handgrip strength measurement at the beginning and at the end of a three-week inpatient rehabilitation. Rehabilitation program included endurance, moderate strength and functional training.
Results: The following results (pre-post-comparison) were obtained:
1. significant improvement of handgrip strength [37.9 (SD 8.7) kg to 40.4 (SD 9.4) kg; $p < 0,001$]
2. subgroup analysis of the age and normative comparison (see table 1)

Tab. 1. Overview of handgrip strength at the beginning and at the end of a 3-week inpatient rehabilitation

		handgrip strength			
	N	**Baseline mean (SD)**	**after 3-weeks mean (SD)**	Sig.	normative reference values
age					
40-60 years	20	**41.5 (7.9)**	**44.7 (8.7)**	p=0.003	49.7 (2.4)
61-70 years	53	**39.0 (8.5)**	**41.8 (9.1)**	p<0.001	46.1 (2.7)
71-90 years	36	**34.3 (8.3)**	**37.6 (9.4)**	p<0.001	39.8 (3.0)

Conclusions: Handgrip strength is a useful diagnostic tool in evaluation of general health improvements due to oncological rehabilitation. A significant increase of handgrip strength was shown however normative reference values are not achieved (1). Therefore, an appropriate training as learned during rehabilitation should be continued after finishing inpatient rehabilitation as a home training program.

Reference:
1. Steiber N. Strong or weak handgrip? Normative reference values for the German population across the life course stratified by sex, age, and body height. PloS one. 2016;11(10):e0163917.

Disclosure: No conflict of interest disclosed.

P965

Influencing factors for post-prostatectomy urinary incontinence

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Introduction: Stress urinary incontinence is one of the side effects after radical prostatectomy. The identification of influencing factors for post-prostatectomy urinary incontinence is of great interest. The purpose of this pilot study was to figure out if the pre-existing body balance and the muscular situation prior to therapy have an impact on the continence situation after surgery.
Methods: 16 incontinent (1h pad test > 50g) and 10 continent (1h pad test < 1g) patients were examined. Study diagnostics included 1-h-PAD-Test, Microswing Balance Test (Posturo Kybernetik Test - PKT), a hand strength dynamometer test and a Staff-drop test (reaction time test).
Results:
1. Incontinent patients have an inferior body balance then continent patients by trend (35.8% to 41.6%; p=0.46)
2. Incontinent patients have a longer reaction time than continent patients (p=0.047)
3. Continent patients have a better muscular situation by trend (46.6kg vs. 42.3kg; p=0.06)
Conclusions: The results show that there are differences between continent and incontinent patients after prostatectomy relating to body balance, muscular strength and reaction (common health condition) prior to surgery. Pelvic floor function and trunk stability are influenced by the existing body balance of the patients. Therefore, a holistic, sensorimotor (oscillation rod treatment (1)) and functional (continence training) rehabilitation program is needed.
Reference:
1. Heydenreich M, Puta C, Gabriel H, Zermann D. Oscillating pole treatment-a new effective treatment option for postprostatectomy urinary incontinence. Oncology Research and Treatment; 2016.

Disclosure: No conflict of interest disclosed.

P966

Improvement of the sense of balance in cancer patients by a specialized oncological rehabilitation program in dependence of patient age

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Introduction: Cancer and cancer therapies (surgery, RT, CT) have a negative impact on physical and mental well-being. The task of rehabilitation is overcoming side effects and regaining good quality of life. Physical training was proven to be very effective (1). The aim of the present prospective study was to evaluate the efficiency of a 3-week rehabilitation program on the sense of balance in dependence of patient age.
Methods: 89 patients (Ø 62 years) after cancer therapy were examined. At the beginning and at the end of a 3-week rehabilitation program a Microswing Balance Test (sense of balance) was performed.
Results: The following results (pre-post-comparison) were obtained:

Tab. 1. Overview of equilibrium sense at the beginning and at the end of a three-week inpatient rehabilitation (subgroup analysis of the age)

		stability right side			stability left side		
age	N	Baseline mean (SD)	after 3-weeks mean (SD)	P value within group after 3-weeks	Baseline mean (SD)	after 3-weeks mean (SD)	P value within group after 3-weeks
<49 years	9	67.4 (12.8)	76.1 (9.2)	p=0.03	71.1 (8.4)	75.9 (6.8)	p=0.02
50-59 years	23	62.0 (13.8)	67.0 (11.6)	p=0.02	64.4 (16.0)	69.2 (10.6)	p=0.03
60-69 years	36	54.7 (19.9)	64.7 (14.2)	p=0.001	55.6 (16.0)	64.6 (11.8)	p=0.001
>70 years	21	39.4 (19.7)	45.0 (20.3)	p=0.05	44.2 (19.1)	50.4 (18.3)	p=0.005

Conclusion: A significant improvement of the sense of balance could be demonstrated in all age groups. Functional training therapy to promote endurance, coordination and strength contributes improving physical function and performance. Patient of all age groups benefit form specialized oncological rehabilitation.

Reference:
1. Zopf E, Baumann F, Pfeifer K. Körperliche Aktivität und körperliches Training in der Rehabilitation einer Krebserkrankung. *Die Rehabilitation* 2014;53(01):2-7.

Disclosure: No conflict of interest disclosed.

P967

How do practicing physicians evaluate the cooperation with oncological rehabilitation?

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Introduction: A tumour disease and its therapies can lead to severe health problems and considerable restrictions on participation in working life as well as in everyday life. Accordingly, a patient-oriented care coordinated between rehab-clinic and general practitioners and specialists for oncological patients should be pursued and accomplished in the long term. The aim of this study is to analyse the cooperation with oncological rehab-clinics and to identify interface problems from the perspective of practicing physicians.
Methods: As part of the EmoR study, 41 physicians (oncologists, gynaecologists, general practitioners) whose patients have gone through oncological rehabilitation were asked by questionnaire about cooperation, rehab-discharge report and suggestions for improvement. In addition, 12 physicians took part in telephone interviews on the topics mentioned.
Results: Overall, 70% of the physicians stated to have (very) good experience with oncological rehabilitation because their patients have benefited from it.
Further, there are no continuous contacts to rehabilitation staff. The rehab-discharge report represented the only form of communication with the rehab clinics for more than 90% of respondents. The physicians expressed the wish to exchange information about patients with an increased need for support during rehabilitation. In addition, after-care recommendations should be discussed together with rehab-physicians for these patients.
The rehab-discharge report was rated by the majority of physicians as ´understandable´ and ´helpful for talking to patient´. Most frequently, the report sections ´rehabilitation result´, ´social medical performance

assessment´ and ´recommendation for aftercare´ were read. It was criticised that the rehab-discharge report was too extensive and contained too many standardised text modules. Furthermore, the recommendation for after-care are too generic, rarely tailored to patient´s needs, and contact addresses or information on ´rehab-after-care services´ are missing.
Conclusions: The majority of physicians assessed oncological rehabilitation as positive and supportive for their patients. In the future, the rehab-discharge report and especially the after-care recommendations should be more tailored to the individual situation of the patient. In addition, strategies should be developed to promote cooperation between physicians and rehab-clinics, especially for patients with increased need for support.

Disclosure: No conflict of interest disclosed.

P968

Influence of specialized sensorimotor rehabilitation on the dysfunction of patients after breast cancer treatment

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Introduction: Around one third of chemotherapy patients develops a neuropathy after their treatment. Even patients without chemotherapy have problems in their fine motor skills ("oncobrain", psychosomatic side effects). The purpose of this study was to find out how breast cancer patients with and without chemotherapy benefit of a 3-week-rehabilitation program with focus on fine motor skills in occupational therapy.

Methods: 66 patients (Ø 59 years) after complex breast cancer treatment were evaluated, 40 patients with chemotherapy and 26 without chemotherapy. All patients completed successfully a 3-week-rehabilitation program. This included occupational therapy (hand baths, design therapy), physiotherapy (cell baths, coordinative exercises) and sports therapy (oscillation rod therapy). Study diagnostics included a Purdue Pegboard Test (PPT) for evaluation of dysfunctions and the small fiber neuropathy screening list (SFNSL) for sensory and pain diagnostics (1, 2).
Results:

Tab. 1. Overview of the results of all patients for SFNSL questionnaire and PPT

			all patients			
		N	Baseline mean (SD)	after 3 weeks mean (SD)	p value within group after 3-weeks	normative reference values
PPT	dominant hand	66	12.8 (2.6)	13.7 (2.7)	p<0.001	14.8 (0.7)
	non dominant hand	66	12.5 (2.6)	13.2 (2.5)	p<0.001	14.1 (0.9)
SFNSL		66	19.8 (13.3)	17.7 (11.9)	p<0.001	

Tab. 2. Overview of the results of patients with and without chemotherapy for SFNSL questionnaire and PPT

			patients with chemotherapy				patients without chemotherapy		
		N	Baseline mean (SD)	after 3 weeks mean (SD)	p value within group after 3-weeks	N	Baseline mean (SD)	after 3 weeks mean (SD)	p value within group after 3-weeks
PPT	dominant hand	40	12.6 (3.1)	13.6 (3.1)	P=0.002	26	13.2 (1.7)	13.7 (2.2)	P=0.022
	non dominant hand	40	12.5 (2.9)	13.1 (2.8)	P=0.03	26	12.6 (2.0)	13.4 (1.8)	P=0.253
SFNSL		40	24.0 (14.7)	21.0 (13.3)	P=0.001	26	13.4 (7.3)	12.5 (6.6)	P=0.002

Conclusions: A specialized rehabilitation program after breast cancer therapy allows the improvement of functional deficits and neuropathic symptoms. Especially chemotherapy patients with polyneuropathy benefit from occupational therapy.

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2. Tiffin J, Asher EJ. The Purdue Pegboard: norms and studies of reliability and validity. Journal of applied psychology. 1948;32(3):234.

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P969

Comparison of different extraction procedures for Chinese plants to support anticancer therapies

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Introduction: In China, mixtures of natural products have been used for thousands of years for the prevention and treatment of diseases. In Germany, some physicians use decoctions in case loss of response to standard treatments, to overcome drug resistance or reduce side effects.
Current research aims to explore the interaction between decoctions and conventional therapeutic approaches in order to understand and potentially improve acting mechanisms. Traditionally the preparation of Chinese plant extracts is performed by boiling. However, lately alternative methods are employed. Our research investigates comparatively different extraction methods and their efficiency on ingredient extraction as well as their effect on human cancer cells.
Materials and methods: Three different extraction methods were used for the preparation (boiling, microwave and granulates). A decoction with two potentially tumor-effective plants and five plants to stabilize the patient was generated by the different methodical approaches. The dissolved plant ingredients were analyzed comparatively by mass spectrometry (MS). Pancreatic adenocarcinoma (PaCa) and one acute lymphoblastic leukemia (ALL) cell line were exposed to increasing extract concentrations (10-100 µg). Modulation of cell metabolic activity was assessed using WST-1 assay after 48h exposure.
Results: With all methods aqueous plant extracts were obtained. Comparative MS showed, that depending on the method the extract varies in number and intensity of the extracted compounds. In comparison, boiling showed the highest number of isolated compounds, granules 25% less and laboratory microwave 60% less.
In total, 13 identical compounds were identified. The amount of these 13 components measured in the MS is on average significantly higher with the traditional boiling decoction method than with the laboratory microwave or the granule. Overall the decoction method has the highest number of isolated compounds.
All extracts reduced metabolic cell activity. Particularly in Patu-02 (PaCa), a dose-dependent effect can be seen within 48h. Microwave extraction reduce the cell activity by 40%, decoction by 35% and the commercial granules by 15%.
Conclusions: Our analyses revealed that the different preparation procedures lead to a significantly differing extraction of ingredients and concentrations. Accordingly, alternative preparation is likely to influence the outcomes and efficacy of decoction intake in cancer patients.

Disclosure: No conflict of interest disclosed.

P970

Cost-effectiveness of Real-World Administration of concomitant Viscum album L. therapy for the treatment of stage IV pancreatic cancer

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Introduction: For patients receiving add-on *Viscum album* L. (VA) treatment for late stage pancreatic cancer an improved overall survival (OS) was observed. Limited information regarding efficacy comparisons between standard of care and standard of care plus add-on VA is available to utilize in comparisons of costs. Therefore the objective of this analysis was to evaluate costs and cost-effectiveness of standard of care plus VA (V) compared to standard of care alone (C) in patients with stage IV pancreatic cancer.
Methods: An observational study was conducted utilizing data from the Network Oncology clinical registry (trial registration: DRKS00013335). Patients included had stage IV pancreatic cancer at diagnosis and received C or V treatment in a certified German Cancer Center. Cost and cost-effectiveness analyses (CEA) including the analysis of the incremental cost-effectiveness ratios (ICER) were performed from the hospital's perspective based on routine data from financial controlling department and observed data on OS.
Results: 88 patients (C: n=34, V: n=54) were included, median age 67.2 years, proportion of male patients 48.9%. Adjusted hospital's total median costs for patients from the C and V group were €9,561.62 (over an adjusted median OS time of 5.63 months) and €11,925.39 (over an adjusted median OS time of 8.43 months), respectively. As to CEA-analysis, relevant total hospital's savings of €283.74/month median OS summing up to relevant €3,403.88/year median OS for V-patients compared to C was calculated. The costs per additional OS month gained with the V-treatment compared to C were €844.20 (ICER). Furthermore, relevant hospital's savings of €710.92 per median hospital stay in the V-group were observed compared to C.
Conclusions: Based on this CEA analysis, from the hospital's point of view, the costs per median month of OS and per median hospital stay were lower for the combinational standard of care plus add-on VA compared to standard of care alone in the treatment of stage IV pancreatic cancer. Further prospective and randomized studies are mandatory to re-evaluate our findings.

Disclosure: Anja Thronicke: No conflict of interest disclosed.
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P971

Chinese medicine for combined treatment of acute myeloid leukemia (AML) - from experience to individualized medicine

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Introduction: New analytical methods allow a better understanding of Chinese Medicine (CM) mediated effects for AML treatment. Data analysis from the Taiwanese National Health Insurance Research Database indicated that patients with AML have a better prognosis when they receive CM in addition to standard therapy (ST). After 1:1 matching of 498 patients using ST plus CM or ST alone the hazard ratio of mortality was 0.29 (95% CI = 0.23 - 0.37, $p < 0.0001$) for the combined treatment regimen. As this is a retrospective analysis different decoctions (watery extracts from plants) were used, three plants and three decoctions dominated.
Methods: A selective literature research using PubMed and the "About Herbs" database from the Memorial Sloane Kettering Cancer Center (www.mskcc.org/about herbs) was used to identify known modes of action as well as possible interactions. We discuss a patient, whose standard therapy had to be stopped because of pancytopenia and was following set on a combined treatment approach.
Results: A female patient of 68 years was diagnosed with AML with maturation (FAB M2) in 2017. For one year she was successfully treated with decitabine, when recurrent pancytopenia and infections, including pulmonary aspergilloses, inhibited further standard therapy. Chinese decoctions (extracts from up to sixteen plants) were started and after two months her condition allowed decitabine to continue. The combined regime was successful for seven months, then relapse of the AML was diagnosed. Modification of the decoction to more nourishing Xue and the

Orbis renalis stabilized again and for two months oral melphalan was used successfully. At present due to her general state only decoctions are used. Salvia miltiorrhiza and Astragalus membranaceus have just been started. Our literature research for the most often used plants identified possible modes of action. Salvia miltiorrhizae inhibits PI3K/Akt, Astragalus membranaceus lectin induces caspase-dependent apoptosis and Spatholobus suberectus causes apoptosis via MiR-657/ATF2 signaling pathway. Possible interactions mainly affect CYP3A4 or the P-glycoprotein.
Conclusions: Preclinical data support the use of CM for the treatment of AML. With our present knowledge it seems reasonable to use decoctions where standard therapy is no longer possible or effective. In future a deeper understanding of CM molecular modes of action will allow more intelligent combination with WM compounds to individualize treatment.

Disclosure: No conflict of interest disclosed.

Posterdiskussion

Tumor- und Zellbiologie

P972

Intrinsic hypoxia of mesenchymal stromal cells in 3D model systems of the human bone marrow niche

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Introduction: The bone marrow niche is essential for the support of human hematopoietic progenitor cells (HPC). In *in vitro* studies, we could demonstrate the functional properties of a co-culture setting with a monolayer of bone-marrow derived mesenchymal stromal cells (MSCs) with HPCs. For more realistic studies, 3D model systems of the niche were developed using a microcavity system and a spheroidic MSC culture assay. Our hypothesis is, that even without applying external hypoxic culture conditions MSCs are capable to create an intrinsic hypoxic micromilieu in 3D culture.
Methods: After obtaining informed consent, MSCs were derived from bone marrow of healthy voluntary donors according to standard protocols.
Cells were inoculated into the microcavity array, which was subsequently mounted into a microbioreactor for long-term culture.A closed loop setup allowed control of medium flow and oxygen saturation. After 10 days the cells were analyzed by immunostaining and confocal microscopy.
In a parallel series of experiments 50,000 MSCs were seeded on a layer of 1% agarose gel in 96 well plates and after 24-48h the formation of spheroid-like cell aggregations could be observed. This process was continuously monitored with time-lapse microscopy. MSC-spheroids were characterized by Western-blot and immunohistology after cryosectioning. Assessment of hypoxia was performed by immunofluorescence microscopy using antibodies after incubation with pimonidazole together with HIF-1alpha detection.
Results: MSCs distributed uniformly inside the microcavities as a scaffold and formed a tissue-like 3D mesh. In comparison, aggregation of MSCs on agarose gel consistently resulted in formation of a single spheroid. Immunohistochemistry revealed that MSC-spheroids consisted of homogeneously aggregated cells, with a similar junction formation as formerly found in 2D monolayer cultures, comprising beta-catenin, N-cadherin, vimentin and actin. We could demonstrate regions of local intrinsic hypoxia in the microcavities as well as in the MSC spheroids.
Conclusions: These 3D model systems allow analyzing key elements of the human bone marrow niche. Intrinsic hypoxia developed in both *in vitro* model systems, supporting the notion that under 3D conditions MSCs - as the main cellular determinant of the stem cell niche - are able to create their own physiologic microenvironment. Spatial effects upon local hypoxia may also play a role and are currently under investigation.

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P973

Identification of TMX2 transmembrane protein network

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Introduction: TMX2 is a thioredoxin-related transmembrane protein that possesses not only a thioredoxin consensus pattern, but also an endoplasmic reticulum membrane retention signal, an N-terminal signal peptide, and a Myb DNA-binding domain repeat signature. The participation of thioredoxin in redox reactions explains its role in cell signaling and homeostasis. Any abnormal regulation could contribute to carcinogenesis. According to previous data, TMX2 overexpressed in breast CSCs and downregulation contribute in downregulation of specific transcription factors involved in stemness. However, no many data about TMX2 pathway and interaction with other proteins exist. The present study aimed to identify potential interactions among TMX2 and other genes and design a potential pathway.
Methods: MDAMB231 and MCF7 breast cancer cell lines tested for TMX2 expression with qPCR and western blot. Then were transfected with siRNA for TMX2 and KD evaluated. RNA extracted from control and siRNA - KD cells and whole gene expression microarrays followed. Genes that downregulated were selected for further analysis. It included clustering analysis and then design of potential interactions among all these genes based on biochemical experimental data.
Results: The qPCR post KD revealed decrease in gene expression of TMX2 up to 82 % for MCF7 and 52% for MDAMB231. More than 200 genes (encoding proteins) downregulated. A potential network designed, including the above proteins and interactions among them or other known proteins. This network consisted of more than 1000 proteins. Sub-networks created, eliminating interactions not correlated direct or indirect with TX2. Approximately 150 proteins participated on the finally network. TMX2 has 13 directed edges and the average shortest path length is approximately 10.7. The closeness is 0.092 and radiality is high enough for TMX2 (0.72) compared with the entire network (max 0.79).
Conclusion: According to experimental data, TMX2 overexpressed in breast cancer and correlated with stemness. Therefore, apart from a potential biomarker TMX2 might be a drug-able target. The identification of TMX2 pathway is required in order to understand the mechanisms of action, since no direct connection with stemness transcription factors revealed from the above data. The TMX2 pathway might be useful for determination other molecules involved in stemness process, and enable the identification of new drug-able targets.

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P974

The oncometabolite 5'-methylthioadenosine (MTA) blocks NK cell functions early after activation

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Introduction: Tumor cells are known to escape the immune system through a variety of mechanism to sustain their survival and expansion. In recent years, oncometabolites, which are secreted by tumor cells due to deregulated metabolic pathways, stepped into the focus of cancer research. 5-methylthioadenosine (MTA), a product of the polyamine biosynthetic pathway, accumulates in the microenvironment of tumor cells

lacking MTA phosphorylase (MTAP), which solely metabolize MTA. We and others have demonstrated that MTA negatively influences the functional activity of T and NK cells. In this project we aim to investigate the molecular mechanism of MTA's negative influence on NK cell functions.
Methods: Isolated and short-term IL-2 activated NK cells from healthy donors were tested for their functional activity in the presence of increasing MTA concentrations *in vitro*. Read-outs include ^{51}Cr release assay to evaluate NK cell cytotoxicity as well as flow-cytometry based methods to analyze degranulation and cytokine production, antibody-dependent cellular cytotoxicity (ADCC) functions, conjugate formation as well as signaling pathways.
Results: NK cell cytotoxicity against the HLA class-I negative target cell line K562 decreased with increasing MTA concentrations, though no direct cytotoxic effect on NK cell viability by MTA was observed. Reduced cytotoxicity was rather the result of decreased NK cell degranulation upon target cell engagement in the presence of MTA. In addition, degranulation and production of cytokines during stimulation with anti-CD16 antibodies, mimicking ADCC function, were both negatively influenced by MTA. Importantly, NK cells from healthy donors with an expansion of the $NKG2C^+$ NK cell subset were less prone to MTA's negative influence on ADCC-dependent cytokine production than those without an expansion. Moreover, we observed that MTA already negatively influence the formation of conjugates between NK cells and their targets. Finally, we could demonstrate that MTA blocks early events of the CD16 receptor signaling cascade such as phosphorylation of AKT, S6, and ERK1/2.
Conclusions: We demonstrate that MTA blocks NK cell functions interfering with early events within the signaling cascade of activating NK cell receptors. Our study broadens the knowledge on tumor escape mechanisms of MTAP deficient tumor cells and will help to develop new treatment strategies for these tumor entities.

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P975

RanBP3L deficiency promotes tumorigenic phenotype

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Introduction: The data from The Cancer Genome Atlas (TCGA) allows identification of factors that are prognostic for patient's outcome. We identified ran binding protein 3 like (RanBP3l) that serves as a favorable prognostic marker for patients with renal cancer. Further analysis showed that high expression level of RanBP3l is associated with overall patient's survival also in the TCGA PANCAN group. Since studies related with function of RanBP3l are rare, we further characterized the cellular und physiological function of RanBP3l.
Materials and methods: We created a RanBP3l deficient epithelial cell line by using CRISPR/Cas9. Single clones with functional deletion of RanBP3l were selected and the knockout was confirmed by Sanger sequencing. First cell morphology studies were analyzed by immune fluorescence. We also analyzed the effect of RanBP3l deficiency on cell proliferation, migration and on colony forming capability.
Results: We successfully generated RanBP3l deficient single clones. RanBP3L knockout results in 30 % less proliferation but nearly 50 % better migration of the cells. Analysis of the colony forming capability showed significantly bigger and more colonies in the knockout cells. Further gene expression analysis revealed that RanBP3l is regulated by the nuclear factor of activated T cells 5 (NFAT5). NFAT5 plays a critical role in the adaptive immune system regulating the B cell proliferation, differentiation and macrophage activation.
Conclusions: Our first cellular und physiological studies indicated RanBP3l as a possible novel tumor suppressor and that its expression is regulated by NFAT5. Further analysis of the cellular actions of RanBP3l using cell lines and studies in knockout mice can be used to develop novel targeting strategies for the treatment of different cancer types.

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P976

The differential role of oncostatin M signaling in the regulation of cell proliferation

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Oncostatin M (OSM) first aroused interest acting as antiproliferative agent on A375 human melanoma cell line. Surprisingly, a proliferative function of OSM was later revealed (e.g. ovarian cancer). The aim of the project is to validate the still unknown mechanism leading to these differential effects.
Cell cycle progression was analyzed using EdU-incorporation and FxCycle™ Violet staining. Isolation of primary MSCs from C57BL/6 mice was performed according to sort protocols previously published, using CD31, Sca-1, CD140, CD166, CD45, CD3, TER-119 and Gr-1 antibodies. Primary human stromal cells have been obtained from the Molecular Diagnostics Lab of the University of Freiburg. We have analyzed the expression of *Osmr* using qRT-PCR. The production of inflammatory cytokines was assessed using cytokine-specific bead arrays.
OSM inhibits the proliferation of all investigated stromal cells (OP9 stromal cell line, primary murine MSCs and primary human stromal cells) *in vitro*, whereas it enhances the proliferation of NIH-3T3 fibroblasts. Both cell lines, OP9 and NIH-3T3 cells, express *Osmr* and upregulate its expression upon OSM treatment. OSM induces the activation of JAK-STAT, MAPK/ERK and PI3K-AKT pathways in both OP9 stromal cells and NIH-3T3 fibroblasts. Interestingly, 1μM ruxolitinib fully restores the proliferative capacity of OSM treated OP9 cells whereas it cannot fully reverse the OSM-induced effect on proliferation in NIH-3T3 cells. Both cell lines respond to OSM with IL-6 production. Only NIH-3T3 fibroblasts react to IL-6 with enhanced proliferation. However, neutralizing IL-6 antibodies cannot reverse the OSM mediated effect.
In the present study, we show that OSM inhibits the proliferation of OP9 stromal cells, whereas the proliferation of NIH-3T3 fibroblasts is promoted by OSM. To investigate further, Western Blots using different concentrations of ruxolitinib (lower than 1μM) together with OSM treatment will be performed.
We hypothesize that the cell lines differ in the expression of master cell cycle regulators like p53 and Rb. Western Blot analysis will be performed to check the cell lines for p53 and Rb expression. The secretion of cytokines by the cell lines concentrating first on M-CSF (OP9 cells lack M-CSF production due to mutation) and their role in the response to OSM will be analyzed in follow-up experiments. Moreover, gene expression arrays will be used comparing both cell lines.

Disclosure: No conflict of interest disclosed.

P977

The Lichen compounds evernic acid and usnic acid synergize with Temozolomide in the glioblastoma cellline U-87

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Introduction: Drug resistance is a serious challenge in the treatment of cancer. Temozolomide (TMZ), an important drug in the treatment of glioblastoma (GBM), frequently causes resistance. Previously we reported about the characterisation and screening of lichen extracts and their fractions for their usnic acid content, their cytotoxic activity alone and in combination with TMZ in U-87 glioma cells. Especially the acetonitrile preparation of *Evernia prunastri L.* could sensitize U-87 glioma cells to TMZ with lower effects on human skin fibroblasts *in vitro* [1,2]. We investigated evernic acid (EA) and usnic acid (UA), main compounds of *E.*

prunastri L., for their antiproliferative activity against U-87 glioma cells and their potential to synergize with TMZ *in vitro*.

Methods: The viability of cells was investigated by the resazurin assay. Combinatory effects were calculated by the Chou-Talalay method (CI) [3] and the ZIP model visualizing synergy scores by 3D-models with SynergyFinder [4].

Results: the IC_{50} for EA, UA and TMZ alone were 61.8 µM, 141 µM and 593.4 µM respectively. EA showed synergistic effects in concentration ranges of 12-40 µM (EA) with TMZ (150-300 µM); UA synergized in concentration ranges of 12-40 µM with TMZ (25-75 µM) (Fig. 1a,b). The effect with the combination of EA-TMZ was higher (cell viability: 49-58%) compared to the combination of UA-TMZ (81-91%) (Fig 1c,d). Different results were obtained using the CI and the ZIP-method.

Conclusion: EA may be a candidate compound for further investigation. Molecular mechanisms at concentration threshold levels for synergism should be investigated.

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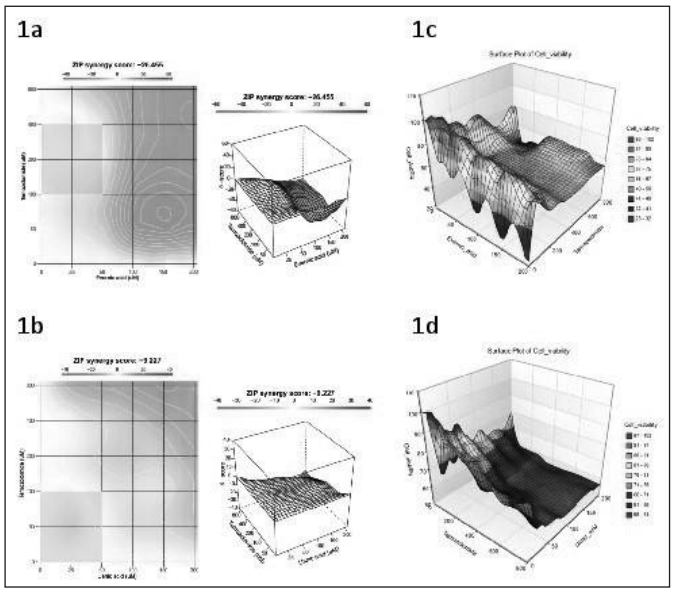

Fig. 1. Graphs of the synergy score (1) and the cell viability (2) of U87 cell line treated with: a) the combination EA/TMZ; b) the combination UA/TMZ

Disclosure: No conflict of interest disclosed.

