SIXTH FRAMEWORK PROGRAMME

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Life Sciences, genomics and biotechnology for health

(LifeSciHealth)

Proposal/Contract no.: 503216

Project acronym: European LeukemiaNet

Project full title: Strengthen and develop scientific and technological excellence in research and therapy of leukemia (CML, AML, ALL, CLL, MDS, CMPD) by integration of the leading national leukemia networks and their interdisciplinary partner groups in Europe

Network of Excellence

# Sixth Annual Activity Report

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Project coordinator: Prof. Rüdiger Hehlmann

Project coordinator organization name: Universität Heidelberg

## Publishable Executive Summary

In 2009 European LeukemiaNet (ELN) entered the 6th year of funding by the European Commission (EC). Years of joint efforts in the management of leukemias have shaped the ELN to what it currently is: An internationally recognized leukemia network, highly motivated and well-focused, grown through mutual trust and independence. 162 institutions from 32 countries participate in 2009 and contribute, each within their particular field of knowledge and expertise. The EC extended the contract with the ELN until February 2011, stating that the ELN is "a very successful network that warrants support and extension". This is indeed a success and motivation for all ELN members and partners. Key results are uniform definitions for diagnosis and treatment in leukemia across Europe manifested in management recommendations for each leukemia entity, enforced activities towards common clinical trials and projects, avoiding duplication and fragmentation, and the spread of excellence in leukemia research and patient care. A comprehensive list of management recommendations and guidelines published during the current funding period for virtually every leukemia entity and interdisciplinary specialty setting uniform standards for all joint activities is shown in table 1 (Section 1.5.).

The ELN offers intellectual diversity. Scientific issues are addressed from complementary points of view with high-level competence in discussions and recommendations. Strong European networks for each leukemia cooperate to enable more clinical trials within Europe to achieve more efficient drug evaluation and a greater diversity of drugs.

The unique infrastructure given by the network management center (NMC, WP1), the European leukemia information center (ELIC, WP2) and the central information and communication services (CICS, WP3 and WP17) provides the basis for internal and external network interactions. Together with the leading national leukemia trial groups of the different leukemia entities (WP4-9) and their interdisciplinary partner groups in diagnostics and therapy research (WP10-15) they are responsible for high quality research and patient care, essential for European excellence in the field of leukemia. This includes:

- Standardized protocols for clinical trials to achieve comparable data, resulting in better and equal treatment options across national borders
- Clinical trials on a European scale
- Development of management recommendations for all leukemias
- Standardized diagnostic procedures, which are in a continuous evaluation and optimization process.
- Networks of reference labs in leukemia diagnostics and pharmacokinetics across Europe (EUTOS for CML public-private patnership)
- Patient registries for information on current treatment as it is, best treatment options and outcome with more certainty (EUTOS for CML, EU-MDS)

- Improvement of patient care due to personalized treatment options
- Spread of excellence and high level training and education to all physicians and researchers interested in leukemia by ELN experts
- Strong infrastructure building on communication and face to face knowledge exchange
- Computational program and technical research support for network members
- Distribution of leukemia news via printed and online media newsletters, (www.leukemia-net.org).
- Patient brochures on each type of leukemia to support public education (in progress)

Sustainability is a key issue to keep this source of interaction and cooperativity alive. The basis for continuation are committed partners and newcomers as well as the expertise and skill for managing organizational development and change.
In 2009 the ELN Foundation was constituted and started its activities. The ELN Foundation is a non-profit charitable organisation. It supports the goals of the ELN to foster science and research and to improve and enhance medical care in acute and chronic leukemias and related diseases. The ELN-Foundation should attract tax deductable donations. It addresses all groups physicians, scientists, health professionals, patients and their relatives, as well as private and public organizations, industry, politicians, other charities and every individual with an interest in leukemia.

Highlights in 2009 include

- The ELN symposium in Mannheim which attracted 439 ELN participants from 30 countries
- Acceptance of fifteen new participants to ELN integrating five additional countries, namely Portugal, Latvia, Slovakia, Slovenia, and Ukraine
- Trials on a European level (CLL, ALL, CML, SCT)
- International awareness of ELN recommendations
- Management recommendations published on AML and APL and updated on CML, in high impact journals
- consensus response criteria in polycythemia vera and myelofibrosis
- Public-private-partnerships between ELN and Novartis successfully continued: standardization of BCR-ABL diagnostics in standardization of BCR-ABL diagnostics in 57 European laboratories in 24 countries, imatinib lood level testing in 28 reference laboratories in 14 countries, European registries with data from 3000 CML patients and 650 MDS patients (in-study, out-study and population-based registries) (www.eutos.org; www.eumds.org).
- Constitution of the ELN Foundation and legalization by authorities to support ELN goals beyond EU funding.
- Spread of excellence by close to 90 educational activities at the annual congresses of ASH, EHA and the German/Austrian/Swiss Societies of Hematology and Oncology, the annual

CML-educational meeting in Barcelona, more than 20 workshops, by publication or completion of more than 590 manuscripts, the 6th information letter, a new information booth, including first time information on the ELN FOUNDATION, an ELN Foundation Newsletter in 7 languages and more than 1000 lectures by ELN-participants.

In 2010, the integration of 14 new participants and one additional country, (Estonia), is planned increasing the number of participants to 176 and the number of countries to 33.

This large partnership is a managerial challenge for the network, but each country has its own areas of activities adding value to joint activities. Spread of excellence to all countries is a key goal of the ELN, supporting local infrastructures to optimize treatment.

The ELN is likely to have a durable impact on leukemia research in Europe. Infrastructure and synergies provided by the ELN create an added value. By promoting cooperation on top of competition the ELN provides a competitive advantage to all participants to the best of every patient with leukemia worldwide.

# Section 1: Project objectives and major achievements during the reporting period

### 1.: Consolidating integration, cooperation, central information and communication structures, central data management and spread of excellence (WP1-3, 17)

Durable integration needs strong governance. The Network management, information and communication centers (NMC, ELIC, CICS and WP 17_Biometry) offer infrastructure, guidance and services.

The NMC facilitated contractual, and financial issues assisting in project management of multinational collaborative leukemia projects and provided organizational support with close to a 77 annual ELN activities at national and international leukemia events, including training of young physicians.

Internal and external communication, within the network's trial or interdisciplinary partner groups, with industry, key stakeholders, patient organizations and public relations as well as the distribution of information on network activities and achievements in research and partnering were major tasks (PR material: flyer, booth).

In 2009, the annual ELN symposium in Mannheim attracted 439 ELN participants from 30 countries. Challenges and new directions in leukemia and related disease entities were highlighted and complemented by a presentation on rare cancers.

Regulatory issues of the new European drug law continue to pose a major hurdle to investigators to initiate international collaborative trials. A special teaching event on the situation of international investigator-initiated trials in Europe was offered. A training course in good clinical practice presented up-to-date information on the actual consequences of changing regulations.

The General Assembly agreed in 2009 on the participation of fifteen new participants integrating five additional countries, namely Portugal, Latvia, the Slovak Republic, Slovenia and Ukraine, increasing the number of participants to 162 and the number of countries to 32. In 2010 the assembly will decide on 14 new participants and 1 new country (Estonia). The ELN network will then include 176 institutions from 33 countries working together in now 105 leading national leukemia trial groups and 105 interdisciplinary partner groups in diagnostics, cytogenetics, MRD-research, gene expression profiling and registry, guidelines and industry (Fig. 1 and 2).

**105 National Leukemia Study Groups**

| European Networks | CML | AML | ALL | CLL | MDS | CMPD |
|---|---|---|---|---|---|---|
| Austria | ● | ● | ● | ● | ● | ● |
| Belgium | ● | ● | | ● | ● | ● |
| Croatia | ● | | ● | | | |
| Cyprus | ● | | | | | |
| Czechia | ● | ● | ● | | ● | |
| Denmark | ● | ● | | ● | ● | ● |
| Estonia | ● | | | | | |
| Finland | ● | | | | ● | |
| France | ● | ● ● | ● | ● | ● | ● |
| Germany | ● | ● | ● | ● | ● | ● |
| Greece | ● | | ● | | | |
| Hungary | ● | | | | ● | |
| Ireland | ● | | | | | |
| Israel | ● | ● | | | ● | |
| Italy | ● | ● | ● ● | ● | ● | ● |
| Latvia | ● | | | | | |
| Luxembourg | ● | ● | | | | |
| Netherlands | ● | ● ● | ● | ● | ● | |
| Norway | ● | | | | | |
| Poland | ● | ● | ● | ● | | |
| Portugal | ● | | | | | |
| Romania | ● | | ● | | ● | |
| Russia | ● | ● | | | | ● |
| Serbia | ● | | | | | |
| Slovakia | ● | | | | | |
| Slovenia | ● | | | | | |
| Spain | ● ● | ● ● | ● | ● | ● | ● |
| Sweden | ● | ● | ● | ● | ● | ● |
| Switzerland | ● | ● | ● | | ● | |
| Turkey | ● | | ● | | | |
| UK | ● | ● | ● | ● | ● | ● |
| Ukraine | ● | | | | | |
| European consortia | EI-CML EBMT | EORTC | EORTC EWALL | ERIC | EBMT EORTC | ECLAP European ET |

**Figure 1**: 105 National Leukemia Study Groups

**105 Interdisciplinary Partner Groups**

| Platform for interdisciplinary specialities | Diagnostics | Cyto-genetics | MRD | Gene profiling | SCT | Supportive Care Infections | Registry | Guidelines |
|---|---|---|---|---|---|---|---|---|
| Austria | ● | ● | ● | | ● | | ● | ● |
| Belarus | | | ● | | | | ● | |
| Belgium | | ● | ● | | ● | ● | ● | ● |
| Croatia | | | | | ● | | | |
| Czechia | | | | | ● | | ● | ● |
| Denmark | | ● | ● | | | | ● | |
| Finland | | ● | ● | ● | ● | | ● | |
| France | ● | ● | ● | ● | ● | ● | ● | ● |
| Germany | ● | ● | ● | ● | ● | ● | ● | ● |
| Greece | | ● | | | | | ● | |
| Hungary | | | | | ● | | ● | |
| Israel | | | | | ● | ● | | |
| Italy | ● | ● | ● | ● | ● | ● | ● | ● |
| Lithuania | | | ● | | | | | |
| Netherlands | ● | ● | ● | ● | ● | ● | ● | ● |
| Poland | | | ● | | ● | | ● | |
| Portugal | | | ● | | | | ● | |
| Russia | | | ● | | | | ● | |
| Serbia | | | ● | | | | | |
| Spain | | ● | ● | ● | ● | ● | ● | ● |
| Sweden | ● | ● | ● | ● | ● | ● | ● | ● |
| Switzerland | ● | ● | ● | | ● | ● | ● | ● |
| Turkey | | ● | ● | | ● | ● | ● | |
| UK | ● | ● | ● | ● | ● | ● | ● | ● |
| European consortia | EGIL | | | EORTC | EBMT CLWP | EBMT | | ESH EHA |

**Figure 2**: 105 Interdisciplinary Partner Groups

WP2 (ELIC) highlights progress within the different leukemias in the ELN homepage. The ELN trial registry database shows information on more than 70 active clinical trials, including research protocols and procedures. Intensive efforts are ongoing to coordinate trials and to harmonize criteria according to European guidelines and to update the trial registry. The performance of European leukemia trials is an area of great promise for the future.


**Figure 3**: ELN Homepage with information on international IIts

The ELN has also established a link to the impact assessment of the European Commission regarding CT-Directive on Good-Clinical-Practice. In the name of the ELN ELIC has prepared a comprehensive comment regarding the public consultation of the CT-directive in collaboration with several national and international working groups. Several ELN members have contributed. The poor situation of academical trials (therapy optimization trials /investigator-initiated trials) was highlighted and changes suggested.
(See http://www.leukemia-net.org/content/international_trials/basic_information/).

The ELIC also cooperates in the name of ELN with the Roadmap initiative for clinical research in Europe for a more efficient Clinical Trial Authorisation (CTA) process that stimulates rather than stifles research and innovation.

http://www.leukemia-et.org/content/international_trials/workshops/the_road_map_initiative/.

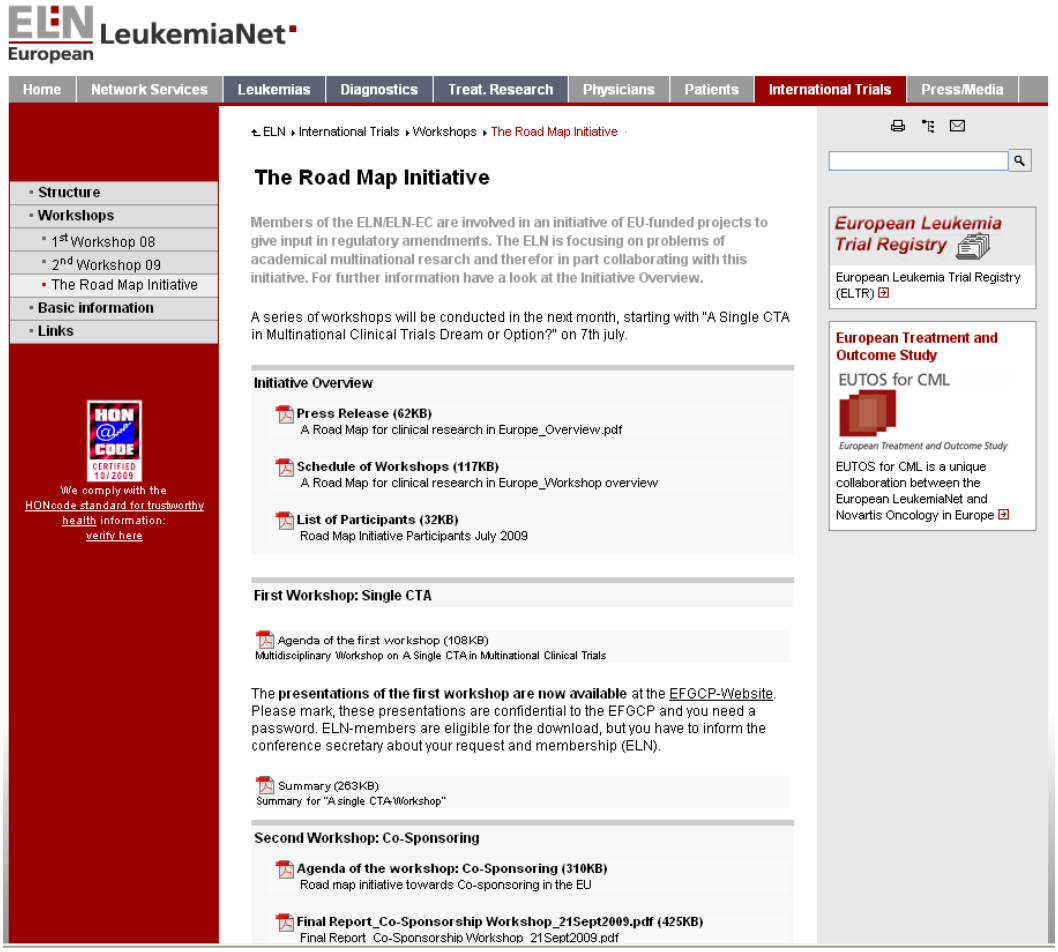



**Figure 4**: ELN Homepage with information on the Roadmap Initiative

The ELN website also offers up-dates and guidance on new trial-legislation and -registration, regulatory requirements and training courses.
(http://www.leukemia-net.org/content/international_trials/links/)

Links to related project websites, like the European treatment and outcome study (EUTOS) for CML, offer information material for download.
The German part of the EUTOS population based registry can be found on the homepage of the German Competence Network.
(http://www.kompetenznetz-leukaemie.de/content/aerzte/studiengruppen/cml/cml_register/).

The ELN Member Database implemented by **ELIC and NMC** together with the German competence net "Acute and chronic leukemias" was further updated with institutions and centers involved in clinical studies or study registration.

The sixth information letter was prepared for the symposium in 2010, highlighting the current progress on projects, collaborations, meetings, website content and lists upcoming meetings (**WP2,** ELIC, in cooperation with **WP1**, NMC). It fosters cooperation amongst network members and informs the public on hot topics in leukemia.

**WP3 (CICS**) offered computational services to the network:
CICS facilitates computational structures for the network, like data management, algorithmic instruments, statistical networks and profiling structures central registry services help to channel international registry data collection through electronic case report forms (eCRFs).
A central randomization facility accompanies clinical trials
In 2009 the range of functions of the software 'RANDOULETTE' was extended. Randoulette allows online randomisation of individual patients in clinical trials according to Good Clinical Practice The randomisation facility is available at no additional costs for trials conducted within the European LeukemiaNet. The GCP-compliant electronic data capture facility MACRO is also available to research groups within the consortium.
In addition WP3 has developed a web-based online electronic case report form (eCRF) for the European Treatment Outcome Study (EUTOS) for CML Registry organised by WP17. Case reports include baseline information and yearly follow-ups. The registry currently covers 52 regions in 23 different countries. More are expected to join in 2010.
A Microarray – Analysis – Pipeline developed in cooperation with the University Regensburg and designed to automate standard working steps was used on 151 CLL samples to develop a prognostic score for patient survival time and time to treatment.
In 2009 WP3 participated in the planning of pseudonymization issues in a large register trial researching outcome of acute myeloid leukemia (AMLSG-BiO Study), which will start in 2010.
Furthermore WP3 (IBE, LMU Munich) participates in the FLAMSA 101, 102, 103 studies in high risk AML patients with IT and biometrical services (RANDOULETTE and statistical analysis).

**An international workshop on "**Advances in Statistical Modeling of High Dimensional Data" took place in September 17-18, 2009 in Munich (48 participants). It was jointly organized by the IBE (representant of the ELN), the German Region of the International Biometrical Society, and the Gene Center of the Munich University. Besides an overview of joint activities of bioinformatics and biostatsitics the workshop also addressed actual research in the field of hemopoietic stem cells.

**WP17, Biometry of registry, epidemiology and prognosis** expanded the registries on CML and MDS in collaboration with WP3, WP4 and WP8, respectively. Together, both registries account for data from more than 3000 eligible CML and more than 650 MDS patients. In CML the population-based-registry started in several countries, collecting baseline and follow up data on new patients

diagnosed with CML, with the goal to develop and validate a comprehensive prognostic model that allows the optimization of individual treatment choices.
Recently, first steps have been taken to start with an AML-registry, beginning in Germany within the AML-Intergroup, but with the perspective of an European AML registry.

**2. Performance of clinical trials (WP4-9, 14-15)**

The implementation of international ELN guidelines and recommendations on treatment of leukemia will help provide patients optimal health care across the globe. By now, 34 recommendations were published in the funding period, eight of these in 2009 (Table 1, below. Section 1.5.) regarding CML, AML, APL, essential thrombocythemia) and polycythemia vera and in stem cell transplantation.
The ELN benchmarks diagnostics and treatment procedures at international levels and evaluates novel concepts and technologies. The ELN defines and applies common standards and protocols and utilizes uniform common data sets established by the interdisciplinary partner groups (WP11-16).
The ELN trial registry shows information on more than 70 active clinical studies.
(http://www.leukemia-net.org/content/leukemias/trial_registry/database/)
Several new clinical trials were started and updates on ongoing trials were presented at conferences (ASH, EHA, DGHO) and published in international journals.

**WP4** has six ongoing collaborative trials on an European level (EICML). Trials with new signal transduction inhibitors, new immunotherapy (vaccination) and with attempts to stop imatinib therapy are running successfully across Europe. The European registry and the subregistries have grown rapidly and now enrolled more than 3500 patients. A European population based registry was launched in 2009. Standardization rounds were completed with 57 ELN laboratories for molecular monitoring of residual CML and consensus recommendations on molecular monitoring were published. In addition an updated and revised version of the ELN recommendations on the management of CML have been published and updated pocket cards for physicians were finalized in December.

During 2009, further progress has been achieved in the European AML network **(WP5).** At the annual Reisensburg Symposium new data on gene mutations (CEBPA, RUNX1) and overexpressions (ERG, BAALC, MN1) have been presented.
Epigenetic changes in AML related to age became the subject of a DFG funded research project.
Aspects of older age AML were elaborated in a large multicenter trial (see Annex Section 3, WP 5-2).
Uniform European recommendations on all clinical aspects of AML were published for both general AML and APL (Table 1, Section 1.5.). APL relapse, data and treatment, were contributed in an own publication (see Annex Section 3, WP 5-9). Multiple approaches and experiences were reported on the field of allogeneic SCT.

The role of growth factor priming in AML could be elucidated in a large multicenter trial as an ELN pilot project (see Annex Section 3, WP 5-2).
Major progress was achieved in setting up an international randomized study in elderly AML patients according to the new EU directive. This is the first randomized study in the elderly using stem cell transplantation (WP 14 and the EBMT). A new definition of inclusion criteria in older patients (frailty index) is under discussion and in preparation.
There is intensive work of representatives of all major European AML trial groups (the AML Intergroup) to coordinate European trials and harmonize various criteria according to European guidelines. Treatment protocols, future strategies and comparability parameters between European AML studies are in discussion
These activities will enhance performance and comparability of trials across Europe leading to better synergies and improved outcomes in research and patient care.

The ALL working group **(WP6)** successfully uses the advent of advanced technologies for monitoring of residual disease and the availability of new drugs and of tyrosine kinase inhibition for BCR-ABL positive cases to optimize outcome of ALL in adults. The rarity of ALL has accelerated the formation of a European Working Party for ALL (EWALL) and the performance of common trials in several European countries. In 2009, WP6 was accepted as a Scientific Working Group of the European Haematology Association (EHA). After approval by the EHA, the first meeting of the EHA-SWG-EWALL will take place during the forthcoming EHA meeting in 2010. EHA president Robin Foà and the president elect UlrichJäger are both members of the EWALL.

In 2009, **WP 7,** ERIC/CLL was approved as a Scientific Working Group of EHA. This acknowledges and fosters scientific credibility, competence and excellence of ERIC as a European non-profit organization. Furthermore, it connects the European LeukemiaNet and EHA as interacting European promoters of competence in hematology and leukemia. In 2009 three ERIC meetings and one ERIC/EHA SWG workshop were held (between 40 and 120 participants). The outcomes of two clinical trials were presented at ASH 2009 in New Orleans.

The MDS working group **(WP8) i**s the second WP that has started a European MDS-registry (EUMDS) with the private partner Novartis. WP8 conducts European trials on all types of MDS including those with demethylating agents. One trial explores the impact of iron chelation on prognosis of MDS.

The CMPD working group **(WP9)** in cooperation with groups in North America explores the impact of JAK-2 mutation on diagnosis and therapy of CMPD. Several consensus protocols deal with risk factors and management of thrombosis in CMPD. In 2009 the group embarked on management

recommendations for P. vera, ET and OMF. European trials are being developed to test JAK-2 inhibitors in OMF and P. vera.

Several meetings between the diagnostic platform (**WP10)** and the minimal residual disease group **(WP12)** allowed to better understand diagnostic strategies used in various European countries for different types of leukemias. A review paper from both workpackages has been completed and published this year (see Annex Section 3, WP 10-3).
Two meetings on the immunophenotype of myelodysplasia by WP8 led to a joint publication on the standardization of flow cytometry in myelodysplastic syndromes. (see Annex Section 3, WP 8-2).
The stem cell transplantation working group **(WP14),** one of the most active groups, makes use of synergies with the European Bone Marrow Transplantation Registry (EBMT). The lead participant of WP14 currently is also president of EBMT. Main activities address adaptation of transplantation conditions to the needs of elderly patients, mainly with AML and ALL. A randomized study in patients with AML over the age of 60 a studying the role of SCT with reduced intensity conditioning (EBMT study) started on January 4th 2010 in Germany. Preceeding ommunication with the Paul Ehrlich Institue was mainly in regards to the procedure and the production of stem cells. An investigators brochure (IB) on stem cell grafts and specifications of stem cell grafts was needed. The study is supported by the Deutsche Krebshilfe. .In CML, an improvement of transplantation outcome has been achieved with low transplantation mortality (<10%) and 3 year survival rates of about 90% in chronic phase and more than 50% in advanced phase patients (see Annex Section 3, WP 4-16).

**WP15**

New guidelines for prevention of infections in stem cell transplant recipients were published in 2009 with a large international collaboration effort in Europe, in the US and Canada. In addition collaboration has been initiated with the infectious disease society of Amnerica (IDSA) regarding guidelines for vaccination of patients with hematological malignancies. A European Conference regarding Infections in Leukemia has been held updating previous guidelines. Manuscripts are in preparation. A multicenter study on the development of common protocols for molecular diagnosis of fungal infections by PCR has been completed and data have been published (see Annex Section 3, WP 15-29). Furthermore work on vaccination of hematopoietic cell transplant recipients (see Annex Section 3, WP15-24), on the treatment of infections in cancer patients (see Annex Section 3, WP15-4) and guidelines on the management of invasive fungal infections, as well as infections with HSV, VZV and infections in patients with hematological malignancies and after SCT were published in 2009 from the Second European Conference on Infections in Leukemia.

## 3. European Leukemia Registries

The registries established by the network will have far-reaching implications for research and public health planning in the future. European registries for CML and ALL started in 2005. The CML registry was expanded in 2007 (EUTOS for CML), a MDS registry started in 2008 (EUMDS), both funded by Novartis.

EUTOS for CML is collecting baseline, treatment and outcomes data for patients with CML and submitting this to the central data centre (CDC) in Munich for analysis. To achieve its objectives, the EUTOS for CML registry is divided into three patient groups: In-study: patients diagnosed between 2002 and 2006 from national study groups enrolled in prospective studies, who are taking imatinib frontline. Out-study: patients diagnosed between 2002 and 2006, already registered in existing data-bases, who are taking imatinib front-line and population-based: newly diagnosed patients from 2009 onwards not previously in registries or clinical studies, irrespective of front-line treatment.

Significant progress has been made with the in-study (DE, DK, ES, FI, FR, IT, NL, NO, SE, UK) and out-study registries (CZ, ES, PL, RO, RU, UK). Data on 1955 patients were presented at ASH 2009.

The population-based registry was successfully launched with the first countries activated in June 2009. To date 27 centres (ELN institutions) from 25 countries across Europe take part in the EUTOS for CML registry. One of the key objectives is to provide a clear epidemiological picture of CML and a real world information on patient treatment and outcomes across Europe. Further objectives are:

- Optimization of individual treatment
- Establishment of new prognostic score in the imatinib era
- Validation of comprehensive prognostic model
- Promotion of quality-controlled molecular monitoring
- Development and update of core data set for CML
- Cooperation with ELN projects ( e.g. imatinib failure registry )
- Detailed analysis of life quality and life expectancy.

The European MDS registry (WP8) has now data on more than 650 patients from 11 countries and and plans to register 2000 patients in 5 years.

In CMPD (WP9), the registry on pregnancies under various treatments and the registry on anagrelide (Exels-study) are continued. Registries and surveys are in development for transplantation in CLL, and leukemic evolution in CMPD. Novel Treatment options: Risk adapted, personalized medicine through improved individual diagnosis and high throughput analysis

A German AML registry will start in 2010. It ist planned to develop this registry into a common European AML registry. In addition, a metadata repository is planned. The ELN offers a basis for collecting data across 33 countries. Comparison of long term clinical trial outcomes throughout Europe and the availability of various treatment options will provide information on differences, on needs,for improvement, and on life expectancy with leukemia across Europe.

**4. Diagnosis / Follow-up (WP10-13)**

International standardisation of diagnostic procedures and the follow up on minimal residual disease are essential for treatment optimisation in each country. The cooperation between the diagnostics WPs was further intensified in 2009: morphology (**WP 10**), cytogenetics (**WP 11**), detection of minimal residual disease (**WP 12**) and gene profiling (**WP 13**).

A good example of the potential of networking is provided by the diagnostics working groups with the Microarray Innovations in Leukemia (MILE) study. The MILE study involves 11 laboratories (7 from ELN, 3 from the US, one from Singapore) and integrates data from morphology, cytogenetics, molecular genetics and immunophenotyping from more than 4000 patients to reveal new patient subgroups with specific prognosis and survival (WP13).

WP12 has focused on minimal residual disease (MRD) monitoring using real-time quantitative PCR (RQ-PCR) for leukemia specific markers and flow cytometry for cases lacking a specific molecular target. Standardization of established assays like *BCR-ABL,* JAK2 V617F was improved in collaboration with WP4 and WP9, respectively, as well as the evaluation of novel RQ-PCR assays (i.e. Wilms' Tumor gene (*WT1*) and nucleophosmin (*NPM1*) mutation). A computer software reporting package of RQ-PCR data to clinicians,was implemented.

Several publications were achieved during the last year in MRD detection in myeloproliferative disorders where it helps to guide therapy with tyrosine kinase inhibitors (Jovanovic *et al*, *Blood* 2007; Metzgeroth *et al*, *Br J Haematol* 2008; see also Annex Section 3, WP 12-13, 4-11, 4-43). In acute myeloid leukemia (AML), MRD detection could lead to improved management and clinical outcome. MRD monitoring could further pinpoint those patients destined to fail first-line therapy, thereby allowing the administration of additional treatment in first remission. Flow cytometry is used in AML cases lacking a leukemia-specific molecular marker. The development of optimized protocols has been a focus of attention for the "Diagnostic Platform" (WP10). Prospective parallel analysis of flow cytometry and optimized RQ-PCR assays is now being evaluated by ELN MRD laboratories within the context of large scale clinical trials.

In collaboration with WP4 accredited reference reagents as a means to facilitate the promulgation of the International Scale (IS) for MRD determination in CML were approved as primary reference reagents in November 2009 by the World Health Organisation (WHO). Over the course of the last year, ELN guidelines on the management of APL and AML have been finalized and published, which both include guidance on the role of MRD monitoring (Table1, Section 1.5.).

Progress in the detection of minimal residual disease, by molecular or cytometric methods, has also been achieved within the ELN WP10 - 15 (see Table 1 and Annex Section 3, WP 10-3).

Quality control rounds and consensus recommendations on a European level were achieved in several of the diagnostics WPs, see Table 1.

## 5. Consensus recommendations and guidelines

The development of standards and guidelines is one of the central aims of ELN. A number of recommendations have been developed and published by ELN in high impact journals, and on the ELN website (see Table 1). Links to abstracts were added on the ELN website at the sub-pages for the respective disease related working groups. Until 2009, ELN participants were involved in the publication of 34 consensual European recommendations or guidelines .

## 6. Synergies, cooperations and sustainability

The ELN has established a network of clinicians and researchers with the aim of 'durable integration'. Many years of successful and fruitful, competitive and synergistic interactions in clinical trials and research have created 'incubators' for excellence and for exploratory activities on new scientific issues in the field of leukemia. The development and sharing of joint infrastructures, integration of research activities and institutions has created structures with good prospects for durability well beyond the period of EU-funding. In addition multinational cooperations with other European working groups including EBMT (European Group for Blood and Marrow Transplantation), EORTC (European Organization on Research and Treatment of Cancer), European School of Hematology (ESH) and ECRIN (European Clinical Research Infrastructure Network) are ongoing. Common issues are trial infrastructure in Europe, trial evaluation criteria, data management and repositories, laboratory standardizations as well as training courses, and educational symposia to spread excellence to as many physicians as possible. Collaborations with industry foster European trials and medical progress. The access to clinical data and innovative research will help industry to speed up drug development and enable novel treatment options to the patient.

An ELN Foundation has been established in 2009. 13 lead participants decided to form the ELN Foundation board, demonstrating personal commitment. The ELN Foundation will use the strength of ELN as a grown and responsible network of excellence to build up new partnerships and ideas and join forces to fight leukemia.

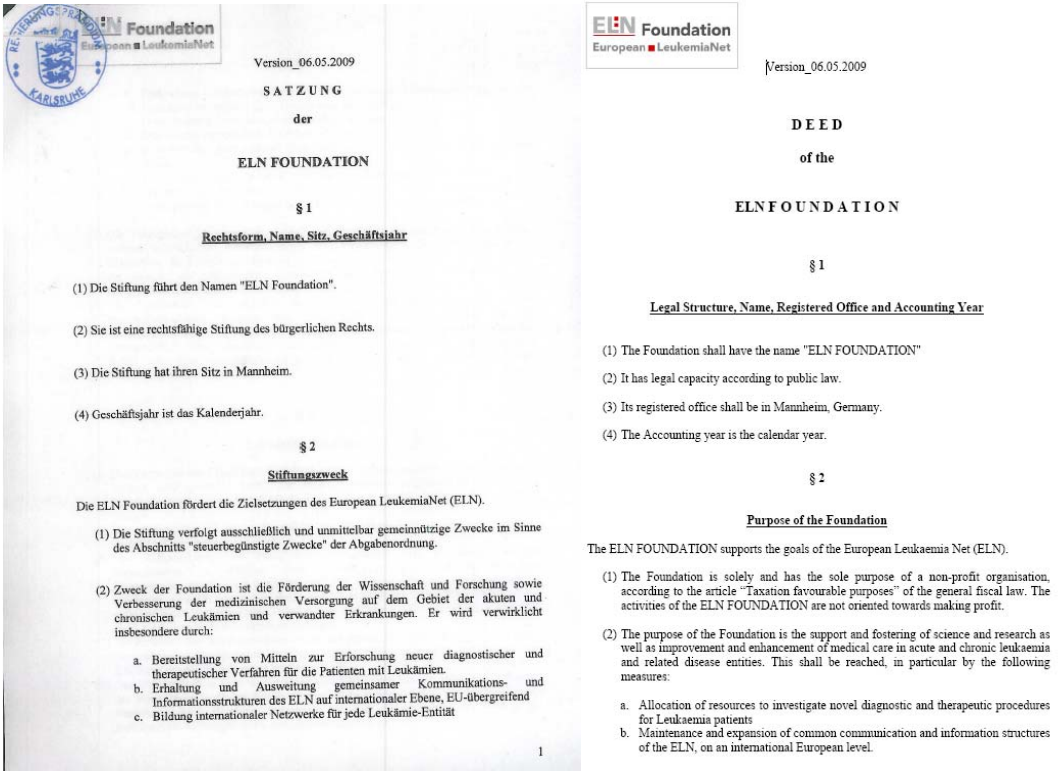
**Table 1:** Recommendations and Guidelines published by the ELN.

| Topic | Reference |
|---|---|
| CML management recommendations | Baccarani et al., J Clin Oncol 2009;27:6041-51<br>Hehlmann et al., Lancet 2007;370:342-50<br>Baccarani et al., Blood 2006 ;108 :1809-20 |
| CML molecular monitoring | Müller et al., Leukemia 2009:1957-63<br>Hughes et al., Blood 2006;108:28-37 |
| CLL guidelines | Hallek et al., Blood 2008;111:5446-56 |
| CLL molecular and Flow cytometric monitoring | Ghia et al.; Leukemia 2007; 21:1-3<br>Rawstron et al., Leukemia 2007; 21 :956-64 |
| AML management recommendations | Döhner et al., Blood 2009, e-pup ahead of print |
| APL management recommendations | Sanz et al., Blood 2009;113:1875-91 |
| APL molecular monitoring | Grimwade et al.; J Clin Oncol 2009;27:3650-3658 |
| Response criteria for ET and PV | Barosi et al., Blood 2009;113:4829-33 |
| Definition of resistance and intolerance to hydroxycarbamide in P. vera and myelofibrosis | Barosi et al., Br J Haematol 2009, e-pub ahead of print |
| Evidence- and consensus-based European guidelines on MDS | ELN Homepage (fourth edition 2008)'<br>www.leukemia–net.org |
| Reference document for four- and five-color flow cytometry | Arnoulet et al. Cytometry B Clin Cytom 2010, 78:4-10 |
| Consensual morphology collection | ELN homepage: www.leukemianet.eu |
| Flow cytometry in MDS | van de Loosdrecht et al.; Haematologica 2009: 94:1124-34 |
| WT1 PCR standardization | Cilloni et al., J Clin Oncol 2009;27:5195-201 |
| FIP1L1-PDGFRA – recommendations for diagnosis & molecular monitoring | Jovanovic et al., Blood 2007;109:4635-40<br>Score et al. Leukemia 2009; 23:332-339 |
| Proposals for standardization of cytogenetic analyses | Haferlach et al., Genes Chromosomes Cancer 2007;46:494-9 |
| BCR-ABL diagnosis recommendations | Branford et al., Leukemia 2006:1925-30 |
| Gene expression profiling recommendations | Kohlmann et al., Br J Haematol 2008;142:802-7 |
| Microarray analyses guidelines | Staal et al., Leukemia 2006;20:1385-92 |
| Transplant-associated microangiopathy recommendations | Ruutu et al., Haematologica 2007;92:95-100 |
| Stem cell transplantation recommendations<br>-in CLL<br>-in MDS | Dreger et al., Leukemia 2007;21:12-7<br>De Witte et al., Haematologica 2006;91:750-6 |
| Recommendations for management of infections<br>-Candida and Aspergillus<br>-Quinolone prophylaxis for bacterial infections in afebrile neutropenia<br>-Empirical antifungal therapy in febrile neutropenic patients<br>-Primary antifungal prophylaxis<br>-Vaccination in stem cell transplant recipients<br>-HSV, VZV and EBV<br>-CMV, HHV-6, HHV-7 and HHV-8 | Herbrecht et al., EJC Supplements 2007 (Vol. 5, 49-59)<br>Bucaneve et al., EJC Supplements 2007 (Vol. 5, 5-12)<br>Marchetti et al., EJC Supplements 2007 (Vol. 5, 32-42)<br>Maertens et al., EJC Supplements 2007 (Vol. 5, 43-48)<br>Ljungman et al., Bone Marrow Transplant 2005;35, 737-746<br>Styczynski et al., Bone Marrow Transplant 2009;43:757-70<br>Ljungman et al. Bone Marrow Transplant 2008;42:227-40 |

Although registered as a non-profit organization in Germany (http://www.rp-karlsruhe.de/servlet/PB/show/1305453/ELN-Foundation.pdf), the ELN Foundation will enable tax-free donations from anywhere in the world. In Europe this is possible since early 2009, based on a European Court decision (C-318/07).