P978

Specific inhibition of PRMT5 suppresses human CD8+ T cells by upregulation of p53 and impairment of the AKT pathway similar to the tumor metabolite MTA

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Genetic alterations in tumor cells provide promising targets for anti-tumor therapy. Recently, loss of methylthioadenosine phosphorylase (MTAP), a deletion frequently occurring in cancer, has been shown to create vulnerability to the inhibition of the protein arginine methyltransferase 5 (PRMT5). MTAP deficiency leads to accumulation of methylthioadenosine (MTA), which reduces PRMT5 activity, and thus sensitizes the tumor cells to further specific PRMT5 inhibition. PRMT5 inhibitors (PRMT5i) are investigated as new strategy to selectively kill MTAP-deficient cells by blocking residual PRMT5 activity, but also to treat PRMT5-overexpressing cancer.

Though many studies investigated the role of PRMT5 in cancer, only little data about the effect of PRMT5 inhibition on immune cells exists. As we could show that the tumor metabolite MTA suppresses human T cells regarding activation, proliferation and viability, we asked if PRMT5 inhibition is detrimental for T cell immune responses. Therefore, we examined the effect of the synthetic PRMT5 inhibitor EPZ015666 on human primary $CD8^+$ T cells in direct comparison to the naturally occurring PRMT5-inhbiting molecule MTA and asked if these molecules share the same mechanisms of action.

Both compounds reduced T cell proliferation, viability, differentiation and expansion of tumor antigen-specific cytotoxic T cells. Western blot analysis revealed reduced symmetric protein arginine di-methylation, which coincided with the induction of p53 expression and MDM4 alternative splicing. Furthermore, we observed reduced AKT/mTOR signaling upon PRMT5 inhibition. Consistently, this was accompanied by impaired T cell metabolism after stimulation, with both activation-induced glycolysis and fatty acid consumption to be involved, as determined by flow cytometry and extracellular flux analysis. Of note, the AKT-activating cytokine IL-7 could rescue AKT signaling-associated processes, but did not restore PRMT5 activity.

In summary, we found PRMT5 activity to be involved in various cellular processes of human $CD8^+$ T cells associated with T cell function. Therefore, PRMT5 inhibitors might critically influence anti-tumor immune responses and hence therapy success. This emphasizes the importance of considering side effects on the immune system when developing new strategies to specifically target not only MTAP-deficient tumors.

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P979

Evidence for a direct LASP1-AKT1 interaction promoting cancer cell progression

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Introduction: LIM and SH3 domain protein (LASP1) was originally identified as a structural cytoskeletal and adaptor protein involved in cell proliferation, migration and adhesion. However, overexpression of LASP1 has been reported in numerous tumor entities and recent data even suggested transcriptional activity. Moreover, LASP1 was described as a novel CXCR4 binding partner and a promoter of the PI3K/AKT/mTORC pathway, and decreased pAKT1-S473 phosphorylation was obseved after LASP1 depletion. The underlying mechanism, however, is unclear: either LASP1/COPS5 synergistically stimulate ubiquitination and degradation of 14-3-3 , resulting in AKT1-S473 phosphorylation, or the protein promotes ubiquitination and degradation of PTEN, thus enhancing PIP2 phosphorylation to PIP3 and concomitant AKT1 activation. Here, we demonstrate a phosphorylation-dependent direct interaction of LASP1 with AKT1.

Methods: Breast cancer cells, mainly showing LASP1-S146 phosphorylation, and CML cells with LASP1 preferentially phosphorylated at Y171, were used to investigate phosphorylation-dependent differences in binding of LASP1 to AKT1 by immunoblotting, pull-down experiments and immunofluorescence staining. Mutations in the C-terminal AKT1 regulatory domain, in combination with LASP1-deletion mutants, allowed LASP1-AKT1 interaction studies. SDF-1 stimulation of macrophages

with knockdown of CXCR4 or LASP1 was performed to analyze CXCR4-LASP1-AKT1 signaling.
Results: LASP1 phosphorylation is transient: Upon CXCR4 stimulation, Gαi inhibits PKA signaling and activates Src family kinases, as seen by the dephosphorylation of LASP1 at the PKA-site (S146) and concomitant phosphorylation at Y171. By deductive binding analysis, the AKT1-C-terminus favors binding to the S146-phosphorylated LASP1 nebulin-linker region. AKT1 also binds to non-phosphorylated LASP1, albeit with lower affinity. Immunofluorescence staining verified AKT1-LASP1 co-localization at the cell membrane and revealed a preferred interaction of AKT1 with pLASP1-S146 in close proximity to the nucleus. The reduced AKT1-S473 phosphorylation, observed after LASP1 knockdown, is not seen for pAKT-T308 phosphorylation. Furthermore, LASP1 depletion has no effect on p38, ERK1/2 and Ca^{2+} pathways.
Conclusions: We propose a model in which LASP1 functions as a central scaffolding protein, accumulating AKT1 and mTORC at the plasma membrane and around the nucleus for optimized protein phosphorylation and nuclear translocation.

Disclosure: Elke Butt: Expert Testimony: Deutsche Krebshilfe, Projektnummer 70112717
Jochen Frietsch: Expert Testimony: Deutsche Krebshilfe, Projektnummer 70112142

P980
Organ infiltration of macro-metastases - a hitherto unnoticed mechanism

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Introduction: Tumor cells are abundantly released into the circulation, but only a very small proportion of these cells successfully colonize distant organs. The colonization itself is subdivided into different steps: first the restart of cell proliferation and forming of a micro-metastasis, then the outgrowth to a macro-metastasis with or without infiltration of the adjacent organ parenchyma and finally the organ destruction and death. Therefore the colonization is the most ineffective but also the most life-threatening step of the metastatic cascade.
Despite its clinical relevance, the mechanisms of organ colonization, especially the infiltration of macro-metastasis into the adjacent organ parenchyma, are almost unknown. In a previous study we demonstrated that metastatic infiltration into the brain parenchyma has a significant impact on prognosis. In this prospective clinical basket trial the 2-year OS with displacing or pushing growth was 43.5%, while that of infiltrative growth was only 6.6%. In brain metastases the infiltrative growth also carried a significant hazard ratio (HR) of 3.3 (P = 0.0097) as opposed to typical clinical parameters. A recent meta-analysis revealed the comparable results of colo-rectal liver metastases. Both observations already led to a change in clinical practice.
Moreover, these studies also revealed at least nine histological patterns at the organ parenchyma/metastatic interface indicating different biological mechanisms.
Results: To define the molecular mechanisms underlying the different patterns seen in human liver and brain metastases, we used syngeneic brain and liver colonization mouse models. Strikingly mouse metastases resembled those patterns seen in human metastases. Finally, we identified the first molecular differences between mesenchymal infiltration and epithelial infiltration besides epithelial mesenchymal parameter (EMT).
Conclusions: These models enable us to investigate the molecular mechanisms of late colonization and identify completely unknown drugable targets to prevent macro-metastatic progression.

Disclosure: No conflict of interest disclosed.

Posterdiskussion

Multiples Myelom III

P981
Case report of a biclonal IgD/IgE multiple myeloma

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Introduction: Only 2 % of multiple myeloma (MM) patients develop a biclonal gammopathy. Reports about patients with IgD or IgE MM are rare.
Case report: We report the clinical course of a 46 years old woman who was full time working as a lawyer till admission to hospital. Reason for hospitalisation was loss of strength since 6 weeks and pain in the left shoulder. We saw a woman in chronical reduced condition (33 kg / 155 cm). Anamnestically vertebral body fractures were detected without a causal connection in the last year. Further examinations showed a hypercalcemia, acute renal failure (Krea 7,3mg/dl, GFR 6ml/min), microcytic anemia with a hemoglobin of 6,8 g/dl and normal leukocytes and platelets and a severe immunoglobulin deficiency (IgG 2,4g/l, IgA 0,13g/l, IgM < 0,05g/l, IgD < 10mg/l IgE 39 IU/ml). Except the distal limbs all pictured bones showed osteolytic / osteodestructive lesions in nuclear spin including a fracture of the left humerus. Specific laboratory showed a biclonal transformation in serum-electrophoresis such as a biclonal paraprotein in IgD kappa and IgE kappa in immunofixation by using mercaptoethanol.
A bone biopsy of the right humerus showed an extended bone marrow infiltration of atypical plasma cells with kappa-light-chain restriction as well as high positive level of zyklin D1 as a potential evidence of a t(11;14) translocation. Further diagnostic arrangements were not done because of rapid clinical worsening and familial decision.
Results: Because of rapid progression in combination with multiple organ failure due to sepsis, caused by a osteomyelitis, patients died 15 days after admission to hospital.
Conclusion: For the first time, we report a finally very adverse clinical course of a 46-year old patient with a biclonal IgDkappa and IgEkappa multiple myeloma stage IIIB according to Durie & Salmon.
Keywords: biclonal multiple myeloma IgD kappa, IgE kappa

Disclosure: No conflict of interest disclosed.

P982
Rate of hospital admissions due to administration of monoclonal antibodies in patiens with multiple myeloma - a retrospective analysis

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Antibodies are an effective therapeutic option in multiple myeloma. In Germany, the SLAMF7-antibody elotuzumab and the CD38-antibody daratumumab are approved. Especially the first administration of daratumumab is associated with a high rate of infusion reactions. Although mostly not severe, administrations are needed due to lower infusion rates. We investigated retrospectively patients who received either elotuzumab or daratumumab for the need of hospital administration in the period from June 2013 until May 2018. 55.6% of patients receiving daratumumab intravenously and no patient after elotuzumab was admitted to hospital.

No life-threatening or lethal infusion reaction occurred, there were only cases with a CTCAE grade 2. There was no case of an infusion reaction after later doses of daratumumab.
In conclusion, different approaches to improve the practicability administration of the first dose of daratumumab are needed. This might be a lower dose of daratumumab at the first day, splitting the dose in two administrations day 1 and 2, and in the future, the usage of daratumumab subcutaneously.

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Axel Nogai: Advisory Role: Celgene, BMS, Janssen, Takeda, Sanofi, Alexxion; Expert Testimony: Celgene, Janssen, BMS

P983

Daratumomab for the treatment of relapsed multiple myeloma involving the central nervous system: a case report

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Introduction: Involvement of the central nervous system is a rare event in multiple myeloma. Since it is associated with advanced stages of the disease and survival of only a few months, standard treatment options have not been defined.
Case report: A 45-year-old female patient with high risk multiple myeloma relapsed with intraspinal and retroperitoneal tumor manifestations 21 months after autologous peripheral blood stem cell transplantation and then proceeded to allogeneic stem cell transplantation following conditioning with treosulfan, fludarabine and ATG. Two months later the patient presented with headache, vomiting, nausea, and gait abnormality. Magnetic resonance imaging (MRI) of the brain showed disseminated intracerebral lesions. Examination of the cerebrospinal fluid revealed pleocytosis with monoclonal plasma cells consistent with an isolated myeloma relapse of the central nervous system (CNS). As the patient presented with a pancytopenia after treatment with ganciclovir because of CMV reactivation she did not qualify for systemic chemotherapy. An intrathecal chemotherapy with methotrexate, cytarabine, and dexamethasone twice weekly and an intravenous daratumumab infusion once weekly was initiated. In the following weeks neurologic symptoms resolved and follow up MRI two weeks after treatment initiation confirmed a major response to treatment. No more plasma cells were detected by cytomorphology of the cerebrospinal fluid at this time. Unfortunately, the patient died three weeks later following an accidental fall with subarachnoid hemorrhage.
Conclusions: Daratumomab in combination with intrathecal chemotherapy was associated with rapid treatment response in a myeloma patient with isolated CNS involvement suggesting daratumumab activity in the brain parenchyma.

Disclosure: No conflict of interest disclosed.

P984

Pomalidomide, Cyclophosphamide and Dexamethasone (PCD) is an effective salvage regimen for multiple myeloma (MM) patients relapsed and/or refractory to Daratumumab (dara)

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Introduction: Dara is approved as monotherapy or in combination with lenalidomide (daraRd) or bortezomib (daraVd) for the treatment of relapsed and/or refractory MM patients (pts). However, treatment options for pts progressing on dara are limited, and little data are available on the efficacy of salvage treatment after dara.
Methods: To evaluate the efficacy of PCD as salvage therapy after dara. Ten pts treated at Jena University Hospital and receiving at least 1 cycle of PCD after dara failure were included in this preliminary analysis. Statistical analysis included descriptive statistics and survival analysis. Progression free survival (PFS) and overall survival (OS) were calculated from the start of PCD. Data cut off was the 25th of April 2019.
Results: Median age at the start of PCD was 63 years (range 51-75). Three pts had extramedullary (EM) disease. The median number of previous lines of therapy was 4 (range 2-8). Nine pts had previously been treated with melphalan, one pt had received allogeneic SCT. All patients had previously received IMiDs (9/10 lenalidomide, 2/10 thalidomide); 8/10 pts progressed during IMiD therapy. Nine pts had been treated with bortezomib and 6/10 with carfilzomib; 7/9 pts were refractory to proteasome inhibitors. Six pts had been treated with dara, 3 pts with daraRd and 1 pt with daraVd. Responses to dara had been limited: 4 partial responses (PR) but 6 pts with primary refractory disease (including 2 pts with EM disease). The median daily dose of pomalidomide was 3 mg (range 1-4 mg), median doses per cycle of cyclophosphamide and dexamethasone were 900 mg/m^2 (range 0-1800 mg/m^2) and 160 mg (range 0-320 mg), respectively. The median number of cycles of PCD was 5 (range 1-27); 4 patients are still on treatment. Overall response rate (≥PR) to PCD was 60% (6/10 pts), including 2 pt with very good PR and 2 pts with complete responses (CR). Clinical benefit (≥minimal response, MR) was seen in 7/10 pts. Of the 3 pts with EM disease 1 achieved a CR and 1 a MR. Responses occurred after a median of 2 cycles (range 1-8). With a median follow up of 17 months, 6/10 patients have relapsed and 4/10 patients have died. Median duration of response was 2 months (95% CI 0.8-3.3), median PFS and OS were 9 (95% CI 2.6-15.4) and 16 (95% CI 7.8-24.2) months, respectively.
Conclusions: PCD is an effective regimen for dara refractory pts, and it seems particularly promising in patients with EM disease.

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Marie von Lilienfeld-Toal: Expert Testimony: Janssen, Celgene, Takeda and Novartis; Other Financial Relationships: Travel support: Janssen, Celgene, Takeda and Novartis

P985

CD38 directed multi-agent therapy is feasible and shows efficacy in CD38 pretreated rrMM

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Introduction: CD38-targeted immunotherapy improved significantly multiple myeloma (MM) therapy, with Daratumumab as its first FDA/EMA approved representative. Additional CD38-targeted therapies are currently in late clinical testing, including the monoclonal antibody MOR202. No data are currently available about CD38 retreatment after disease progression. Here we provide first evidence about feasibility and efficacy of a Daratumumab-based combination therapy in an advanced patient progressing on CD38 targeted therapy in prior treatment line.
Case report: Our 74-year old patient was diagnosed with genetic standard risk Ig A lambda MM in 2002. After having progressed to various treatment regimen, including tandem autologous stem cell transplantation, first and second-generation proteasome inhibitors and immunomodulator therapy, she was included into the MOR201C101 trial (MOR202/Pomalidomide/Dexamethasone). VGPR was achieved as best response and after 13 cycles of therapy disease progressed in an intra- and extramedullary manner. In addition, invasive breast cancer was diagnosed and then resected in curative intention. Thus, treatment options were highly limited for this organ-fit patient, and no further clinical trial participation was possible due to the secondary cancer. We therefore treated the patient with an in-house experimental multiagent POM-PAD-DARA combination therapy ('Einzelheilversuch').

Results: After 7 cycles of POM-PAD-Dara therapy the patient achieved MRD negative CR and no major toxicity occurred. PET imaging was negative for EMD and sFLC ratio was normalized. Treatment was then stopped for an ongoing watch & wait treatment strategy.
Conclusions: To best of our knowledge this is the first description of treatment response to a Daratumumab based 5-agent combination therapy after prior CD38 targeted treatment failure. POM-PAD-DARA therapy was safe and seems to hold high antitumor effectivity in relapsed refractory MM that needs to be further evaluated in clinical trials.

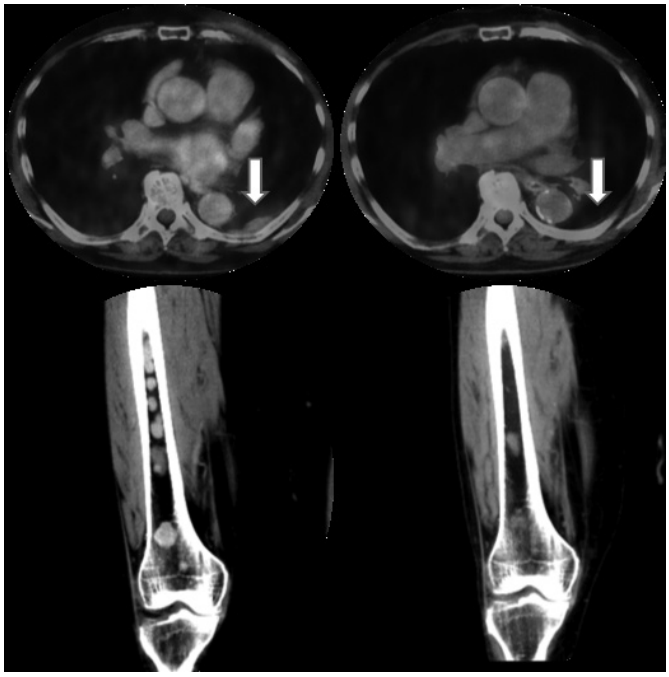

Fig. 1. PET and CT reconstructions of EMD and bone marrow infiltration after MOR202 and DARA

Figure: PET and CT reconstructions of EMD (upper row) and bone marrow infiltration (lower row) after MOR202 (left) and 12 cycles DARA (right).

Disclosure: No conflict of interest disclosed.

P986

Biochemical markers of metabolism of bone tissue and their significance at monoclonal gammapathia and multiple myeloma in the patients of the Gomel region of Belarus

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Introduction: The destructive syndrome MM is based on the processes of disruption of the normal ratio of bone resorption and recovery, which is accompanied by deviations in the level of biochemical markers.
Objectives: Assess the role of biochemical markers of bone metabolism and cytokines in MM and MGUS patients for predicting lytic lesions.
Materials and methods: The study has included 100 patients: 64 MGUS patients (60±4 years) and 36 patients with newly diagnosed MM (65±5 years). All patients underwent biochemical examination of osteocalcin, BAP,β-CrossLaps,IL-6,TNF-α, phosphorus, X-rays of the skeleton bones.
Results: Bone tissue destruction was found in 75% of MM patients (most often IgG secretion - 75%), and in 25% of MGUS (appeared during observation), (of which most often IgA secretion 67.7%).
A decrease in osteocalcin relative to the norm was observed in 41.2% of MM patients, which was accompanied by the presence of a destructive syndrome. In MGUS patients, a decrease in osteocalcin was detected in 29% and in 31.6% of this group, destruction was detected in course of observation by method of low-dose CT.
A decrease in BAP was observed only in MM patients who had significant bone damage (multiple foci of destruction) and there was no change in the level of BAP in MGUS. There was not observed correlation between osteocalcin and BAP in MGUS patients (p=0.419). In MM patients, there was determined a correlation of the average force between the indicated indicators (Spearman r=0.40;p=0.045), which is confirmed by the literature data.
In 28.6% of MM patients with bone tissue destruction, there was an excess of β-CrossLaps and 20% of patients from this group had no lesions. In MGUS patients only in 7% an excess of the level of this indicator was detected, and in the process of observation, isolated lytic lesions were detected, and 18.2% of patients had no destructive manifestations.
Despite a slight excess of serum IL-6 level in MM patients, there were no significant differences between MM and MGUS groups (p=0.299).
There was a significant excess of the TNF-α in MM patients (59.5%) and MGUS (39.1%).
There were not identified disorders from the level of phosphorus in the serum.
Conclusions: There was found that a certain percentage of MGUS patients already have irregularities in the ratio of these markers in different variations, which may be harbingers of MGUS patient progression in MM, which requires more careful monitoring of this group.

Disclosure: No conflict of interest disclosed.

P987

Rheumatologic diseases impact the progression risk of MGUS patients

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Introduction: Monoclonal gammopathy of undetermined significance (MGUS) is an asymptomatic pre-malignant condition with an inherent risk of progression into overt multiple myeloma (MM) or related haematological disorders. Chronic inflammation is a known risk factor for cancer initiation and progression. Whether chronic inflammation associated with rheumatologic diseases may impact the risk of progression of MGUS has not been systematically explored so far. Our study provides data on the prevalence of rheumatic impairment in MGUS pts., their clinical features as well as their impact on long-term outcome with focus on progression to myeloma or other plasma cell disorders.
Patients and methods: 2935 MGUS patients diagnosed between 1/2000 and 8/2016 were identified. The rheumatic disorders were grouped as follows: rheumatoid arthritis (RA), collagenoses, polymyalgia rheumatica (PMR), spondyloarthropathy (SpA), and arthritis urica.
Results: 255 of 2935 MGUS patients suffered from an additional rheumatologic co-morbidity. The progression-risk between MGUS patients with *versus* without rheumatic co-morbidity differs significantly. MGUS patients suffering from PMR, SpA or arthritis urica have a doubled progression-risk when compared to MGUS patients without a respective concomitant rheumatologic disorder (HR=2.1 [95%CI 1.1-3.9], P< 0.02). In contrast, MGUS patients suffering from RA or other collagenoses tend to have a lower progression risk (HR=0.4 [95%CI 0.1-1.2], P=0.09), which however does not reach statistical significance. This data translates into a 5-year progression-risk of 4%, 10% and 2% in MGUS patients without rhaumatologic co-morbidity, MGUS patients with co-existing PMR, SpA

or arthritis urica and MGUS patients suffering from collagenoses or RA, respectively.

Conclusions: Chronic inflammatory diseases impact the progression risk of MGUS into overt MM. However, the prognostic impact is not consistently negative, as some rheumatic co-morbidities (e.g. RA) are even protective, whereas others clearly increase the risk of progression (e.g. arthritis urica). It remains unclear how the underlying inflammatory conditions and/or treatment of the rheumatic disorder impacts the progression risk. Our current aim is to define in more detail potential disease- or treatment-associated variables impacting the MGUS progression risk. The ultimate goal is to further refine the currently applied prognostic scores in MGUS by including rheumatologic co-morbidities.

Disclosure: No conflict of interest disclosed.

P988

Use of pomalidomide-based regimens in relapsed/refractory multiple myeloma (RRMM) in four European countries - findings from PREAMBLE

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Introduction: Pomalidomide plus dexamethasone (Pd) is indicated for patients (pts) with RRMM after lenalidomide and proteasome inhibitors (PIs) fail, but responses are not durable and median overall survival is about 1 year (y). Pd-based triplets have improved outcomes, including duration of response. We analyzed the use of pomalidomide-based regimens for RRMM in 4 European countries.

Methods: Adults with RRMM from France, Germany, Italy, and the UK were identified from PREAMBLE (NCT01838512), an ongoing, prospective, observational study. Pts with ≥1 prior therapy who began therapy with a PI, immunomodulatory drug (IMiD), IMiD+PI, or newer agent (monoclonal antibody, Akt or histone deacetylase inhibitor, or novel combination) 90 days (d) before to 30 d after informed consent were followed for ≤3 y. Data were summarized with descriptive statistics.

Results: Baseline characteristics and treatment at enrollment for 824 pts with available data are shown in the Table.

Table: Demographics and baseline characteristics

	Europe (N=824)
Country, n (%)	
France	239 (29.0)
Germany	171 (20.8)
Italy	235 (28.5)
UK	179 (21.7)
Median age (range), y	
At MM diagnosis	65 (29, 88)
At study enrollment	70 (34, 92)
Male, n (%)	467 (56.7)
Race, n (%)	
White	559 (67.8)
Black	10 (1.2)
Other	16 (1.9)
Missing/unknown	239 (29.0)
Disease status, n (%)	
Relapsed	640 (77.7)
Refractory	165 (20.0)
Missing/unknown	19 (2.3)
Treatment at enrollment, n (%)	
IMiD	446 (54.1)
PI	299 (36.3)
IMiD+PI	54 (6.6)
Newer agent	25 (3.0)
Number of prior therapies, n (%)	
1	383 (46.5)
2	207 (25.1)
3	100 (12.1)
4	63 (7.6)
5 or more	71 (8.6)

At data cut-off (27 April 2018; median [range] follow-up 14.0 months [7.3-25.8]), 51.6% of pts remained in the study. Of pts receiving IMiD-based regimens (n=500), 14.2% received Pd-based regimens (90.1% Pd; 9.9% Pd triplets). Similar proportions of pts received an IMiD in second-line (2L; 39.1%, n=322), 3L (46.9%, n=279), 4L (44.3%, n=170), 5L (45.6%, n=110), and 6L+ (36.3%, n=157) settings. Use of Pd-based regimens increased, but

use of Pd triplets decreased, from 2L to 6L+: 4.6% (n=17; Pd vs Pd triplets: 64.7% vs 35.3%), 14.5% (n=45; 93.3% vs 6.7%), 27.5% (n=52; 94.2% vs 5.8%), 34.5% (n=41; 95.1% vs 4.9%), and 39.9% (n=69; 98.6% vs 1.4%). More pts received newer agents with increasing lines of therapy (LoT): 1.3% (n=11; 2L), 2.7% (n=16; 3L), 3.6% (n=14; 4L), 6.2% (n=15; 5L), and 10.6% (n=46; 6L+).

Conclusions: In France, Germany, Italy, and the UK, use of Pd-based regimens was rare as 2L therapy, but increased with successive LoTs, with >25% of pts receiving Pd-based regimens in 3L+. Few pts received Pd triplets, particularly in 3L+. As Pd triplets are associated with durable improvements in outcomes, they may be an option for pts with ≥2 prior therapies and MM refractory to lenalidomide and PIs.

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Gordon Cook: Advisory Role: Amgen, Bristol-Myers Squibb, Celgene, Glycomimetrics, Janssen, Sanofi, Takeda; Financing of Scientific Research: Amgen, Bristol-Myers Squibb, Celgene, Glycomimetrics, Janssen, Sanofi, Seattle Genetics, Takeda; Expert Testimony: Amgen, Celgene, Janssen, Takeda; Other Financial Relationships: Speakers bureau: Amgen, Celgene, Janssen, Sanofi, Takeda

P989

Prospective monitoring of immune signatures in newly diagnosed high risk multiple myeloma patients under treatment with Isatuximab, Carfilzomib, Lenalidomide and Dexamethasone (I-KRd): first results of the GMMG-CONCEPT trial

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Minimal residual disease (MRD) negativity is correlated with improvement in progression-free (PFS) and overall survival (OS) for standard and high-risk multiple myeloma (MM). Reconstitution of the immune system might play a crucial role in long-term disease control. The GMMG-CONCEPT trial investigates combination treatment of isatuximab, carfilzomib, lenalidomide and dexamethasone in induction, consolidation and maintenance for first-line treatment of high risk MM. Primary endpoint is MRD negativity after consolidation. In a prospective scientific program, prospective immune monitoring is performed in order to correlate response outcomes with distinct immune signatures. Here, we report on results of the first 12 patients of the ongoing trial. Immune monitoring consists of a 13-colour flow using 40 markers to define B, T and natural killer (NK) subsets in peripheral blood (PB) and bone marrow (BM). Response is determined by IMWG criteria. Analysis was performed at baseline (bs), during induction, prior consolidation and prior maintenance (pm). Longitudinal analysis from baseline until start of maintenance treatment showed a marked decrease of absolute numbers of mature CD57+CD56^{dim}NK cells in PB (bs: median 7.77x10*4/ml, range 0.0 - 78.7 x 10*4/ml; pm 0.416 x 10*4, 0.0- 2.13 x10*4) and BM (bs: 19x10*4/ml, 4.42 - 393 x 10*4/ml; pm 0.695 x 10*4, 0.00-2.85x10*4) with a subtotal loss of the CD57+CD56^{dim} population. NK cells in PB and BM showed baseline expression of PD-1, which significantly decreased under treatment resulting in a loss of PD-L1 expression (median MFI at bs 130, median MFI pm 36). Furthermore, we detected decrease of CD4$^+$CD25$^+$CD127$^-$FoxP3$^+$regulatory T cells (bs 0.3x10*5/ml, 0.07 - 7.942 x 10*5/ml; pm 0.1 x 10*5, 0.08-0.413x10*4) in PB and BM with a markedly reduced number of proliferating Ki67$^+$regulatory T cells . Prior maintenance a substantial increase of gdT-cells (bs 4.22x10*3/ml, 1.316 - 59.67 x 10*3/ml; pm 10.69 x 10*3, 2.89 - 187.56 x10*3) was observed in BM. All patients analyzed showed response under treatment achieving at least very good partial remission (VGPR).
Prospective immune monitoring under optimized first-line MM treatment shows distinct quantitative and phenotypically changes in NK-cell and T-cell populations over time. Continuous analysis is aimed to prospectively identify distinct immune signatures correlating with durable, MRD negative responses in high-risk MM patients.
*AMA and SEA contributed equally

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Katja Weisel: Advisory Role: Amgen, Celgene, Janssen, Sanofi; Financing of Scientific Research: Amgen, BMS, Celgene, Janssen, Novartis, Takeda; Expert Testimony: Amgen, Celgene, Janssen, Sanofi

P990

Isatuximab, Carfilzomib, Lenalidomide and Dexamethasone (I-KRd) in front-line treatment of high-risk multiple myeloma: results of the safety run-In cohort in the phase II, multicenter GMMG-CONCEPT trial

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High-risk multiple myeloma (MM) disease still has a significant impaired prognostic outcome. Achievement of minimal residual disease (MRD) negativity correlates with favorable progression-free (PFS) and overall survival (OS) including high-risk patients. Combination treatment with proteasome inhibitor, immunomodulating agent and dexamethasone in first-line treatment results in high response rates and deep remissions. It was shown, that addition of monoclonal anti-CD38 antibody further improves depth of response and MRD-negative rates. The multicenter, phase II GMMG-CONCEPT trial investigates combination treatment with Isatuximab, Carfilzomib, Lenalidomide and Dexamethasone (I-KRd) for front-line, high-risk MM. Here, we report on the results of the safety run-in cohort.
153 patients with newly-diagnosed MM are planned to be included into the trial and receive 6 cycles of I-KRd induction followed by high-dose melphalan, 4 cycles of I-KRd consolidation and I-KR maintenance. The safety-run in phase included the first 10 patients to assess dose-limiting toxicities during the first two I-KRd cycles. In addition, early responses are reported.
10 patients (42-67 years) contributed to the analysis. All patients experienced at least one treatment-emergent adverse event (TEAE), in total 49 TEAE were reported, 15 were classified as Grad 1, 14 as Grade 2, 17 as Grade 3 and 3 as Grade 4. Main ≥ Grade 3 toxicities were hematologic with neutropenia in 6 patients, leukopenia in 5 patients, lymphopenia in 2 patients, anemia in 2 patients and thrombocytopenia in 1 patient. Non-hematological toxicities Grade ≥ 3 were cerebral vascular disorders in 2 patients, self-limiting ventricular tachycardia in 1 patient and diarrhea in 1 patient. 3 patients experienced infusion reaction grade 2 during the first Isatuximab infusion. In total, 5 SAE occurred. The 2 cerebral events were classified as non-related due to preexisting comorbidities. 9/10 patients completed 6 cycles of induction. 10/10 patients had documented responses during induction phase with all patients achieving ≥ VGPR.