The first ELN Foundation Newsletter is available in 7 languages and was presented at the annual ELN-Symposium in February 2010.

The new partners, that joined the ELN in 2009 or will join in 2010, demonstrate the interest in and the international acceptance of the ELN. A network like the ELN with its transnational 'integration' in research, diagnosis, treatment and education provides transparency in research, the critical mass for excellence and a competitive advantage for participants and their partners, including industry, setting the stage for future activities and progress.



Version_06.05.2009

SATZUNG

der

ELN FOUNDATION

§ 1

Rechtsform, Name, Sitz, Geschäftsjahr

(1) Die Stiftung führt den Namen "ELN Foundation".

(2) Sie ist eine rechtsfähige Stiftung des bürgerlichen Rechts.

(3) Die Stiftung hat ihren Sitz in Mannheim.

(4) Geschäftsjahr ist das Kalenderjahr.

§ 2

Stiftungszweck

Die ELN Foundation fördert die Zielsetzungen des European LeukemiaNet (ELN).

(1) Die Stiftung verfolgt ausschließlich und unmittelbar gemeinnützige Zwecke im Sinne des Abschnitts "steuerbegünstigte Zwecke" der Abgabenordnung.

(2) Zweck der Foundation ist die Förderung der Wissenschaft und Forschung sowie Verbesserung der medizinischen Versorgung auf dem Gebiet der akuten und chronischen Leukämien und verwandter Erkrankungen. Er wird verwirklicht insbesondere durch:

a. Bereitstellung von Mitteln zur Erforschung neuer diagnostischer und therapeutischer Verfahren für die Patienten mit Leukämien.
b. Erhaltung und Ausweitung gemeinsamer Kommunikations- und Informationsstrukturen des ELN auf internationaler Ebene, EU-übergreifend
c. Bildung internationaler Netzwerke für jede Leukämie-Entität

1

Version_06.05.2009

DEED

of the

ELN FOUNDATION

§ 1

Legal Structure, Name, Registered Office and Accounting Year

(1) The Foundation shall have the name "ELN FOUNDATION"

(2) It has legal capacity according to public law.

(3) Its registered office shall be in Mannheim, Germany.

(4) The Accounting year is the calendar year.

§ 2

Purpose of the Foundation

The ELN FOUNDATION supports the goals of the European Leukaemia Net (ELN).

(1) The Foundation is solely and has the sole purpose of a non-profit organisation, according to the article "Taxation favourable purposes" of the general fiscal law. The activities of the ELN FOUNDATION are not oriented towards making profit.

(2) The purpose of the Foundation is the support and fostering of science and research as well as improvement and enhancement of medical care in acute and chronic leukaemia and related disease entities. This shall be reached, in particular by the following measures:

a. Allocation of resources to investigate novel diagnostic and therapeutic procedures for Leukaemia patients
b. Maintenance and expansion of common communication and information structures of the ELN, on an international European level.

**Figure 5:** First page of the ELN Foundation Deed in its German and English version.

## Section 2: Workpackage progress of the period

**NMC (WP 01)**

*Objectives and starting point of work at the beginning of the reporting period*

*Progress towards objectives – tasks worked on and achievements made with reference to planned objectives*

**1.3e**

**Operating management of networking, i.e.legal and contractual, dissemination and knowledge (including 1.14, 1.20)**

In 2009 the NMC offered again managerial services:

- Contractual-, financial issues and organizational support (25 EUTOS subcontracts prepared and signed)
- Project management of multinational collaborative leukemia projects
- Communication within the network's study or -interdisciplinary groups, but also with industry, key stakeholders, patient organizations and public relations
- Training of health care personnel and spread of excellence to institutions and countries not yet participating in the network
- Spread of information on network activities and achievements in research and partnering
- External visibility of the network to everyone with an interest in leukemia
- Information on participating centers
- Integration of new members into the network
- Provision of a networking and meeting platform to enhance knowledge transfer from bench to bedside with close to a 100 annual ELN activities at international leukemia events: organization of the international annual ELN symposium (Figure 2) or presence at major hematology and oncology congresses with WP meetings, brainstorming events and workshops, but also educational events, training courses and exchange visits for young scientists
- PR activities, like press conferences, and provision of PR materials (exhibition booth, flyers, newsletters and posters)
- The 6th Annual ELN Symposium in February 2009 with 439 participants from 30 countries, the WP-meetings at EHA in Copenhagen in June 2009 (more than 200 participants), and the ELN-breakfast meeting at ASH in New Orleans in December 2009 (over 150 participants).
- A new ELN flyer and poster including the ELN foundation and the EUTOS for CML project were presented at ASH 2009. The ELN exhibition booth was updated with a new section representing the ELN Foundation. The 6th ELN newsletter was prepared for the Symposium 2010.
- Presentations on the ELN Foundation at the General Assembly during the annual symposium 2009 and at the ELN breakfast meeting at ASH in 2009

- The EUTOS for CML Homepage was updated.

Meetings were organized at the following occasions:

- Annual ELN-Symposium in Mannheim, January 2009
- Educational day for young hematologists in conjunction with EUTOS for CML, Naples, May 2009
- WP meetings at EHA Conference, Berlin, June 2009
- 18th International CML-Workshop with EUTOS meeting in Mannheim, July 2009
- ESH-ELN joined CML meeting in Bordeuax, September 2009
- ELN-CML educational with EUTOS for CML with a press conference, Barcelona, September 2009
- Presentation of the new booth at the ASH Congress Exhibition, New Orleans 2009
- ELN Breakfast meeting and WP meetings at ASH, New Orleans, December 2009

**1.4e**

**Operating financial infrastructure and support of initiatives to build up sustainability and durability of the network**

The NMC gave again advice for the preparation of the financial reports i. e. which costs are eligible and how Forms C are prepared. Due to the number of participants, this is time consuming but rewarding due to the growing impact of ELN. A new financial plan of budget allocation for the sixth period is being prepared and will be part of the updated Technical Annex 2010.

During 2009 all institutions were informed on their remaining budget and their expenses. Institutions which did not spend their money were asked to pay it back. 50.000€ were returned to the NMC. Together with the payment from the EU for this year (total sum of 364.932,36 €) one meeting per WP can be sponsored.

In addition the NMC centrally managed the reimbursement of all travel costs arising from the Annual Symposium and all WP meetings and workshops.

Several subcontracts (so far 25) to the EUTOS for CML contract were signed between the University of Heidelberg and the ELN on one hand and ELN member countries on the other hand, concerning data for the European CML registry as contracted in the Scientific collaboration agreement between the University of Heidelberg and Novartis.

The legal documents for establishing the ELN Foundation were signed in June 2009 and the Foundation received official status as a non-profit-organisation by the German authorities (http://www.rp-karlsruhe.de/servlet/PB/show/1305453/ELN-Foundation.pdf).

The ELN applied to the European Science Foundation for funding. The evaluation is still ongoing. So far 74% funding could be reached. 80 % are necessary to have the application accepted.

**1.5e Organization of internal and external reporting ensuring that milestones are effectively reached**

Progress reports, meeting minutes, presentations and summary notes of meetings and symposia are collected and available at the management center for external reporting.

**1.6e Organization of regular meetings held by the Steering Committee**

Two SC meetings were organized in 2009: in February 2009 in Mannheim and in June 2009 in Berlin. Discussed and agreed issues were communicated to all participants for information and coordination of the annual meetings, deliverables, reporting and contractual affairs (see Annex Section 3, WP1-5 and 1-6).

**1.7e Organizing of the Annual Network's Symposium 2009**

The sixth Annual Symposium was held on 2-4. February 2009 in Mannheim (Fig. 1.1). It was preceded by a workshop on good clinical practice (GCP), which was organized jointly by WP1 and WP3, offering GCP-certificates to the participants. A special event was presented by WP2 following the scientific symposium giving insight into the latest development on Investigator initiated Trials (IITs) in Europe. Speakers from EMBT, ECRIN and ELN were invited.


**Figure 1.1.** The invitation and program of the joint annual symposium of the European LeukemiaNet and the German Competence Network "Acute and chronic Leukemias", February 2009

The NMC organized the scientific program and provided the operational and organizational structure of symposium and workshops. This includes scientific program, meeting facilities, catering, accommodations and reimbursement of travel costs. In total, 439 participants attended the Symposium.

The programme was available for download via the ELN homepage, and the event was announced through several media and organizations like the Telematik Platform in Berlin (TMF) (Fig. 1.2) and the German Society for Hematology and Oncology (DGHO).


**Figure 1.2.** A link on the German TMF (Telematik Platform für medizinische Forschungsnetze) homepage to the joint annual symposium of the European LeukemiaNet and the German Competence Network "Acute and chronic Leukemias".

**1.7f Organization of the Annual Network's Symposium 2010**

In November and December 2009 the preparations for the Annual Symposium 2010 were carried out. All activities around reservation of the meeting venue and planning of logistics and technical issues as well as the scientific program and invitations were initiated already in Q1 2009 and progressed through the year. The seventh Annual ELN Symposium will be held together with the 11th German Competence Network (KNL) on February 1-3, 2010 in Mannheim.

**1.9e Continuation of delivering all integrated trials to the integrated web site, progress report in conjunction with ELIC**

The trial list and charts were updated in 2009 through ELIC and the NMC and the help of all leukemia clinical trial WPs. Continuous updating of the trials is promoted by the NMC.

**1.10e Annual reports to the EC**

i) The **activity report** informing and summarizing on the scientific activities of the project. Reports of all 16 workpackages were collected, edited and combined.

ii) The **management report** (including Form C, Summary Form C and the "Report on the Distribution of the Community's contribution") providing the administrative and financial information. Collecting forms C of 59 funded participants and financial audits of two participants funded with >150.000€ was again a tremendous and time-consuming effort. Again, extensive advice had to be provided. Requests especially on Forms C by the EC were answered ASAP; iii) the **new implementation plan (D1.18)** with the new list of deliverables was prepared in agreement with the workpackage leaders with approval of the General Assembly; iv) the **financial planning for the sixth period (D1.18)** was prepared on the basis of the new implementation plan) **updated CPF** (contract preparation form) **file, updated Annex I** and **updated list of researchers** were prepared.

**1.10f Annual reports to the EC**

Organizational work for the report 2009 started in November 2009 with completion of templates for activity and management reports. Due to the cost-neutral prolongation of the financing period to March 2011 further planning of deliverables and financial issues are in progress.

## 1.11f Continuation of public relations activities to enhance public visibility of the European LeukemiaNet

The ELN-booth was updated in 2009 with highlights and current research as well as a new map of Europe including the newly participating countries Estonia, Latvia, Portugal, Slovenia, Slovakia and Ukraine. A new panel presenting the ELN Foundation was introduced (Fig. 1.3).


**Figure 1.3:** The ELN Booth 2009 including a new map of European collaboration, an update on EUTOS for CML and the newly founded ELN Foundation. The booth was presented first at ASH in New Orleans (December 2009).

ELN Flyer

An updated ELN flyer was prepared highlighting changes in the platforms and workpackages as well as the addition of new participants (Fig. 1.4).

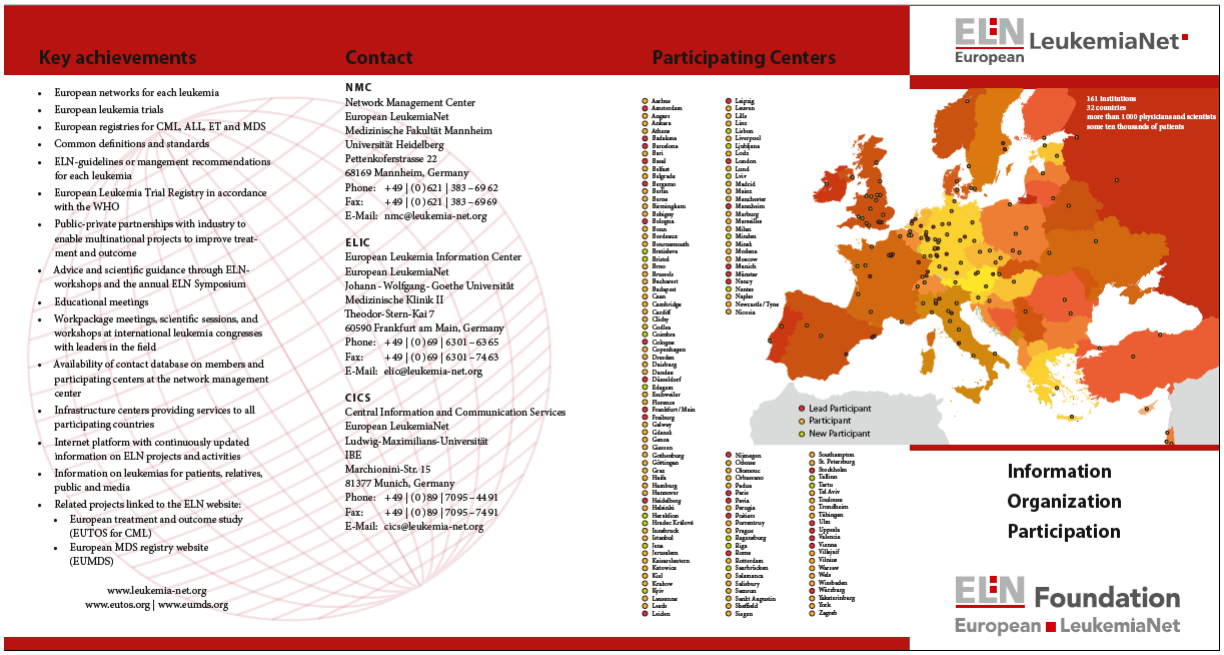
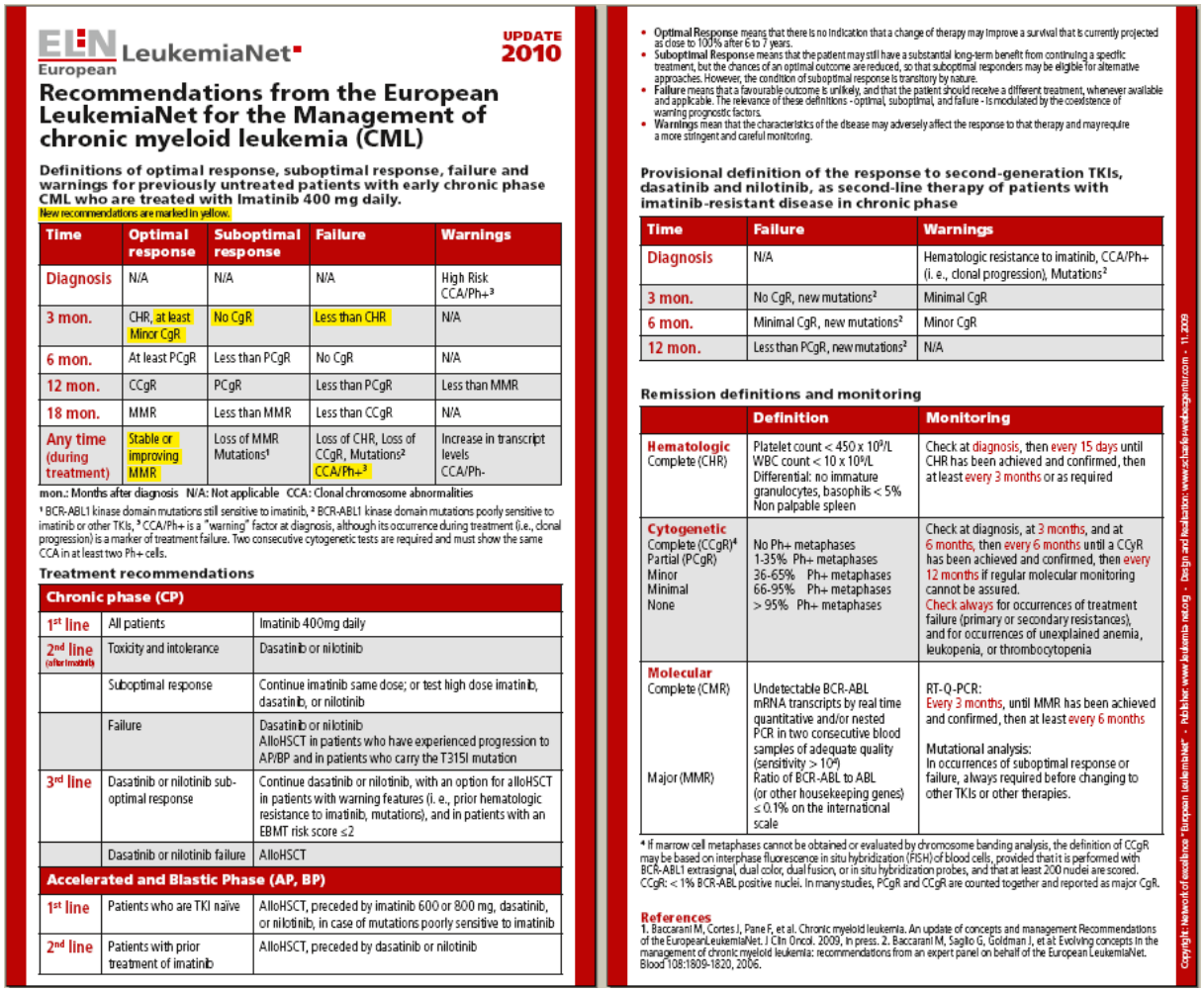



**Figure 1.4**: The ELN Flyer 2009 including ELN key achievements, a new map of European collaborations and an update on EUTOS. The logo of the newly founded ELN Foundation is already present.