Conclusions: The 4-drug combination of I-KRd was administered for the first time for treatment of MM patients. Overall, toxicity was manageable with an overall safety profile consistent with prior experience with KRd and anti CD38 antibody treatment. After completion of the safety run-in, the trial continued as planned. First response rates are encouraging and will be followed continuously.

Disclosure: Katja Christina Weisel: Advisory Role: Amgen, Adaptive Biotech, Bristol Myers Squibb, Celgene, Janssen, Juno, Sanofi, Takeda; Financing of Scientific Research: Amgen, Bristol Myers Squibb, Celgene, Janssen, Takeda; Expert Testimony: Amgen,Celgene, Janssen, Sanofi
Hartmut Goldschmidt: Advisory Role: Amgen, Adaptive Biotech, Bristol Myers Squibb, Celgene, Janssen, Sanofi, Takeda; Financing of Scientific Research: Celgene, Janssen, Novartis, BMS, Chugai, ArtTempi; Expert Testimony: Amgen, Bristol Myers Squibb, Celgene,Chugai, Janssen, Mundipharma, Sanofi, Takeda, Novartis

Posterdiskussion

Sonstige Onkologie II

P991

Despite intervention with Alemtuzumab steroid-refractory acute GvHD leads to tumor control

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Introduction: Steroid-refractory acute graft versus host disease (aGvHD) is the major complication of allogeneic hematopoietic stem cell transplantation. For this life-threatening complication no therapeutic standard exists. We and others have demonstrated that treatment with CD52 antibody alemtuzumab leads to a significant improvement. Despite concerns in CMV-positive individuals that subsequent lymphocyte depletion may lead to virus reactivation, it remains unclear whether this may not also lead to loss of tumor control. Therefore, we evaluated the relapse rate in these alemtuzumab treated patients.
Methods and patients: Fifty-four consecutive patients treated with alemtuzumab between the years 2006 and 2018 were included in a**r**etrospective single-center analysis. The mean age was 51 years (range from 13 to 68 years)and the indication forallogeneic stem cell transplantation were lymphatic (n=16) or myeloid (n=38) malignancies. Patients developed severe acute GvHD (Grade III-IV) with at least intestinal involvement stage 3 that was refractory to high-dose corticosteroids. Typically, a first dose of 5 mg (3-5 mg) given intravenously was followed by 2 or 3 doses of 5 mg (5 to 10 mg) alemtuzumab approximately every 14 days while concurrent immunosuppressive therapy was reduced to a calcineurin inhibitor.
Results: Two-year survival after stem cell transplantation was 34 % (n=18). Sixty-seven percent (n=37) of all alemtuzumab treated patients survived more than 6 months after first application of alemtuzumab. One patient relapsed early within 2 months. Notably, only 11 % (n=4) of long-term-survivors relapsed at a later time point (17 to 143 months after 1st dose of alemtuzumab). Treatment complications were infections, particularly in CMV-positive patients.
Conclusions: These data indicate that severe aGvHD may lead to strong immune mediated tumor control not abrogated by alemtuzumab mediated severe lymphocyte depletion.

Disclosure: No conflict of interest disclosed.

P992

Reduced-intensity conditioning regimen with fludarabine/ melphalan versus sequential melphalan, fludarabine and total body irradiation conditioning in acute myeloid leukemia patients with active leukemia or measurable residual disease

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In patients with relapsed/refractory acute myeloid leukemia (AML) encouraging results have been reported after allogeneic hematopoietic stem cell transplantation (HSCT) following a conditioning regimen with sequential melphalan, fludarabine and total body irradiation (FMTBI) (Steckel et al.,Br. J. Haematol. 2018;180:840-853). However, non-relapse mortality (NRM) was up to 45% in patients >59 years. We hypothesized that in elderly AML patients with active leukemia/measurable residual disease (MRD) FM alone might enable similar long-term graft-versus-host-disease (GVHD) and relapse-free survival (GRFS).
Between 1/2011-2/2019, 72 consecutive AML patients with active disease (n=45)/MRD (n=27) received conditioning with FMTBI (n=42) or FM (n=30) and a T cell-repleted graft from an HLA-matched donor. Active disease was defined as ≥5% bone marrow blasts or extramedullary disease; MRD was defined as ratio of oncogene to control gene (ABL1) >0.01% determined by qPCR analysis of mutated NPM1 (n=22), CBFB-MYH11 (n=2), MLL-PTD (n=2) or JAK-V617F (n=1). FMTBI was the standard conditioning regimen in patients ≤60 years of age; in patients >60 years (n=13), Hematopoietic Cell Transplantation-specific Comorbidity Index (HCT-CI)>3 (n=14), intensive pretreatment prior to AML therapy (n=2), prior/current severe infection (n=2) and/or persistent aplasia (n=2) FM was used.
With a median follow-up of 31.0 months (range, 1-94), probability of overall survival at 3 years was not significantly inferior in the FM group compared to FMTBI (61.2±9.3% vs. 78.8±7.5%; p=0.440) with similar cumulative incidences (CI) of relapse (20.8% vs. 26.6%, p=0.667), but higher CI of NRM in the FM group (2.3% vs. 21.1%, p=0.032). Despite higher NRM in the FM group, GRFS did not differ between groups (42.2±9.2% vs. 49.0±9.7%, p=0.882, respectively).
Our data suggest that FM is well tolerated and associated with similar outcomes compared to FMTBI in patients who proceeded to transplant with active AML/MRD. Thus, FM is a valid option for elderly patients or patients with an HCT-CI>3/intensive pretreatment/infection/aplasia, who face a high risk of NRM, resulting in a median GRFS of 29 months in this cohort.

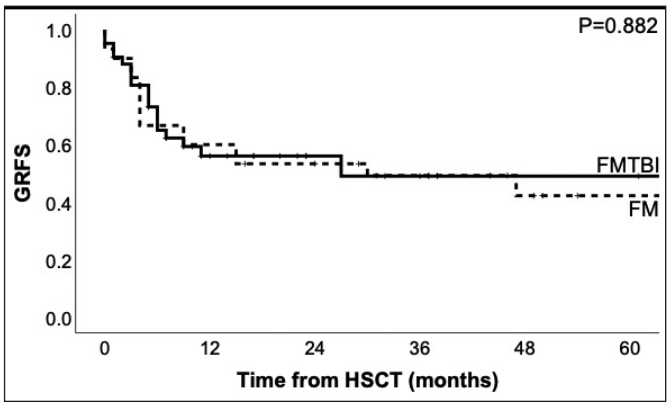

Fig. 1. Probability of GRFS by conditioning regimen

Disclosure: No conflict of interest disclosed.

P993

Outcome and reconstitution after allogeneic hematopoietic stem cell transplantation in patients with secondary myelofibrosis - a retrospective cohort study

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Introduction: Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is the only curative treatment for secondary myelofibrosis (sMF). The course of sMF is characterized by a longer interval between initial diagnosis of essential thrombocythemia (ET) /polycythemia vera (PV) and transformation into sMF with subsequent allo-HSCT. We conducted a single-center retrospective analysis of the long-term outcome of allo-HSCT with respect to engraftment and overall survival (OS) in patients (pts) with sMF.

Methods: This analysis comprised the data of from 60 pts (29 male and 31 female) with sMF evolved from ET (n=29) and PV (n=31) who received allo-HSCT from HLA-matched sibling (n=39) or unrelated (n=21) donors between 1994 and 2018. The median age was 56 (range, 22-70) years. A myeloablative conditioning regimen was performed in 53 pts, while 7 pts were treated with a reduced intensity conditioning regimen. Peripheral blood stem cells (n=55) or bone marrow (n=5) with a median of $7.2x10^6CD34^+$ cells/kg bodyweight (BW) (range, 1.3 to 25) were transplanted.

Median time between initial diagnosis to allo-HSCT was 118 months (range, 19-414). For analysis the cohort was divided into two into two groups: < 120 months between initial diagnosis and allo-HSCT (group I, 30 pts) or >120 months between diagnosis and allo-HSCT (group II, 30 pts).

Results: For the entire cohort, the median follow-up after allo-HSCT was 13 months (range, 1-274) and the 2- and 5-year OS was 50% and 38%, respectively. The rate of complete hematological engraftment was 92% (55 of 60 pts). The median time to recovery was 20 days (range, 12-130) for neutrophils and 25 days (range, 11-180) for platelets.Hematologic reconstitution significantly differed between groups I and II: platelets: 23.9 versus 37.1 days (p=0.003) and neutrophils 23.1 versus 33.1 days (p = 0.02), respectively. Estimated 10-year OS was 52% in group I and 21% in group II (p=0.025) (Figure 1).

Conclusions: Our data showed that longer time to allo-HSCT negatively affected overall survival and hematopoetic reconstitutionin pts with sMF after allo-HSCT.

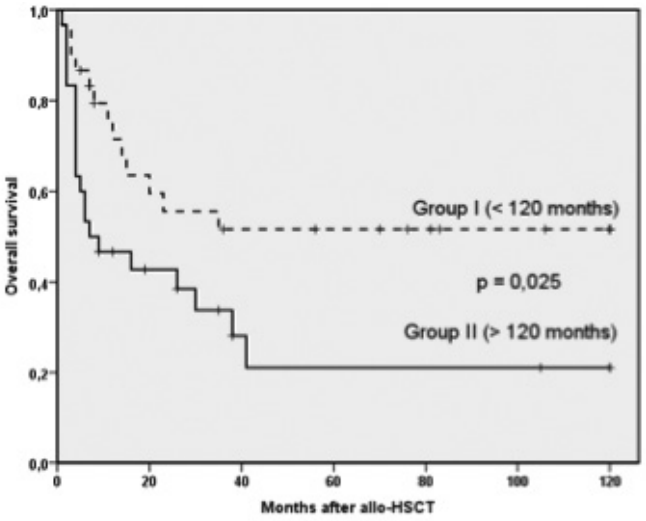

Fig. 1. OS according to interval between initial diagnosis and alle-HSCT

Disclosure: No conflict of interest disclosed.

P994

The extracellular CTLA-4 domain fusion protein abatacept as salvage therapy in the treatment of severe chronic GvHD after allogeneic stem cell transplantation: a retrospective analysis

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Introduction: Chronic graft-versus-host disease (cGvHD) poses the most relevant factor impairing survival and quality of life after allogeneic hematopoietic stem cell transplantation (alloHSCT) and besides corticosteroids there exists no established therapy. Abatacept has shown efficacy in a phase I/IIa trial in cGvHD. We retrospectively analyzed the efficacy and safety for salvage treatment of cGvHD with abatacept since 2018.

Methods: 11 patients (pts) with severe steroid refractory cGvHD and a median age of 54 years (range 35-70 yrs) received abatacept for at least one dose (dosage: 10 mg/kg iv, maximum: 800mg). NIH consensus criteria grading for cGvHD and the immunosuppressive regimen were noted at the time of the first abatacept administration and after 3, 6 and 12 months of therapy. All patients received additional immunosuppression (IS) already given at least 4 weeks without response before start of abatacept. No further IS was added in parallel to abatacept and response assessment was stopped at start of any additional new IS. All patients had received peripheral stem cell grafts. The median number of days between alloHSCT and onset of cGvHD was 294 (range 76-597). The median number of days between alloHSCT and initiation of abatacept therapy was 2103 days (range 188-7953). At cGvHD onset, 10/11 patients had severe cGvHD and 1/11 patients had mild cGvHD. 4/11 patients are still receiving abatacept at the time of analysis.

Results: As abatacept was given fairly recently in most pts, 6-month follow-up was only reached in 4/11 pts and 12 month follow-up has not been reached for any patient yet. Abatacept administration was well tolerated, however one patient showed nausea, vomiting, diarrhea and fever repeatedly upon infusion.

At 3-month follow-up of abatacept therapy, 3/11 pts showed a partial remission, 4/11 pts stable disease, and 1/11 patient progressive disease of cGvHD. Three pts have not yet reached 3-month follow-up.

During abatacept therapy none of the pts suffered from recurrence of the underlying malignancy. Three pts developed significant infections requiring hospital admission with a median of 40 days after the last abatacept dose (range 24-70) and two of them succumbed to sepsis. Of note, 3 pts with severe lung involvement experienced stabilized lung function and improved functional capacity on abatacept.

Conclusions: Abatacept is a promising treatment option in advanced cGvHD but further evaluation within a phase II trial is required.

Disclosure: No conflict of interest disclosed.

P995

Recovery of T cells and their subsets in peripheral blood following donor lymphocyte infusion in patients after allogeneic stem cell transplantation

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Donor lymphocyte infusion (DLI) after allogeneic stem cell transplantation is an established method to enhance the graft-versus-leukemia (GvL) effect. DLI can be administered prophylactic in high-risk patients, pre-emptively in patients having a mixed chimerism and/or a molecular

relapse/persistence or as a therapeutic option in a hematologic relapse. However, what happens on cellular basis in detail and how the GvL effect is triggered after applying CD3+ cells of the donor to the patient is not well understood.
We used immunophenotyping to measure the absolute numbers of CD4+, CD8+, NK (CD56+) and NK-like T (NKT) (CD3+ and CD56+) cells and their respective subsets in peripheral blood of 16 patients receiving up to 3 DLI in increasing dosages ($2x10^5$, $1x10^6$ and $5x10^6$ CD3+ cells/kg bodyweight [bw]). By using Wilcoxon test for associated samples, we compared the results of one day and seven days post DLI each to the measurement before DLI.
After the administration of $1x10^6$ CD3+ cells/kg bw we were able to detect an increase of CD8+ and NKT cells. We determined significant changes between day -1 and day +1, and day +7 respectively, in CD8+ cells, various of their subsets and NKT cells. Among CD8+ subsets we observed a significant increase in naïve, effector memory, effector memory RA+, terminal effector, activated memory, early, intermediate and late, exhausted and terminal effector CD8+ cells. Regarding CD4+ cells, we did not detect significant changes. Further, we did not see significant changes in CD8+ cells after DLI with a lower dosage ($2x10^5$ CD3+ cells/kg bw). Applying a higher dosage ($5x10^6$ CD3+ cells/kg bw) led to a significant increase one day post DLI in CD8+ cells and in CD4+ cells as well as in several of both their subsets. 7 days later this increase was not detected anymore. In NK cells we observed a significant increase only 7 days post DLI with the highest dosage of $5x10^6$ CD3+ cells/kg bw. As internal negative control we measured absolute B cells and their subsets (naïve, memory, class-switch and transitional) not registering any changes after DLI.
Our data show a longer-lasting increase of CD8+ cells and their subsets after the application of DLI. The significant increase of NK cells 7 days post DLI with $5x10^6$ CD3+ cells/kg bw can possibly be explained by the recruitment of NK cells by the at this time point already increased CD8+ cells. This data can give a deeper insight which CD8+ subtypes might play a role for the GvL effect after DLI.

Disclosure: No conflict of interest disclosed.

P996

Pathogen epidemiology of blood stream infections in a cohort of allogeneic hematopoietic stem cell transplant patients treated in Cologne from 2009 - 2018

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Introduction: Due to severe immunosuppression, patients undergoing allogeneic hematopoietic stem cell transplantation (aSCT) are at increased risk of infection and especially blood stream infections (BSI) remain a major cause of death. Knowledge of the specific epidemiology of pathogens and resistances is of utmost importance to optimize antimicrobial treatment strategies.
Methods: Based on the Cologne Cohort of Neutropenic Patients (CoCoNut), we conducted a retrospective analysis of blood cultures collected within 100 days following aSCT in patients treated between 01/2009 and 12/2018 at the University Hospital of Cologne, Germany. Contamination of coagulase-negative Staphylococci (CoNS) isolates (single positive isolate within 5 days) was considered within the analysis.
Results: In total, 843 aSCT patients were available for analysis (484/843 [57%] male). Median age was 53 (interquartile range [IQR] 43-62) years, predominant underlying diseases were acute myeloid leukemia (47%, 397/843), lymphoma (14%, 117/843), and acute lymphoblastic leukemia (11%, 89/843). Median inpatient stay was 39 (IQR 34-50) days, while 67/843 (8%) patients died. Antibacterial prophylaxis was administered in 289/843 (34%) and antifungal prophylaxis in 738/843 (88%) patients. BSI was microbiologically diagnosed in 233/843 patients (28%). In total, 5,489 pairs of blood cultures were taken (median 4 per patient, IQR 2-8), while a pathogen could only be detected in 922/5,489 (17%). Most frequent pathogens were CoNS (259/922, 28%), *Enterococcus spp*. (219/922, 24%), E. *coli* (132/922, 14%), *Klebsiella spp*. (44/922, 5%), *P. aeruginosa* (39/922, 4%), S. *aureus* (37/922, 4%), and *Candida spp*. (42/922, 5%). In 58/922 (6%) cases polymicrobial infection was detected. Within *Enterococci* isolates, 24/219 (11%) were VRE. None of the *Klebsiella*, but 9/132 (7%) of E. *coli* isolates were ESBL positive. In 4/37 (11%) cases S. *aureus* isolates were MRSA.
Conclusion: Patients in the early phase after allogeneic hematopoietic stem cell transplantation are at high risk of BSI with a predominantly gram-positive spectrum. Empirical antimicrobial treatment must consider epidemiology and resistance patterns of pathogens while waiting for blood culture results.

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P997

Cyclophosphamide for salvage therapy of chronic graft-versus-host disease: a retrospective analysis

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Background: Chronic Graft-versus-Host disease (cGvHD) occurs frequently after allogeneic stem cell transplantation (alloSCT) leading to significant morbidity and mortality and lacking approved second line treatment options. We retrospectively analyzed the safety and efficacy of cyclophosphamide (cyclo) for salvage treatment of cGvHD or cGvHD-associated glomerulonephritis (GN) between 2010 and 2019.
Methods: We identified 12 patients (pts) at median age of 57 yrs (range 28-67) receiving cyclo for treatment of moderate (3/12) and severe (5/12) steroid-refractory cGvHD, cGvHD-associated GN (3/12) or CNS manifestation of cGvHD (1/12). All except one received a matched donor graft (11/12 PBSC) with related and unrelated donors in equal parts. Median onset of cGvHD was on day 230 (range 102-571), a median of 5 (range 1-8) organs/sites were involved. Cyclo was started on day 464 (median, range 49 - 2297) after cGvHD onset, the median duration of application was 140 days (range 14-275) with 4/12 currently continuing treatment. 11/12 pts received a continuous oral dose of 50 mg daily (6/12) or every 2-3 days (5/12). One patient was treated with pulse therapy (7 applications, each 500 mg intravenously). NIH organ grading and the intensity of immunosuppression (IS) were assessed at cyclo start and repeated after 3, 6 and 12 months. Response assessment was stopped at start of any additional new IS.
Results: Up to now 3-month follow-up was reached by 9/12 pts. 3/9 showed partial remission (PR), 3/9 no change (NC) and 3/9 required new IS treatment. After 6 months 1/9 showed PR, and 2/9 NC. Mixed response (MR) and progressive disease (PD) were observed each in 1/9 and new IS was required in 4/9. 12-month follow-up was reached by 7/12 pts with 1/7 showing PR and 2/7 NC. Assessment was stopped in 4 cases due to new IS. Best response was 1/11 complete remission (CR), 4/11 PR, 4/11 NC, 1/11 MR and 1/11 PD with one patient not having reached the first follow-up yet. Infectious complications ≥CTCAE grade °III were observed in 3/12 pts. Further adverse events observed each in single pts were a Parainfluenza infection (2 weeks therapy discontinuation), early neutropenia and fever (therapy break-off) and an occipital alopecia. During cyclo therapy none of the pts suffered from recurrence of underlying malignancy.

Conclusions: Overall, cyclo was relatively well tolerated and showed responses in heavily pretreated patients but requires further evaluation within clinical trials.

Disclosure: No conflict of interest disclosed.

P998

Evaluation of safety, tolerability and activity of Sunitinib in patients (pts) with advanced or metastatic renal cell carcinoma (mRCC) in routine clinical practice: the STAR-TOR registry

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Introduction: Sunitinib (SUN), an oral tyrosine kinase inhibitor, is approved in the EU for the treatment of pts with mRCC. A pivotal study had demonstrated significantly increased progression-free survival (PFS) with SUN compared to the former standard interferon alpha (11 vs. 5 months (mo); HR 0.42, p< 0.001). To evaluate the safety profile and efficacy of SUN in a clinical routine setting, a non-interventional trial was conducted.

Methods: A German multicenter registry for pts with mRCC (NCT00700258) was amended to include SUN pts in June 2010 with regulatory and ethic committee´s approval. Objectives are the evaluation of the safety profile, the tolerability and anti-tumor activity of SUN as well as the profile, comorbidity and characteristics of pts and the sequence of systemic therapies in pts with mRCC. Inclusion criteria are histologically confirmed mRCC treated with SUN and written informed consent.

Results: From July 2010 to February 2019, 114 active study sites recruited 665 pts for this interim analysis. Characteristics: 72.6% male, median age 66.9 years (range 23.0-87.7), median Karnofsky index 90% (range 40-100%). Histological subtype: 81.5% with clear cell component, 18.5% other histologal entities. In 82.8% of pts SUN is used as first-line therapy. 435 pts were evaluable with regard to MSKCC criteria: 11.5% favorable, 63.2% intermediate, 25.3% poor risk. For all 665 pts, drug related adverse and serious adverse events were observed in 64.1% and 13.8% of pts, respectively. Most common drug-related toxicities (incidence ≥ 15%) of any grade were gastrointestinal disorders (37.7%), general disorders including fatigue, edema, mucosal inflammation and pain (28.3%), skin and subcutaneous tissue disorders including hand-foot syndrome (23.3%), blood and lymphatic system disorders (18.9%), and nervous system disorders (18.3%). Median PFS for clear-cell mRCC pts (n=542) was 7.8 mo, for pts with other histologies 5.1 mo. The subgroup of clear-cell mRCC pts for which SUN was first-line therapy (n=448) had a PFS of 8.0 mo, for second-line clear-cell pts (n=61) 7.0 mo, ≥ third-line (n=31) 6.4 mo. Overall survival (OS) for all SUN-treated pts was 24.0 mo.

Conclusions: The patient population in the registry represents the expected pattern in pts with mRCC regarding distribution of age, sex, and histology. Efficacy and tolerability of SUN in routine clinical practice confirm published data.

Disclosure: Lothar Bergmann: Advisory Role: BMS, Ipsen, Novartis, Pfizer, Roche, Eusa; Expert Testimony: BMS
Michael Woike: Employment or Leadership Position: Pfizer Pharma GmbH

P999

A randomized phase II study of Nivolumab plus Ipilimumab versus standard of care in previously untreated and advanced non-clear cell renal cell carcinoma (SUNIFORECAST)

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Non-clear cell renal cell carcinomas (nccRCC) are heterogeneous entities and account for approximately 25% of RCC patients (pts.). Since most clinical trials focus on clear-cell RCC (ccRCC) only, data on treatment strategies for nccRCC are limited. Recently, the combination of Nivolumab and Ipilimumab has been investigated in the Checkmate-214 phase-III trial in ccRCC showing a significant improvement in overall survival (OS) and overall response (ORR) in intermediate and high-risk pts. compared to sunitinib. As PD-L1 is expressed in nccRCC on tumor cells and/or tumor infiltrating mononuclear cells (TIMCs) as well, treatment with immune checkpoint-inhibitors in nccRCC appears promising.

In this prospective randomized phase-II multicenter European trial, adults with advanced or metastatic nccRCC without prior systemic therapy are eligible. Other key inclusion criteria include: available tumor tissue, Karnofsky >70% and measurable disease per RECIST 1.1. All histological diagnoses are reviewed by a central pathologist. The study plans to randomize ~306 pts. stratified for papillary or non-papillary non-clear cell histology and by the International Metastatic RCC Database Consortium (IMDC) risk score. Pts. will be randomized 1:1 to either i) Nivolumab 3mg/kg intravenously (IV) plus Ipilimumab 1mg/kg IV every 3 weeks for 4 doses followed by Nivolumab fixed dose 240mg IV every 2 weeks or ii) standard of care agent according to the approved schedule. Treatment will be discontinued in case of unacceptable toxicity or withdrawal of informed consent. Pts may continue treatment beyond progression, if clinical benefit is achieved and treatment is well tolerated. Primary endpoint is the OS rate at 12 months. Secondary endpoints include OS rate at 6 and 18 months, median OS, PFS, ORR and quality of life. The trial is in progress and 69 patients have been randomized up to now.

Clinical trial identification NCT03075423

Disclosure: Lothar Bergmann: Advisory Role: Teilnahme an Advisory Boards BMS, Ipsen, EUSA, Roche, Pfizer; Expert Testimony: Grant von BMS (Goethe Universität)
Bernard Escudier: Advisory Role: Diverse Adboards; Stock Ownership: unbekannt; Honoraria: unbekannt; Financing of Scientific Research: Diverse honorierte Adboards; Expert Testimony: unbekannt; Other Financial Relationships: unbekannt

P1000

Expression of Prostate-specific Membrane Antigen (PSMA) in papillary renal cell carcinoma (pRCC)

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Introduction: The expression of the type 2 transmembrane glykoproteine PSMA is not only specific to prostate cancer tissue but also expressed in the neovascular endothelium of different types of cancer. Among them are breast cancer, colorectal cancer, non-small cell lung carcinoma, and different types of RCC. 68Ga-PSMA-labeled hybrid imaging (CT/ MRI) is used for the detection of PSMA-positive primary tumors and metastases with high sensitivity and specificity. Therapeutic applications such as Lutetium-177-PSMA or Actinium-225-PSMA radionuclid therapy or bispecific antibodies that target PSMA are currently investigated within clinical trials for the treatment of PSMA positive tumors. The aim of our investigation was to determine the expression of PSMA in pRCC and to evaluate PSMA as a potential diagnostic or therapeutic target.
Methods: n=374 patients with pRCC type 1 (n=245; 65,5%) and type 2 (n=129; 34,5%) from the multicentric PANZAR consortium were analyzed. Immunohistochemistry was performed on formalin-fixed, paraffin-embedded tissue samples of primary tumors. Results were correlated with clinical data. PSMA expression of endothelial vessels within tumor tissue was evaluated dichotomously (positive/ negative). Descriptive statistics were performed with SPSS v25.
Results: In pRCC type 1, tissue was positive for PSMA staining in 3/245 (1,2%) of cases whereas 0/129 (0,0%) of the pRCC type 2 samples were positive for PSMA. In all 3 cases where PSMA was detected tumor stage was pT1 cN0 cM0 and grading was G2 (according to Fuhrmann and WHO).
Conclusions: No significant PSMA expression was detected in the PANZAR consortium cohort of pRCC. In light of PSMA-directed treatment strategies and tumor agnostic therapeutic concepts the determination of PSMA expression in pRCC should be limited to individual cases only.

Disclosure: No conflict of interest disclosed.

P1001

TITAN, a phase 3 study of apalutamide (APA) versus placebo (PBO) in patients (pts) with metastatic castration-sensitive prostate cancer (mCSPC) receiving androgen deprivation therapy (ADT)

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Introduction: TITAN evaluated whether APA, a selective next-generation androgen receptor inhibitor, plus ADT improves overall survival (OS) and radiographic progression-free survival (rPFS) compared with PBO plus ADT in pts with mCSPC.
Materials and methods: In this double-blind, phase 3 study, pts with mCSPC regardless of disease extent were randomized 1:1 to APA (240 mg/d) or PBO, added to continuous ADT, in 28-day cycles. Pts with prior treatment for localized disease or prior docetaxel for mCSPC were allowed. Dual primary end points were OS and rPFS. Secondary end points were time to: a) initiation of cytotoxic chemotherapy, b) pain progression, c) chronic opioid use, d) skeletal-related event. Time-to-events were estimated by Kaplan-Meier and Cox proportional hazards methods.
Results: 525 pts were randomized to APA, 527 to PBO. APA significantly improved OS (HR, 0.67; $p = 0.0053$), with a 33% reduction in risk of death. Median OS was not reached, APA or PBO. APA significantly improved rPFS (HR, 0.48; $p < 0.0001$); benefit was observed across all subgroups analyzed. Median rPFS was not reached (APA) and 22.1 mos (PBO). Time to initiation of cytotoxic chemotherapy was significantly improved with APA (HR, 0.39; $p < 0.0001$). Based on these results, TITAN was unblinded to allow crossover of PBO pts to receive APA. Rates of grade 3/4 adverse events (AEs) were similar (42% APA, 41% PBO); discontinuations due to AEs (8% APA, 5% PBO) were low.
Conclusion: In TITAN, addition of APA to ADT significantly improved OS and rPFS in pts with mCSPC, and treatment was tolerable.