ELN Pocket Cards, with updated recomendations on CML management

In 2009 the Recommendations for the management of CML were updated by the ELN in JCO, 2009 (see Annex Section 3 WP 4-2 and Table 1). New pocket cards for physicians were printed (Fig.1.5).



ELN European LeukemiaNet

UPDATE 2010

**Recommendations from the European LeukemiaNet for the Management of chronic myeloid leukemia (CML)**

**Definitions of optimal response, suboptimal response, failure and warnings for previously untreated patients with early chronic phase CML who are treated with Imatinib 400 mg daily.**

New recommendations are marked in yellow.

| Time | Optimal response | Suboptimal response | Failure | Warnings |
|---|---|---|---|---|
| Diagnosis | N/A | N/A | N/A | High Risk CCA/Ph+[3] |
| 3 mon. | CHR, at least Minor CgR | No CgR | Less than CHR | N/A |
| 6 mon. | At least PCgR | Less than PCgR | No CgR | N/A |
| 12 mon. | CCgR | PCgR | Less than PCgR | Less than MMR |
| 18 mon. | MMR | Less than MMR | Less than CCgR | N/A |
| Any time (during treatment) | Stable or improving MMR | Loss of MMR Mutations[1] | Loss of CHR, Loss of CGgR, Mutations[2] CCA/Ph+[3] | Increase in transcript levels CCA/Ph- |

mon.: Months after diagnosis N/A: Not applicable CCA: Clonal chromosome abnormalities

[1] BCR-ABL1 kinase domain mutations still sensitive to imatinib, [2] BCR-ABL1 kinase domain mutations poorly sensitive to imatinib or other TKIs, [3] CCA/Ph+ is a "warning" factor at diagnosis, although its occurrence during treatment (i.e., clonal progression) is a marker of treatment failure. Two consecutive cytogenetic tests are required and must show the same CCA in at least two Ph+ cells.

**Treatment recommendations**

| Chronic phase (CP) | | |
|---|---|---|
| 1st line | All patients | Imatinib 400mg daily |
| 2nd line (after 3 months) | Toxicity and intolerance | Dasatinib or nilotinib |
| | Suboptimal response | Continue imatinib same dose; or test high dose imatinib, dasatinib, or nilotinib |
| | Failure | Dasatinib or nilotinib<br>AlloHSCT in patients who have experienced progression to AP/BP and in patients who carry the T315I mutation |
| 3rd line | Dasatinib or nilotinib sub-optimal response | Continue dasatinib or nilotinib, with an option for alloHSCT in patients with warning features (i. e., prior hematologic resistance to imatinib, mutations), and in patients with an EBMT risk score ≤2 |
| | Dasatinib or nilotinib failure | AlloHSCT |
| **Accelerated and Blastic Phase (AP, BP)** | | |
| 1st line | Patients who are TKI naïve | AlloHSCT, preceded by imatinib 600 or 800 mg, dasatinib, or nilotinib, in case of mutations poorly sensitive to imatinib |
| 2nd line | Patients with prior treatment of imatinib | AlloHSCT, preceded by dasatinib or nilotinib |

- **Optimal Response** means that there is no indication that a change of therapy may improve a survival that is currently projected as close to 100% after 6 to 7 years.
- **Suboptimal Response** means that the patient may still have a substantial long-term benefit from continuing a specific treatment, but the chances of an optimal outcome are reduced, so that suboptimal responders may be eligible for alternative approaches. However, the condition of suboptimal response is transitory by nature.
- **Failure** means that a favourable outcome is unlikely, and that the patient should receive a different treatment, whenever available and applicable. The relevance of these definitions - optimal, suboptimal, and failure - is modulated by the coexistence of warning prognostic factors.
- **Warnings** mean that the characteristics of the disease may adversely affect the response to that therapy and may require a more stringent and careful monitoring.

**Provisional definition of the response to second-generation TKIs, dasatinib and nilotinib, as second-line therapy of patients with imatinib-resistant disease in chronic phase**

| Time | Failure | Warnings |
|---|---|---|
| Diagnosis | N/A | Hematologic resistance to imatinib, CCA/Ph+ (i. e., clonal progression), Mutations[2] |
| 3 mon. | No CgR, new mutations[2] | Minimal CgR |
| 6 mon. | Minimal CgR, new mutations[2] | Minor CgR |
| 12 mon. | Less than PCgR, new mutations[2] | N/A |

**Remission definitions and monitoring**

| | Definition | Monitoring |
|---|---|---|
| **Hematologic** Complete (CHR) | Platelet count < 450 x $10^9$/L<br>WBC count < 10 x $10^9$/L<br>Differential: no immature granulocytes, basophils < 5%<br>Non palpable spleen | Check at diagnosis, then every 15 days until CHR has been achieved and confirmed, then at least every 3 months or as required |
| **Cytogenetic**<br>Complete (CCgR)[4]<br>Partial (PCgR)<br>Minor<br>Minimal<br>None | No Ph+ metaphases<br>1-35% Ph+ metaphases<br>36-65% Ph+ metaphases<br>66-95% Ph+ metaphases<br>> 95% Ph+ metaphases | Check at diagnosis, at 3 months, and at 6 months, then every 6 months until a CGyR has been achieved and confirmed, then every 12 months if regular molecular monitoring cannot be assured.<br>Check always for occurrences of treatment failure (primary or secondary resistances), and for occurrences of unexplained anemia, leukopenia, or thrombocytopenia |
| **Molecular**<br>Complete (CMR)<br><br><br><br>Major (MMR) | Undetectable BCR-ABL mRNA transcripts by real time quantitative and/or nested PCR in two consecutive blood samples of adequate quality (sensitivity > $10^4$)<br>Ratio of BCR-ABL to ABL (or other housekeeping genes) ≤ 0.1% on the international scale | RT-Q-PCR:<br>Every 3 months, until MMR has been achieved and confirmed, then at least every 6 months<br><br>Mutational analysis:<br>In occurrences of suboptimal response or failure, always required before changing to other TKIs or other therapies. |

[4] If marrow cell metaphases cannot be obtained or evaluated by chromosome banding analysis, the definition of CCgR may be based on interphase fluorescence in situ hybridization (FISH) of blood cells, provided that it is performed with BCR-ABL1 extrasignal, dual color, dual fusion, or in situ hybridization probes, and that at least 200 nuclei are scored. CCgR: < 1% BCR-ABL positive nuclei. In many studies, PCgR and CCgR are counted together and reported as major CgR.

**References**

1. Baccarani M, Cortes J, Pane F, et al. Chronic myeloid leukemia. An update of concepts and management Recommendations of the European LeukemiaNet. J Clin Oncol. 2009, in press. 2. Baccarani M, Saglio G, Goldman J, et al: Evolving concepts in the management of chronic myeloid leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet. Blood 108:1809-1820, 2006.



**Figure 1.5**: The updated recommendations from the ELN for the management on CML.

ELN links on the EUTOS for CML Website

The EUTOS for CML website was updated with presentations from the EUTOS educational meetings and workshops in 2009 (http://www.eutos.org/content/home/) (Fig.1.6).

One educational meeting EUTOS for CML was held in Barcelona in September 2009 (Invitation see Fig. 1.7), another one for young hematologists took place in Naples, May 2009.

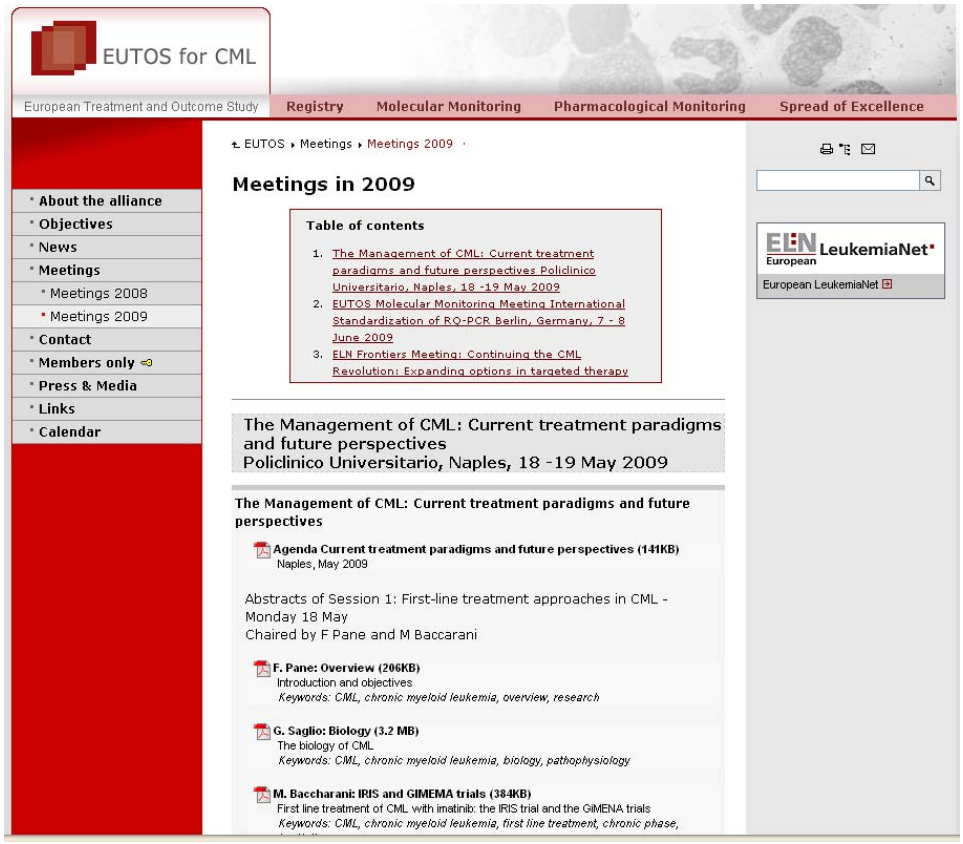



**Figure 1.6**: The updated EUTOS Homepage including presentations for download.


**Figure 1.7**: The invitation to the EUTOS educational meeting on CML in Barcelona 2009.

**International Article about the ELN**

An article on the ELN was published in the December issue of the TELEGRAFT Newsletter by the International Society for Cellular Therapy under the Eurocells column with the title: "European LeukemiaNet, A Model of Transnational Collaboration". The Eurocells column is dedicated to broadening the exposure for EU consortia by providing them with a platform to present their focus, goals, history, organization, workpackages, collaborators and achievements (Fig. 1.8).

International Society for Cellular Therapy
ISCT

TELEGRAFT

VOLUME 16 NO.4 :: WINTER 2009 — A QUARTERLY NEWSLETTER



## ISCT 2010 Annual Meeting Speakers Featured on 60 Minutes

Anthony Atala of the Wake Forest University Institute for Regenerative Medicine and Stephen Badylak of the McGowan Institute for Regenerative Medicine at the University of Pittsburgh were recently featured in a 60 Minutes TV story on Regenerative Medicine entitled 'Growing Body Parts'. Both Dr. Atala and Dr. Badylak will be speaking in the Strategies for Commercialization track at the ISCT Annual Meeting in Philadelphia May 23-26, 2010. The text of the 60 Minutes story can be found at http://www.cbsnews.com/stories/2009/12/11/60minutes/main5968057.shtml ?tag=contentMain;contentBody. In addition, regenerative medicine will be featured in a plenary session at the Annual Meeting chaired by Chris Mason of the University College London, and with Robert Nerem and Paolo Macchiarini as speakers. These high caliber speakers are just a part of a varied and exciting program for the Annual Meeting. Please see the preliminary program starting on page 15 of this issue and our meeting web page at www.CellTherapy2010.com. We hope to see you in Philadelphia!

Bruce Levine and David Porter
ISCT 2010 Co-Chairs

## EUROCELLS: European LeukemiaNet A Model of Transnational Collaboration


Schroitz-King P; Saussele S; Gökbuget N; Guilhot F; Mansmann U; Simonsson B; Büchner T; Ossenkoppele G; Hoelzer D; Hallek M; De Witte T; Baccarani M; Barbui T; Serve H; Béné MC; Fonatsch C; Grimwade D; Haferlach T; Niederwieser D; Ljungman P; Hochhaus A; Hasford J and Hehlmann R.


### Summary


The ELN is an established network of excellence, composed of internationally recognised clinicians and scientists, medical study groups and interdisciplinary research centers reaching across four continents (Europe, North America, Asia and Australia). The ELN has a landmark history of enabling the best therapeutic options


### EUROCELLS

*The European Union (EU) Framework Programme (FP) is the EU's main instrument for research funding in Europe. Each FP is proposed by the European Commission and adopted by Council and the European Parliament following a co-decision procedure. FPs cover a period of five years with the last year of one FP and the first year of the following FP overlapping. FPs have been implemented since 1984 and focus on establishing cooperative groups or consortia, both within the EU and globally. The Sixth FP (FP6, 2003-2007) funded numerous projects involving cellular therapeutic approaches or stem cell research, some of which are in their final year of funding. FP7 (2007-2013) is now underway, and already 100 projects involving stem cells have been funded.*

*This Eurocells column is dedicated to broadening the exposure for these consortia by providing them with a platform to present their focus, goals, history, organization, work packages, collaborators and achievements.*


continued on page 4




**Figure 1.8**: The article "European LeukemiaNet, A Model of Transnational Collaboration" in the Telegraft Newsletter in December 2009.

**The ELN Foundation Newsletter in 7 languages**

The ELN Foundation has planned during 2009 a newsletter in 7 languages to be published at the annual symposium in 2010 (Fig.1.9).

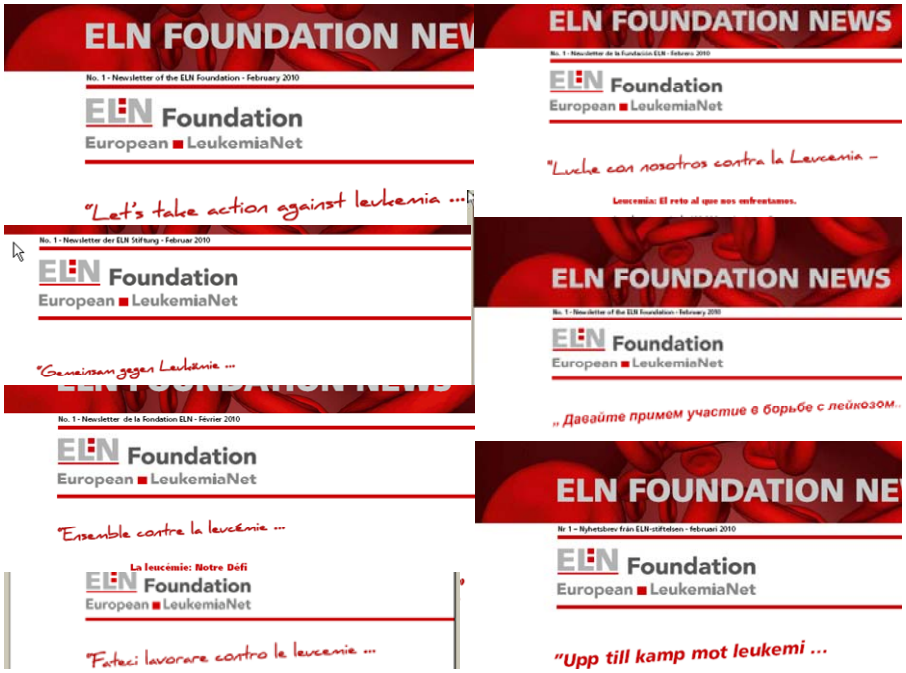



**Figure 1.9**: The ELN Foundation newsletter in 7 languages as presented at the annual symposium in 2010.

**1.12e Issue of the biannual network's information letter in conjunction with ELIC**

The sixth ELN information letter was prepared in 2009 to be available at the ELN Symposium in 2010

**1.14e, 1.21f Continuation of organization of workshops, seminars, conferences etc.**

The ELN was presented at multiple national and international congresses. Time slots for WP meetings were arranged at the Annual ELN Symposium in February, the EHA congress in June 2009 and at the ELN breakfast meeting at ASH conference in New Orleans, December 2009.