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P1002

Can isoflavones influence prostate specific antigen serum levels in localized prostate cancer? A systematic review

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Introduction: Low risk prostate cancer does not always necessitate aggressive or invasive intervention and is best monitored through active surveillance, but in daily practice a majority of men seek a more proactive approach. Therefore, tertiary chemoprevention is an attractive option for men seeking a way to slow disease progression. Several natural anti-carcinogens have been identified in soy beans, especially isoflavones. Case series have been published, demonstrating a positive influence of isoflavones on PSA serum levels in prostate cancer. Consequently, we decided to perform a systematic review about the effect of isoflavones compared to placebo on PSA levels in localized prostate cancer.
Methods: We followed the recommendations provided in the Cochrane Handbook of systematic Reviews and the PRISMA reporting guidelines. On the whole, the primary aim of this review is to summarize the evidence for the use of isoflavones in localized prostate cancer in terms of PSA response.
Results: As a result, in all randomized controlled trials identified for this review (n=5), isoflavones have no influence on PSA levels in localized prostate cancer. Due to heterogeneity of the included studies, we were not able to perform a meta-analysis of the data. On the whole, none of the studies showed a significant difference in PSA levels or a reduction of risk in of PSA failure. The influence of isoflavones on overall survival in localized prostate cancer remains unclear. Reporting of methodological quality parameters was incomplete in 3 of the studies. Overall, risk of bias was assessed as low and the quality of evidence was rated good.
Conclusions: Isoflavones have no influence on PSA levels in localized prostate cancer. The influence of isoflavones on overall survival in localized prostate cancer remains unclear. Furthermore, isoflavones are interesting substance for further research, for example in lipid metabolism and cholesterol.

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P1003

PROpel: A randomized, Phase III trial evaluating the efficacy and safety of olaparib combined with abiraterone as first-line therapy in patients with metastatic castration-resistant prostate cancer (mCRPC)

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Background: A Phase II trial (Study 8, NCT01972217) showed olaparib (300 mg bid) in combination with abiraterone (1000 mg od + prednisolone 5 mg bid) significantly prolonged radiologic progression-free survival (rPFS) compared with abiraterone alone (median 13.8 vs 8.2 months; hazard ratio 0.65, 95% CI 0.44-0.97, *P*= 0.034) in patients (pts) with mCRPC in the second-line metastatic setting who received prior docetaxel (Clarke *et al. Lancet Oncol* 2018). Treatment benefits were achieved irrespective of homologous recombination repair (HRR) mutation status, suggesting potential synergy between the two treatments that could impact a broader patient population. PROpel (EudraCT:2018-002011-10) is the follow-on study to this, and the first Phase III to assess a PARP inhibitor in combination with abiraterone as first-line treatment in a genetically unselected mCRPC population.
Methods: PROpel is a double-blind, placebo-controlled, global multicenter study of pts randomized (1:1) to abiraterone (1000 mg od + prednisolone 5 mg bid) plus either olaparib (tablets, 300 mg bid) or placebo. Pts must not have received prior chemotherapy, new hormonal agents or other systemic treatment at mCRPC stage (except docetaxel at mHSPC stage). Randomization is stratified according to site of metastases (bone only *vs* visceral *vs* other) and docetaxel treatment at mHSPC stage (yes, no). The primary endpoint is investigator-assessed rPFS (RECIST v1.1 [soft tissue] and Prostate Working Cancer Group 3 [PCWG-3 criteria; bone]). Secondary objectives include time to first subsequent therapy or death, time to pain progression, overall survival, safety, tolerability and health-related quality of life. Exploratory endpoints include HRR subgroup analyses to confirm that efficacy is independent of HRR status.

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P1004

Successful targeting of BRAF V600E mutation with vemurafenib in a treatment-resistant extragonadal non-seminomatous germ cell tumor

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Introduction: In contrast to the very good prognosis of testicular germ cell tumors, cure rates of primary extragonadal non-seminomatous germ cell tumors (NSGCT) are considerably lower with 5 year overall survival rates of approximately 50% due to an increased rate of resistance to chemotherapy. Recent studies identified actionable genomic alterations including BRAF-mutations in up to half of the cisplatin-resistant GCT suggesting that these patients may benefit from targeted therapy. Here we report, to our knowledge for the first time, the successful targeting of a cisplatin-refractory primary extragonadal NSGCT harboring a BRAF mutation with vemurafenib.
Methods: A panel of 170 genes was investigated by next generation sequencing (NGS; TruSight Tumor 170 Gene Panel and Next Seq550, Illumina) in cells isolated from tumor tissue by microdissection. Resulting sequences were analyzed for single nucleotide mutations, insertions, deletions, splice variants and gene fusions using human genome hg19 as reference (BaseSpace Sequence Hub, Illumina). Copy number variations were analyzed by comparing the normalized target gene coverage to the whole genome.
Results: A 39-year-old male patient was diagnosed with pT0 N3 M1b S3 stage IIIC, IGCCCG poor risk, primary extragonadal NSGCT. After failure of multiple lines of chemotherapy including high dose chemotherapy with autologous stem cell support and salvage surgery, molecular profiling of a resected liver metastasis was performed by NGS and an actionable BRAF V600E mutation was identified. Targeted treatment with vemurafenib lead to a dramatic decrease of the tumor marker α-Fetoprotein and a very good partial remission with response of all tumor masses except for a single mediastinal lymph node (LN). Therefore, therapy was switched to a combined BRAF/MEK1-inhibition using trametinib plus dabrafenib and salvage surgery of the LN was performed. The molecular profiling of the LN showed an activating MEK1 C121S mutation resistant to currently available BRAF and allosteric MEK inhibitors.
Conclusions: The presented case illustrates that BRAF-inhibition of the classical BRAF V600E mutation can lead to a very good response even in heavily pretreated primary cisplatin-refractory NSGCT. Therefore, although BRAF mutations are rare events in GCT, testing for BRAF mutation should be performed especially in platin-resistant tumors. Further

evaluation of NGS to identify targetable mutations in cisplatin-refractory GCT is warranted.

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P1005

Mechanistic insights into the interaction of Hodgkin lymphoma cells with macrophages

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Introduction: There is growing evidence that macrophages are abundant immune cells in the tumor microenvironment and are predictive in solid tumors and defined lymphoma subtypes. The main unknowns are the functional repertoire, mechanism by which macrophages are recruited and more importantly mechanism leading to their M2-like phenotype. Therefore, further functional studies are required to predict biologic mechanisms associated with human tumor associated macrophages.
Methods: Lymphoma conditioned media were used to differentiate monocytes into macrophages. RNA-Seq und global protein amounts by mass-spec analysis was performed. A chorio-allantois membrane assay was established to monitor lymphoma-macrophage interaction in ovo.
Results: We compared the capacity of conditioned media from aggressive lymphoma cells to affect the migration and differentiation of monocytes and macrophages.We revealed differences in global gene expression and proteom of macrophages derived from CSF1or stimulation with lymphoma conditioned media. Especially conditioned media from Hodgkin lymphoma cells are effective in supporting macrophage differentiation and specifically upregulating a number of surface antigens. Mainly the mannose receptor 1 is higher as in classically derived M2-like macrophages and is partially regulated by specific Hodgkin lymphoma derived autocrine growth factors. The functional consequence is enhanced mannose dependent endocytosis but also collagen I uptake. The collagen I uptake and high MMP9 secretion by macrophages supports the view that these macrophages are actively participating in matrix remodeling. Preclinical models further showed that co-culture of Hodgkin lymphoma cells with monocytes or macrophages support invasion of lymphoma cells into lymphatic vessels although the tumor size and vessel destruction is decreased when compared to lymphoma only tumors.
Conclusions: our analysis facilitates a better understanding of the lymphoma macrophage interaction also in view of drugs targeting this interaction.

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Posterdiskussion

Solide Onkologie

P1006

Health-related quality of life in MONARCH 3: Abemaciclib plus an aromatase inhibitor as initial therapy in women with HR-positive (HR+), HER2-negative (HER2-) advanced breast cancer

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Introduction: In the MONARCH 3 trial, abemaciclib plus an aromatase inhibitor (AI) significantly improved progression free survival and overall response rate with a tolerable safety profile vs placebo (PBO) plus AI. We report patient-reported outcomes (PRO) including health-related quality of life, functioning and symptoms.
Methods: MONARCH 3 (NCT02246621) was a phase 3 study of abemaciclib or PBO plus AI in 493 women with HR+/HER2- advanced breast cancer with no prior systemic therapy for metastatic disease. The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-Core 30 and QLQ-Breast 23 questionnaires were completed at baseline, every 2 cycles through cycle 19, then every 3 cycles until treatment discontinuation, and at short-term follow up. Between-arm comparisons of change from baseline were analysed by mixed model methods. Statistical significance was set at 0.05 and clinical meaningfulness at ≥10 points on a 0-100 scale.
Results: PRO completion rates were >91% through cycle 19; treatment duration was longer for abemaciclib plus AI (median 19 vs 15 cycles). The highest symptom burden was reported during early visits. Diarrhea scores in the abemaciclib arm showed a clinically meaningful (18.68 points) and a statistically significant ($p< 0.001$) increase (worsening) vs PBO; group mean diarrhea scores returned to near-baseline levels post-therapy. Other symptoms with statistically significant differences were fatigue: 4.96, $p=0.004$; systemic therapy side effects: 4.48, $p< 0.001$; appetite loss: 4.03, $p=0.034$; nausea/vomiting: 2.77, $p=0.013$, consistent with investigator-reported treatment emergent adverse events (AE). Several non-symptom results were also statistically significant including global health/health status (-4.36, $p=0.003$), role function (-4.25, $p=0.025$), social function (-3.41, $p=0.047$) and body image (-5.11, $p=0.009$). No statistically significant between-arm differences were noted for physical, emotional and cognitive functioning, or for symptoms of pain, dyspnea, insomnia or constipation, or financial difficulties.
Conclusions: Abemaciclib plus AI resulted in clinically meaningful and statistically significant changes in diarrhea, and clinically not meaningful differences in other symptom scores. Increased GI-related symptoms were consistent with the manageable, reversible AE profile. No clinically

meaningful differences in global health status or functional scores were observed.

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P1007

Management of abemaciclib-associated adverse events in patients with HR+/HER2- advanced breast cancer: analysis of the MONARCH trials

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Introduction: Abemaciclib is a CDK4/6 inhibitor dosed continuously, with demonstrated efficacy and an acceptable safety profile in patients (pts) with HR+/HER2- advanced breast cancer (ABC) alone (MONARCH 1, NCT02102490) or in combination with fulvestrant (MONARCH 2, NCT02107703) or non-steroidal aromatase inhibitors (MONARCH 3, NCT02246621). Most frequent adverse event (AE) was low-grade diarrhea; neutropenia was the most frequent grade 3/4 AE. We describe the timing and management of common AEs in the MONARCH trials.
Methods: MONARCH 1,2,3 trial designs and eligibility criteria have been previously reported. Pts were advised to initiate antidiarrheal therapy at first sign of diarrhea and notify the investigator and drink fluids. If not improved within 24 h to ≤grade 1, treatment was suspended until diarrhea resolved. Dose reductions were required for grade ≥3 or persistent grade 2 diarrhea. For grade 3 neutropenia, abemaciclib was held until ≤grade 2; dose was reduced for recurrent grade 3/4 neutropenia.
Results: This analysis included a total of 900 pts who received abemaciclib in the MONARCH trials. Any-grade diarrhea was reported by 769 (85.4%) pts; grade 3 by 116 (12.9%) pts. Median time to onset of diarrhea was between day 6 and 8; diarrhea was not recovered/resolved in 191 (9.3%) of events. Pts with 1, 2 or ≥3 diarrhea events were: 369 (41.0%), 171 (19.0%) and 229 (25.4%), respectively. Abemaciclib treatment changes occurred in 210 (23.3%) pts (dose reduction, 155 [17.2%]; dose omission, 166 [18.4%]; discontinuation, 20 [2.2%]). First dose reductions for diarrhea occurred at a median of 28-41 days. Dose holds for diarrhea were brief, constituting 1.7-3.8% off total treatment time. Antidiarrheal medications were given to 639 (71.0%) pts. Any-grade neutropenia occurred in 395 (43.9%) pts; grade 3/4 in 227 (25.2%) pts. Median time to onset of grade 3/4 neutropenia was 29-36.5 days and resolved at a median of 11-15 days. Due to neutropenia, 100 pts (11.1%) required dose reduction, 150 pts (16.7%) required dose omission and 16 pts (1.8%) discontinued.
Conclusions: Abemaciclib dose adjustments and/or supportive medication were effective in managing AEs in pts with ABC in the MONARCH trials. Understanding the safety profile of abemaciclib can inform AE management and can extend time on treatment. Previously presented at ESMO 2018, FPN 339P, Rugo HS et al. Reused with permission.

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P1008

Abemaciclib in combination with fulvestrant in patients with HR+/HER2- advanced breast cancer that had exhibited primary or secondary resistance to prior endocrine therapy

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Introduction: Abemaciclib is a selective inhibitor of CDK4/6 that is dosed on a continuous schedule and is approved for the treatment of HR+/HER2- advanced breast cancer (ABC). In the intent-to-treat (ITT) population, abemaciclib with fulvestrant (F) demonstrated improved progression-free survival (PFS) and objective response rate (ORR) vs placebo (P)+F (PFS: 16.4 vs 9.3 months, hazard ratio [HR]:0.553, P< .0000001; ORR in measurable disease: 48.1% vs 21.3%, P< .001). The ITT population was stratified into primary endocrine therapy resistance (ETR), including patients (pts) with ABC whose disease relapsed while receiving the first 2 years of (neo)adjuvant endocrine therapy (ET) or progressed while receiving the first 6 months of ET (Cardoso et al 2014), and secondary ETR. Here, we compare the efficacy and safety of abemaciclib+F vs P+F in the primary and secondary ETR subgroups.
Methods: MONARCH 2 (NCT02107703) was a phase 3 randomized, double-blind study of abemaciclib+F vs P+F in pts with HR+/HER2- ABC that progressed on ET. Pt eligibility criteria have been published (Sledge et al 2017). Pts received oral abemaciclib 150mg twice daily + 500mg F (per label) or P+F. Pts were stratified by sensitivity to ET and metastatic site. Primary objective was investigator-assessed PFS. Secondary objectives included efficacy, safety and tolerability.
Results: In pts with primary ETR (n=169; 25.3%), abemaciclib+F prolonged PFS vs F+P (median PFS: 15.3 vs 7.9 months; HR [95% confidence interval (CI)]:0.45 [0.31, 0.67]; P< .001); ORR in measurable disease was 53.9% vs 17.9% (P< .001). In pts with secondary ETR (n=489;73.1%), abemaciclib+F prolonged PFS vs F+P (median PFS: 16.6 vs 9.6 months; HR [95% CI]:0.59 [0.46, 0.75], P< .001); ORR in measurable disease was 46.2% vs 22.6% (P< .001). Most frequent adverse events (AEs; any grade) in primary and secondary ETR populations were similar. In the primary ETR population, AEs for abemaciclib+F vs P+F were diarrhea (87.3% vs 22.4%), neutropenia (43.6% vs 5.2%), nausea (41.8% vs 25.9%), abdominal pain (36.4% vs. 13.8%), anemia (31.8% vs 5.2%) and leukopenia (30.9% vs 1.7%).
Conclusions: Abemaciclib+F improved PFS and ORR with a generally tolerable safety profile in pts with HR+/HER2- ABC and primary/secondary ETR. Although pts with primary ETR typically have poor prognosis, the benefit from abemaciclib+F was maintained in this population. Previ-

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P1009

Pathological complete response after neoadjuvant chemotherapy in high-risk, early breast cancer patients- a retrospective, single centre analysis from the St. Josef Hospital in Vienna

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Introduction: Pathologic complete response (pCR) following neoadjuvant chemotherapy (NAC) is associated with improved outcomes among patients (pts.) with early-stage, high-risk breast cancer (BC) and serves as a potential surrogate endpoint for long-term survival. The aim of this study was to retrospectively compare pCR rates between the different intrinsic subtypes of BC.
Methods: A review of the data of all pts. treated with NAC for early BC at the St. Josef Hospital Vienna between 2016-2018 was performed. Invasive BC was diagnosed and staged according to national consensus guidelines. NAC usually consisted of epirubicin, cyclophosphamide and docetaxel (EC-T) and Her2-neu directed therapy in case of Her2-neu positive disease.
Results: The data of 144 pts. consecutively treated with NAC were available for analysis (143 female). Median age was 52 years (range 26-78). Baseline clinical characteristics are displayed in table 1. Rates of pathological remission were available from 109 pts. (69.4%) at the time of analysis. pCR defined as ypT0/is ypN0 was 10.9% (n=7) in luminal B Her2- tumours, 39.3% (n=11) in luminal B Her2+ tumours, 63.6 % (n=7) in Her2+ and 58% (n=23) in triple negative tumours. One pt. with luminal A subtype did not show a significant tumour regression. During the observation period one (0.7%) pt. had local disease recurrence and one pt. (0.7%) relapsed and died from metastatic disease.
Conclusions: The results of our retrospective analysis demonstrate high pCR rates in Her2neu positive and triple negative early stage breast cancer similar to recently published data in a large cohort of unselected patients. These real world date underscore the importance of a neoadjuvant treatment approach also in a non academic breast cancer centre.

Table 1. Baseline patient characteristics (n=144)

	%	N
All patients	100	144
Histology		
Ductal invasive	83.8	120
Lobular invasive	5.6	8
Other type	11.1	16
Subtype		
Luminal A	0.7	1
Luminal B Her2+	19.5	28
Luminal B Her2-	44.5	64
Her2+	7.6	11
Triple negative	27.8	40
Tumor stage		
cT1	32.6	47
cT2	57.6	83
cT3	7.6	11
cT4	2.7	4
Nodal status		
cN0	56.3	81
cN1	39.6	57
cN2	-	-
cN3	1.4	2
Missing	2.8	4
Tumor grade		
1	1.4	2
2	36.1	52
3	61.2	88
Missing	1.4	2

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P1010

Large single-center safety and outcome analyses of dual anti-Her2 treatment with Trastuzumab and Pertuzumab for breast cancer

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Her2-positive breast cancer (Her2pos-BCa) is the second most fatal molecular subtype of breast cancer. Clinical trials have led to the approval of the combination of trastuzumab (T) and pertuzumab (P) in neoadjuvant, adjuvant and palliative settings of Her2pos-BCa. While outcomes from multicenter clinical trials were published, single-center institutional or academical outcome as well as safety data of patients treated with T+P, in combination with or without chemotherapy, is sporadic for all settings currently approved.In our retrospective analysis, we compare outcome and safety data from Austrias biggest academic cancer center with those reported in clinical trials. Using drug order protocols and patient records, we present data of approximately 1500 cycles of T+P received and report pathological complete response (pCR) rates for neoadjuvant and progression-free survival (PFS) for palliative patient treatment. Additionally, we address the topic of cardiac toxicity by reporting ejection fraction (EF)

drops observed in our patient cohort. Further, we carefully describe both neoadjuvant and palliative patient groups by assessment of body weight/size, tumor stage, histology including immunohistochemistry (IHC), prior lines of oncological therapies received and deaths observed.Summarizing, we present a large academic single-center database of patients treated with T+P across all treatment settings and lines and report descriptive, outcome and safety data for this breast cancer patient cohort.

Disclosure: No conflict of interest disclosed.

P1011

Dose specific treatment of anti-cancer drugs induce features of EMT in pancreatic cancer cells

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Background: Pancreatic ductal adenocarcinoma (PDAC) is estimated to be the second leading cause of cancer-related death in Germany and the USA by the year 2030. In contrast to other solid tumors, the prognosis of PDAC remains unchanged and clinical therapies are not satisfactory. Within an aggressive subtype, different characteristic molecular pathways are found, some of which are MYC-dependent. The activation of MYC pathways are associated with epithelial to mesenchymal transition (EMT) signatures and certain therapeutics are known to activate MYC may induce increased aggressiveness. Our aim is to dissect the MYC-EMT axis to identify new target structures to treat PDAC.
Methods: A total of 12 murine and human cell lines were treated for 72h with Irinotecan, Gemcitabine, Paclitaxel, 5-Fluorouracil and Oxaliplatin and viability was determined by MTT-Test (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide. Analysis of motility and morphologic changes upon treatment with Paclitaxel and TGF-beta has been performed by fluorescence based microscopy, wound healing assays and Boyden-chamber invasion assays in one human and two murine PDAC cell lines. Relative mRNA expression of CDH1, CDH2, VIM, ZEB1, ZEB2, SNAIL, SLUG, PRRX1 and MYC expression has been determined by qPCR (DDCt). Protein expression of VIM, MYC and CDH1 was analyzed by Western-Blot. Analysis of transcriptomic profiles (metadata) has been performed by analytical tools from the GenePattern repository (Broad Institute).
Results: An epithelial-to-mesenchymal transition (EMT) is activated in pancreatic cancer cell lines upon treatment with specific dosages of the taxane paclitaxel. Moreover, we could also notice a stronger mesenchymal shaping, possibly enhancing the metastatic capacity of the cells and drug resistance, arguing for the amplification of the EMT program. Our results show that at certain anticancer drug concentrations mesenchymal features and EMT are activated along with MYC activation.
Conclusions: Different molecular networks are activated in pancreatic cancer cells, whereas activation of certain pathways, such as MYC-pathways may worsen the therapeutic outcome. In the future, individualized therapeutic approaches have to take subtype specific leading molecular mechanisms into account to improve the therapeutical outcome.

Disclosure: No conflict of interest disclosed.

P1012

Identification of novel subtype-specific therapeutic approaches by high throughput drug screening in PDAC

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Background: Pancreatic ductal adenocarcinoma (PDAC) is the most frequent type of pancreatic cancer and one of the most lethal malignancies with a 5-year survival rate of less than 8%. Genetic heterogeneity is a crucial contributor towards the failure of current clinical treatments. Recent studies have shown distinct molecular subtypes of PDAC associated with different prognosis and therapy response. The most aggressive subtype shows a high mRNA expression of the pro-apoptotic protein NOXA correlating with worse overall survival. The aim of this study is to identify unknown vulnerabilities by an unbiased pharmacological screening.
Methods: Two human PDAC cell lines -with contrasting NOXA expression- were used in addition to two murine PDAC cell lines harboring a CRISPR/Cas9-mediated NOXA knock out together with its wild type isogenic cell line. All of these six cell lines were used for a drug screening of 1842 compounds (FDA approved and experimental drugs) at a single dose concentration of 600 nM. The cells were seeded onto 96-well plates to maintain cell line characteristics and grown for 24 h. After 72 h of treatment, the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) reaction was performed and absorbance was read at 570 nm on a plate reader to measure viability. Multivariate analysis of variance (MANOVA) was performed with the software Infostat using a confidence interval of 95% (α=0,05).
Results: Comparison of $NOXA^{high/wildtype}$ and $NOXA^{low/knockout}$ showed a significant increased sensitivity towards 2% of all substances in the $NOXA^{high/wildtype}$ cell lines. Of those, we found hits involved in DNA-synthesis (20%), Cytoskeleton dynamics (17,5%), PLK1 (10%), Epigenetic modulators (7,5%), Proteasome inhibition (5%), mTOR/PI3K (2,5%) among other pathways. In the latter, two hits were exclusively present: a glucocorticoid steroid and Raltitrexed, an inhibitor of thymidylate synthase. Our screening results were corroborated by comparing it with public data.
Conclusions: Our data supports the notion that high-throughput drug screenings represent a powerful tool to elucidate new pathways involved in malignant diseases and to give the first steps towards the development of subtype-specific strategies for personalized treatment approaches in PDAC.

Disclosure: No conflict of interest disclosed.

P1013

Seemingly stable quality of life due to return rate bias in patients with locally advanced or metastatic pancreatic cancer - data from the TPK clinical cohort study

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Introduction: A main goal in the treatment of locally advanced or metastatic pancreatic cancer (mPC) is stabilization of quality of life (QoL) by palliation of tumor symptoms. Analysis of patient-reported outcomes (PRO) in routine care can reveal important information on the quality of care, but missing data present a key challenge. PanLife - a sub-project of the Tumor Registry Pancreatic Cancer (TPK) investigates longitudinal PRO to better understand the real-life situation of patients (pts) with mPC.
Methods: TPK is a prospective, multicentre, cohort study of pts with mPC receiving systemic palliative therapy. Starting in February 2014, 104 study sites in Germany recruited >1500 evaluable pts with mPC at the start of their 1st-line treatment. In the sub-project PanLife PRO are measured with the validated questionnaires (Q) EORTC QLQ-C15-PAL and EORTC-QLQ-PAN26. PRO Q were collected at the start of 1st-line treatment (BL) and every two months thereafter. Here, interim data on QoL are reported with focus on the risk of misinterpretation due to missing data (return rate bias).
Results: Q return rate, mean change from baseline for all pts and mean values according to the number of returned Q are shown in Table 1 for the global health status. While mean change results over all pts indicated stable QoL, mean values by return rate showed deterioration of QoL in all subgroups with QoL being lowest in pts with lowest number of returned Q. Similar results were observed for the scales pain and loss of appetite, In contrast, deterioration of the physical health status scale was so strong that it was detectable in the total sample (-10 points at 4-10 months) and in the subgroups by returned Q.

Tab. 1. Mean change and mean values of the global health status (EORTC QLQ-C15-PAL)

	Start of pal. 1st-line (BL)	2 Mo	4 Mo	6 Mo	8 Mo	10 Mo
Return rate	83%	63%	60%	56%	51%	46%
All patients (mean change, range +50 : -50)	-	-1	-1	-1	-2	-2
Mean values						
Pts with 6 Q	54.9	56.4	57.4	56.7	55.2	52.7
Pts with 5 Q	52.1	53.7	50.5	48.0	42.6	
Pts with 4 Q	48.2	49.2	48.0	43.4		
Pts with 3 Q	50.3	48.0	45.0			
Pts with 2 Q	46.8	40.0				
Pts with 1 Q	42.6					

Conclusions: Changes in QoL in pts with mPC should be presented in total and by subgroup according to returned Q. Pts with low QoL will more likely not return their Q leading to non-random missing data and skewed representation of QoL if not addressed. PRO data from the TPK show that QoL and physical health deteriorate and pain remains a challenge in treatment of mPC pts.

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P1014

Ex vivo drug testing in patient-derived pancreatic cancer organoids (PDOs) - challenges and potential applications

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Introduction: The identification of individual therapeutic vulnerabilities in pancreatic cancer (PDAC) based on tumor molecular profiling is extremely challenging. 92%-95% of PDACs harbor oncogenic KRAS mutations and there is currently no successful targeting strategy for KRAS-driven tumors. Patient-derived pancreatic cancer organoids (PDOs) preserve genotype and phenotype of individual tumors and therefore uniquely allow for testing drug sensitivities *ex vivo* in a co-clinical setting.
Methods: For this project, we generated a large living biobank of PDOs derived from patients undergoing resection or surgical biopsy of pancreatic adenocarcinoma at the University of Freiburg Pancreatic Cancer Center. Organoid cultures undergo a standardized work-up including histology and quantitative KRAS mutational analysis by digital droplet PCR (ddPCR), followed by NGS panel or whole exome sequencing.
Results: For drug testing, we have been optimizing an *ex vivo* drug screening protocol for individual drugs and rational drug combinations. We present and discuss findings from drug testing in 2D vs. 3D culture as well as in the presence and absence of stroma cells. Drug testing results are aligned with individual tumor's molecular profiles. We discuss challenges and further optimization with a future co-clinical trial in mind.
Summary: Ex vivo drug testing of patient-derived organoids holds great potential as a novel tool for pancreatic cancer precision oncology

Disclosure: No conflict of interest disclosed.

P1015

MARkers for ImmunotherApy in sarcomas (the MARIAchIS-project) - what can we learn from responders?

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Introduction: Immune checkpoint inhibitors (ICIs) have shown clinical activity and gained approval in multiple cancer entities. However, few studies have been conducted in soft tissue sarcomas (STS) and most of did not stratify for histology and biomarkers. In these unselected groups response rates are less than 10%. Nevertheless, some patients derive substantial benefit and predictive biomarkers for selection of those patients are urgently needed.
Methods: We have established a multicenter database with patients diagnosed with STS who received ICIs within or outside of clinical trials. Patients were categorized in those with immediate progression and those with at least 12 weeks of disease stabilization or unequivocal sign of tumor shrinkage. Analyses from tumor tissue of patients, if available, were started looking for immune cell infiltrates, PD-L1 expression, microsatellite instability and mutational load.
Results: Up to now, the database consists of 12 cases with different histological subtypes of STSs (1 undifferentiated pleomorphic sarcoma, 3 alveolar soft part sarcomas, 2 malignant peripheral nerve sheath tumors, 3 angiosarcomas, 2 clear cell sarcomas and 1 myxofibrosarcoma). In this highly select cohort, clinical benefit was seen in 9 cases. Preliminary analyses associate PD-L1 expression with response. Nonetheless, lack of PD-L1 expression surprisingly did not preclude clinical benefit.
Conclusions: Patients with best clinical benefit from ICIs seem to exhibit a high rate of PD-L1 expression. Moreover, certain histological subtypes may have a particular benefit from immunotherapy and deserve a systematic screen. But additional biomarkers are needed and have to be validated. Hereby, outlier (non-) responders could provide crucial insight for future, biomarker-driven studies. The MARIAchIS-Project is an ongoing initiative and seeks national wide collaborations.

Disclosure: No conflict of interest disclosed.

P1016

Olaratumab in combination with Doxorubicine in advanced or metastatic soft tissue sarcoma -the Charité experience

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Introduction: Two years after approval from the FDA due to the promising results of a phase Ib/II trial, the anti-PDGFRA antibody olaratumab could not be proven additionally beneficial to doxorubicine treatment in the phase III ANNOUNCE trial. We hereby share our experience at Charité-Universitätsmedizin Berlin with olaratumab in combination with doxorubicine in soft tissue sarcoma (STS).
Methods: N=32 STS patients treated with olaratumab/doxorubicine between 2016 and 2019 at our institution were included. In n=9 of the patients the intention was to possibly enable surgery, the remaining patients

received palliative treatment. The median age was 63 years (range 44-81), there were n=21 male and n=11 female patients included. In the majority of patients, it was the first systemic therapy (n=25) and n=7 had received 1-4 previous treatments. All of the patients received at least 1 cycle, 28% of the patients completed 6-8 cycles. N=5 patients with localized disease received additional regional hyperthermia.
Results: In our limited single-center patient population, mean PFS was 3.1 months (range 0.6-16.2). A response [complete remission (CR), partial remission (PR) or stable disease (SD)] was seen in n=11 (34%) cases whereas n=21 (66%) patients showed progressive disease (PD). In n=9 patients surgery was performed subsequently in an individual therapeutic approach. 4 out of 5 patients receiving additional regional hyperthermia achieved PR or SD. The combination treatment was well tolerated with no grade 3/4 toxicity related to olaratumab.
Conclusions: The efficacy data in our limited patient population compares to the previous results for the olaratumab/doxorubicine combination therapy in STS. Therefore, we might contribute to a further understanding for the heterogenous efficacy results of olaratumab in this entity. Additionally, our findings suggest that a combination therapy with this substance might be valuable in a neoadjuvant setting or in combination with hyperthermia

Disclosure: No conflict of interest disclosed.

P1017

Impact of a specialised palliative care intervention in patients with advanced soft tissue sarcoma - a retrospective analysis

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Introduction: Soft tissue sarcomas (STS) are rare diseases accounting for less than 1% of all malignancies. Half of patients (pts) develop metastases with limited survival after the beginning of first-line palliative chemotherapy. While there is still a high unmet need for modern effective therapies to prolong survival, the aims of palliative treatment include symptom relief and improvement of quality of life. Data about symptom burden and palliative care of these pts are limited. In this analysis we assess the effectiveness of a palliative care intervention focusing on symptom relief and quality of life in pts with STS.
Methods: We conducted a retrospective analysis of pts with symptomatic advanced STS who were admitted to our palliative care unit from 2012 until 2018. Symptom burden was measured with a standardized palliative base assessment questionnaire at admission and discharge including ECOG performance status, pain (numeric rating scale), distress thermometer, MIDOS (minimal documentation system for patients in palliative care) and personal situational challenges. Additional information was collected from the hospital patient records.
Results: We analysed 52 hospitalisations of 33 pts with STS. Median disease duration until admission was 24 months (range 1-125), 85% of pts were metastasised at admission. The majority of pts were admitted from home (69%). The predominant indication for admission was pain, concomitant severe symptoms were mainly weakness and fatigue. Palliative care intervention led to a significant reduction of pain (median NRS for acute pain was reduced from 3 to 1, pain within the last 24hrs from 5 to 2) and of the median MIDOS symptom score (18 to 13). In addition, the median stress level according to the distress thermometer was reduced significantly (7.5 to 5), whereas no change in ECOG performance status was observed (median 3 at admission and discharge). The majority of pts (58%) could be discharged, 30% of them with palliative home care. 25% died on the palliative care unit.
Conclusions: Our analysis demonstrates that specialised palliative care intervention leads to a significant symptom relief and appears effective for pts with advanced STS. Further exploration of the effect of an early integration of palliative care on improvement of overall survival and identification of particularly affected subjects of this heterogeneous group of pts is warranted.

Disclosure: No conflict of interest disclosed.

P1018

Extraordinary response to a combination therapy with Dabrafenib and Trametinib in a malignant extrarenal rhabdoid tumor of the liver in adult - a call for precision oncology in sarcomas

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Introduction: Malignant rhabdoid tumor (MRT) of the kidney is an uncommon renal tumor in children. This tumor has a very aggressive behavior and poor prognosis. In adults MRTs are extremely rare. We report a 35-year old male patient with a MRT of the liver showing an extraordinary response to dabrafenib and trametinib.
Methods: For identification of potential targetable mutations, a therapy-orientated next-generation sequencing (NGS) panel (GeneRead DNAseq Custom Panel V2, Qiagen) was performed. Tumor cell content was minimum 60%. For library preparation, the NEBNext Ultra DNA Library Prep Kit for Illumina (NEB) was used and sequencing was performed on Illumina MiSeq.
Results: In October 2018, a 35-year old male patient underwent emergency surgery in an external hospital due to acute liver bleeding. He was referred to our center with the diagnosis of a MRT. Post-operative staging revealed residues of tumor in liver segments VI and VII as well as local lymph node metastasis, peritoneal sarcomatosis and bone metastasis. Due to reduced performance score (ECOG 3) and significant comorbidities, a monotherapy with doxorubicin 75mg/m^2 was started. There was no clinical benefit from treatment and chronic tumor bleeding required >12 blood transfusions. Consequently, the first scan showed tumor progression. Based on mutations in BRAF Exon 15 (c.1799T>A) and MAP2K2 Exon 7 (c.856G>A) an off-label therapy with a combination of dabrafenib and trametinib was initiated. Clinically, tumor bleeding ceased, the patient improved rapidly from tumor symptoms as well as in performance score (ECOG 1). The follow-up CT scan also showed an ongoing extraordinary tumor response with a PFS of >4 months.
Conclusions: For extremely rare tumors standard treatment recommendations do not exist. In our case of adult MRT comorbidities prohibited standard chemotherapy according to the European Rhabdoid Registry Study (EU-RHAB). Precision oncology may provide individual treatment approaches, which optimize treatment outcome and should be available early during the course of treatment. Customized therapy-orientated NGS-panels are a useful a tool for identification of targetable mutations. In this case, the NGS-panel helped to successfully guide the therapy using a combination of the MAPK inhibitor dabrafenib and MEK inhibitor trametinib in this rare case.

Disclosure: No conflict of interest disclosed.

P1019

Uncommon location of Kaposi`s sarcoma in human immunodeficiency virus (HIV) infection

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Introduction: The most frequent symptoms of acute HIV infection are fever, skin rash, fatigue, lymphnode swelling and loss of appetite. In advanced stages there are often uncommon infections, that leads to diagnosis of HIV-infection.
We reported about an unusual tumour and location as first manifeation of HIV-infection.
Case-Report: A-48-year old caucasian male was admitted to our emergency department complaining of dysphagia, weight loss and a small tumour of the maxilla (Picture 1)

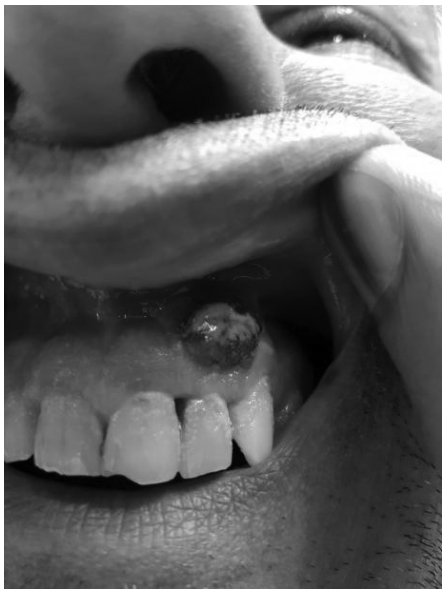

Fig. 1. Kaposi sarcoma left maxilla

The physical examination was unremarkable. A full blood count showed a mild anaemia with a haemoglobin of 12.2g /dl. The leucocyte and thrombocyte counts were normal. Transaminases were not elevated. A gastroscopy showed an extended oesophageal candidiasis and a histological examination of the tumour revealed a Kaposi`s sarcoma.
The HIV 1 serology was positive. The viral load was found to be 91000 copies per µl and the CD4 count was 30 per µl (normal range 400 to 1200). We initiated therapy with fluconazol and triple antiretroviral therapy with efavirenz, tenofovir, emtricitabine. Additionally, a pneumocystis jiroveci prophylaxis with trimethoprim/sulfametoxazol was started.
The oesophageal candidiasis resolved in 10 days. Under the treatment with efavirenz, tenofovir and emtricitabine the viral load sunk below the level of detection within 6 months. There were no side effects of the medical therapy.
The Kaposi`s sarcoma regressed spontaneously by antiretroviral therapy within 4 months (Picture 2)

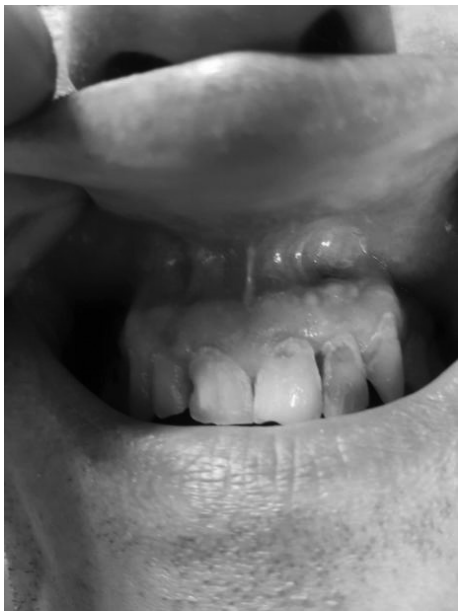

Fig. 2. Kaposi sarcoma left maxilla after 4 months antiviral therapy

The patient condition continues to be good and the antiretroviral therapy is ongoing.

Conclusions: In all patients with signs of weight loss and dysphagia the oral cavity should also particular examine to avoid overlooking first indications of HIV-infection.

Disclosure: No conflict of interest disclosed.

P1020

Integration of circulating tumor DNA (ctDNA) and novel protein biomarkers for stratification and therapy monitoring in stage IV pancreatic cancer

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Introduction: The clinical course and response to chemotherapy of stage IV pancreatic cancer patients are highly heterogeneous. Prognostic stratification and early identification of treatment failure are therefore critical goals to improve patient outcome. Liquid biomarkers hold great potential to deepen the insight into individual patient's tumor biology and treatment response. However, the analysis of single biomarkers such as CA19-9 or circulating mutated KRAS typically lack sensitivity or specificity, while more comprehensive NGS-based liquid biopsies are costly, particularly when performed repeatedly.
Methods: We collected and analyzed plasma samples from 50 individual patients undergoing systemic chemotherapy for stage IV pancreatic cancer at our institution. Cell-free DNA was extracted and screened for cfKRAS^{mut} using in-house designed generic discriminatory multiplex digital droplet PCR (ddPCR) assays. Established and experimental protein biomarkers developed in own previous work (Klett et. al, Frontiers Genetics, 2018) were assayed in parallel und results were integrated and correlated to treatment response, progression-free and overall survival.
Results: Both cfKRAS^{mut} copy numbers and concentrations of selected protein markers correlated with disease stage. ctDNA copy numbers and, with a distinct pattern, protein biomarkers were enriched in patients with liver metastases, suggesting distinct mechanisms of release into circulation. Integration of protein biomarkers and cfKRAS^{mut} in untreated metastasized patients increased prognostic and predictive power when compared to each parameter individually in preliminary analyses. Dynamic changes of cfKRAS^{mut} and biomarker proteins during 1st line chemotherapy were highly predictive of PFS and OS. Integration of cfKRAS^{mut} and protein biomarker further enhanced robustness and power of the individual assays.
Conclusion: The integrated analysis of ctDNA and novel protein biomarkers in patients undergoing systemic treatment for stage IV pancreatic cancer holds great potential to predict overall survival and identify treatment failure.

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V1021

Gilteritinib significantly prolongs overall survival in patients with FLT3-mutated relapsed/refractory acute myeloid leukemia: results from the phase 3 ADMIRAL trial

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Introduction: Gilteritinib is a potent/selective oral FLT3 inhibitor. Based upon interim analysis response rates from the ADMIRAL phase 3 study of gilteritinib vs salvage chemotherapy (SC) in patients (pts) with relapsed/refractory (R/R) *FLT3*-mutated (*FLT3*$^{mut+}$) AML (NCT02421939), gilteritinib was approved as single-agent therapy in this population. We present the final results of this pivotal trial.

Methods: Adults with confirmed *FLT3*$^{mut+}$ AML (*FLT3*-ITD or *FLT3*-TKD D835/I836 mutations) refractory to induction chemotherapy, or in untreated first relapse, were randomized (2:1) to receive continuous 28-day cycles of 120-mg/day gilteritinib or prerandomization-selected SC: low-dose cytarabine (LoDAC), azacitidine (AZA), mitoxantrone/etoposide/cytarabine (MEC), or fludarabine/cytarabine/granulocyte colony-stimulating factor/idarubicin (FLAG-IDA). Prior FLT3 inhibitor use, other than midostaurin or sorafenib, was excluded. Overall survival (OS) and the combined rate of complete remission/complete remission with partial hematologic recovery (CR/CRh) were co-primary endpoints. Safety/tolerability was also examined.

Results: A total of 371 pts were randomized: 247 to gilteritinib and 124 to SC (MEC, 25.7%; FLAG-IDA, 36.7%; LoDAC, 14.7%; AZA, 22.9%). Median age was 62 years (range, 19-85). Baseline *FLT3* mutations were: *FLT3*-ITD, 88.4%; *FLT3*-TKD, 8.4%; both *FLT3*-ITD and *FLT3*-TKD, 1.9%; unconfirmed, 1.3%. Overall, 39.4% of pts had refractory AML and 60.6% had relapsed AML. Patients assigned to gilteritinib had significantly longer OS (9.3 months) than SC (5.6 months; hazard ratio for death=0.637; *P*=0.0007); 1-year survival rates were 37.1% and 16.7%, respectively. The CR/CRh rates for gilteritinib and SC were 34.0% and 15.3%, respectively (nominal *P*=0.0001); CR rates were 21.1% and 10.5%. Common adverse events (AEs) in all randomized pts were febrile neutropenia (43.7%), anemia (43.4%), and pyrexia (38.6%). Common grade ≥3 AEs related to gilteritinib were anemia (19.5%), febrile neutropenia (15.4%), thrombocytopenia (12.2%), and decreased platelet count (12.2%). Exposure-adjusted serious treatment-emergent AEs were less common with gilteritinib (7.1/patient-year) than SC (9.2/patient-year).

Conclusions: In pts with R/R *FLT3*$^{mut+}$ AML, gilteritinib demonstrated superior efficacy compared with SC and had a favorable safety profile. These results change the treatment paradigm for R/R *FLT3*$^{mut+}$ AML and establish gilteritinib as the new standard of care.

Disclosure: Alexander E Perl: Advisory Role: Astellas US Pharma, Inc., Daiichi Sankyo, Arog, AbbVie; Financing of Scientific Research: Novartis, Pfizer, Actinium Pharmaceuticals, Jazz Pharmaceuticals, Takeda Oncology, AbbVie, NewLink Genetics, Asana Biosciences, Seattle Genetics, Agios; Expert Testimony: Astellas US Pharma, Inc., Daiichi Sankyo, Novartis, Bayer, FujiFilm, BioMed Valley Discoveries

Mark J. Levis: Expert Testimony: Astellas, Novartis, FujiFilm; Other Financial Relationships: Daiichi-Sankyo

V1022

Clinical characteristics and outcome in *IDH1/2* mutant AML patients - analysis of 5213 newly diagnosed patients with Acute Myeloid Leukemia

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Purpose: Mutations of the *IDH1* and *IDH2* genes are frequent alterations in AML. Previous analyses have reported differential impact on outcome, depending on the *IDH*-mutation type.

Patients and methods: AML pts. consecutively enrolled into intensive AML treatment protocols of the SAL, AMLCG or into the SAL registry were included in this analysis. Screening for mutations was performed either by NGS based sequencing of exon 4 for IDH1 and 2 or DHPLC, followed by NGS.

Results: Samples of 5213 pts. were analyzed. Median FU was 87 months. Pts.' characteristics are shown in Table 1. 446 pts. (8.6%) had *IDH1* and 608 (11,7%) had *IDH2* mutations.

Of the *IDH1* variants, the most common ones were the R132C found in 195 pts. (44%) and R132H in 182 pts. (41%). For *IDH2*, 463 pts. had the R140Q (77%) and 116 pts. the R172K (19%) variant.
In *IDH1*-mutated pts., we observed significant differences in baseline characteristics between the two most common mutation types. Pts. carrying the R132C mutation were older (61 vs. 55 years, $p< .001$), had lower WBC (3.6 vs. 21 Gpt/L, $p< .001$) and were less likely to have *NPM1* (25% vs. 70%, $p< .001$), and *FLT3*-ITD mutations (10% vs. 25%, $p< .001$) than those with the R132H variant.
In univariate cox regression, the CR rate (54% vs 74%, $p\leq.001$) and OS (12.9 months vs. 21.8 months) was significantly lower in pts. with *IDH1* R132C compared to those with the R132H variant. In multivariate analysis including age, WBC, *NPM1* and *FLT3*-ITD status, and ELN2017 risk, the CR rate was also significantly lower ($p=.038$).
For IDH2, OS was in trend more favourable for pts. with *IDH2* R172K (26 vs. 18 months) as compared to those with R140Q. In Pts. w/o *NPM1*/*FLT3*-ITD mutation, those with *IDH2* R172K (n=51) had a highly significant better OS than pts. (n=84) with *IDH2* R140Q (52 vs. 17 months, $p=.017$).
Conclusion: In this large cohort of AML pts. with *IDH1*/2 mutations, we found significant and so far not reported differences for the most prominent mutations types of *IDH1*. In case of *IDH2* we confirmed findings on co-mutations and showed a favorable outcome for intensively treated pts. without *NPM1*/*FLT3*-ITD mutation and *IDH2* R172K.

Tab. 1. Baseline characteristics

Parameter	IDH WT	IDH1 R132C	IDH1 R132H	IDH1 other	IDH2 R172	IDH2 R140	p-value
Number of pts., n (%)	4176 (100)	195 (100)	182 (100)	68 (100)	116 (100)	470 (100)	
Age (years), median	57	63	54	61	61	60	<0.001
WBC in Gpt/l, median	15.2	3.8	20.7	15	2.3	16.7	<0.001
NPM1 mut; n (%)	1145 (28)	48 (25)	127 (70)	44 (65)	2 (2)	229 (49)	<0.001
FLT3-ITD; n (%)	917 (22)	19 (10)	46 (25)	17 (25)	5 (4)	113 (24)	<0.001

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Christian Thiede: Employment or Leadership Position: Agendix GmbH; Stock Ownership: Agendix GmbH

V1023

Routine care of advanced breast cancer: the prospective, national research platform OPAL for patients with advanced breast cancer in Germany

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Introduction: The Tumor Registry Breast Cancer (TMK) has prospectively documented treatment and outcome of patients (pts) with breast cancer (BC) by oncologists in Germany since 2007 and provided insight into treatment in routine practice where pts' sociodemographic and medical characteristics often differ from those treated in clinical trials. OPAL continues this successful work focusing on changes in treatment reality of advanced BC (ABC), patient-reported outcomes (PROs) and representation of all specialists (medical and gynecologic oncologists) treating ABC in Germany.
Methods: OPAL like the TMK is a prospective, observational, open, multicentre clinical registry. In addition to the 4500 pts from the TMK, at least 2000 pts will be recruited in OPAL, stratified into 3 cohorts: 1000 pts with hormone receptor positive, HER2-negative, 500 pts with HER2-positive and 500 pts with triple-negative ABC. In total, up to 200 sites (comprehensive cancer centres, clinics and office-based gynaecologic and medical oncologists) will be participating. All pts are recruited at start of their first palliative systemic treatment (≤6 weeks after start of treatment, PRO-Module: before/at start of treatment), to avoid an overestimation of outcome data. There is no treatment specification.
OPAL collects detailed information on all (sequential) treatments, patient and tumor characteristics, physician-reported factors potentially influencing treatment decision, biomarker testing and additional treatments (surgery, radiotherapy, osteoprotective therapy). Follow-Up is until death or up to 5 years.
Associated satellite projects are a decentralized biobank for future investigational translational research and the collection of PROs in clinical routine (every 3 months for 3.5 years). The data remain in Germany.
Results: By April 2019, a total of 5076 pts had been recruited, 434 since the start of OPAL in December 2017. 2105 pts with ABC recruited by 116 sites are now available for analyses of the combined TMK/OPAL database. First results from the interim analysis 2019 will be presented.
Conclusions: OPAL will show how pts with ABC in Germany are treated and how the choice of treatment changes over time, which sequential treatments are applied and what the effectiveness (e.g. best response, progression-free and overall survival) and PROs are in a "real world" setting. It will reveal the impact of new treatments in pts in routine care and allow to identify areas for improvement of care.

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Anja Welt: Employment or Leadership Position: Oberärztin am Universitätsklinikum in Essen; Advisory Role: Amgen, Roche, Novartis, Pfizer, Tesaro; Financing of Scientific Research: Roche, Eisai, Amgen, AstraZeneca, iOMEDICO, Pfizer, Daiichi Sankyo, Interplan; Expert Testimony: Novartis

V1024

Pet positivity after 2 cycles of abvd is a risk factor in patients with early-stage favorable Hodgkin lymphoma treated in the phase 3 GHSG HD16 study

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Background: PET-adapted therapy is the standard treatment for advanced-stage Hodgkin lymphoma (HL). The role of interim PET in early-stage favorable disease is still unclear.
Aims: In our HD16 study (NCT00736320) for early-stage favorable HL, we evaluated the use of PET after 2 cycles of ABVD (PET-2) to guide involved-field radiotherapy (IFRT). Furthermore we investigated if a positive PET-2 is a risk factor for progression-free survival (PFS) in these patients.
Methods: From 2009-2015, we recruited 1150 patients with newly diagnosed early-stage favorable HL aged 18-75. Patients were randomly assigned to receive standard combined-modality treatment (CMT) with 2xABVD and 20 Gy IFRT or PET-guided treatment, where IFRT was restricted to patients with DS ≥3 after 2xABVD. A central objective of the trial was to test whether a Deauville score (DS) ≥3 was associated with PFS impairment among patients treated with CMT (i.e. those randomized to the standard group and those from the PET-guided randomization group with DS ≥3). We also explored the association of DS with baseline characteristics and treatment outcomes considering different cutoffs for positivity.
Results: Among 1007 randomized patients with regular PET, 667 (66%), 218 (22%) and 122 (12%) had DS 1-2, 3 and 4, respectively. Of those, 693 were assigned to treatment with CMT (353, 218 and 122 with DS 1-2, 3 and 4, respectively). Clinical stage II and bulky disease at initial staging were associated with an unfavorable DS after 2xABVD. With median follow-up of 46 months, estimated 5-year PFS was 93.2% (90.2-96.2) among patients with DS1-2, 92.8% (88.8-96.9) for those with DS3 and only 80.9% (72.2-89.7) in the DS4 subgroup. Considering DS ≥3 as cutoff, the PFS difference missed statistical significance (HR adjusted for baseline factors 1.73 [0.99-3.02], p=0.055). With DS4 as cutoff, the difference became more pronounced, indicating a threefold risk for treatment failure in patients with DS4 after chemotherapy (adjusted HR 2.94 [1.63-5.31], p=0.0004). Overall survival was on a high level with no differences between any subgroups defined by DS.
Conclusions: In early-stage favorable HL, a positive PET after 2xABVD is associated with a larger tumor volume and represents a risk factor for PFS among patients treated with standard CMT, particularly when DS4 is considered as cutoff for positivity. PET-guided treatment intensification in this high-risk subgroup might help to reduce the frequency of relapses.

Disclosure: Michael Fuchs: Employment or Leadership Position: Uniklinik Köln Andreas Engert: Employment or Leadership Position: Uniklinik Köln; Expert Testimony: Takeda, Bristol-Myers-Squibb, Affimed

V1025

One-Year Efficacy of Ravulizumab (ALXN1210) in adult patients with paroxysmal Nocturnal hemoglobinuria naive to complement inhibitors

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Introduction: Ravulizumab is a novel C5 complement inhibitor for treating paroxysmal nocturnal hemoglobinuria (PNH). In a phase 3 study in complement inhibitor-naive PNH patients (pts), qw8 ravulizumab was non-inferior to qw2 eculizumab for all endpoints after 26 wks. The efficacy profile of ravulizumab after switching from eculizumab in adult PNH pts was characterized in an extension study (NCT02946463).
Methods: In this phase 3, active-controlled, open-label study (123 centers, 25 countries) pts were randomized to eculizumab (n=121) or ravulizumab (n=125) for 26 wks. Then, pts on ravulizumab continued ravulizumab maintenance (R-R arm), and pts on eculizumab switched to ravulizumab (E-R arm). Data for lactate dehydrogenase normalization (LDH-N), transfusion avoidance, breakthrough hemolysis (BTH), LDH levels and plasma free C5 levels were obtained through 52 wks
Results: In the R-R-arm, 74% (26 wks) vs 77% (27-52 wks) of pts avoided transfusion. Over 90% (n=83) of pts avoiding transfusion in wks 0-26 maintained this response through 52 wks; 38% (n=12) requiring transfusion in wks 0-26 avoided it in wks 27-52. In E-R, 66% (26 wks) vs 67% (52 wks) avoided transfusion; 87% (n=69) avoiding transfusion for 26 wks maintained this response through 52 wks and 28% (n=11) (E-R) requiring transfusion in wks 0-26 avoided it in wks 27-52. LDH-N occurred in 48% (R-R)/42% (E-R) of pts at 26 wks and 44%/40% at 52 wks. Pts on ravulizumab had a 77% mean LDH reduction from baseline at 26 and 52 wks. All R-R pts (n=119) maintained free C5 < 0.5mg/mL through 52 wks (Figure). No E-R pts had free C5 >0.5mg/ml after the switch. BTH occurred in 4% (R-R)/11% (E-R) of pts at wks 0-26 and 3%/2% at wks 27-52. No BTH event (wks 27-52) was associated with free C5 >0.5mg/ml. This demonstrates maintenance of free C5 control in pts on ravulizumab. The drug was well tolerated and the most common treatment-related adverse events decreased in frequency during treatment.
Conclusions: Ravulizumab showed consistent and durable efficacy over 52 wks. All pts with suboptimal free C5 control on eculizumab achieved complete free C5 inhibition after switch to ravulizumab, associated with a decreased BTH incidence.

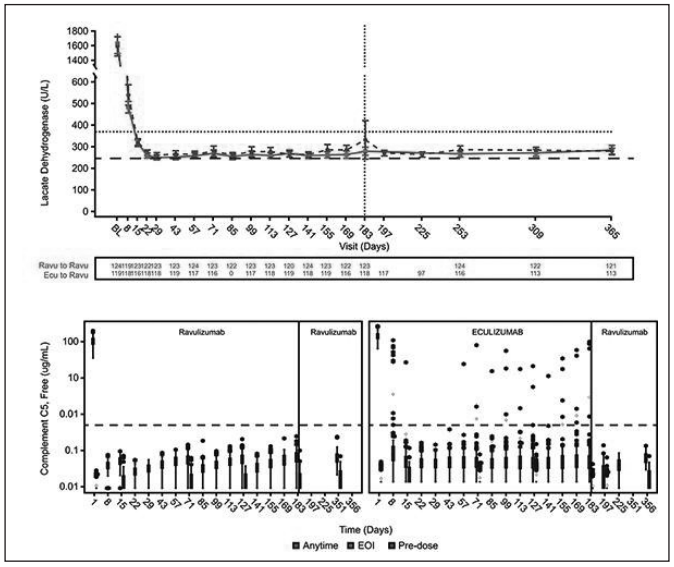

Fig. 1. LDH and free C5 concentration in the R-R and E-R arm

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Gerard Socie: Advisory Role: Alexion Pharmaceuticals, Inc.; Financing of Scientific Research: Alexion Pharmaceuticals, Inc.

V1026

GADD45b plays an essential role in the G-CSF triggered granulocytic differentiation of hematopoietic stem cells

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The mechanism of maturation arrest of myeloid progenitors in severe congenital neutropenia (CN) patients is not fully elucidated. We identified GADD45b as a stress sensor downstream of G-CSF signaling which was shown to be essential in stress-induced murine myelopoiesis. In CN patients G-CSF fails to activate GADD45b expression which might be a reason of diminished granulopoiesis in CN patients. To test this hypothesis, we inhibited GADD45b expression in CD34$^+$ cells and iPSCs of healthy donors using specific CRISPR/Cas9 RNP. We evaluated G-CSF-triggered myeloid differentiation of GADD45b-deficient iPSCs using embryoid body (EB)-based method and found that iPSCs present with severely diminished granulocytic differentiation upon *GADD45B* knockout, as assessed by FACS, CFU assay and morphological examination of cytospin slides. We also observed reduced G-CSF-mediated granulocytic differentiation of GADD45b-deficient CD34$^+$ cells of healthy individuals in CFU assay and liquid culture differentiation. Importantly, rescue of GADD45b in HSPCs of CN patients (n = 2) by lentivirus-based transduction of *GADD45B* cDNA restored defective granulocytic differentiation, as compared to control transduced cells. To determine the role of GADD45b *in vivo*, we performed transient gadd45bb knockout in zebrafish and found that gadd45bb-deficiency in zebrafish embryos resulted in drastically reduced numbers of mpo-expressing myeloid cells. These data strongly support the essential role of GADD45b in G-CSF-mediated granulocytic differentiation.
In silico analysis of *GADD45B* promoter revealed putative binding sites for C/EBP transcription factors. Reporter gene assay and ChIP confirmed C/EBPα binding to the *GADD45B* promoter. Intriguingly, C/EBPα expression is severely diminished in myeloid cells of CN patients. To study the mechanism by which GADD45b mediates myeloid differentiation, we performed RNA sequencing and EPIC methylation array of WT or GADD45b-deficient CD34$^+$ HSPCs treated or not with G-CSF. Interestingly, in GADD45b-deficient cells, G-CSF failed to induce hypomethylation and mRNA expression of genes important in granulocyte differentiation and functions, such as *RXRA*, *MEFV*, *CXCR1*, *FPR2*, *SERPINA1*.
In summary, our data suggest that GADD45b plays an essential role in granulocytic differentiation and inability of G-CSF to induce *GADD45B* expression in CN patient cells might be a reason for the defective granulopoiesis.