**1.17f Continuous support of quality control measures, e.g. consensus protocols, quality control rounds, and reference laboratories** (see also 1.21.e)

Quality control measures are a major topic at all ELN meetings. They are also a key topic of the EUTOS for CML project regarding all 4 subprojects, registry, molecular and pharmacological monitoring and spread of excellence. The ELN is supporting the spread of information to physicians across Europe. A table of over 34 recommendations and guidelines on leukemia management is available in the 2010 issue of the ELN newsletter and on the ELN homepage. A summary table is also shown on the exhibition booth. Recommendations can be ordered by clinicians as pocket card via the ELN homepage. Slide kits for physicians on all four EUTOS subprojects are available on the EUTOS homepage.

**1.20f Integrating new partners, industry and key stakeholders including patient organizations, support activities that constitute synergism, e.g. cooperations, partnership, funds**

In 2009, fifteen new institutions were included into the consortium after approval by the Assembly on 2. February 2009 (see Annex Section 3, WP1-7). All documents were adapted accordingly.

1. SymbioTec GmbH, Germany, represented by Prof. Michael Zeppezauer, WP 5
2. Riga Eastern Clinical University Hospital, clinic Linezers, National Haematolog Centre, Latvia, represented by Prof. Sandra Lejniece, WP 4.
3. Instituto Portugues de Oncologia Francisco Gentil de Lisboa, Portugal, represented by Dr. Antonio Almeida, WP 4
4. Johannes Wesling Klinikum Minden, Germany, represented by Prof. Martin Griesshammer, WP 9
5. University Hospitals Bristol NHS Foundation Trust, UK, represented by Prof. David Ian Marks, WP 6
6. Antwerp University Hospital (Universitair Ziekenhuis Antwerpen), Belgium, represented by Dr. Zwi Berneman, WP 4
7. Institute of Molecular Genetics and Genetic Engineering, Serbia, represented by Dr. Sonja Pavlovic, WP 12
8. University of Crete, Medical School, Greece, represented by Prof. Maria Kalmanti, WP 4
9. Fakultní nemocnice, Czech Republic, represented by Prof. Jaroslav Malý, WP4
10. Institut Paoli-Calmettes, France, represented by Dr. Marie-Joelle Mozziconacci, WP11/12
11. RCRM of AMS of Ukraine, Ukraine, represented by Dr. Iryna Dyagil, WP4
12. Clinical Center, Slovenija, represented by Prof. Peter Cernelc, WP4
13. Clinic of Hematology, Slovak Republic, represented by Dr. Martin Mistrík, WP4
14. Universität Regensburg, Germany, represented by Prof. Reinhard Andreesen, WP14
15. Centro Hospitalar de Coimbra, EPE, Portugal, represented by Dr. Jaspal Kaeda, WP12

Contacts to potential new participants were arranged. The inclusion of 14 new institutions for 2010 was prepared including approval by the Workpackage leaders. CPFs and Forms B were collected.

**1.22b Organization of panel meetings and preparation of ELN management recommendations:**

The NMC organized a panel meeting for WP9 at ASH to start work on recommendations for CMPN.

*Deviations from the workprogram and corrective actions taken: identify the nature and the reasons for the problem, identify contractors involved*

None

**Table 1.1** List of deliverables WP 1, 2009

| Deliv. No. | Deliverable Name | Date due | Actual/Forecast delivery date | Estimated indicative person months*) | Used indicative person months*) | Lead contractor |
|---|---|---|---|---|---|---|
| WP 1 | NMC | | | | | |
| **1.3e** | Operating management of networking, i.e.legal and contractual, dissemination and knowledge | 61-78 | 61-72 | 0 | 6 | Saußele, Huber Weinreich Friedrich |
| **1.4e** | Operating financial infrastructure and support of initiatives to build up sustainability and durability of the network | 61-78 | 61-72 | 0 | 6 | Saußele Hehlmann Hochhaus Weinreich Schrotz-King |
| **1.5e** | Organization of internal and external reporting ensuring that milestones are effectively reached | 66,78 | 66 | 0 | 1 | Saußele |
| **1.6e** | Organization of regular meetings held by the Steering Committee | 61,66,73 | 61-72 | 0 | 1 | Hehlmann Saußele |
| **1.7e** | Organization of Annual Network's Symposium 2009 | 61 | 61 | (14) | 14 | Saußele Hehlmann Hochhaus |
| **1.7f** | Organization of Annual Network's Symposium 2010 | 73 | ongoing | 0 | 14 | Saußele Hehlmann Hochhaus |
| **1.9e** | Continuation of delivering all integrated trials to the integrated web site, progress report in conj. with ELIC | 61-78 | 61-72 | 0 | 4 | Saußele |
| **1.10e** | Annual reports to EC | 62 | 62 | (14) | 14 | Saußele Hehlmann |
| **1.10f** | Annual reports to EC | 74 | ongoing | 0 | 14 | Saußele Hehlmann |
| **1.11f** | Continuation of public relations activities to enhance public visibility of the European LeukemiaNet | 61-78 | 61-72 | 0 | 4 | Saußele Hehlmann |
| **1.12e** | Issue of the biannual network's information letter in conj. with ELIC | 69 | 72 | (4) | 4 | Saußele Schrotz-King |
| **1.14e** | Continuation of organization of work-shops, seminars, scientific meetings, conferences to enhance knowledge transfer from bench to bedside, from research centers to clinical institutions in conjunction with WP 4-9 | 61-78 | 61-72 | 0 | 2 | Saußele Hochhaus Hehlmann |
| **1.17f** | Continous support of quality control measures, e.g., consensus protocols, quality control rounds, reference laboratories | (39)-78 | 61-72 | 0 | 4 | Reiter, Hochhaus |
| **1.20f** | Integrating new partners, industry and key stakeholders including patient organizations, support activities that constitute synergism, e.g. cooperations, partnership, funds | 61-78 | 61-72 | (6) | 4 | Hehlmann Hochhaus Saußele |
| **1.21f** | Continuous update of project presentations | 61-78 | 61-72 | 0 | 6 | Hehlmann Saußele |
| **1.22b** | Organization of panel meetings and preparation of ELN management recommendations:<br>• CML update<br>• AML<br>• APL | 61-78 | 72 | 0 | 1 | Hehlmann Saußele |

*) if available

**Table 1.2** List of milestones WP 1, 2009

| Milestone No. | Milestone Name | Date due | Actual/Forecast delivery date | Lead contractor |
|---|---|---|---|---|
| WP 1 | NMC | | | |
| **1.4e** | Operating financial infrastructure and support of initiatives to build up sustainability and durability of the network_Setting up the ELN Foundation. | 61-78 | 61-72 | Saußele<br>Hehlmann<br>Hochhaus<br>Weinreich<br>Schrotz-King |
| **1.7e** | Organization of Annual Network's Symposium 2009 | 61 | 61 | Saußele<br>Hehlmann<br>Hochhaus |
| **1.7f** | Organization of Annual Network's Symposium 2010 | 73 | ongoing | Saußele<br>Hehlmann<br>Hochhaus |
| **1.10e** | Annual reports to EC 2009 | 62 | 62 | Saußele<br>Hehlmann |
| **1.10f** | Annual reports to EC 2010 | 74 | ongoing | Saußele<br>Hehlmann |
| **1.12e** | Issue of an annual network information letters in conjunction with ELIC in 2009 and 2010 | 69 | 72 | Saußele<br>Schrotz-King |

**Section 3: Consortium management**

14 new institutions including 1 new country (Estonia) were presented at the General Assembly on 2. February 2010 in Mannheim for accession to the contract:

1. Russian Research Institute of Hematology and Transfusiology, St. Petersburg, Russian Federation, Prof. K. Abdulkadyrov (WP 4)
2. Haematology and Oncology Clinic, Tartu University Hospital, Tartu, Estonia, Prof. H. Everaus (WP 4)
3. SA Pohja-Eesti Regionaalhaigla (foundation North Estonia Medical Centre), Tallinn, Estonia, Dr. E. Laane (WP 4)
4. State Institution "Institute of Blood Pathology and Transfusion Medicine of UAMS", Lviv, Ukraine, Prof. Z. Maslyak (WP 4)
5. Hellenic Society of Haematology, Athens, Greece, Prof. P. Panayiotidis (WP 4)
6. Universitätsklinikum Jena, Germany, Prof. A. Hochhaus (WP 4)
7. Centre Hospitalier Universitaire de Nantes, Nantes, France, Dr. S. Hermouet (WP 9)
8. Stockholm South Hospital, Stockkholm, Sweden, Pr. Dr. J. Samuelsson
9. TYKSLAB at Tyks-Sapa utility unit of Hospital District of Southwestern Finland, Turku, Finland, Dr. V. Kairisto
10. Universitätsklinikum Aachen, Aachen, Germany, Prof. Dr. T. Brümmendorf
11. Université de Liège, Liège, France, Prof.. V. Bours
12. Rostov State Medical University, Rostov-on-Don, Russion Federation, Prof. S. Kutsev
13. Hospices Civils Ce Lyon, Lyon, France, Dr. F. Nicolini
14. University of Copenhagen, Danmark, Prof. H. Hasselbalch

**Section 4: Other Issues**

Ethical issues - none

Competitive calls - none

**Section 5: WP-Performance**

| Performance indicators | Status |
|---|---|
| Number of participating trial groups, centers, researchers | 164 institutions |
| Annual symposia | done |
| 6-monthly workshops of trial groups and interdisciplinary partners | done |
| Collection and distribution of information on ongoing projects | done |

**ELIC (WP 02)**

*Objectives and starting point of work at beginning of reporting period*

- Maintenance of current website with a content-management-system (CMS)
- Maintenance of the European Leukemia Trial Registry
- Browser-based opportunity of editing special parts of the website by web-editors
- Web-contents for all different user groups and all parts of the website
- Questionnaires for the evaluation of user needs, gender issues and for determination of the actual state in the field of research in Europe
- Preparation of information letters and e-mail newsletters, to present the network towards the network members, as well as to spread information to public, press and media

**2.2 LP reports to NMC regarding structure, activities (1 page, bullet point style)**

Reports were regularly prepared as agreed.

**2.24d Maintenance of existing website-contents**

Existing content was continuously revised. ELIC verified and corrected all links from the website.
User rates and usage characteristics of the website have been analysed continuously throughout 2009. There was a 15% increase of visits compared to 2008. Around 40.000 visits from 137 countries were registered in 2009. 22% of the users came from referring sites. This result indicates that improved cross-linking is required.

**2.25d Telephone advisory service for web-editors**

This service was not requested in 2009.

**2.26d Coordination and monitoring of new contents**

New contents could be added in specific parts of the website.

Contact information

The contact data of WPs 4 to 6 and 8 has been updated by inserting lists with the WP members. This is essential information to initiate and maintain the crosslinking between workpackages and contacts with groups out of the ELN.

Abstracts of recent papers and recommendations available online

Since start of the ELN a number of important manuscripts, specifically recommendations and guidelines has been published. Essential information on these publications has been added to the website in order to increase visibility and recognition of the ELN. Taking copyright rules into consideration abstract and bibliographical reference and a link to PubMed of each publication has been included in the respective sections of the website. A request to the authors to provide additional material for the website e.g. tables, graphics or ppt-slides is ongoing.

Multilingual Website Contents and Collaboration with Web Advisors

In order to improve recognition of the work of the ELN in different European countries, to enhance the international character of the ELN, to offer basic information to non-English speaking users and to improve GOOGLE ranking WP2 increased multilingual information on the website. A section with a description of the ELN in various European languages (Czech, Danish, Dutch, Finnish, French, German, Greek, Italian, Polish, Spanish and Turkish) has been included to the ELN website.

The idea to support the ELN website as webadvisor has been suggested to the ELN members. Several members took over this task. They collaborate with ELIC as webadvisors, help with translation and crosslinking with national and international websites.

Information on ELN in Wikipedia

Wikipedia is one of the worldwide most frequently used information systems. In order to improve visibility of the ELN and to attract users to the website short information on the ELN and a backlink to the ELN website has been introduced to different national Wikipedia sites.

**2.35b Maintenance of ELTR**

The completion of the European Leukemia Trial Registry (ELTR) was intensified and this was a major work topic. All study leaders were contacted and requested to insert their leukemia trials into the ELTR. ELIC kept on screening the NCI register www.clinicaltrials.gov for listed leukemia trials to transfer them to the ELTR. All leukemia-diseases and all countries, represented in the ELN, were included into that survey. Responsible study leaders were contacted to update the studies, before integrating them into the ELTR. This process is still ongoing.

At present up to 65 European Leukemia trials were provided in the ELTR:

- Acute Lymphoblastic leukemia (ALL)
- Acute myeloblastic leukemia (AML)
- Chronic Lymphoblastic leukemia (CLL)
- Chronic myeloblastic leukemia (CML)
- Chronic Myelodysplastic Disease (CMPD)
- Myelodydysplastic Syndrome (MDS)
- Stem Cell Transplantation (SCT)

**2.50 6th information letter and e-mail newsletters**

The Medline application of the ELN information letter has unfortunately been declined in 2009. In order to improve the chances of acceptance in the future the structure of the newsletter and the procedures have been standardized. It will be separated into information on the ELN foundation, about EUTOS, original articles and short messages from the ELN, list of ongoing studies.

The 6th information letter has been prepared to be presented at the LeukemiaNet meeting (February 1, 2010). All WP leaders were contacted to contribute articles from their present field of research. The information letter contributions were reviewed and edited. Furthermore the WP leaders of WP 4 to 9 were motivated to update the ELTR to have an actual list of active trials and to offer the user of the ELTR a current issue of the trial status in Europe.

In addition seven electronic e-mail newsletters were prepared and sent out up to 600 ELN members. The aim was to inform ELN members on new developments in the ELN, to increase binding to the ELN and to attract users to the website.

- February 2009: New content regarding international IITs and Expert Committee on IITs
- March (1/2) 2009: New participants ELN, members of the Expert committee and web-advisors, dates and meetings
- March (2/2) 2009: Presentations slides ELN, EUTOS-Project
- June (1/2): First information on Road Map Initiative on clinical research in Europe, results of EFGCP (Before and after CT-Directive; Report), new ELIC staff
- June (2/2): EHA-Meeting information
- October: Abstracts and presentations of CML/EUTOS, workshop information (Road map initiative on clinical research in Europe), a multilingual website ELN, update on ELN contacts
- December: Chance for contribution to CT-Directive amendment

Contents of the information letters were extracted and added to the respective parts of the websites in order to achieve a quicker availability of the respective information to internet users.

Information on ELN


**Figure 2.1:** ELN website.

In order to improve user rates of the Website and to distribute information on the ELN a promotion slide has been suggested and provided to the ELN members. All members are asked to integrate such slides into their educational presentations.

### 2.47 Cooperation concerning website-linking with European institutions

Cross-linking with all major hematology associations and patient groups was continued. The idea of taking the ELN website forward with a project for GOOGLE optimization and backlinking was conceived, so the help of ELN members in terms of linking the ELN website to national websites was requested. A project for enhancing the backlinks of the ELN by external technical assistance was prepared but cannot be realized without further funding.

### 2.48 Sustainability concept for ELN website and ELTR

A sponsor-concept including fundraising was developed by ELIC. It has been discussed with the network center and the ELN fundraiser at several occasions intensively with regard to integration in the future ELN fundraising strategy. Options to include additional technical features, particularly new technologies as web2.0, have been discussed intensively as means to attract potential sponsors. The realization will depend on final decision on the fundraising strategy for the ELN and the available funds.

### 2.51 Organisation of a workshop on “Quality of Life and Late Effects”

The organisation of a third workshop on international IITs was not required since the ELIC – together with other European Organisations – initiated a series of joint international workshops in several European countries (see below).

Therefore the ELIC has addressed another topic which is a major cross-sectional scientific issue for the different disease related workpackages. With better cure rates for leukemias it is of increasing importance for the scientific community to collect and analyse information on the condition of patients. Also quality of life and late effects are potential new endpoints for clinical trials. Research may help to optimise trial design and aftercare of the patients. The idea of the workshop was to inform about current and planned activities in the ELN and to improve collaboration and initiate joint projects. A survey was sent out to the ELN members to analyse interest of the members in the topic and to identify topics and speakers. The resonance was extremely positive. The workshop was prepared (agenda below).

**Table 2.1:** Workshop (Chaired by N. Gökbuget, F. Efficace).

| TOPIC | SPEAKER |
|---|---|
| • Welcome | N. Gökbuget |
| ***Quality of Life*** | |
| • QoL in MDS: what have we learned so far? | F. Efficace |
| • Impact of different post-remission strategies on quality of life according to age and affected life cycle phase at initial diagnosis in patients with AML | R. Schlenk |
| • QoL in patients with MDS or MM: home versus hospital treatment | O. Rauzy |
| ***Quality of Life and Late Effects*** | |
| • Long-term patient-reported symptoms and QoL in CML patients treated with Imatinib | F. Efficace |
| • QoL and late effects in ALL: a retrospective study of long-term survivors | N. Gökbuget |
| ***Late Effects*** | |
| • Long-time follow up after stem cell transplantation | H.-J. Kolb |
| • Second malignancies occurring during treatment of chronic myeloid leukemia with tyrosine kinase inhibitors: a retrospective study in the Czech Republic | E. Faber |
| ***Preliminary data/Planned projects*** | |
| • Pregnancy cases in CML patients: Pregnancy Registry in Russian Federation. | E. Chelysheva |
| • Quality of life: Project proposal from the German CML Group | U. Kossak |

### 2.49. Participation in an international expert group for novellation of the Clinical Trial Directive (CT-Directive 2001/20/EC) and coauthorship for recommendations

The EU-directive 2001/20/EC aimed to implement good clinical practice in the conduct of clinical trials on medicinal products for human use in the EU member states. But it turns out that the changes have caused huge and negative effects for investigator-initiated ("investigator-driven"; "investigator-

sponsored") trials (IITs): administrative burden and costs were extremely rising and independence and trial performance particularly in an optimum-use scenario are dramatically damaged.

To react on the poor situation ELIC is participating in the Road Map Initiative for Clinical Research in Europe, which organizes workshops for stakeholders in the area of clinical trials. The aim is to build a strong lobby group and to elaborate detailed suggestion for changes in the legislation.

**Working schedule:**

- March 2009: Meeting in Sweden, Göteburg at the EBMT/CLINT-Meeting: Forming the group and first strategies
- June 2009: Meeting in Berlin and Telephone Conference: Defining workshops and responsibilities
- Further correspondence: Comments on content and speakers of the workshop agendas:

**Workshop schedule:**

1. A Single CTA in Multinational Clinical Trials – Dream or Option?' held in Brussels on 7 July 2009
2. Innovative Approaches to Clinical Trials Co-Sponsorship in the EU" held on London on 21 September 2009

**Further workshops planned for 2010:**

3. Risk based approach in clinical trials, 18 January 2010, Barcelona
4. Research Ethic Committees and Ethical Review in Europe, 19 January 2010, Barcelona
5. Towards a better Future for Pharmacovigilance in Clinical Trials, 8 February 2010 in Brussels
6. Designing the Future Conditions for Clinical Research in Europe, 17 march 2010 (Final Workshop)

**2.52NEW. Contribution to the impact assessment of the EU directive on clinical trials**

The ELIC group has prepared in collaboration with other European societies a comprehensive contribution to the impact assessment of the CT directive. The document which places a focus on the specific tremendous problems of academic clinical trials is made available on the website (http://www.leukemia-net.org/content/international_trials/basic_information/).

**2.45. Information on conduct of international trials**

Information on international trials was added to the website. In collaboration with another EU funded project (ECRIN) we attempted to identify available SOPs and guidelines. However the documents prepared by ECRIN are non-public. The project seemed to be not helpful to support and strengthen individual and independent academic investigators. Support is only offered via national research infrastructure networks for selected projects. Information on procedures to get in collaboration with ECRIN – which is only via national ECRIN coordinators - was added to the website.

*Deviations from the work program and corrective actions taken: identify the nature and the reasons for the problem, identify contractors involved*

WP2 is a workpackage with mainly service purposes for other WPs – in contrast to the other scientific workpackages. Since in 2009 no funding was available to pay staff and technical equipment the planned deliverables had to be reduced and limited. The payment of staff had to be made from other projects at the University of Frankfurt, which cannot be continued in 2010. Nevertheless we tried to maintain and extend the function of the website as the essential communication and information platform and even started new projects.

**Table 2.2** List of deliverables WP 2, 2009

| Deliv. No. | Deliverable Name | Date due | Actual/Forecast delivery date | Estimated indicative person months*) | Used indicative person months*) | Lead contractor |
|---|---|---|---|---|---|---|
| **WP 2** | **ELIC** | | | | | |
| **2.2** | LP reports to NMC regarding structure, activities (1 page, bullet point style) | **-78+** | 2009 | 0 | 1 | Gökbuget |
| **2.24d** | Maintenance of existing website-contents | **-78+** | 2009 | 0 | 10 | Ihrig |
| **2.25d** | Telephone advisory service for Web-Editors (content-oriented) | **-78+** | Not required | 0 | 0 | Ihrig |
| **2.26d** | Survey of new contents offered by the WPs | **-78+** | 2009 | 0 | 10 | Gökbuget |
| **2.35b** | Maintenance of ELTR (entry of new studies provided by the WPs) | **-78+** | 2009 | 0 | 5 | Ihrig |
| **2.50** | 6th information letter | **-78+** | 2009 | 0 | 10 | Ihrig |
| **2.45** | Update of information on international IITs | **-78+** | 2009 | 0 | 5 | Gökbuget |
| **2.47** | Continuous website-linking with European institutions | **-78+** | Reduced; 2009 | 0 | 2 | Ihrig |
| **2.48** | Realization of website sponsoring and acquisition of support | **-78+** | Reduced; 2009 | 0 | 4 | Gökbuget |
| **2.51** | Organisation of the 3rd workshop for international IITs; replaced: Workshop on Quality of Life | **-78+** | 2009 | 0 | 4 | Ihrig |
| **2.49** | Participation in an international expert group for novellation of the European Drug Law and coauthorship for recommendations | **-78+** | 2009 | 0 | 5 | Gökbuget |
| **2.52** | NEW. Contribution to the impact assessment of the EU directive on clinical trials | **-78+** | 2009 | 0 | 2 | Gökbuget |

*) if available

**Table 2.3** List of milestones WP 2, 2009

| Milestone No. | Milestone Name | Date due | Actual/Forecast delivery date | Lead contractor |
|---|---|---|---|---|
| **WP 2** | **ELIC** | | | |
| **2.24d** | Maintenance of existing website-contents | **-78+** | 2009 | Ihrig |
| **2.26d** | Coordination and monitoring of new contents | **-78+** | **2009** | Gökbuget |
| **2.35b** | Maintenance of ELTR | **-78+** | **2009** | Ihrig |
| **2.45** | Information on international IITs | **-78+** | **2009** | Gökbuget |
| **2.48** | Sustainability concept for ELN website and ELTR | **-78+** | **2010** | Gökbuget |

**Section 3: Consortium management**

**Section 4: Other Issues**

Ethical issues: none

Competitive calls: none

**Section 5: WP-Performance**

| Performance indicators | Status |
|---|---|
| Number of questionnaires and results | 1 questionnaire on gender related issues; 140 answers |
| Number of studies in the ELTR | About 65 European Leukemia Trials |
| Education and Training | 2 Workshops on IITs in January 2008 and 2009; workshop on quality of life prepared |
| Number of pageviews & visits / year | 171.236 pageviews/32.443 |
| Number of questionnaires | 2 comprehensive questionnaires, including evaluation in 2008 |

**Publications:**

**WP2 – ELIC:**

EL IC for impact assessment of EU -directive on good clinical practice (Information Letter 6), see Annex Section 3 WP 1-2-1

**CICS (WP 03)**

*Progress towards objectives – tasks worked on and achievements made with reference to planned objectives*

**3.3 LP reports to NMC regarding structure, activities and integration of national groups**

Reports were sent as requested.

**3.31 Operation of central web-based recruitment and randomisation facility**

This deliverable covers operation of the facility from project month 67 (1.7.2009) to month 72 (31.12.2009). See also deliverable D3.7, D3.12, D3.16 and D3.18.

The central web-based facility 'RANDOULETTE' for conducting randomisation in clinical trials has been developed, operated and provided for use in clinical trials of the network. Randoulette allows for online randomisation of individual patients at any time using a standard web browser.

The software Randoulette has been implemented as a java web application and is hosted on a server at the IBE, LMU Munich. Randoulette provides a randomisation result for patients in stratified, blinded clinical trials with block randomisation with or without stratification or alternatively full randomisation. The block lengths can be defined as randomly variable. The number of appliable treatment arms and study centers is unlimited and treatment arms can be parametrized by weighting. Stratification by centers or other factors is also possible limitless. Lists of blinded labels of drug packages can be created and provided for blinded drug manufacturing. The sections of a list are assignable to one or more trial sites for random assignment. Breaking of single blinded codes is supported and available online. In all processes Randoulette offers full conformity to concerns of Good Clinical Practice (GCP).

In 2009 the range of functions of the software 'RANDOULETTE' was extended. Reporting facilities were implemented and are now available for authorized trial coordinators. Quality assurance measures are customable for each trial. The user interfaces were redesigned. Randomisation notifications can be sent by email to all authorized persons.

The randomisation facility is available at no additional costs for trials conducted within the European LeukemiaNet. Interested trial group leaders should contact WP3 participant A. Fischer by randoulette@ibe.med.uni-muenchen.de or the Network Management Center.

**3.32 Operation of central electronic data capture facility**

This deliverable extends the results of deliverables D3.8, D3.13, D3.17, D.3.19 and D3.27 and covers operation of the facility from project month 67 (1.7.2009) to month 72 (31.12.2009).

The GCP-compliant electronic data capture facility MACRO has been installed. Both services are available to research groups within the consortium, but there will be extra license-costs for additional users. For further information see deliverable D3.8 and D.3.14.

In addition WP3 has developed a web-based online electronic case report form (eCRF) for the European Treatment Outcome Study (EUTOS) for CML Registry organised by WP17. Case reports include baseline information and yearly follow-ups. The registry currently covers 52 regions in 23 different countries. More are expected to join in 2010. The system is based on proven open source software components such as the Linux plattform, the Apache webserver, and the PostgreSQL database as well as several tools stemming from in-house development that have been sucessfully used in a number of web-based projects and continuously enhanced. Due to pre-existing structures, the allocation of responsibilities differs in various member countries and regions. This is accommodated by a simple and yet versatile role-based authorisation scheme.

### 3.33 Operation of the PID-Generator

This deliverable extends the results of deliverables D3.21, D3.25 and D3.28 and covers operation of the facility from project month 67 (1.7.2009) to month 72 (31.12.2009).

The second version of the PID-Generator developed by the TMF has been installed on a server at the IBE Munich. The various configuration possiblities the software offers have been deployed and tested by WP3 participants.
The software which implements an algorithm providing unique pseudonyms for subjects of research collectives such as trials and disease registers is available for all ELN member projects.
WP3 offers interested research projects guidance in concerns of data protection and pseudonymization.

In 2009 WP3 participated in the planning of pseudonymization issues in a large register trial researching outcome of acute myeloid leukemia (AMLSG-BiO Study). An implementation scenario integrating the PID service in the existing data collection plattform has been developed. In this context the PID-Generator service has been custom-configured and was tested against available real-life datasets. The planning of the AMLSG-BiO study is nearly finished and it will be starting in 2010.

### 3.34 Enhancement and Operation of the analysis pipeline for DNA-Microarrays

This deliverable extends the results of deliverables D3.23 and D3.29 and covers operation of the facility from project month 67 (1.7.2009) to month 72 (31.12.2009).

The Microarray – Analysis – Pipeline has been designed to automate standard working steps in microarray data analysis such as preprocessing, assessment of differentially expressed genes or annotation. In 2009 it was used on 151 CLL samples to create preprocessed and normalized data which were then used to develop a prognostic score for patient survival time and time to treatment.
The pipeline was developed in cooperation with the "Computational Diagnostics Group" at the University Regensburg (http://www-compdiag.uni-regensburg.de).

### 3.35 Workshop for statistics-specialists

Title: "Advances in Statistical Modeling of High Dimensional Data: Variable selection and Challenges in Image Analysis"
The statistical workshop took place in September 17-18, 2009 in Munich. It was jointly organized by the IBE (as representant of the ELN), the German Region of the International Biometrical Society, and the Gene Center of the Munich University. It aimed at presenting new methodological development to interpret complex molecular data and data gained from observing single cells.
Besides an overview of the state-of-art in joint activities of Bioinformatics and Biostatistics the workshop also addressed actual research on the field of hemopoietic stem cells. This international workshop had 48 participants.

**Table 3.1**: Programme of the statistical workshop.

| Thursday Sep 17th, 2009 (13:00 – 18:00) | |
|---|---|
| Indirect comparison of interaction graphs | Ulrich Mansmann |
| Estimating high-dimensional intervention effects from observational data | Marloes Maathuis / Peter Bühlmann |
| Minimal Gene Set Enrichment | Julien Gagneur |
| Deep sequencing of a mixed sample | Osvaldo Zagordi/ Niko Beerenwinkel |
| Integrated analysis of copy number alterations and gene expression | Martin Schäfer/ Katja Ickstadt |
| Estimating Networks in a Huge Microarray Meta-Analysis with 60 Experiments and more than 7000 Microarrays | Markus Schmidberger |
| Analysis of cellular genealogies | Ingo Röder |
| Dynamic Nested Effects Models | Rainer Spang |

| Friday Sep 18st, 2009 (9:00 – 12:30 ) | |
|---|---|
| Reverse Engineering of Signaling Pathways from RNAi Data | Bettina Knapp/ Lars Kaderali |
| Prediction of gene function by automated cellular phenotyping and genome-wide RNAi. | Grégoire Pau |
| Heterogenous population context determines cellular activity and virus infection patterns | Berend Snijder/ Lucas Pelkmans |
| Reconstruction of signaling networks from gene intervention data | Tim Beissbarth |
| Bayesian Modelling for Perfusion Imaging | Volker Schmid |
| Bayesian parameter estimation in signalling networks | Fabian Theis |

**Table 3.2** List of deliverables WP03, 2009

| Deliv. No. | Deliverable Name | Date due | Actual/Forecast delivery date | Estimated indicative person months*) | Used indicative person months*) | Lead contractor |
|---|---|---|---|---|---|---|
| **WP 3** | **CICS** | | | | | |
| **3.3** | LP reports to NMC regarding structure, activities and integration of national groups (1 page, bullet point style) | 69, 72, 75 | **69, 72, 75** | 0 | 1 | Mansmann |
| **3.31** | Operation of central web-based recruitment and randomization facility | 67 - 78 | 72 | 0 | 3 | Mansmann |
| **3.32** | Operation of central electronic data capture facility | 67 - 78 | 72 | 0 | 3 | Mansmann |
| **3.33** | Operation of the PID-Generator | 67 - 78 | 72 | 0 | 2 | Mansmann |
| **3.34** | Enhancement and Operation of the analysis pipeline for DNA-Microarrays | 67 - 78 | 72 | 0 | 5 | Mansmann |
| **3.35** | Workshop for statistics-specialists | 69 | 69 | 0 | 0.5 | Mansmann |

**Table 3.2** List of milestones WP3, 2009

| Milestone No. | Milestone Name | Date due | Actual/Forecast delivery date | Lead contractor |
|---|---|---|---|---|
| **WP 3** | **CICS** | | | |
| **3.35** | Operation of central web-based recruitment and randomisation | 67-78 | 72 | Mansmann |

**Section 3: Consortium management**

None

**Section 4: Other Issues**

In cooperation with Prof. Dr. med. Hans-Jochem Kolb (LMU Munich, WP14: Stem Cell Transplantation) three studies in AML high risk patients (the EudraCT number has not been applied yet) were started.

**FLAMSA 101, 102, 103:** Due to a lack of funding, there was no progress in the FLAMSA studies in 2008. A decision on further sponsoring by the "Deutsche Krebshilfe" was scheduled for February 2009. Now two of the planned three studies did start in 2009.

**FLAMSA 101**

- Sponsor: GMIHO (Gesellschaft für med. Innovation Hämatologie und Onkologie mbH)
- Principal investigator: Prof. H-J Kolb (LMU München)
- Non-randomised prospective multi centre trial - Phase II
- Early allogeneic SCT for refractory Acute Myeloid Leukemia.

To evaluate whether early allogeneic stem cell transplantation (SCT) following the FLAMSA-RIC conditioning without repeated prior attempts for remission induction can improve the results of patients with chemo-refractory AML, as compared to the historic control group of EBMT.

- Possible cooperating centres in Munich, Augsburg, Wiesbaden, Hannover, Ulm, Münster, Cologne, Berlin, Marburg, and Regensburg (Cooperation centres are not selected yet).

**FLAMSA 102**

- Sponsor: GMIHO
- Principal investigator: Prof. H-J Kolb (LMU München)
- Non-randomised prospective multi centre trial - Phase II.

To evaluate whether substitution of busulfex for TBI will be able to reduced treatment related mortality without loss of antileukemic activity as compared to a historical control group treated by the classic FLAMSA-RIC including TBI.

- Possible cooperating centres in Munich, Augsburg, Wiesbaden, Hannover, Ulm, Münster, Cologne, Berlin, Marburg, and Regensburg

All three studies use the IT and biometrical services offered by the WP3 (IBE, LMU Munich): Patient randomisation with the well-proven randomisation software RANDOULETTE. Furthermore statistical analysis will be done at the IBE (LMU Munich).

**CML (WP 04)**

*Objectives and starting point of work at beginning of reporting period*

Cooperation between European study groups on CML has a longstanding tradition since establishment of the group of "European investigators on CML" (EICML) in 1992. Thus, EICML represents one of the founding collaborative groups for the European LeukemiaNet. Another important background structure is the "German Comptence Network Leukemias", which was founded in 1999. WP4 has now (2009) 62 participants representing 28 countries. Major goals of the WP with regard to the optimization of treatment strategies in CML are:

- Establishment of a comprehensive registry for CML patients across Europe
- Elaboration and updating of common definitions and guidelines for diagnostic and therapeutic procedures
- Creation of an European trial platform
- Standardization and harmonization of molecular methodologies for diagnosis and follow up of CML patients
- Laboratory and experimental studies of different aspects of CML
- Spread of excellence

This sixth period was characterized by an active communication process with five WP meetings and several meetings of specific groups working on particular deliverables (e.g registry, sub-registries, standardization and harmonization of molecular monitoring, different clinical trials, implementation of guidelines, spread of excellence activities).

WP4 is closely networking with WPs 1-3, 10-14, 17, CML Study Groups outside EU and the pharmaceutical industry. The collaboration atmosphere is indeed creative. The five WP lead participants have a tight communication by mail and phone and at meetings.

Highlights of the cooperative work include:

- EUTOS (European Treatment and Outcome Study)
- Standardization round with 57 ELN laboratories for molecular monitoring of residual CML
- Consensus manuscript on molecular monitoring published and a follow up paper is published
- Trials with new signal transduction inhibitors, new immunotherapy (vaccination) and with attempts to stop imatinib therapy are running successfully across Europe
- Six ongoing collaborative trials on an European level (EICML)
- The European registry and the subregistries have grown rapidly and now enrolled more than 3500 patients
- A European population based registry was launched in 2009
- Several multicenter upfront clinical trials have been reported
- An updated and revised version of the ELN recommendations have been published and an updated version of the pocket card was finalized in December

*Progress towards objectives – tasks worked on and achievements made with reference to planned objectives*

**4.5 Regular WP meetings**

Three WP meetings were organized in February, June and December (see Annex section II).