Disclosure: No conflict of interest disclosed.

Wissenschaftliches Symposium

Immunonkologie: Aktuelle Herausforderungen

V1028

Possibilities and limitations of cellular therapies in immune oncology

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Zellbasierte Immuntherapien und molekulare, zielgerichtete Therapien bilden inzwischen die vierte Säule in der Immunonkologie. Dabei hat insbesondere die Behandlungen mit CAR (chimärer Antigen Rezeptor) T-Zellen weltweit zu großen klinischen Erfolgen bei Patienten mit CD19-positiven Leukämien und Lymphomen geführt. Seit 2017 sind die ersten CAR-T-Zelltherapien in den USA und seit August 2018 in Europa zugelassen. Die individualisierte Herstellung der autologen Präparate ist ein aufwendiger und komplexer Prozess - die Behandlungskosten liegen bei >300.000 €. Inzwischen ist das Management der zum Teil schweren Nebenwirkungen in dafür spezialisierten Kliniken gut etabliert. Darüber hinaus wird intensiv geforscht, diese Zell-und Gentherapeutika auch für Patienten mit hochmalignen Tumoren einzusetzen. Neben einer Übersicht zu den Möglichkeiten und Grenzen der personalisierten CAR T-Zelltherapien werden auch neue Wege aufgezeigt, genmanipulierte, allogene Effektorzellen als „off the shelf" Präparate einzusetzen. Darüber hinaus erfordert die Komplexität von Krebserkrankungen meist ein multimodales Konzept, um mögliche Resistenzentwicklungen gegen molekulare und zellbasierte Therapien zu überwinden und eine nachhaltige Elimination der Krebszellen zu erreichen.

Disclosure: No conflict of interest disclosed.

Wissenschaftliches Symposium

B-NHL aggressiv: Neue Strategien

V1030

New Molecular DLBCL Subtypes - Ready for the Clinic?

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Diffuse large B-cell lymphoma is a clinically and molecularly heterogenous disease that is transcriptionally subdivided into activated B-cell (ABC)- and Germinal Center B-cell (GCB)-subtype. Comprehensive

genomic analyses revealed now 5 robust genetically defined DLBCL subtypes, that provided insights into prognosis prediction and lymphomagenesis and most importantly provided a roadmap for future rational design of targeted treatment combinations. This presentation will summarize our current understanding of DLBCL subtypes and discuss the relevance for the clinics.

Disclosure: No conflict of interest disclosed.

Fortbildung

Joint Symposium (mit GTH): Update Hereditäre und erworbene Hämophilie

V1037

Options for replacement therapy in hemophilia A and B

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Hemophilia A and B continue to be major challenges for afflicted patients, affecting both their survival and quality of life, mainly through breakthrough bleeding and chronically progressive joint disease but also by governing many aspects of their daily life. In severe cases, life-long replacement therapy, substituting coagulation factor VIII and IX, respectively, is necessary in order to prevent or treat bleeding, placing patients at risk for transmitted diseases and autoimmunity and limiting their daily activities, such as sports and recreation, from early ages on. And even patients with less severe hemophilia may require substitution of blood coagulation factors in special circumstances (i.e. during surgery, after injury, and during intense physical activity). Today, most patients are treated with conventional recombinant or plasma-derived human factors. However, recent clinical developments have included coagulation factors with longer half-lives and decreased immunogenicity, oral and subcutaneous formulations, porcine factors, but also novel agents such as monoclonal antibodies bridging factors IXa and X and gene therapy approaches. In this educational session, I will review the conventional and novel options for hemophilia treatment and weigh their potential risks and benefits. Further research is needed in order to enable hemophilia patients to lead their lives with the same quality and life expectancy as healthy individuals.

Disclosure: Steffen Koschmieder: Advisory Role: Pfizer, Incyte/Ariad, Novartis, AOP Pharma, BMS, CTI, Roche, Baxalta, Sanofi, Bayer; Financing of Scientific Research: Novartis, BMS, Pfizer, Incyte/Ariad, Shire, Roche, AOP Pharma, Janssen; Expert Testimony: Novartis Foundation, BMS, Novartis, Janssen; Other Financial Relationships: Alexion, Novartis, BMS, Incyte/Ariad, AOP Pharma, Baxalta, CTI, Pfizer, Sanofi, Celgene, Shire, Janssen, Bayer

V1040

Acquired von Willebrand syndrome

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Primary hemostasis is critically dependent on the function of von Willebrand factor (VWF), a multimeric plasma glycoprotein stored inside platelet α-granules and Weibel-Palade bodies of endothelial cells, where it is rapidly released from upon activation. VWF mediates the adhesion of platelets to the damaged vessel wall and serves as a protective carrier protein for coagulation factor VIII. Congenital quantitative and/or qualitative abnormalities of VWF define the most common inherited bleeding disorder, von Willebrand disease. Various pathogenic mechanisms, however, may also result in an acquired von Willebrand syndrome (AVWS). These mechanisms include, but are not limited to, impaired synthesis in patients with severe hypothyreosis, increased ADAMTS13-mediated proteolysis under conditions of elevated shear forces (e.g. in patients with severe aortic valve stenosis or with extracorporeal life support systems such as ECMO or LVAD), enhanced non-specific proteolysis by enzymes such as plasmin or leukocyte elastase in the context of hyperfibrinolysis, acute leukemia or liver damage, accelerated immunologic clearance in patients with VWF autoantibodies or monoclonal gammopathy of unknown significance (MGUS), non-specific complex formation with plasma IgM in patients with Waldenström's macroglobulinemia, and increased adsorption to (aberrantly expressed) GPIb with subsequent proteolytic degradation in patients with essential thrombocythemia or solid tumors. No single laboratory test is sufficient to prove or rule out AVWS, but multimer analysis is usually required to detect subtle qualitative abnormalities in patients with massively elevated VWF plasma levels. Therapeutic measures to improve hemostasis depend on the underlying pathomechanism and should always take into account the opposing risks of bleeding and thromboembolism in a typically elderly patient population.

Disclosure: No conflict of interest disclosed.

Wissenschaftliches Symposium

Frauen in Führungspositionen in der Hämatologie und Onkologie - Ein Ziel - Viele Wege.

V1042

Rehabilitation medicine - a niche?

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Introduction: Rehabilitation offers an exciting and family-friendly working environment. There are many design options with regard to working time models.
Methods: The different areas of activity in oncological rehabilitation will be highlighted.
Results: The aim of rehabilitation treatment is to ameliorate patients existing illnesses or therapy-related restrictions and thus to improve their quality of life. The persons receiving rehabilitation treatment usually stay 21 days. Hospitalization is scheduled. This leaves a lot of room for flexible working time models. In addition, oncological rehabilitation has become an evidence-based part of oncological therapy. Drug therapies will also be administered as needed. Internal basic diagnostics and disease-specific special diagnostics are performed.
In addition, a socio-medical assessment is required, which evaluates the ability to work and possible limitations in the patient´s professional capacity. Where necessary, retraining or applying for a pension is recommended. Participation in both working and social life are important rehabilitation goals. If necessary, the planning of vocational reintegration takes place during the patient's stay in a convalescent home. Clinical research and health services research are also realizable in rehabilitation and expand the possible scope of tasks for doctors.
Conclusions: Overall, oncological rehabilitation offers an attractive field of work that is compatible with many working time models. The satisfaction of doctors working in rehabilitation is high. This makes it a niche especially for women in haematology and oncology who want to reconcile family and work.

Disclosure: No conflict of interest disclosed.

V1043

Need for a women´s quota? Experience from the pharmaceutical industry

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Introduction: The pharmaceutical industry offers promising career options for women: the proportion of women in the workforce is 40 percent and 15 out of 44 of the vfa member companies in Germany are led by women (*vfa 03/2019*). Increasing the share of women in management positions is a strategic goal for Novartis. Heterogeneous teams are proven to be more innovative, more effective and more economically successful (*McKinsey Quarterly, April 2012*).

Methods: To fill management positions balanced supporting frameworks and attractive working conditions are necessary. Novartis provides an environment that encourages women to apply for higher management positions. Measures of career promotion are mentoring, networking events and campaign days. Female executives face challenges that their male colleagues do not. These include equal pay, self-confidence, and appearance in a male-dominated field, and returning to work after parental leave. Novartis offers a variety of measures including trust based working time, flexible part-time models, home-office options and support in caring for relatives and childcare. The job sharing pilot project *Leadership in Tandem* provides flexibility at management level and allows managers to share the working hours and responsibilities of a position.

Results: The share of woman at Novartis worldwide is 50% as a whole and 43 % at management level.

At Novartis Germany the share of women increased continuously during the last five years: from 61,7% in 2014 to 64,2% in 2018 and the share of women at management level as well: from 31% in 2014 to 38% in 2018.

Conclusions: Equality is a social consensus but not yet reality in many companies. Often it is still the woman who takes care of her family on the costs of her professional career. Novartis offers women and men opportunities to reconcile work and private life in the best possible way. A quota, the objective to reach gender equity at management level is necessary and needs to be tracked to ensure that teams are diverse and the share of women is further increased. The advantages of diversity are the positive influence on motivation and performance, strengthening creativity and innovation and a better understanding of the different needs of male and female patients.

Disclosure: Ulrike Haus: Employment or Leadership Position: Novartis Pharma GmbH; Stock Ownership: Novartis AG

Wissenschaftliches Symposium

AML: von aktuellen präklinischen Forschungsergebnissen in der Epigenetik zur klinischen Anwendung

V1053

Progressive DNA methylation programming defines hematopoietic lineage committment

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Recent single-cell RNA sequencing (scRNAseq) data have revised our view on hematopoiesis and suggested a continuous rather than a step-wise differentiation process. However, while differentiation trajectories can be inferred from scRNAseq data, it is impossible to discern whether discreet lineage commitment decisions occur at specific points along these trajectories. The existence of such commitment points could still be compatible with a step-wise differentiation model and their characterization at the molecular level would be essential for our understanding of hematopoiesis.

We hypothesized that DNA methylome analysis facilitates the identification of such molecular commitment marks due to the progressive nature of DNA methylation programming during differentiation.

This study investigated DNA methylation programming in normal hematopoiesis using whole-genome bisulfite sequencing of 26 murine hematopoietic cell populations. Across all cell populations studied, we identified 147232 differentially methylated regions (DMR). Hierarchical clustering revealed co-regulated DMRs that show progressive DNA methylation programming during hematopoietic differentiation. These regions can be interpreted as specific DNA methylation programs: pan-hematopoietic-, lineage- and cell type-specific programs. These programs were strongly enriched in hematopoietic transcription factor binding sites as well as in lineage and cell type-specific enhancers. Integration of DNA methylome programs with comprehensive multi-tier scRNAseq data revealed a strong anti-correlation of DNA methylation dynamics and cell-state specific gene expression patterns. The progressive and lineage-specific nature of DNA methylation programming during hematopoietic differentiation, allowed us to infer a phylogenetic tree of the hematopoietic system, which is solely based on DNA methylation dynamics. Furthermore, the identified DNA methylation programs are conserved across different mouse strains which underlines the broad applicability of this resource.

We provide a novel view on the regulation of hematopoiesis that is solely based on DNA methylation dynamics, and which complements recent findings from scRNAseq studies. We show that DNA methylation patterns enable the dissection of tissue hierarchies in regenerating tissues. Furthermore, our work provides a rich resource to investigate DNA methylation in normal as well as in abnormal hematopoiesis across a broad range of conditions and mouse strains.

Disclosure: No conflict of interest disclosed.

V1055

Why do we need genetic/epigenetic analyses of AML at the single-cell level?

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Cell-to-cell heterogeneity in acute myeloid leukemia (AML) and other malignancies impact the clinical characteristics of the disease and its response to treatment. Next generation sequencing of the entirety of leukemic cells (cell bulk) is able to provide a rough estimate of the cell-to-cell heterogeneity, but analyses at the single-cell level are required to really capture the differences among the leukemic clones. In the recent years, major technological advances have been made in our ability to analyze molecular features of individual cells. These advances led to unprecedented insights into normal and malignant hematopoiesis (see Review Series in Blood 2019:133). We have used such approaches to decipher the genetic clonal architecture of AML by single-cell mutation analyses (Stosch et al. Br J Haematol 2018:132) or to study phenotypic characteristics of genetically-defined AML by single-cell RNA sequencing (Becker et al. Blood Adv 2019:3). Furthermore, recent studies have begun to correlate the genetic and phenotypic features of single leukemia cells (Rodriguez-Meira et al. Mol Cell 2019:73). Future research will expand this to the combined characterization of genetic aberrations, gene and protein expression and the epigenetic regulation in single cells of the AML and its microenvironment before and, importantly, under treatment as well as at relapse. This will help us to understand the biology of the disease and the mechanisms of resistance in order to improve our clinical decisions and our research on how to overcome the resistance mechanisms.

Disclosure: Heiko Becker: Financing of Scientific Research: Roche, Servier, Novartis, BMS

V1056

Genomic landscape of Acute Myeloid Leukemia (AML) in the elderly

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AML is a disease of the elderly with a median age at diagnosis of ~70 years. Outcome of older patients (pts) has remained very poor due to unfavorable patient- and disease-related factors. With regard to disease-related factors, older pts more often exhibit adverse karyotypes as defined by European LeukemiaNet 2017 and a distinct mutational pattern, e.g. in genes encoding epigenetic modifiers, such as DNMT3A, TET2, ASXL1, RUNX1, IDH1/2, as well as more often mutations in TP53. These genomic alterations significantly influence treatment response and overall survival (OS). Consistent with mutations in epigenetic regulators, older patients display a distinct pattern of DNA methylation that is not driven by physiologic changes in age-associated CpGs (Silva et al, Leukemia 2017).

In the pivotal AZA-AML-001 study of 488 older pts with newly diagnosed AML, azacitidine (AZA), a hypomethylating agent (HMA), prolonged median OS vs conventional care regimens (CCR). In exploratory post-hoc analyses, AZA in particular improved outcome of patients with adverse genetics, e.g., high-risk karyotypes and TP53 mutations (Döhner et al, Leukemia 2018). Treatment with HMA has now emerged as a preferred treatment option in older patients who are not eligible for intensive therapy, in particular in AML with adverse genetic features.

We are currently performing larger-scale next-generation sequencing (NGS)-based analyses in patients treated with HMA, both in the general care landscape and within controlled clinical trials. As an example, recently, a large phase 3 randomized trial has been completed comparing the second-generation HMA guadecitabine vs physician´s choice (mostly HMA) in 815 treatment-naïve AML patients not eligible for intensive chemotherapy (Fenaux et al. EHA 2019). The trial failed to reach its co-primary endpoints improvement of response and overall survival. To identify patients who potentially benefit from the different HMAs used in this randomized trial we are currently performing NGS using a panel of 264 genes involved in hematologic malignancies. Furthermore, an interrogation of methylation patterns at the genome-wide level is planned. Preliminary data from patients randomized in this trial stand in line with previous studies showing high prevalence of mutations in TP53 (~25%), TET2 (24%), DNMT3A (22%), ASXL1 (21%), SRSF2 (20%), RUNX1 (17%), U2AF1 and IDH2 (mostly R140) in 13% each, and NRAS (11%).

Disclosure: No conflict of interest disclosed.

Freier Vortrag

Nicht maligne Hämatologie (excl. Anämie)

V1057

Interim results from the phase 3 Northstar-2 and Northstar-3 studies of LentiGlobin gene therapy for the treatment of transfusion-dependent β-thalassemia

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Introduction: Transfusion-dependent β-thalassemia (TDT) is a severe genetic disease with serious comorbidities and is managed by lifelong red blood cell (RBC) transfusions which results in iron overload. LentiGlobin gene therapy contains autologous CD34+ hematopoietic stem cells (HSCs) transduced *ex vivo* with the BB305 lentiviral vector (LVV) encoding β-globin with a T87Q substitution and is being evaluated in patients with TDT. The phase 1/2 Northstar study demonstrated initial safety and efficacy; all 18 patients had polyclonal integration with up to 4 years follow-up. LentiGlobin is further being evaluated in two ongoing phase 3 studies, Northstar-2 (NCT02906202; non-β^0/β^0 genotypes) and Northstar-3 (NCT03207009; β^0 or β^+ IVS-I-110 mutations on both *HBB* alleles).
Methods: HSCs were mobilized and collected by apheresis after a combination of G-CSF and plerixafor and transduced with the BB305 LVV. Patients received busulfan myeloablative conditioning before transduced cells were infused. Statistics represent median (min-max).
Results: As of 14 Sept 2018, 16 and 3 patients have been treated in Northstar-2 (follow-up: 9.3 [0.7-20.4] months; age: 19 [8-34] yrs) and Northstar-3 (follow-up: 4.2 [1.4-9.2] months; age: 17 [7-26] yrs), respectively. All patients with >2 months follow-up had HSC engraftment.

In Northstar-2, 10/11 patients with ≥3 months follow-up stopped RBC transfusions. Hemoglobin (Hb) ranged from 11.1-13.3 g/dL with 7.7-10.6 g/dL HbA^{T87Q} at last visit. Transfusion independence (weighted average Hb ≥9 g/dL without RBC transfusions for ≥12 months) was achieved by 2/3 evaluable patients. In Northstar-3 as of 19 Nov 2018, Pt 1 with a β^0/β^0 genotype had no RBC transfusions after LentiGlobin infusion; Hb was 13.8 g/dL at month 12. Pt 2 had a Hb of 10.1 g/dL at month 6 and last RBC transfusion was at month 1.9. Pt 3 had a Hb of 11.6 g/dL at month 3 and last RBC transfusion was at month 1.4.

Post-infusion non-hematologic grade ≥3 adverse events (AE) that occurred in ≥3 patients were stomatitis, febrile neutropenia, epistaxis, pyrexia, and veno-occlusive liver disease in Northstar-2. Stomatitis was the only non-hematologic grade ≥3 AE post-infusion in >1 patient in Northstar-3.

Conclusions: In Northstar-2, 10/11 patients with TDT and ≥3 months follow-up stopped RBC transfusions following treatment with LentiGlobin. Early Northstar-3 data suggests patients also may stop transfusions. The safety profile is consistent with myeloablative busulfan conditioning.

Disclosure: Joachim Kunz: No conflict of interest disclosed.
Alexis Thompson: Advisory Role: bluebird bio; Expert Testimony: Amgen, Baxalta/Shire, bluebird bio, Celgene, Novartis, Biomarin, La Jolla Pharmaceutical

V1058

A zebrafish model for severe congenital neutropenia with HAX1 deficiency

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Introduction: Inherited deficiency of HCLS1-associated protein X1 (HAX1) in human leads to the development of a severe congenital neutropenia (CN). Patients with *HAX1* deficiency are characterized by impaired maturation of neutrophil granulocytes. They are also predisposed to myelodysplasia and acute myeloid leukemia development, yet the underlying mechanisms are not fully understood. Our current knowledge of *HAX1*-associated neutropenia is predominantly derived from clinical observations and *in vitro* studies. Thus far, no reliable *in vivo* model has been established. Mice lacking *Hax1* are characterized by normal granulopoiesis. Hence, a major motivation for this study was our desire to establish a zebrafish model to study the consequence of *HAX1* deficiency in granulopoiesis.
Methods: To interfere with zebrafish Hax1 function, we used two approaches. First, we injected antisense morpholino that efficiently blocked the translation of *hax1*. As a second approach, we used CRISPR-Cas9 technique to introduce loss-of-functions mutations in the zebrafish *hax1* gene. To analyze the number of neutrophils, HSPCs and monocytes, whole-mount in situ hybridization against different marker genes was performed. The expression levels of downstream components of G-CSF signaling pathway were then compared between wild-type and *hax1* morphants using qRT-PCR. TUNEL assay was used to assess whether *hax1* knockdown affects the cell survival. In addition, a granulopoiesis rescue experiment was carried out by the induction of G-CSF using a heat-inducible construct.
Results: The zebrafish *hax1* gene is specifically expressed in the hematopoietic tissue. Both knockdown and mutations in *hax1* decreased the number of neutrophils, without affecting HSPCs and monocytes, mimicking the phenotype of CN patients with *HAX1* deficiency. Similar to human, we observed that the expression levels of downstream target genes of G-CSFR signaling were reduced in zebrafish *hax1* morphants. The observed neutropenic phenotype could be then rescued by induction of either zebrafish or human G-CSF indicating that G-CSFR signaling is evolutionarily conserved between human and zebrafish.
Conclusions: We have successfully established an *in* vivo model for studying the HAX1 role in the granulopoiesis. This model might open new avenues for developing tailored therapeutic strategies for severe congenital neutropenia as well as in vivo studying the role of HAX1 in the leukemogenesis.

Disclosure: No conflict of interest disclosed.

V1059

A phase 3 study of Ravulizumab (ALXN1210) vs. Eculizumab in adults with paroxysmal nocturnal hemoglobinuria currently treated with Eculizumab: subgroup analysis by transfusion history and demographics

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Introduction: Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, life-threatening hematologic disorder caused by uncontrolled activation of the complement system, leading to intravascular hemolysis. The treatment goal for PNH is to inhibit complement activation, thereby preventing the risk of severe thrombosis, reducing symptoms caused by free hemoglobin and alleviating anemia. Ravulizumab is a novel C5 inhibitor administered every 8 weeks shown to be non-inferior to eculizumab (administered every 2 weeks) in two phase 3 trials. Due to PNH's rarity, little data is available evaluating treatment in unique patient populations. This study examined the safety and efficacy of the two drugs in specific patient subgroups on the basis of transfusion history and demographics.
Methods: ALXN1210-PNH-302 was a phase 3, open-label, randomized, active-controlled, multicenter study assessing the switch from eculizumab to ravulizumab. Adult patients with a history of PNH, previously treated with eculizumab for ≥6 months and lactate dehydrogenase (LDH) levels ≤1.5 times the upper limit of normal prior to baseline were enrolled. Patients were randomly assigned to switch to ravulizumab or continue on eculizumab. The primary efficacy endpoint was LDH change (%) from baseline to day 183. We examined the impact of observed transfusion history, sex, age at first study treatment exposure, race and geographic region subgroups on LDH change (%) using descriptive statistics.
Results: A total of 195 patients received treatment with ravulizumab (n=97) or eculizumab (n=98). Baseline characteristics between treatment groups were similar. Subgroup analyses results are shown in the plot below. Point estimates for percent change from baseline in LDH favored ravulizumab overall and across all patient subgroups.
Conclusions: This prespecified subgroup analysis showed point estimates favoring ravulizumab in normalizing LDH levels in PNH patients at day 183. The findings confirm the results of the phase 3 study and support the use of ravulizumab in patients previously treated with eculizumab, irrespective of transfusion history, sex, age at first study treatment exposure, race or geographic region.

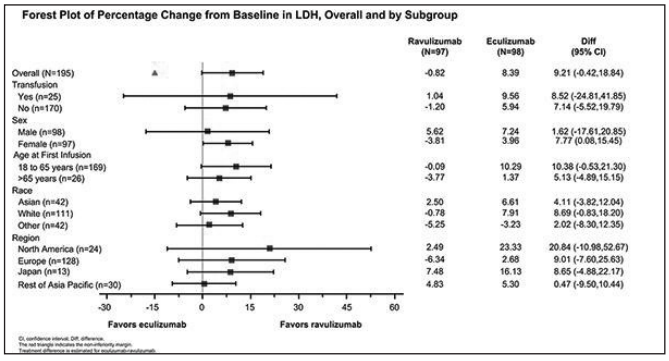

Fig. 1. Forest Plot of Percentage Change from Baseline in LDH, Overall and by Subgroup

Disclosure: Antonio Risitano: Advisory Role: ja; Financing of Scientific Research: ja Austin Kulasekararaj: Advisory Role: ja; Financing of Scientific Research: ja

V1060

The role of gene polymorphisms of the mannose binding lectin 2 in severe acquired hemophilia

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Introduction: Acquired haemophilia (AH) is a rare autoimmune disease in which spontaneously occurring autoantibodies directed towards coagulation Factor VIII (FVIII) lead to severe bleedings. Recently a pro-coagulant activity of the mannose binding lectin (MBL) pathway of complement activation was discovered. We examined associations of *MBL2* gene single nucleotide polymorphisms (SNPs) and the severity of HA as well as the coagulation product consumption during treatment.
Methods: *MBL2* SNPs in exon 1 at codons 52, 54 and 57 (C, B, D-Alleles respectively) were determined in 30 AH patients with high-titre inhibitor levels (>5 Bethesda Units (BU)) and life threatening bleedings requiring intensive care monitoring. Clinical data of patients treated by the Bonn-Malmoe protocol were analysed retrospectively.
Results: *MBL2* SNPs were present in ten of 30 patients. Patients with *MBL2*-SNPs required a higher number of (i) immuneadsorptions (IA) (21.5 vs 16.6), (ii) of days until the inhibitor activity was first undetectable (4.9 vs 2.8), (iii) of IAs until the factor substitution could be discontinued (19.5 vs 15.2), (iv) of hospital days (35.8 vs 33.4) and had a higher FVIII consumption (2.24 vs 0.47 10^6 IU) as well as higher inhibitor titres (557 vs 161 BU). However, none of these differences reached significance. A significant difference was only observed in the consumption of rFVIIa (5.53 vs 1.0 10^3 kIU, p>0.05). Two patients with *MBL2* SNPs required FEIBA, none of the wildtype group.
Conclusions: An association of *MBL2* SNPs with treatment responses should be systematically investigated in a larger patient collective of HA considering the role of MBL in complement activation and in the coagulation cascade.

Disclosure: No conflict of interest disclosed.

V1061

Characterization of idiopathic multicentric castleman disease (iMCD) in Europe from ACCELERATE, the first-ever castleman disease natural history registry

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Introduction: Idiopathic multicentric Castleman disease (iMCD) is a rare and heterogeneous disorder involving multiple regions of lymphadenopathy and systemic inflammatory symptoms. Siltuximab, an anti-interleukin (IL)-6 monoclonal antibody, is the only European Medicines Agency-approved drug treatment for iMCD based on a 34% response in a randomized phase 2 clinical trial; identification of additional effective treatments is urgently needed. ACCELERATE is a two-armed natural history registry of Castleman disease (CD) comprised of a patient-powered arm (PPA), operating out of the United States, and a physician directed arm (PDA), operating out of 9-sites in Europe.
Methods: We use the ACCELERATE registry to characterize iMCD in a European cohort and to identify the treatments most frequently used by European physicians.
Results: To date, 33 iMCD patients have met inclusion criteria (Germany 10, France 8, Italy 4, Spain 6, and Norway 5). The cohort is 48% female, and median age at diagnosis is 47.5 yrs (38.1,57.1). In this cohort, histopathology is strongly consistent with that defined in the 2017 International Consensus Diagnostic Criteria. Clinical and laboratory characteristics at diagnosis are also consistent with Consensus Criteria with 85% of assessed patients demonstrating constitutional symptoms, 28% organomegaly, and 19% fluid retention; laboratory abnormalities include hypoalbuminemia (median: 33.0 (25^{th} %: 27.0, 75^{th} %: 35.0) g/L), inflammation (CRP: 115.0 (12.2, 127.0) mg/L), anemia (hemoglobin: 10.1 (8.5,12.1) g/dL), and hypergammaglobulinemia (17.3 (10.1, 33.4) g/L)). In this cohort, twenty unique drugs have been used to treat iMCD, including antineoplastic agents, corticosteroids, immunosuppressive agents, anti-IL6 therapy, and immunoglobulins. Rituximab and siltuximab are the most frequently administered drugs, administered to 50% and 39% of treated patients, respectively.
Conclusions: European iMCD patients in the ACCELERATE registry demonstrate clinical, laboratory, and pathological features consistent with iMCD found in other regions of the world. One agent is EMA-approved, and many agents are used off-label. Rituximab is most frequently administered in patients in both the US and European centers, and siltuximab is among the top three drugs across both arms of the registry. Data collection is ongoing, and further work and additional patients are needed to assess the effectiveness of treatments in this cohort.

Disclosure: Christian Hoffmann: Advisory Role: Janssen-Cilag; Financing of Scientific Research: Janssen-Cilag (für Vorträge); Expert Testimony: Janssen-Cilag David Fajgenbaum: Expert Testimony: Janssen Pharmaceuticals

V1062

The association of clonal hematopoiesis of indeterminate potential with chronic ischemic heart failure

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Cardiovascular diseases (CVD) are one of the leading causes of death. Beside established risk factors, clonal hematopoiesis of indeterminate potential (CHIP) is associated with a higher risk of CVD and has therefore recently gained high medical intertest. CHIP is defined as the expansion of a blood cell clone by somatic mutations in individuals without hematologic abnormalities.
Our studies focused on the questions, whether there is a different disease progression in chronic ischemic heart failure (CHF) patients with CHIP and what the consequences are on blood cell lineages and hematopoietic stem and progenitor cells (HSPC) in these CHF patients.
Therefore, we investigated a clinically well-characterized cohort of 200 CHF patients and correlated disease progression with CHIP-mutations and investigated alterations of peripheral blood (PB) and bone marrow (BM) cells.
We found a high incidence of CHIP (22% of patients) in our CHF patient cohort. The most recurrent mutations occurred in DNMT3A and TET2, which both epigenetically control gene expression and regulate inflammation. We demonstrated a strong association of poor prognosis in CHF and CHIP-mutations in these genes leading to increased death and/or hospitalization due to CHF in our cohort, which remained significant after multivariate correction. These mutations may causally contribute to disease progression since there was a striking dose-response between the variant allele fraction and clinical outcome. By analyzing PB and BM in CHF patients, we detected an increased number of monocytes in the BM of CHIP carriers. In patients harboring TET2 mutations, we determined an increase in BM leukocyte numbers and HSPCs without a bias in the distribution of leukocyte lineages. Surprisingly, we did not determine any

alterations in HSPCs in patients with a DNMT3A mutation, which contrasts the results in knock-out mouse models, showing an increased stem cell self-renewal.
Whether non-mutated HSPCs are also affected in individuals with TET2 mutations in a paracrine, cell-extrinsic fashion, caused by an inflammatory milieu due to altered cytokine production, requires further investigation.

Disclosure: No conflict of interest disclosed.

Freier Vortrag

Tumor-/Zellbiologie II

V1063

Targeting mitotic exit and Mcl1 in solid tumors

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Introduction: Tumor cells may survive treatment with antimitotic drugs due to residual anaphase-promoting complex (APC/C) activity and continuous cyclin B-degradation leading to mitotic exit. Thus, blocking cyclin B-proteolysis via additional APC/C-inhibition may induce much more efficient tumor eradication. We assumed that blocking cyclin B-degradation non-selectively by approved proteasome inhibitors (PI) may be likewise efficient as specific APC/C-inhibitors, proved this concept in AML and showed that the PI bortezomib (B) enhanced a volasertib-induced mitotic arrest (Schnerch et al, Oncotarget 2017). We now analyzed this approach in solid tumors, also in respect of suspected entity-specific differences in response.
Methods: Patient-derived tumor cells (PDX) from breast and non-small cell lung cancer (NSCLC) were treated with the antimitotic agent paclitaxel (T), the APC/C-inhibitors proTAME/Apcin (pT/A) or B, and the Mcl1-inhibitor S63845 and analyzed via flow cytometry, ATP-measurement, life-cell-imaging, soft-agar colony assays and western blot.
Results: HeLa cells treated with T showed higher rates of G2/M-arrest after addition of pT/A, a similar effect was achieved with sequential addition of B. In different PDX, the combination of T with B led to a stronger reduction of the rate of successful mitoses, cell viability and cell growth than T alone. However, in NSCLC, cell growth was reduced most efficiently with the combination of T with pT/A, and pT/A alone already had a strong effect. This effect was not observed in breast cancer due to an overexpression of the anti-apoptotic regulator Mcl1. Here, the most efficient reduction was achieved with the combination of APC/C- and Mcl1-inibition.
Conclusions: The efficacy of antimitotic treatment depended on the different biology of the tumor entities. In NSCLC highly efficient mitotic arrest with subsequent apoptosis in mitosis was reached by combining an antimitotic agent and a direct APC/C-inhibitor, blocking cyclin B-proteolysis and mitotic exit using low doses achievable in vivo. A similar effect was reached with the combination with an unspecific PI. Breast cancer cells were more sensitive to B and resistant to pT/A, probably due to overexpression of the anti-apoptotic regulator Mcl1. Thus, the combination of APC/C- and Mcl1-inhibition was most effective. After further verification in mouse models, our data provide the basis for phase I/II trials with clinical approved drugs and APC/C-inhibitors.

Disclosure: No conflict of interest disclosed.

V1064

WNT11 integrates PI3K and Rho/Rock signaling to mediate breast cancer invasion

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Introduction: Breast cancer is one of the most common tumor entities worldwide. One limiting factor for human life span is the emergence of distant metastasis. Previous studies have identified the WNT signaling pathway to be frequently aberrantly activated in breast cancer. Especially β-catenin independent, non-canonical WNT signaling seems to play a role in metastasis. Therefore, the aim of this study was to identify novel non-canonical WNT proteins involved in breast cancer progression.
Methods: Publicly available gene expression data sets of patients with primary breast cancer (n=2075) as well as own RNA sequencing data of breast cancer brain metastases (n=42) were analyzed for the expression of different non-canonical WNT ligands and receptors. Interesting genes were validated in breast cancer cell lines and analyzed for their associated signaling by qRT-PCR, Western Blots and knockdown/overexpression approaches as well as for their functional relevance in invasion and migration assays.
Results: Gene set enrichment analysis identified activation of non-canonical WNT signaling in breast cancer primaries and metastases in which it was both associated with poor patient survival. A non-canonical WNT signature was applied to the data sets and clustered the patients into three groups, among which the patient group with the poorest overall survival was characterized by high expression of the non-canonical ligand WNT11. Overexpression and knockdown studies in human and murine breast cancer cells confirmed WNT11 as a major factor regulating tumor invasiveness. Characterization of WNT11-stimulated cells by RNA sequencing as well as reverse phase protein array (RPPA) identified the PI3K signaling pathway as a master regulator of WNT11 signaling. In line with this finding, phosphorylation of Akt and mTOR was increased after WNT11 stimulation. Additionally, Akt phosphorylation was involved in the upregulation of RhoA/Rock which mediated invasion in WNT11-overexpressing breast cancer cells, thereby suggesting a link between both pathways. The inhibition of the PI3K-Akt pathway, by using inhibitors commonly used in the clinic, led to a decrease of the pro-invasive effect of WNT11 on breast cancer cell invasion.
Conclusions: Taken together, our results identified WNT11 as an important tumor protein regulating breast cancer metastasis through integration of PI3K and Rho/Rock signaling.

Disclosure: No conflict of interest disclosed.

V1065

Vitamin D enhances Rituximab-mediated NK-cell cytotoxicity via the Interferon-a pathway

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Introduction: Vitamin D deficiency has been associated with decreased OS of patients with DLBCL treated with R-CHOP. We hypothesized that rituximabmediated NK-cell cytotoxicity is more effective at higher vita-

min D levels. Vitamin D substitution in deficient healthy volunteers increased their rituximab-mediated NK-cell cytotoxicity in vitro against the lymphoma cell line 'Daudi'.
Methods: We collected PBMCs from the afore mentioned vitamin D deficient, otherwise healthy volunteers before and after 25-OH vitamin D3 substitution to > 30 ng/ml. NK cells were separated by magnetic depletion. After isolating total RNA, we performed a microarray analysis using an Affymetrix Gene-Chip 2.0™. For pathway analysis, gene set enrichment analysis was used in a two-step approach. First, we selected 7.705 genes due to their involvement in the NK cell-mediated immune response. These were used for specific analysis of the NK-cell cytotoxicity pathway. Next, the complete data set of 48.145 genes was used in an exploratory analysis to screen further dysregulated pathways. Gene sets were provided from the Molecular Signature Database. A significance level of $p < 0.05$ and False Discovery Rate were chosen. Affymetrix data were confirmed by RT-PCR.
Results: The NK cell-associated cytotoxicity pathway was found to be upregulated after restoration of normal vitamin D levels. The most significantly overexpressed genes in this gene set were IFN-a2, IFN-a4, IFN-a6, IFN-a7, IFN-a10 as well as IFN-κ. An exploratory analysis showed an upregulation of type I interferon-related pathways. Other pathways involved in the immune response were found to be downregulated after vitamin D substitution. The common feature of these pathways was downregulating of the toll-like receptor genes TLR-8, TLR-7, and TLR-2.
Conclusions: Increased expression of IFN-a subtypes may explain the increased rituximab-mediated NK-cell cytotoxicity after vitamin D substitution in deficient individuals. TLRs, known as positive regulators of IFNa production in NK cells, were upregulated during vitamin D deficiency and downregulated after vitamin D substitution and restoration of IFN-a production, representing a negative feedback mechanism. Thus, for the first time, we were able to show how vitamin D increases the ADCC potential of NK cells.

Disclosure: No conflict of interest disclosed.

V1066

Improving tumor integrating of multipotent mesenchymal stromal cells (MSC) as basis for their application as potential vehicles for tumor therapy

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Introduction: Tumor-integrating mesenchymal stromal cells (MSC) with expression of anti-tumor factors like tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) may serve as vehicles for tumor therapy. Our previous studies showed that TRAIL-expressing MSC were able to reduce the tumor growth not only of TRAIL sensitive but also of selected TRAIL resistant colorectal carcinoma (CRC) cell lines in vitro and in mixed xenograft mouse models. A fundamental requirement for potential clinical efficacy is the integration of the modified MSC into the tumors which we aimed to improve within this study.
Methods: MSC with co-expression of lentivirally introduced TRAIL and luciferase (TRAIL/Luc-MSC) were generated. We performed direct 2D cocultures and 3D mixed spheroids using CRC cell lines with different TRAIL sensitivity (HCT8, DLD1, HT29) mixed with MSC and partly cotreated with low dose chemotherapeutic substances and analyzed apoptosis induction. Tumor integration of MSC was analyzed in vitro using a 3D CRC spheroid-model. Studying tumor integration in vivo was realized using intraperitoneally (i.p.) established xenografts of CRC cells. MSC were injected i.p. following application of chemotherapeutic agents or vascular disrupting agents.
Results: TRAIL/Luc-MSC showed stable protein expression over several passages and no changes in MSC characteristics (multipotent differentiation, immunophenotype) nor signs of malignant transformation were observed. In 2D and 3D cocultures with CRC cell lines TRAIL/Luc-MSC induced apoptosis in adjacent TRAIL sensitive (DLD1) and TRAIL resistant (HCT8) tumor cells. Also, TRAIL resistant HT29 cells underwent apoptosis in coculture with TRAIL/Luc-MSC if sensitized by a preceding exposure with oxaliplatin or 5-fluorouracil at subapoptotic doses. In vitro integration studies revealed a slight increase of MSC integration into CRC spheroids after preceding exposure with low dose chemotherapeutic substances.
Preliminary in vivo data suggest an increased tumor integration of systemically applied MSC in CRC xenografts depending on specific pretreatment of tumors in a model of peritoneal carcinosis.
Conclusions: We generated MSC co-expressing TRAIL and luciferase which were functional in apoptosis induction in adjacent tumor cells and could be monitored during in vivo experiments. The improved tumor integration induced by specific tumor pretreatment represents the basis for further functional studies using MSC as therapy vehicles.

Disclosure: No conflict of interest disclosed.

V1067

Identification of recurrent somatic mutations at canonical and alternative upstream translational initiation codons in malignant melanoma

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Ribosome profiling studies revealed that cis-regulatory upstream open reading frames (uORFs) in the 5′-region of eukaryotic mRNAs are frequently initiated by alternative near-cognate translational initiation sites (aTISs), deviating in a single base from the canonical AUG initiation codon (uAUG). Deregulated protein translation due to genetic defects at AUG-initiated uORFs has been linked human diseases, including cancer, yet the role of aTIS-initiated uORF regulation in tumorigenesis is unknown. Here, we analyzed whole exome sequencing data of `The Cancer Genome Atlas′ to determine the genetic variability at canonical and alternative uORF initiation codons in malignant melanoma. Mutect2-generated `variant call format′ files of 470 individual patients suffering from malignant melanoma were downloaded from the Genomic Data Commons data portal. Files were computationally screened for genetic variation at 65410 uAUGs and 933983 aTISs, as identified in human genome assembly 38. Minimal requirements for a positive call were ≥10 total reads, ≥3 alternative reads (alt) deviating from the reference base (ref), and the alt/ref ratio being ≥4-times higher in the tumor vs. the normal control sample. Recurrent somatic mutations affecting ≥2 melanoma patients were identified at 217 uAUGs and 2018 aTISs. Among the aTIS variants, CTG codons were most frequently mutated (23.5%), followed by ACG (21.6%) and AGG codons (21.0%). Overall, somatic mutations affecting ≥1% of melanoma patients were found at 6 uAUGs and 162 near-cognate translational initiation codons. The uORF start variants showing highest rates of recurrence within the patient cohort were observed for NBPF20 (loss of UUG in 4.7% of patients), EIF2B1 (loss of AAG in 3.3%), and SMG8 (loss of AAG and gain of AUG in 3.2%). Similar to the latter mutant, 348 more mutations resulted in a gain of a uAUG, affecting MRPL21, MPCH2, PIGC, and PCF12 in ≥1% of melanoma patients. These data reveal substantial somatic genetic variability at canonical and alternative uORF initiation codons in malignant melanoma. Ongoing functional analyses of the newly identified uORF variants will define the role of defective uORF-mediated translational control in the development and course of the disease.

Disclosure: No conflict of interest disclosed.

V1068

Characterization of the interaction between Wnt-bearing extracellular vesicles and their receptors in the context of tumor progression

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Deciphering the crosstalk of tumor cells and the surrounding stromal cells during cancer progression and metastasis is of high importance to further optimize therapeutic strategies and prevent recurrence. Regarding this tumor-stroma interaction our group showed a functional role of the activation of Wnt5a-mediated β-catenin-independent signaling cascades for breast cancer progression and metastasis (Pukrop et al. 2006, Pukrop et al. 2010, Klemm et al. 2011). To mediate this interaction, Wnt5a is shuttled on two types of extracellular vesicles (EV), namely microvesicles (MV) and exosomes (Exo), to the tumor cells where they induce enhanced invasiveness (Menck et al. 2013).

Although EV as communicators between cells attract an increasing interest in the scientific society, currently little is known about how exactly Wnt-bearing EV interact with the receiving cells and potential receptors.

To quantitatively address these questions, we analyze receptor-ligand interactions with advanced and super-resolution fluorescent microscopy (dual-color axial line-scanning FCS, STED/SMLM) . We developed expression constructs for the Wnt5a receptor ROR2 as well as for two Wnt5a-isoforms labeled with easy exchangeable fluorophores. With a newly designed pipeline consisting of an indirect TCF-Luciferase-Assay as well as Boyden Chamber invasiveness assays we prove functionality of the Wnt5a fusion proteins and show that they are indeed shuttled on both MV and Exo. CRISPR/Cas9 is used to transfer this tagging strategy in the endogenous protein context.

This tools will not only help to further understand the progression and metastasis of breast cancer but will also give a mechanistic insight into the role and function of EV to use them effectively as diagnostic, prognostic and therapeutic agents.

Disclosure: No conflict of interest disclosed.

Freier Vortrag

Magenkarzinom

V1069

HER2positive gastric cancer: intermediate HER2 expression levels are related to high test deviation rates between local and central pathology and worse survival

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Background: For HER2+ Gastric Cancer (GC) trastuzumab is the only approved targeted therapy addressing the membrane-bound receptor tyrosine kinase HER2. Trastuzumab is used for 1st line treatment of stage IV HER2+ GC, but not all treated patients respond and almost all initial responders eventually experience progression. The resistance mechanisms for trastuzumab in GC are poorly understood. The aim of the VARIANZ study (NCT02305043, grant: BMBF 01ZX1610E) was to investigate the biological background of resistance to anti-HER2 therapy in GC.

Methods: Patients receiving medical treatment for stage IV GC were recruited in 34 German sites. HER2 status was verified centrally according to algorithm of the ToGA study using immunohistochemistry and chromogenic-in-situ hybridization. Patients were followed up to 48 months.

Results: 548 pts were enrolled and 514 samples were characterized for HER2. 90 of 514 samples were found HER2+ in central testing. In 69 samples the locally assessed HER2+ status could not be centrally confirmed. The deviation rate between local and central testing was 21.4%. In confirmed HER2+ GC more tumor cells stained positive for HER2 (57.93 ± 31.23% [SD] vs. 15.61± 24.05% [SD]; p< 0.001) and a higher HER2/CEP17 ratio was found (7.42 ± 5.85 [SD] vs. 1.53 ± 0.88 [SD]; p< 0.001). Also HER2 gene expression (ΔCt) was higher in confirmed HER2+ GC (41.83 ± 1.63 [SD] vs. 39.05 ± 1.78 [SD]; p< 0.001). Other EGFR family members as EGFR, HER3 or HER4 were not differently expressed, but gene expression of TGFα (33.55 ± 3.06 vs. 31.30 ± 4.69 p= 0.043) and MET (36.59 ± 1.03 vs. 35.78 ± 1.74; p=0.044) was slightly elevated in confirmed HER2+ GC samples.

Only patients with confirmed HER2+ status seem to benefit from trastuzumab in addition to chemotherapy with an overall survival of 19.2 months (95%-CI 14.6 - 31.2; n=55) versus 10.5 months (95%-CI 8.2 - 14.4, n=55) for patients with unconfirmed HER2-positivity (HR for death 0.71, p< 0.001).

Conclusions: Discrepancies between local and central HER2 assessment in GC were significant and mostly found in tumor specimens with intermediate HER2 expression levels. Borderline HER2-positivity and heterogeneity of the marker expression should be considered as a resistance factor for HER2-directed therapy. HER2-cut-offs should be reconsidered and a more detailed reporting of the HER2 status including the quantification of stained tumor cells might be of value.

Disclosure: No conflict of interest disclosed.

V1070

Association of PD-L1 combined positive score (CPS) and immune gene signatures with efficacy of Nivolumab (NIVO) ± Ipilimumab (IPI) in patients with metastatic gastroesophageal cancer (mGEC)

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Introduction: In the CheckMate 032 phase 1/2 study, NIVO±IPI demonstrated clinically meaningful antitumor activity in patients with chemotherapy-refractory mGEC. Archival or fresh tumor biopsies were analyzed to determine whether expression of PD-L1 and selected immune gene signatures were predictive of efficacy with NIVO±IPI.
Methods: Pooled analyses included patients from all treatment regimens (NIVO 3 mg/kg, NIVO 1 mg/kg + IPI 3 mg/kg, and NIVO 3 mg/kg + IPI 1 mg/kg, as well as NIVO 1 mg/kg + IPI 1 mg/kg from the dose-escalation phase). PD-L1 expression on tumor and tumor-associated immune cells was examined using PD-L1 immunohistochemistry (IHC; Dako PD-L1 IHC 28-8 pharmDx assay). CPS was determined by evaluating PD-L1 expression on tumor and tumor-associated immune cells on previously stained IHC slides. Gene expression profiling (GEP) by RNA sequencing was used to evaluate immune cell activation and infiltration signatures, a Bristol-Myers Squibb (BMS) 4-gene inflammatory signature, and PD-L1 gene expression.
Results: Pooled PD-L1 CPS (N=104), tumor PD-L1 (N=130), and GEP (N=40) cohorts were representative of the overall CheckMate 032 mGEC cohort (N=163). At a median (range) follow-up of 23.4 (17.0-35.4) months, PD-L1 expression by CPS at higher cutoffs correlated better with efficacy and had higher prevalence than PD-L1 expression on tumor cells in all analyses (Table). For all immune gene signatures examined, responders had higher signature scores in aggregate. For the BMS 4-gene inflammatory signature, the association between signature score and response was significant (P=0.004; false discovery rate =0.037).
Conclusions: PD-L1 expression by CPS demonstrated stronger association with efficacy of NIVO±IPI at higher cutoffs than PD-L1 expression on tumor cells in mGEC. Prevalence of PD-L1 expression by CPS was higher than PD-L1 expression on tumor cells. The BMS 4-gene inflammatory signature showed the strongest association with response and warrants further investigation.

Tab. 1.

All regimens				
Method	**N**	**Cutoff**	**ORR, %**	**Prevalence, %**
PD-L1 CPS	104	≥ 10	27	33
		≥ 5	19	50
		≥ 1	14	68
		< 1	3	32
Tumor PD-L1	130	≥ 10	9	8
		≥ 5	8	10
		≥ 1	18	31
		< 1	8	69
NIVO1 mg/kg + IPI3 mg/kg				
Method	**N**	**Cutoff**	**ORR, %**	**Prevalence, %**
PD-L1 CPS	33	≥ 10	55	33
		≥ 5	41	52
		≥ 1	28	76
		< 1	0	24
Tumor PD-L1	42	≥ 10	0	2*
		≥ 5	0	2*
		≥ 1	40	24
		< 1	19	76

CPS, combined positive score (number of PD-L1–staining tumor cells, lymphocytes, and macrophages relative to all viable tumor cells x 100); ORR, objective response rate. *Only 1 patient had tumor PD-L1 ≥ 5% and ≥ 10%.

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Zachary Boyd: Employment or Leadership Position: Roche/Genentech, and Bristol-Myers Squibb; Stock Ownership: Roche/Genentech, and Bristol-Myers Squibb

V1071

Efficacy and safety of trifluridine/tipiracil (FTD/TPI) in patients (pts) with metastatic gastric cancer (mGC) with or without prior gastrectomy: results from a phase III study (TAGS)

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Background: The phase 3 study TAGS demonstrated that the novel oral therapy FTD/TPI (TAS-102) represents an effective treatment option with a manageable safety profile for pts with heavily pretreated mGC. In an earlier single-arm Japanese phase 2 trial in mGC, no differences were found in the pharmacokinetics of either FTD or TPI in pts with or without prior gastrectomy. We evaluated the efficacy and safety of FTD/TPI in pts with or without prior gastrectomy within the TAGS study.
Methods: In this global phase 3 study of adult pts with mGC who had received ≥2 prior regimens of chemotherapy, pts were randomized 2:1 to receive FTD/TPI (35 mg/m^2 BID on days 1-5 and 8-12 of each 28-day cycle) or placebo, plus best supportive care. We performed a preplanned analysis of efficacy and safety endpoints in pt subgroups with or without prior gastrectomy.
Results: Of 507 randomized pts, 221 (44%) had a prior gastrectomy (FTD/TPI, 147/337; placebo, 74/170). Baseline pt characteristics were balanced across pt subgroups. FTD/TPI prolonged survival versus placebo regardless of gastrectomy (table). The frequency of neutropenia/leukopenia appeared to be higher among FTD/TPI-treated pts with vs without gastrectomy, but this did not result in more treatment discontinuations (table).
Conclusions: In the TAGS study, subgroup analysis demonstrated that FTD/TPI is an effective treatment option with a manageable safety profile for pts with heavily pretreated mGC, regardless of prior gastrectomy. Clinical trial information: NCT02500043.

	Gastrectomy		No gastrectomy	
	FTD/TPI	Placebo	FTD/TPI	Placebo
ITT population, n	147	74	190	96
Median OS (95% CI), mo	6.0 (4.6–7.0)	3.4 (2.7–3.8)	5.6 (4.6–6.2)	3.8 (3.1–5.9)
HR (95% CI)	0.57 (0.41–0.79)		0.80 (0.60–1.06)	
OS rate (95% CI), %	50 (41–58)	24 (15–35)	44 (37–52)	39 (30–49)
6 mo				
12 mo	20 (12–28)	9 (3–19)	22 (16–30)	16 (8–26)
Safety population, n	145	73	190	95
Grade ≥3 AEs of any cause, % Any	84	60	76	56
Most common[a],				
Neutropenia	28	0	19	0
Anemia	21	4	17	11
Decreased neutrophil count	17	0	7	0
Leukopenia	10	0	4	0
Fatigue	2	5	11	6
Leading to dosing modification	65	21	53	23
Leading to treatment discontinuation	10	16	15	17

AEs of any grade or cause, %; [a]Occurring in ≥ 10% of pts in any group

Fig. 1.

Disclosure: Peter Thuss-Patience: Advisory Role: Servier, Merck, MSD, Pfizer, Roche, BMS, Astellas, Lilly; Expert Testimony: Merck, Novartis
Kohei Shitara: Advisory Role: Astellas, Lilly, BMS, Takeda, Pfizer, Ono,; Financing of Scientific Research: Novartis, AbbVie, Yakult; Expert Testimony: Lilly, Ono, Sumoitomo Dainippon, Daiichi Sankyo, Taiho, Chugai, MSD

Freier Vortrag

AML III

V1072

Impact of epigenetic therapies on the immunopeptidome of primary acute myeloid leukemia cells

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In recent years, therapeutic options for acute myeloid leukemia (AML) have improved, but the disease is still characterized by high relapse rates and a poor overall survival calling for the development of novel therapies. Among the novel treatment options, epigenetic modifying therapies have shown promising results for the treatment of AML and recent data showed their ability to induce gene expression of various cancer/testis antigens (CTAs). This might lead to the presentation of novel CTA-derived peptides on human leukocyte antigen (HLA) molecules, which could serve as prime targets for combinatorial T-cell based immunotherapy. Therefore, we here investigated the impact of the DNA methyltransferase inhibitor decitabine (DEC) and the histone deacetylase inhibitor vorinostat (VOR) on the immunopeptidome of primary AML cells.
We treated primary AML cells from 5 patients *in vitro* with DEC, VOR, or a combination of both for 72 h and 96 h. Flow cytometry-based quantification of HLA surface expression showed no significant influence of treatment. Implementing label-free quantitation mass spectrometry, we quantitatively assessed HLA class I ligand presentation after treatment and observed only minor quantitative effects on the whole immunopeptidome. Of 37,925 identified unique HLA ligands, 2,078 peptides showed exclusive presentation in treated samples compared to untreated controls (959 after DEC, 465 after VOR, and 654 after combination treatment). The most frequently presented treatment-exclusive antigens represent products of epigenetic regulated genes (BACH1, USP20, NAPRT). Focusing on alternated CTA-expression, we found HLA ligands from 4 CTAs (CAGE1, KDM5B, CNOT9 and SPAG9) to be exclusively presented after epigenetic modifying treatment. Notably, overlap analysis with our in-house benign tissue (n=404, >140,000 HLA ligands) and untreated malignant tissue (n=552, >240,000 HLA ligands) database revealed that 130 of the 2,078 treatment-exclusive peptides where never identified on benign or malignant tissue before, confirming the treatment-association of these HLA ligands.
Our results reveal a modulatory effect of DEC and VOR on the immunopeptidome of primary AML cells, inducing therapy-exclusive HLA ligands, which will be further evaluated for their eligibility as suitable targets for immunotherapeutic approaches in AML patients.

Disclosure: No conflict of interest disclosed.

V1073

AML: final remission status prior to post-remission therapy overrides negative prognostic impact of early blast persistence during induction therapy

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Introduction: In AML, the prognostic role of remission status/blast clearance after induction 1 (day 14-21) has not been consistently clarified so far. In this analysis, we provide long-term survival data from 1008 intensively treated AML-patients (diagnosed between 2000-2017, aged 18-86 years) in association with their early remission status after induction 1.
Methods: Data were acquired from our local AML database. Remission status and cytogenetic/molecular risk were determined according to ELN (2010) criteria. At baseline, patients [pts] were characterized by ECOG score, comorbidity [CCI] and age. Pts were grouped according to their early remission status after induction 1 (d14-21) and prior to further therapy (chemotherapy and/or allo-HSCT). Survival was analyzed using Kaplan-Meier- and Cox regression models.
Results: In the entire cohort, early remission status was as follows: 57% CR/CRi, 19% PR, 24% RD. The different remission groups did not significantly differ in age, ECOG-score or CCI, but with regard to ELN risk groups. 62% of all pts received a double induction, 61% consolidation therapy and 47% allo-HSCT (as a part of first-line therapy). 85% were in 1st CR/CRi prior to HSCT. Amongst pts receiving HSCT, early PR/RD was converted into CR/CRi prior to HSCT in 72% of cases. Pts not receiving HSCT achieved CR/CRi after an additional cycle of chemotherapy in 40%. In the whole group, early PR/RD was associated with inferior OS as compared to CR/CRi ($p < 0.001$). After conversion into CR/CRi prior to post-induction therapy, early PR lost its negative prognostic impact whereas early RD remained an adverse prognostic factor for OS and RFS ($p=0.002$), particularly in pts receiving HSCT. In transplanted pts., early PR with blast clearance beyond induction 1 had no significant impact on RFS and OS, whereas in pts without HSCT it resulted in impaired RFS ($p=0.045$) but not OS.
Conclusions: Our results clearly confirm a favorable prognostic impact of early blast clearance in a large cohort of intensively treated AML pts. However, the negative prognostic impact of early PR on OS can be overcome by later achievement of CR/CRi, whereas RD after induction 1 remains an adverse prognostic variable. Our results suggest that the time point of CR/CRi achievement is less important with regard to OS than the final remission quality prior to post-remission treatment. Consequently, MRD-guided therapy prior to allo-HSCT might improve outcome of first-line AML therapy.

Disclosure: No conflict of interest disclosed.

V1074

TGF-β1 as candidate molecule for the functional inhibition of healthy CD34+ hematopoietic stem and progenitor cells (HSPC) in acute myeloid leukemia (AML)

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Introduction: AML is a blood stem cell disorder that is characterized by hematopoietic insufficiency. Since the bone marrow (BM) of patients with AML is dominated by a leukemic blast population we surmised a direct pathophysiological link between leukemic cells and disruption of normal hematopoiesis. In the light of recent experimental evidence we considered soluble factors secreted by leukemic cells to be responsible for suppression of healthy CD34+ HSPC.
Methods: As a model for the BM infiltration *in vitro* we exposed healthy BM-derived CD34+ HSPC to cell-free supernatants derived from 3 AML cell lines (THP-1, HL-60, MV4-11) as well as from 24 newly-diagnosed AML patients. Following 3 days of incubation in leukemic or control media CD34+ HSPC were analyzed for proliferation, cell cycle state and colony-forming capacity. Additionally, we screened soluble candidate molecules involved in myelosuppression by PCR and tested their impact on the functionality of healthy CD34+ HSPC in cell-culture systems.
Results: Exposure to conditioned media derived from AML cell lines and primary patients' cells significantly inhibited proliferation of healthy CD34+ HSPC. In line with this, we observed a shift of the cell cycle state of these healthy CD34+ HSPC towards a resting phenotype and a lower colony-forming capacity. The latter was mainly reflected by a reduction of the erythroid colonies (CFU-E and BFU-E) rather than for the myeloid ones. Experiments with paired patient samples showed that these inhibitory effects on healthy CD34+ HSPC were markedly related to the immunomagnetically enriched CD34+ leukemic cell population, but not to the MNC fraction. PCR-screening revealed a significant overexpression of TGF-β1 in leukemic cells suggesting a potential role of TGF-β1 for suppression of healthy hematopoiesis by leukemic cells. Accordingly, blocking of TGF-β receptor signaling by SD-208 enabled a partial restoration of differentiation and colony forming capacity in healthy CD34+ HSPC.
Conclusions: Overall, these data indicate that leukemic blasts mediate direct suppressive effects on important functions of healthy CD34+ HSPC thereby contributing to hematopoietic insufficiency in AML and TGF-β1 may be a potential candidate molecule, which is at least in parts responsible for the observed effects.