**4.6 LP reports to NMC regarding structure, trial activities and integration of national leukemia trial groups (1 page, bullet point style)**

Reports on the status of the deliverables have been sent to NMC.

**Deliverables**

*Registry*

**4.14d Report of study patients to registries (n > 400 per year)**

Registry for prognosis of imatinib treated patients: All new cases of CML registered at the Italian GIMEMA, the German, the Nordic, the Spanish and the French CML study groups have been made available to the European Registry of CML. Total number of registered cases over a 5-year period (2004-2008) amounts to more than 3500. Reports were given at ISH and ASH 2009. For more details see also Annual Activity Report of WP17.

The database of the GIMEMA CML group has been linked via Internet with the central secretariat of the European CML Registry in Munich, so that the Registry Group has free realtime access to all online data.

National/international based registries are running in Czech Republic, Finland, Netherlands, Poland, Sweden, and Spain and a new common European population based registry was started in 2009. Further, a subregistry of patients with additional cytogenetic abnormalities in Ph-positive and Ph-negative hematopoiesis after imatinib therapy has enrolled 40 patients. Over 918 patients from more than 50 centers have been enrolled into the subregistry of patients failing imatinib therapy. Data were presented at WP4 meetings during EHA and ASH 2009.

**Direct results out of registries:**

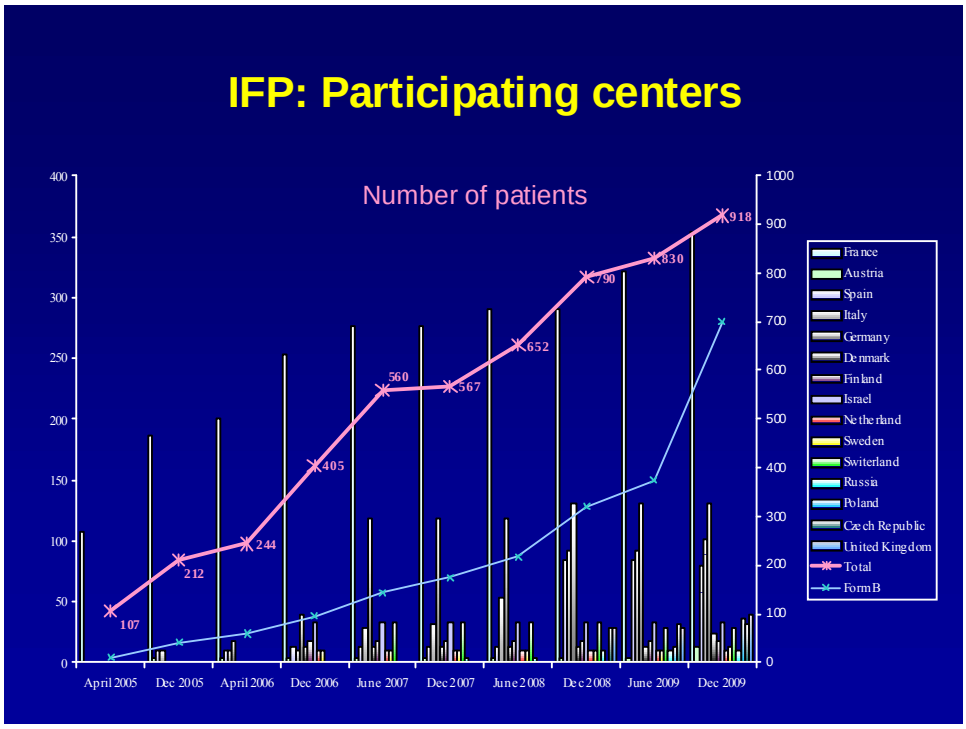
See also Annual Activity Report from WP 17.

**Imatinib-discontinuation registry:**

The Registry was reorganized within the project of the registry of Imatinib failure patients (IFP-Registry). An additional project is defined under D4.46 and 4.49.

The IFP is organized as a sub-registry under the CML European Registry (WP4). IFP registry is supported by a grant from the 6th European Framework program and by Novartis Pharma. French authorities approved this study in accordance with the European Community and the Helsinki protocol.

The first annual information letter has been generated on January 2008. The research plan and the case report forms have been posted on the web site of ELN. Currently 918 cases have been recorded and 757 cases fully documented; 15 European countries are participating. The first analysis of this registry is now planned for 2010.



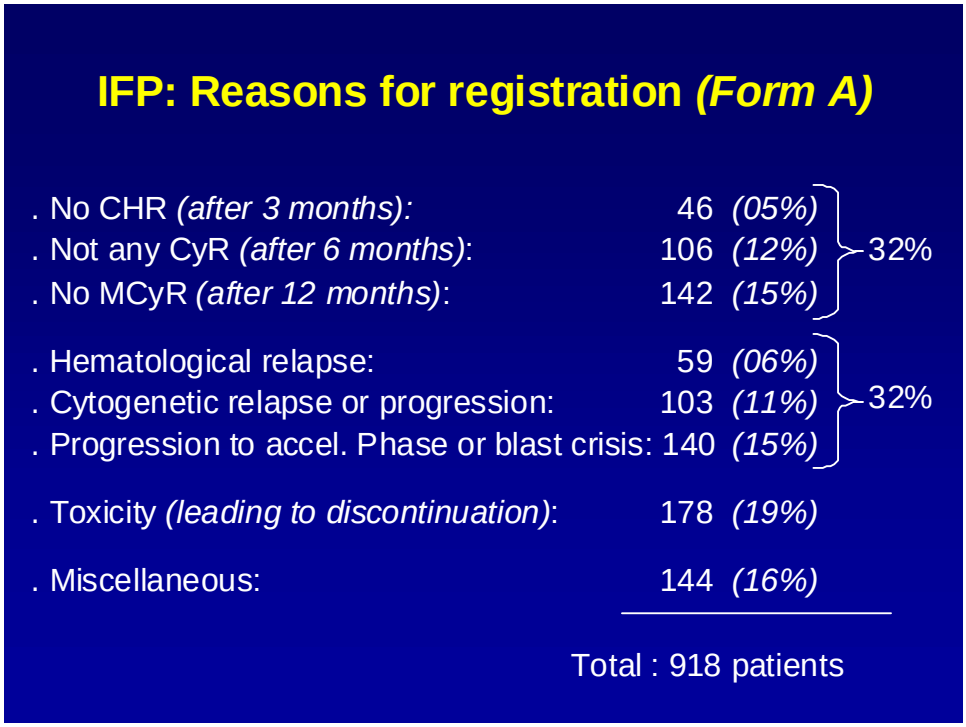




**Figure 4.1:** Participating centers and reasons for registration in the CML registry.

*Studies*

**4.19e Study imatinib + IFN or AraC, progress reports**

The prospective phase II study of Imatinib and Peg-Intron, front-line, in 76 early chronic phase patients, that was already published in 2004 (Baccarani et al., Blood 2004; 104: 4245-51).This study has been updated and presented at ASH 2009 (see Annex/Section 3, literature WP4-80).

Prospective studies investigating standard dose imatinib and the combination of imatinib and interferon alpha or imatinib and ara-C are running in Germany (recombinant IFN, ara-C) and France (pegylated IFN, ara-C), the Nordic countries (Denmark, Finland, Norway and Sweden; pegylated IFN), and UK (pegylated IFN). In total, more than 2500 patients had been enrolled Q4 2009. Analyses from Germany and France have been presented at several international meetings (see Annex/Section 3 WP 4-89, -107, -108, -112) and demonstrate the feasibility of the combinations.

The phase III prospective randomized trial investigating the impact of higher dose imatinib and of the combination of imatinib and interferon alpha or imatinib and Ara-C is still running in France (pegylated IFN) i.e. the SPIRIT trial. As of October 2009, 636 patients have been recruited and followed at least 24 months. The data were presented for the first time at ASH 2008 and a follow up was presented at ASH 2009. The molecular response rate at 24 months is significantly improved with combination of Imatinib plus Peg IFN.

An update of the first 636 patients followed at least 24 months has been recently presented during ASH 2009. The molecular responses are significantly higher with the combination of imatinib plus pegylated IFN. Thus imatinib 600mg and imatinib 400mg plus cytarabine have been closed for accrual. The trial is still recruiting in the imatinib 400mg and imatinib 400mg plus pegylated IFN.

In the Nordic study (n=112), also reported at ASH 2009, Imatinib was compared with Imatinib + peg-interferon. The 12 month rate of Major Molecular Response was also here significantly improved in the combination arm. The German group found no effect on 24 months molecular or cytogenetic reponses by adding regular interferon to imatinib (n=562) (GEIST-study, reported at ASH 2009 (see Annex/Section 3 WP 4-91).

**4.20e Study consecutive vs parallel imatinib/IFN combination (German CML IV), progress report**

5-year survival and response results of the pilot phase of the randomized German CML Study IV

The German CML Study IV was designed as a randomized trial to compare standard imatinib vs. imatinib + interferon alpha (IFN) vs. imatinib + low dose araC vs. imatinib after IFN-failure. By the end of 2005, 670 patients were randomized, 14 had to be excluded. 656 patients were evaluable. OS of all patients is 91% (see Figure 4.2), CCR is 94% and MMR is 88% at 5 years without significant differences between the four treatment arms. To verify possible differences in survival, e.g. imatinib 400 mg vs. imatinib + IFN, longer observation is planned. Although cytogenetic and molecular responses in the imatinib after IFN failure arm at 5 years are inferior to that in the other treatment

arms, the question of whether the consecutive therapy with IFN first and imatinib after IFN-failure provides a survival advantage requires long term follow-up.

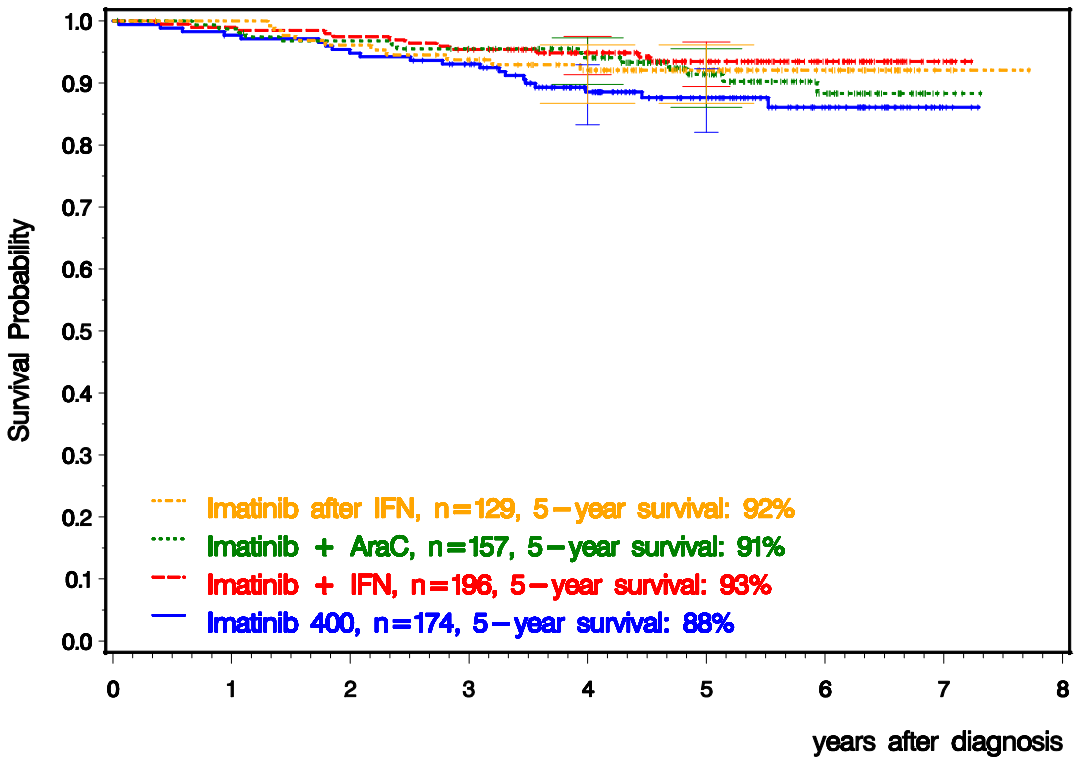



**Figure 4.2:** Overall survival at 5 years. Results of the pilot phase of the German CML Study IV.

### 4.21e Study high dose imatinib in high-risk chronic phase CML, final report

The data of this ELN, international study of Imatinib 400 mg vs 800 mg daily, front-line in Sokal high risk patients, have been analyzed (all patients have completed the study as of April 2008) and have been reported at EHA 2008, at the 8th Congress of the Italian Society of Experimental Hematology, Bari, 2008 and at ASH 2008. The final report has been published in Blood (see Annex/Section 3 WP 4-3). The study has not shown any detectable significant differences between 400 and 800 mg as it concerns cytogenetic response, molecular response, compliance, and survival.

### 4.22c Study high dose imatinib vs imatinib in standard dose (CML-Study IV), progress report

The German CML Study Group compared imatinib 800 mg (IM 800) with standard dose imatinib +/- IFN (IM 400, IM 400 + IFN). By April 30, 2009, 1022 chronic phase CML patients have been randomized (326 for IM 400, 338 for IM 800, 351 for IM + IFN). The cumulative incidences of achieving CCR and MMR between treatment arms are summarized in the Table 4.1. MMR at 12 months was reached faster with IM 800 than with IM 400 (p=0.0001) or IM400+IFN (p=0.0009). At the time of this evaluation, OS (92%) and PFS (88%) at 5 years showed no difference between treatment arms. In conclusion, these data show a significantly faster achievement of MMR and CCR

with IM 800 as compared to IM 400 +/- IFN up to 24 months after start of treatment. The data indicate that the optimal imatinib dose in CP may be higher than 400 mg per day. Longer observation is required to determine whether this more rapid achievement of MMR and CCR will translate into better OS or PFS.

**Table 4.1** Cumulative incidences of achieving a CCR and MMR

| Time after start of treatment | Cumulative incidences of achieving a | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | CCR(%) | | | | | MMR(%) | | | | |
| | IM400 n=273 | *Δ* | IM800 n=268 | *Δ* | IM400 +IFN n=304 | IM400 n=279 | *Δ* | IM800 n=283 | *Δ* | IM400 +IFN n=309 |
| 6 months | 21.5 | *12.0* | 33.5 | *15.1* | 18.4 | 6.1 | *11.3* | 17.4 | *11.2* | 6.2 |
| 12 months | 49.8 | *13.4* | 63.2 | *13.7* | 49.5 | 31.1 | *24.7* | 55.8 | *22.8* | 33.0 |
| 18 months | 66.6 | *7.2* | 73.8 | *3.8* | 70.0 | 51.5 | *18.7* | 70.2 | *15.5* | 54.7 |
| 24 months | 74.5 | *8.5* | 83.0 | *6.6* | 76.4 | 64.2 | *13.3* | 77.5 | *14.7* | 62.8 |

**4.27c Optimization of imatinib based therapies (high dose imatinib, imatinib + lonafarnib, imatinib + RAD001), final report**

Molecular mechanisms such as compensatory Akt/mTor activation may represent a novel mechanism for the persistence of BCR-ABL-positive cells in IM-treated patients. Treatment with mTor inhibitors may thus be particularly effective in IM-sensitive patients, whereas Akt-pathway activation variably contributes to clinically overt IM resistance. Studies for treatment optimization in patients on imatinib therapy lacking any cytogenetic response after 6 months, a complete cytogenetic response after 12 months or a major molecular response after 12 months of therapy were initiated in Germany at 13 centers. Options are the use of high dose imatinib (800 mg/day), the combination of imatinib and lonafarnib, or the combination of imatinib and RAD001. The study was running at 13 centers in Germany, 20 patients have been enrolled and the recruitment was stopped in 2008 due to toxicity.

**4.28d Optimization of Imatinib/IFN combination therapies in CML, manuscript in preparation**

A phase I/II study combining Imatinib with pegylated IFN alpha 2a (Pegasys) has been closed for recruitment after enrollment of 76 patients. Immunologic and molecular analyses were performed during therapy to demonstrate the differences in T-cell activation between consecutive and parallel Pegasys therapy. A study on imatinib discontinuation after imatinib/interferon alpha combination therapy was analysed and accepted for publication: Imatinib induces sustained remissions in chronic myelogenous leukemia (CML) patients, but fails to eradicate CML stem cells. This is of major concern to the issue of cure, long-term imatinib tolerability and imatinib resistance. We therefore asked whether interferon alpha 2a (IFN) alone could maintain molecular remissions achieved by a

prior combination therapy with imatinib and IFN. Imatinib therapy was stopped in twenty patients that had concomitantly been pretreated with imatinib and IFN for a median of 2.4 years (range, 0.2-4.8) and 2.5 years (range, 0.2-4.9), respectively. After imatinib discontinuation, the remission status was monitored monthly by quantitative analysis of the peripheral blood BCR-ABL mRNA levels using real time polymerase chain reaction. Proteinase-3 expression and proteinase-3-specific T-cells were longitudinally measured to assess putative markers of IFN response. With a median time of 2.4 years after imatinib withdrawal (range 0.5-4.0), 15 of 20 patients (75%) remained in remission. The number of patients in complete molecular remission increased under IFN from two at baseline to five after two years. Relapses occurred in five patients within 0.4 years (range, 0.2-0.8), but were rescued with imatinib, re-establishing molecular remission. IFN therapy was associated with an increase in the expression of leukemia-associated antigen proteinase 3 and induction of proteinase-3-specific CTL. Treatment with IFN enables discontinuation of imatinib in most patients after prior imatinib/IFN combination therapy and may result in improved molecular response. Induction of a proteinase-3-specific CTL response by IFN may contribute to this effect (see Annex Section 3, WP 4-30).

**4.29d Dynamics of response and resistance in CML patients treated with tyrosine kinase inhibitors beyond imatinib (AMN 107, BMS 354825): Progress reports.**

Nilotinib (AMN107) and dasatinib (BMS354825) are novel BCR-ABL inhibitors and are tested in clinical phase II/III trials. Levels of residual disease, BCR-ABL mutation analysis, and proportion of phosphorylated CRKL are determined in laboratories in Mannheim, Torino and Bologna.