Disclosure: No conflict of interest disclosed.

V1075

In vivo kinetics of early, hypomethylating agent-induced methylome and transcriptome changes in primary AML blasts: random or specific?

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The therapeutic effect of DNA-hypomethylating agents (HMAs) in AML has been broadly studied in cell line models, but only few studies have addressed the global effects in primary blasts serially isolated from AML patients (pts) undergoing HMA treatment. We therefore conducted serial methylome and transcriptome analyses on AML blasts from pts of the DECIDER trial (NCT00867672), hypothesizing that both random and non-random effects of the HMA may be observed *in vivo*.
We obtained peripheral blood samples from 28 pts of the DECIDER trial at 3 time points (days [d] 0, 8 and 15 from decitabine treatment start) to allow a "triplet analysis" of matched samples. Blasts were sorted using anti-CD34, CD117 MACS microbeads. Methylomes and transcriptomes were obtained using Infinium Human Methylation 450K and GeneChip Human Gene 2.0 ST array, respectively.
Significant demethylation ($\Delta\beta < -0.1$, FDR< 0.05) at d8 was achieved for 69384 CpGs (15% of all 462165 CpGs). Of these, 536 CpGs (representing 227 genes) became demethylated in all 28 pts. Gene Ontology (GO) analysis showed a strong enrichment for genes involved in adhesion, including genes with (putative) tumor suppressor function. By d15, 40129 CpGs (58% of the 69384 CpGs) became at least partially remethylated. We next asked whether these CpG methylation changes were random or specific: Compared to 1000 randomly chosen sets of CpGs, the number of CpGs significantly demethylated at d8 (vs. day 0) in all 28 pts was much higher, indicating non-random demethylation. Similar results were obtained for CpGs demethylated at d15 (vs. d0). In contrast, CpGs remethylated at d15 (vs. day 8) were similar to the random controls, indicating random remethylation. Next, we investigated in 12 of the 28 pts whether demethylation at d8 was associated with gene expression changes. A total of 870 genes showed a significant inverse correlation between expression and DNA methylation, thus being both induced and demethylated. GO analysis revealed enrichment for immune response genes.
In our study, a subset of genes was specifically targeted by demethylation in all pts, arguing against a completely random effect on the methylome. However, only a limited number of demethylating events was associated with gene induction. A better understanding of de- and remethylation kinetics *in vivo* may aid in schedule optimization of HMA therapy.

Correlative studies on demethylation kinetics and treatment outcome in the DECIDER trial are therefore ongoing.

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V1076

Characterization and transfer of extracellular vesicles (EVs) within the bone marrow niche in acute myeloid leukemia (AML)

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Cellular crosstalk between leukemic stem/progenitor cells and the bone marrow niche is important for the development and maintenance of myeloid malignancies. These compartments can communicate via bidirectional transfer of extracellular vesicles (EVs), which contain proteins, lipids, RNA, and DNA. EVs derived from leukemic cells can deliver immunosuppressive signals that promote cancer escape mechanisms to recipient cells. It has also been shown that they play a role in niche remodeling in several tumor models. We aim to characterize AML EVs and to examine their impact on cellular crosstalk between leukemic cells and their microenvironment in AML.
After purifying EVs from primary material via differential centrifugation or ExoEasyKit (Qiagen), EV characterization was performed. Transmission electron microscopy, western blotting and nano tracking analysis (NTA) showed a pure isolated EV fraction, inter alia, expressing common EV markers (e.g. CD63, CD81). For further characterization, EVs isolated from AML patients with and without Flt3-ITD mutation were compared to healthy donor EVs. As an in-vitro model of the bone marrow niche mesenchymal stem cells (MSCs) treated with AML EVs were analyzed in terms of differentiation, growth, apoptosis and whether they support haematopoietic stem cells.
NTA showed no difference in EV number released by AML cells compared to healthy ones. However, AML EVs were significantly larger than those from healthy donors. Moreover, EV surface markers of AML and healthy EVs were compared through flow cytometry and showed significantly altered expression of surface proteins. Using immunofluorescence, we proved that AML-derived EVs are internalized by healthy EVs, suggesting the deposition of specific EV-cargo in MSCs, which might induce functional effects. First results of in-depth analysis of AML EV-cargo as proteomics and RNA-sequencing showed a remarkable difference between AML and healthy EVs. Ongoing analysis will help to further elucidate the role of EVs in bone marrow niche modulation and might contribute to new clinical approaches for cancer diagnosis and therapy.

Disclosure: No conflict of interest disclosed.

V1077

Cooperativity of the oncoprotein SKI and the mutated receptor tyrosine kinase FLT3ITD in acute myeloid leukemia patients with normal karyotype

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Introduction: The FLT3 internal tandem duplication (FLT3ITD) is observed in 30% of acute myeloid leukemias (AML) and is often associated with a normal karyotype (CN). FLT3ITD-positive CN AML with a high allelic ratio but without mutated NPM1 have a poor prognosis. The nuclear oncoprotein SKI is overexpressed in solid tumors and AML (Ritter 2006). It is part of a histondeacetylase (HDAC)-recruiting repressor complex and can be inhibited by HDAC inhibitors (HDACi) (Nomura 1999; Frech 2018). We have described that SKI induces *FLT3* (Feld 2018). In mice, SKI overexpression induces a myeloproliferative disease (Singbrandt 2014). Hence, it is important to further analyze the role of SKI in CN AML with FLT3ITD.
Methods: 50 bp single-read RNA sequencing (RNAseq) of FLT3ITD-positive CN AML patients (7 -SKI, 6 +SKI) before treatment was carried out. For validation, RT-qPCR of putative SKI target genes were performed in MV4-11 control clones and clones, in which *SKI* was deleted by CRISPR/Cas9. In patient or MV4-11 cells protein levels of SKI, FLT3ITD or downstream targets were analyzed by Westernblot. After HDACi treatment, cell viability assays and flow cytometric analyses of differentiation markers were used to analyze MV4-11 clones ± SKI.
Results: Survival analysis of 15 CN FLT3ITD-positive AML patients showed a significant ($p \leq 0.036$) shorter overall survival (OS) with high SKI protein levels compared to AML with low levels. RNAseq results of 13 of these patients further showed an enrichment of gene sets associated with FLT3ITD-positive AML, hematopoietic stem cells and MYC in SKI-positive cells, while ERK, RUNX1 and TGFβ gene sets were inhibited. Westernblots of the AML patients and MV4-11 clones revealed that SKI is important for induction of FLT3ITD expression. Here, SKI expression was accompanied by STAT pathway activation; interestingly, ERK signalling was impaired. In line with activated STAT signalling also IL2RA was induced in SKI-positive MV4-11 clones. Interestingly, viability assays and flow cytometric analyses of differentiation markers showed that SKI-positive MV4-11 cells responded better than SKI-negative cells to a HDACi treatment.
Conclusion: SKI induces FLT3ITD expression in CN AML and is associated with a shorter OS. Since FLT3ITD-positive AML cells with a high SKI expression respond better to HDACi, an additional treatment with HDACi may provide a therapeutic benefit for FLT3ITD-positive CN AML patients with a high SKI expression.

Disclosure: No conflict of interest disclosed.

Freier Vortrag

Patientensicherheit

V1078

Development of tumor disease-specific PRO-CTCAE item sets

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Introduction: In oncology, adverse events (AE) are mainly documented using the Common Terminology Criteria for Adverse Events (CTCAE) (1). This physicians´ assessment can be supported by patient-reported outcomes (PRO) (2). For this reason, the NCI has developed a PRO version of the CTCAE criteria, consisting of a pool of 78 symptoms and 124 items (3). A core item set containing 31 items for patients with chemotherapy has already been validated in German (4).
The aim of the this is to develop tumor disease-specific PRO-CTCAE item sets for different tumor entities with 30 to 40 items and high content validity.

Methods: Patients treated at three outpatient centres were asked for the occurrence and relevance of the 78 PRO-CTCAE symptoms using a questionnaire. In order to select the most relevant PRO-CTCAE items for each tumor entity, clinical impact scores were calculated on the basis of occurrence and relevance for every symptom.
Results: Data of 101 patients with breast cancer (BC) and 47 with multiple myeloma (MM) have been analysed so far. The BC item set contains 39 items representing 23 symptoms, the MM item set 40 items for 21 symptoms. 24 items for 14 symptoms are included in both item sets. Although scores for MM are in general higher than for BC, four out of the five main symptoms with the highest scores in both item sets are fatigue (BC 8.92, MM 19.52), hair loss (BC 8.43, MM 18.82), sleep disorders (BC 7.96, MM 18.20) and numbness and tingling (BC 7.85, MM 18.16). The symptom with the highest score included only in one item set is nail ridging and discoloration in the MC item set (6.98) and general pain in the MM item set (16.84). 16 Items of the core item set are included in the MM item set, 19 items in the BC item set.
Conclusion: Based on patient-reported differences in symptom pattern, specific PRO-CTCAE item sets were developed for breast cancer and multiple myeloma. Their psychometric criteria will be analysed in a validation study.

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V1079

Application of therapeutic drug monitoring of fluorouracil in an ambulatory setting

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Introduction: Numerous studies have demonstrated that dosing of Fluorouracil (5-FU) based on body surface area leads to a wide range of pharmacokinetic variability, resulting in a risk of under- and overdosing. So far, a target 5-FU exposure of 20-29 mg•h/L (area under the curve) and a dosing algorithm have been established [1]. In a prospective multicenter study, Wilhelm et al. showed that TDM results in a significantly higher fraction of patients reaching the proposed target AUC range [2]. However, the utility of 5-FU TDM has not been examined in the routine of an ambulatory setting.
Methods: TDM of 5-FU was established at the oncological practice 'Onkologie UnterEms' in Leer, Germany. It was applied to patients receiving 5-FU based chemotherapy for the treatment of several cancer types e.g. colorectal, stomach and esophageal cancer. 5-FU plasma concentrations were measured using a nanoparticle immunoassay (My5-FU™; Saladax Biomedical, Bethlehem, PA) and the AUC was calculated. Data was analyzed retrospectively.
Results: TDM was applied to 168 patients (35-85 years) and 553 dose adjustments were recorded. 5-FU exposure variability was high with AUC values ranging between 5 and 41 mg•h/L in the first cycle of chemotherapy. Compared to the study of Wilhelm et al. [2] there was a higher fraction of patients in the target exposure range already in cycle 1. However, the application of TDM did not lead to a reduction of the fraction of underdosed patients which was achieved under study conditions. This might be due to the fact that only 41% of all dose adjustments were made according to the recommendations of the dosing algorithm. 19% and 40% of the dose adjustments were performed either applying a higher or lower than the suggested dose, respectively.

Tab. 1. Proportion of patients above, within and below the target AUC range stratified by cycle

Onkologie UnterEms				
	Cycle 1 (n=175)	**Cycle 2 (n=75)**	**Cycle 3 (n=40)**	**Cycle 4 (n=8)**
AUC ≥ 30*	7 %	9 %	12 %	12 %
AUC 20 – 29*	54 %	59 %	53 %	48 %
AUC ≤ 19*	39 %	32 %	35 %	40 %
Wilhelm et al. [2]				
	Cycle 1 (n=67)	**Cycle 2 (n=64)**	**Cycle 3 (n=65)**	**Cycle 4 (n=63)**
AUC ≥ 30*	3 %	6 %	10 %	24 %
AUC 20 – 29*	33 %	47 %	65 %	54 %
AUC ≤ 19*	64 %	47 %	25 %	22 %

*AUC unit: mg·h/L

Conclusions: Although the application of 5-FU TDM has been shown to be effective in clinical trials, the performance in clinical routine is still limited. Medical staff should be trained in the correct application of the dosing algorithm in order to fully exploit the potential of 5-FU TDM.

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[1] Kaldate et al. Oncologist 2012; 17:296-302.
[2] Wilhelm et al. Clin Colorectal Cancer 2016; 15:381-8.

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V1080

Use of standardized supportive care protocols improves patient safety during high-dose methotrexate therapy

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Introduction: High-dose methotrexate (HD-MTX) is a cornerstone of treatment protocols in ALL, osteosarcoma and lymphomas. Due to its toxicity profile, several supportive measures (urine alkalization, leucovorin rescue/measurement of MTX plasma levels) and precautions (avoidance of pharmakokinetic interactions, detection of third space fluids) are neccessary to ensure safe administration of HD-MTX. If supportive care measures are not strictly followed, life-threatening toxic side effects of HD-MTX are possible. The implementation of a standard operating procedure (SOP) containing structured, standardized documentation for supportive care to improve safety of HD-MTX was investigated.
Methods: A checklist containing items for preparation of HD-MTX therapy and a protocol for timely defined control and documentation of urine alkalization was implemented into clinical care and was used in all patients receiving HD-MTX since 05/2017. Checklist items included: detection of third space fluid, renal function, control of pharmacokinetic interactions with preexisting medication, preparation of a urine alkalization protocol, actual status of urine alkalization and hyper-hydration therapy. Rates of defined adverse drug reactions (renal failure, prolonged elevation of MTX plasma levels, need to use glucarpidase) in 118 patients

(414 cycles of HD-MTX since 05/2017) were compared to 108 patients (332 treatment cycles) who received HD-MTX therapy without the use of a SOP (01/2015-04/2017). The incidence of adverse events was calculated per treatment cycle.
Results: The use of a safety checklist and standardized documentation of urine alkalization improved safety of HD-MTX and reduced adverse effects. The rate of renal failure was 6.2 % in patients treated without SOP intervention and 0.7% in the intervention group ($p < 0,001$). Inadequate decrease of MTX serum levels was observed in 51 treatment cycles (15.2%) in the control group and in 11 cycles (2.6%) of the intervention group ($p < 0,0001$).Five patients in the control group (1.47%) and two in the intervention group (0.48%) received glucarpidase.
Conclusions: SOPs including a checklist for the documentationof supportive care prior to HD-MTX and a strict protocol for urine alkalization during HD-MTX therapy are able to significantly improve safety and reduce the rates of adverse effects.
Use of these rigorous safety tools is encouraged to prevent unneccessary, life-threatening toxicity in patients undergoing HD-MTX.

Disclosure: No conflict of interest disclosed.

V1081

Implementation of a new chemotherapy management software - promises potential challenges and future perspectives

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Introduction: After 10 years of electronic chemotherapy (CTx) ordering via an in-house-database (Chemo AS), a new transferable (CTx) management software (ChemoCompile®) was introduced at Freiburg university medical center (FUMC). The established workflow, involving a pharmacovigilance check of each prescription by a surveillance team: the Clinical Cancer Research-Group (CCR-G), in close cooperation with our clinical pharmacy, was maintained. Detected errors are instantly corrected and recorded electronically. Our restructured error-score allows comparing the potential error consequences prior and after initiation of our new software. Further, we aim to facilitate other centers to be part of our reliable safety structure.
Methods: Our current software ChemoCompile®, was developed based on its predecessor Chemo-AS. Via database query, all prevented errors in 2018 (1-12/2018) were retrieved and categorized. Results were compared to our prior analyses (2013/2014) with Chemo AS.
Results: Over 1 year after implementation of the new ChemoCompile® software with increased automated safety features, the amount of errors remains gratifyingly low: with 2.2%, the error rate in 2018 was comparable to 2013/2014 (1.7-2.7%). With the new software, errors of ´incorrect CTx-timing´ and ´CTx not ordered´ decreased (-9%/-5%), and ´errors of incorrect substance´ and ´study cohort´ remained stable. Notably, an increase in underdosing errors by +9% (from 15%→24%) and slight increase in overdosing errors by +3% (51%→54%) was observed. Importantly, however, all errors analyzed were efficiently prevented by our CCR-Group. For other centers, using ChemoCompile® and wishing to share our efficient pharmacovigilance service, we are in the process to offer an electronic connection with a "satellite CCR-Group service" as a novel research-cooperation project.
Conclusions: Although the new software is based on the preceding database we observe a change in error structure. This highlights the need for 1) ongoing cooperation between clinicians and IT-specialists, currently constructively pursued; 2) analysis of potential improvements also of system-induced errors and 3) supports the expansion of an additional pharmacovigilance check to other centers. We have applied for funding to realise this multi-center pharmacovigilance project and will report details at the meeting.

Disclosure: No conflict of interest disclosed.

V1082

Extended Medication Plan for patients with ORal Tumortherapy (EMPORT)

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Introduction: Due to the increasing number of oral anticancer agents the responsibility for the management of oncologic therapies shifts more towards the patient. In 2016 a national medication plan (Bundeseinheitlicher Medikationsplan, BMP) was introduced in Germany and has the potential to assist patients in the management of their therapy and to inform all healthcare providers about the medication.
The aim of this project is to identify relevant information on oral anticancer drugs that should be added to the BMP in order to increase its value for cancer patients.
Methods: To evaluate which information should be added to the BMP, we conducted a needs assessment among oncologists, specialized oncology pharmacists and cancer patients. Oncologists were invited to participate by the Scientific Institute of Office-Based Hematologists and Oncologists (WINHO) and the Central European Society for Anticancer Drug Research (CESAR), oncology pharmacists by the German Society of Oncology Pharmacy (DGOP). Patients were recruited in the University Hospital Cologne.
Based on the results we developed an oncological extension to the BMP. To detect whether this extended medication plan is feasible in routine, it was piloted in 10 patients who were observed for at least 3 months.
Results: 130 pharmacists, 167 oncologists and 50 patients participated in the needs assessment. Information that should be added to the BMP is amongst others how to take the drug (oncologists: 87.8%, pharmacists: 97.0%) followed by the therapy regimens (oncologists: 75.5%, pharmacists 67.0%), symptoms when the patients need to see a doctor (oncologists: 49.0%, pharmacists: 82.0%,) and how to proceed with missed doses (oncologists: 42.18%, pharmacists: 74.0%). Most important for patients is the interaction of their anticancer drugs with OTC medicines (83.0%).
The 10 patients recruited in the pilot phase were treated with ruxolitinib (5), lenalidomide (4) or lenalidomide/ixazomib (1). In total, the BMPs of 6 patients have been updated. Updates were made by pharmacists (3) and by the patients themselves (3). Some updates have been made on additional forms e.g. notepads written by patients (3), doctor´s letters (2) or other medication plans (1).
Conclusions: The results of this project suggest that the extended BMP is a useful tool to provide patients with relevant information on their oral anticancer therapy. It will be further optimized based on patient interviews and process mapping.

Disclosure: No conflict of interest disclosed.

V1083

Structural Iatrogenesis - Too Little, too Late

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Mrs. S. was a 69-year-old woman with thyroid cancer treated initially in 2009 and for relapse in 2013. In 2016 a new lesion developed. Biopsy,

however, revealed a new histology: Follicular Dendritic Cell Sarcoma. After 2 cycles of an anthracycline containg regimen the tumor had progressed. She underwent rescue surgery and remained in remission for 2 years. In spring 2018 she developed pulmonary metastases. Biopsy confirmed follicular dendritic cell sarcoma with high PD-L1 expression. We applied for health insucrance coverage of checkpoint inhibitor treatment. 1st petition 9/2018: refusal 10/18 (after 5 weeks): no data for checkpoint-inhibitor treatment. 2nd petition 11/18, refusal received 1/19 (after 10 weeks): other chemotherapy agents, even if off-label, should be tried first. 3rd petition filed 1/19 and eventually granted approval 2/19 (after 3 weeks). Meanwhile the patient developed aspiration pneumonia. One day before health insurance's approval the patient died, presumably from pulmonary embolism.
Structural iatrogeneis is the causing of harm by bureaucratic systems within medicine, including those intended to benefit patients (e.g. quality control measures by health insurance).[1] How can we avoid structural iatrogenesis: (1) Recognize and change bureaucratic structures that harm patients, e.g. patients with life-threatening or rapidly progressive diseases should not wait for health insurance approval for expensive treatments but instead be covered until disapproval. (2) Speed decision processes, e.g. change policies that prevent the treating physician to contact medical expert from the "Medizinische Dienst der Krankenkasse" directly (e.g. by mail, phone). (3) Prioritize individualized treatment over standardized care: Guidelines and choosing wisely recommendations are based on studies with younger, less sick, and more competent patients than those seen in daily practice. Instead, guidelines should explicitly indicate which patients were not included in the underlying studies to which recommendations consequently do not apply. (4) Extend quality of care assessments onto health insurances. Besides hospitals, also health insurances should be ranked by their patients' outcome, e.g. survival and quality of life compared to patients insured by other public or private health insurances. These and additional suggestions will be discussed during the presentation at the meeting.

References: [1]Stonington S. N Engl J Med 2019;380:701-3

Disclosure: No conflict of interest disclosed.

Studententag

Studententag: Karriere in der Hämatologie und Onkologie

Career at a non-university hospital

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Introduction: The specialty of hematology/oncology is relatively young. It developed from internal medicine in the 1960s meanwhile with one of the highest number of publications and many new approved drugs every year. Thus, it requires the willingness to constantly keep up to date, to accept often changing diagnostic and treatment recommendations and to work interdisciplinaryly. In addition, caring for individuals in critical life-situations, and perhaps raising a family at the same time, makes it challenging to maintain a work-life balance and to avoid burn-out.
Methods: Results presented are based on literature research in pubmed, ESMO, ASCO and DGHO publications as well as on own experiences as head of a hematology/oncology department.
Results: Fellows working in a community based hospital are not expected to be involved in research projects, acquire funding or take part in teaching activities. Only senior physicians and the head of the department have teaching obligations if the hospital is an academic teaching hospital. Thus, fellows can focus on their clinical training including special diagnostics such as cytology, immune cytology, and ultrasound, as well as on intensive and palliative care. Non-university hospitals often treat a broad spectrum of internal and oncological diseases. Staying for a minimum of 24 months at the hospital and for at least 6 months at an outpatient clinic are required during the training. Afterwards, there are opportunities to continue as a senior physician or even as head of a department. A good child-care system, especially for children under the age of 3, part-time contracts and flexible working hours are important to ensure that the steadily increasing number of female fellows remain integrated in the hospital system and complete the training for hematology/oncology. For financial reasons, this is more likely to be offered at hospitals with a maximum support level. In line with the demographic development, cancer rates increase. Therefore, depending on the region, 6-25% more hematologists/oncologists will be needed in 2020, while at the same time >25% of hematologists/oncologists will turn >65 .
Conclusions: Due to the demographic development, there are increasing career options at non-university hospitals for young hematologists/oncologists who aim to treat a broad spectrum of oncological diseases. To be seen as attractive employers, non-university hospitals need to offer flexible contracts as well as child support.

Disclosure: No conflict of interest disclosed.

Career Path in Translational and Basic Research

Chapuy B.

Universitätsmedizin Göttingen, Hämatologie und Onkologie, Göttingen, Germany

Prof. Chapuy is an advanced clinical scientist, who trained at the University Medical Center, spend 10 years abroad to do ever-exciting translational research at the Dana-Farber Cancer Institute/Harvard Medical School, and works now as physician and group leader of a translational lymphoma biology laboratory. Prof. Chapuy will present typical and (not so typical) career paths for academically interested clinical scientists.

Disclosure: No conflict of interest disclosed.

Studententag

Symposium Lehre&Weiterbildung

iLearn onco: tackling the challenges of interdisciplinary teaching in medical oncology

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Interdisciplinary teaching in Medical Oncology challenges both students and their respective teachers.
At the University Medical Center of Göttingen Medical Oncology is taught as part of the 6-week course "Erkrankungen des Blutes, des Knochenmarks und Grundlagen der Tumorerkrankungen" with 14 institutes and clinics involved in the curriculum and/or exam generation.
To offer the students guidance through the broad and dramatically developing field of Oncology in the very limited duration of the course as well as in the preparation for the second and third state examination we designed the eLearning platform iLearn Onco in cooperation with Amboss. iLearn Onco provides versatile tools to prepare for lectures and practical courses, revise and recapitulate old and new knowledge and implicates small group learning approaches.
Furthermore, the students have the option to use an integrated learning plan to deal with the enormous contents of the course. iLearn Onco is accessible on all kinds of mobile devices.

Its blended learning approach aims to support longitudinal learning and elaborate the students own research skills by providing direct links to peer-reviewed guidelines and regularly updated websites such as Onkopedia and Amboss instead of offering a classical, briefly outdated lecture script.
For the teachers with diverse professions such as surgery, radiology, pharmacology, psychology or palliative medicine iLearn Onco offers the possibility to be used in a flipped-classroom setting.This allows not only to remove the slag from the oftentimes content-overloaded lectures but also to acknowledge the students individual level of proficiency in the various fields.
After the launch of the pilot in the winter semester 2018/2019 we evaluated iLearn Onco with an online evaluation system as well as a focus group discussion.
Step-by-step expansion of the contents, further integration in the pre-existing curriculum and raising the acceptance in the teaching staff will be priorities for the following semesters.

Disclosure: No conflict of interest disclosed.

Collegiate tumor board: teaching of decision making

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Introduction: In the context of rapid progression in development of different treatment modalities - especially in oncology - interdisciplinary decisions for treatment concepts obtain central importance. Interdisciplinary discussions in tumor boards will become a main competence in being a medical doctor. Teaching the experience of decision making is underrepresented in current curricula.
Methods: All medical students at the Goettingen University pass a sequence of lectures and seminars in their third clinical semester in oncology. In the setting for lung cancer the students are divided into six groups defining an affiliation to special seminars to become an ´expert´ in one of the following specialties: pneumonology, radiology, pathology, oncology, thoracic surgery, and radiation oncology. With the experience of ´being an expert´ in one of these specialties they join a collegiate tumor board for lung cancer. In this setting the students experience to be an expert and advocate for the patient.
Results: In four 3rd clinical semesters we have implemented the new module successfully. The teaching included 6 disciplines and senior experts in the seminars and the collegiate tumor board. The concept of divided seminars and the tumor board was well rated by students ant doctors.
Conclusions: The new concept was successfully implemented in the curriculum and positively rated. Competences in decision making are addressed in an early stage of learning and are a cornerstone for success in an interdisciplinary cooperation.

Disclosure: No conflict of interest disclosed.

Setting an individual focus with longitudinal electives in medical school - "Interdisciplinary oncology" and the Heidelberg curriculum medicinale (HeiCuMed)

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Introduction: Compared to other academic disciplines such as social sciences and humanities, medical school curricula are known to be very "school-like" leaving limited opportunities to meet individual interests of students. Freedom of choice within the clinical part of MD education traditionally consists in choosing training locations for internships and practical year placements, the subject of doctoral thesis and one elective of 1-3 weekly lecture hours. To allow students to set an individual focus in their MD education, longitudinal electives ("tracks") were introduced within the Heidelberg Curriculum Medicinale (HeiCuMed) in 2017. The volume of training consists of 2 weekly lectures hours for at least 3 semesters. Participation in the program has been on a voluntary basis until 2019 and will be obligatory starting from winter semester 2019/2020. 11 different tracks are offered to students. Subjects covered are e.g. "Immunology", "Emergency Medicine", "Global Health" and "Interdisciplinary Oncology (IO)".
Results: More than 50 % (roughly 730/1360) of eligible students decided to participate voluntarily in a longitudinal elective track. Of those, 13% of participants chose IO. Within the IO elective, more than n=30 optional courses are offered each semester covering subjects such as scientific methods (e.g. statistic seminars, training in laboratory methods, journal clubs), ethics and communication skills training, practical courses (e.g. image diagnosis, ultrasound, port-a-cath puncture, lumbar puncture) and clinical seminars on topics such as CAR T cells, clinical trial design, and toxicity management among many others. The modular system of the IO elective allows for a wide selection of topics for the students that are registered as participants within the track.
Conclusions: The longitudinal elective track "Interdisciplinary Oncology" has a high voluntary participation rate and very positive feedback from students. This indicates that our teaching concept is very well suited to address the call for increased choice and specialization in medical curricula in Germany.

Disclosure: No conflict of interest disclosed.

Pflegekongress Vortrag

Unterstützende Angebote im Akut- und Rehabereich

Music therapy in oncological care

Moser D.

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Stellt man einen gesellschaftlichen Exkurs zur Wirkung der Musik an, stellt man fest, dass nahezu jeder Mensch Erfahrungen dazu in seiner Biographie sammeln konnte. Je nach Zeitpunkt und Art der angebotenen Musik kann Freude, Erhabenheit, Aufmunterung, Glück, Ergriffenheit, Geborgenheit, Beruhigung, aber auch Depression, Unruhe oder Angst ausgelöst werden. Seit Menschengedenken wird aus diesem Grund Musik zweckgebunden eingesetzt. In unserer Kultur findet diese insbesondere Eingang bei Lebensübergängen (Geburt, Taufe, Einschulung, Konfirmation/Firmung, Hochzeit, Sterben). Alle Übergänge und die damit verbundenen Veränderungen im Leben eines Menschen stellen Herausforderungen dar, die gemeistert werden wollen. Aus dieser Sicht liegt es auf der Hand, dass ein musiktherapeutisches Angebot ein bedeutendes und hochwirksames Potential in der Patientenbegleitung darstellt und einen wichtigen Platz im onkologischen Behandlungskonzept einzunehmen vermag. Neben eingehenden theoretischen Erläuterungen liegt ein Fokus des Referates auf Fallbeispielen, sowie wird auf Möglichkeiten und Grenzen des musiktherapeutischen Arbeitens im Bereich der onkologischen Versorgung eingegangen.

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