Dasatinib efficacy was analyzed in patients recruited to phase 2/3 trials with chronic-phase chronic myeloid leukemia with or without BCR-ABL mutations after prior imatinib. Among 1043 patients, 39% had a preexisting BCR-ABL mutation, including 48% of 805 patients with imatinib resistance or suboptimal response. Sixty-three different BCR-ABL mutations affecting 49 amino acids were detected at baseline, with G250, M351, M244, and F359 most frequently affected. After 2 years of follow-up, dasatinib treatment of imatinib-resistant patients with or without a mutation resulted in notable response rates (complete cytogenetic response: 43% vs 47%) and durable progression-free survival (70% vs 80%). High response rates were achieved with different mutations except T315I, including highly imatinib-resistant mutations in the P-loop region. Impaired responses were observed with some mutations with a dasatinib median inhibitory concentration (IC(50)) greater than 3nM; among patients with mutations with lower or unknown IC(50), efficacy was comparable with those with no mutation. Overall, dasatinib has durable efficacy in patients with or without BCR-ABL mutations (see Annex Section 3, WP 4-63).

In a subanalysis of a phase II study of nilotinib in patients with imatinib-resistant or imatinib-intolerant CML-CP, the occurrence and impact of baseline and newly detectable BCR-ABL mutations were assessed. Baseline mutation data were assessed in 281 (88%) of 321 patients with CML-CP in the phase II nilotinib registration trial. Among imatinib-resistant patients, the frequency of mutations

at baseline was 55%. After 12 months of therapy, major cytogenetic response (MCyR) was achieved in 60%, complete cytogenetic response (CCyR) in 40%, and major molecular response (MMR) in 29% of patients without baseline mutations versus 49% (P = .145), 32% (P = .285), and 22% (P = .366), respectively, of patients with mutations. Responses in patients who harbored mutations with high in vitro sensitivity to nilotinib (50% inhibitory concentration [IC(50)] <or= 150 nM) or mutations with unknown nilotinib sensitivity were equivalent to those responses for patients without mutations (not significant). Patients with mutations that were less sensitive to nilotinib in vitro (IC(50) > 150 nM; Y253H, E255V/K, F359V/C) had less favorable responses, as 13%, 43%, and 9% of patients with each of these mutations, respectively, achieved MCyR; none achieved CCyR. For most patients with imatinib resistance and with mutations, nilotinib offers a substantial probability of response. However, mutational status at baseline may influence response. Less sensitive mutations that occurred at three residues defined in this study, as well as the T315I mutation, may be associated with less favorable responses to nilotinib (see Annex Section 3, WP 4-46).

**4.30d Preclinical and phase 1 – 2 clinical studies of tyrosine kinase and Src inhibitors**

Several studies are in progress, focusing on the gene expression profile and on single nucleotide polymorphisms of Ph+ cells, including CD34+ cells, and on their relationship with response to imatinib and prognosis (see Annex Section 3, WP4-20, -25, -26, -115,-117).

The first, preliminary analysis of studies of BCR-ABL kinase domain mutations was presented orally at the 2009 meeting of the EHA in Berlin (see Annex Section 3, WP4-80, -116).

**4.36c Phase II study of peptide vaccine to potentiate and stabilize imatinib effect in CP**

The first interim analysis of a phase 2 prospective study evaluating the effect of a B3A2 and B2A2 peptidic vaccine on the BCR-ABL transcript level of patients in stable complete cytogenetic response has been reported at the ASH 2009 meeting. Seventy patients have been enrolled in the B3A2 study, and 26 in the more recent B2A2 study. A molecular improvement (a reduction of the BCR:ABL ratio of 50% or more) has been reported in 50% of patients (see Annex Section 3, WP4-81).

**4.38c Nilotinib upfront in CP.**

A prospective, multicentric study of Nilotinib 400 mg twice daily, front-line, has been completed, with the enrollment of 76 pts who have been followed for one year or more. The results have been reported at the EHA and ASH 2009 meetings, and have been published (see Annex Section 3, WP4-3, -18, -109). All patients but one tolerated Nilotinib at doses ranging between 400 mg and 800 mg daily. All patients but two were in complete cytogenetic response (CCgR) at 12 months, and 80% of them were also in major molecular response. The response was very rapid, with 50% CCgR already at 3 months.

### 4.40 Long term effects of imatinib therapy

Imatinib is an effective first line therapy for chronic myeloid leukemia (CML) and has substantially changed its biological and clinical behavior. Durable complete cytogenetic responses (CCyR) were reported in the majority of patients, with a rather benign side effect profile, despite the 'off target' inhibition of several other kinases, including Kit, PDGFR and Lck. Since available information is largely based on sponsored trials and long-term field studies are lacking, the ILTE study was conceived as an independent, academic, multicenter trial supported by the Italian Drug Safety Agency (AIFA) and Regione Lombardia. ILTE is an international study on a retrospective cohort and includes 31 centers in Europe, North/South America, Africa, Middle East and Asia; therefore it is uniquely positioned to present a global picture of imatinib long-term effects. Consecutive patients with Ph+ CML who started imatinib between 01 September 1999 and 31 December 2004 were eligible if they were in CCyR after two years of imatinib treatment. Study endpoints were (a) survival, (b), serious adverse events (SAE, including second cancers), (c) toxicities not qualifying as SAE (NSAE) but judged by the referring physician as substantially impacting quality of life, (d) loss of CCyR, and (e) development of PCR negativity. A total of 948 patients were enrolled, 88% of which met eligibility criteria after centers were visited and monitored. The median age of eligible patients was 51 (range 18-92) years; 59% of patients were males and the median follow-up was 4.0 years (excluding the first two years of treatment). As of Dec. 31 2008, 3255 persons years were available for analysis. Twenty one deaths were observed (only 6 of them [28%] caused by relapsed CML), with a standardized rate of 0.6/100 person years and an observed/expected ratio of 0.7 (95% CI = 0.43-1.07, p=ns). A total of 138 SAE was recorded (rate 4.2/100 person years, most frequent type "heart failure"), with 19.5% being considered related to imatinib. Second cancers were documented in 29 patients (rate 0.9/100 person years), with an observed/expected ratio of 1.02. Among the 761 NSAE recorded (rate 23.4/100 person years) the most frequent types were cramps, asthenia, edema, skin fragility, diarrhea; 69% of them were considered related to imatinib. A total of 18 patients (2.2 %) discontinued imatinib because of toxicities during the period of observation. Forty patients lost CCyR, corresponding to a rate of 1.3/100 person years (1.0 in patients with imatinib as first-line treatment, 1.4 in patients who were treated with imatinib >6 months after diagnosis), with stable or increasing rates over time. Finally, 256 patients (36.0%) developed durable (>1year) PCR negativity.

In conclusion, this report from ILTE shows that CML patients on imatinib die unfrequently of CML related causes, do not appear to have substantially higher second cancer rates than the general population, have mortality rates similar to an age/sex matched population and do not show new types of imatinib-related adverse events. They also experience a low but steady rate of loss of CCyR and develop PCR negativity in approximately 1/3 of cases. Follow-up and further analysis are ongoing.

### 4.41 Allo-SCT after second generation TKI

Work in progress. See report under deliverable D14.48b.

### 4.44 Imatinib +/- hydroxyurea

After a phase I study in newly diagnosed (n=18) or interferon alpha refractory (n=2) CML patients, 80 newly diagnosed patients were randomized 2:1 for the combination treatment IM 400mg + HU 500mg (n=53) with a progressive escalation of the HU dose to attain mild leucopenia (3-4 Gpt/l) or IM 400mg alone (n=27). The primary endpoint of the study is the achievement of a major molecular response (MMR) after 18 months.

Until now the combination of IM 400 mg with HU doses up to 3000 mg results in a low toxicity profile compared to other combination treatment strategies. Preliminary response data indicate that the combination therapy has the potential to increase the frequency of patients achieving major molecular responses. Therefore a complete interim analysis for the primary endpoint has been planned for 2010.

### 4.45 Allo-HSCT in low risk patients

In the context of the German CML IV prospective controlled study, patients with an allogeneic transplant for CML were analyzed. The data show clearly that patients with low EBMT risks score (0-2) transplanted for defined indications had an excellent outcome with a survival not different from age and sex matched patients in the same prospective study. These data document the ongoing role of allogeneic HSCT in a very well defined subcohort (see Annex Section 3, WP4-19).

### 4.46 European study on imatinib withdrawal

A large ELN multicentre “Stop Imatinib” (STIM) study will be launched in 2010. A study protocol has been translated to English. The working group (chaired by F.X. Mahon) will present and discuss a final protocol draft at the next WP4 meeting February 2, 2010 in Mannheim. It should include patients in CMR for 2 years under TKI treatment (imatinib, nilotinib or dasatinib). Prerequisit will be that complete baseline information at diagnosis is available.

### 4.49 Imatinib D/C in patients with CMolR (STIM)

This French study on imatinib discontinuation has included the 69 planned patients and the first results were presented at ASH 2008 and 2009.

The data from 69 pts (34 had at some stage received IFN) showed that imatinib can be stopped in patients who have been in CMR (with at least 5 consequetive neg PCR-analyses) for two years without immediate negative effects. Molecular relapse free survival was 46% (Sokal low risk better, IFN vs no IFN not different). Relapses occurred within 6 months and were easily retreated to CMR. In total 658 patient months without any CML treatment. More females were included, while more males remained in CMR.

**4.50 Optimization of imatinib treatment based on plasma imatinib level (OPTIM)**

The French group started in 2009 a new trial entitled: ”A prospective randomized phase II study evaluating the optimization of the residual plasmatic level of dasatinib (sprycel®) in patients newly diagnosed with chronic phase chronic myelogenous leukaemia (cp-cml).”

Dasatinib is a new, multitargeted, tyrosine kinase inhibitor with a 300 fold more potent activity on the BCR-ABL tyrosine kinase in vitro comared to imatinib mesylate. Dasatinib has been extensively studied in the setting of imatinib failure with a rate of 40% of CCR in case of failure to imatinib. The dose of 100 QD of dasatinib is now labelled for patients with CP CML. Based on preliminary results of dasatinib in de novo CML, the estimated rates of MMR at 6 and 12 months are 19% and 33% respectively. The estimated rates of CCR at 3, 6 and 12 months are 72%, 94% and 100% respectively. A CCR rate of 81% is expected from the assumption made for the sample size calculation of the BMS 056 dasatinib front line study.

Adverse events observed with dasatinib include fluid retention, pleural effusions and cytopenia (especially thrombocytopenia). These adverse events require dose reduction or dasatinib interruption.

A subanalysis of the BMS 034 study indicated that the main factor associated with these adverse events is the level of the residual dosage of dasatinib (Cmin). Cmin correlates with the risk of adverse events such as fluid retention, pleural effusion and thrombocytopenia. In this study, the cut off value for Cmin was below 5nM. This analysis demonstrated also that the cumulative duration of dasatinib interruption is an independent factor inversely correlated to the quality of the response (Nicaise et al. EHA 2008).

We propose to prospectively assess the Cmin values of patients with de novo chronic phase CML treated with dasatinib as a first line therapy. Patients with a dasatinib plasmatic Cmin over 5nM will be randomized between a prospective adaptation strategy of the dasatinib daily dose based of the monitoring of the Cmin value (arm A1) versus observation only (arm A2). The other patients with a dasatinib plasmatic Cmin value below 5nM will be follow up according the ELN recommendation (arm A3). Dasatinib plasmatic Cmin will then be rechecked at two weeks interval (arms A1 and A2) until reaching the optimal dosage of dasatinib (arm A1) and every month in arm A3. The objective of the study is to reduce the rate of adverse events in arm A1 compare to arm A2. Patients in arm A3 will provide an estimate of the best expected difference between arm A1 and arm A2.

**4.51 IFN to patients in MMolR after 2 years imatinib (INTERIM)**

This trial is still under discussion with Roche, waiting for the dispensation of Peg IFN.

**4.52 Optimization of imatinib treatment based on plasma imatinib level (OPTIM)**

The design of the trial has been approved by the French CML Group. First patients should be included this year.

### 4.53 Auto-SCT in CML

The numbers of autologous transplants in Europe have declined to less than a dozen per year. The indications are clearly extremely limited. Autologous HSCT is not considered a standard procedure. It should only be undertaken in the context of a clear defined study (see Annex Section 3, WP4-7).

*Lab*

**4.34c European control round for BCR-ABL mRNA quantification (overlap with WP 12), progress report**

The rationale for the development of this subproject was to

(i) improve the early recognition of relapse

(ii) provide prognostic information

Thus this project aims to bring about the standardization of RQ-PCR throughout Europe ensuring an alignment with the International Scale (IS). A good network of standardized labs currently exists across Europe: 57 labs are participating in this project with 26 national reference labs (including Mannheim) validated across Europe so far (see Figure 4.3). Preliminary conversion factors (CF) are calculated using standard samples sent from the central laboratory in Mannheim to national labs and then validation of these CFs occurs by sending patient samples from the national labs to the central lab. Once validated, the national reference labs are equipped to propagate validated CFs and allow local labs in their respective countries to express their BCR-ABL levels on the IS. Recommendations for the propagation of the IS by national or regional laboratory networks were recently published in Leukemia (see Annex Section 3, WP4-11).

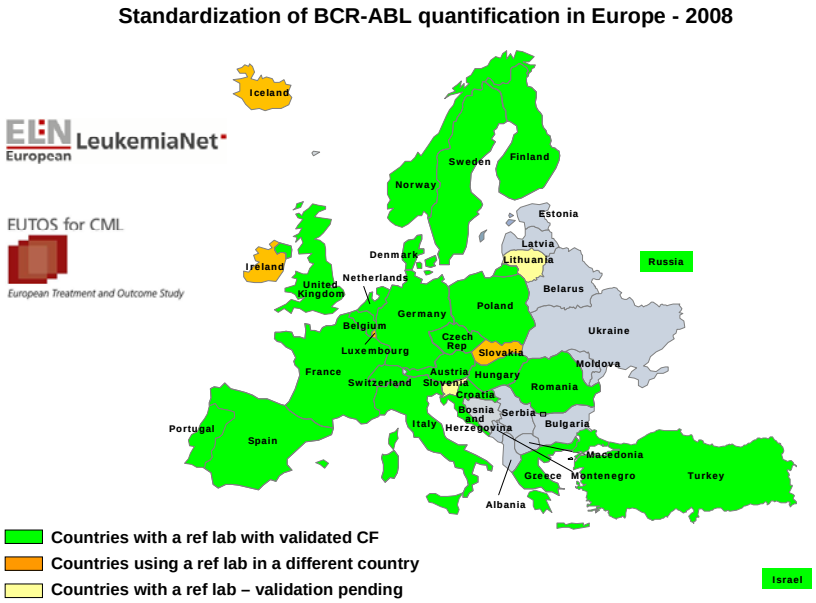



**Figure 4.3:** A summary of the standardization progress of BCR-ABL quantification in Europe between 2006 and 2008.

The plan moving forward is to expand the project to include around 200 labs across Europe, to perform regular certified control rounds in validated labs and to initiate exchange programs to educate laboratory personnel on RQ-PCR and mutational analysis, allowing rapid implementation of the standards in all participating European countries. Within in the EUTOS program the IS was established during 2008 to 28 laboratories within Europe. Additional meetings are planned to further distribute the IS from these central laboratories to the countries, to control performance of mutation analysis and to standardize CMR assessment.

**4.35 Mutated bcr-abl clones - In vivo sensitivity on a transcriptional level**

Various techniques to detect BCR-ABL kinase domain mutations in imatinib resistant patients with CML have been employed, resulting in different frequencies of mutations and a heterogeneous pattern of individual mutations.

We sought to compare direct sequencing (DS), denaturing high-performance liquid chromatography (D-HPLC) and two different quantitative allele-specific (ASO) PCR approaches for analysis of BCR-ABL mutations in 200 blinded cDNA samples within three different European laboratories. Comparing DS and D-HPLC, 114 mutations were detected by both methods and 13 additional mutations were detected by D-HPLC. Eighty of 83 mutations (96%) within a selected panel of 11 key mutations were confirmed by both ASO PCR techniques and 62 mutations with a median of 1.68 (range 0.04-100) % BCR-ABLmutant/BCR-ABLtotal were identified additionally to D-HPLC. Furthermore, 125 mutations were detected by one ASO PCR technique only with a median of 0.73 (range 0.01-100) % BCR-ABLmutant in BCR-ABLtotal.

We conclude: (i) D-HPLC identifies more mutations compared to DS. (ii) ASO PCR further increases the number of detected mutations and confirms mutations at low level. (III) Quantitative mutation monitoring should be considered for in vivo mutation kinetic studies.

The study has been published (see Annex Section 3, WP4-6).

**4.47 DNA microassays in CD34 + CML cells**

The aim of the project is to find changes in gene expression caused by TKIs in CD34+ cells. These cells are obtained from CML patients via CD34+ magnetic sorting and grown in primary cultures. These cultures are subsequently treated with TKIs. The differences in gene expression based on dose and time of exposure will be observed. In addition, differences in cell behaviour, such as apoptotic progression, will be analyzed.

Year 2008: Biological material collection and storage as well as primary cell culture technique testing on first samples. Optimization and verification of statistical methods used in consecutive phases of the project.

Year 2009: Testing and assessment of minimal proper concentration and time of exposure of TKI dasatinib on the level of gene expression changes in Bcr-Abl positive cells. K562 cell line was used as a model of homogenic Bcr-Abl positive cell population and consequently primary CD34+ cells.
We focused on apoptotic changes caused by TKI-mediated Bcr-Abl inhibition using flow cytometry (pCrkl, Annexin) and PCR (Bcl-2 protein family).
Plans for 2010: Further investigate the mechanism of action on microarrays (Affymetrix) and by modulating selected signalling pathways in the cell (MEK-ERK pathway, Caspases and proteasome inhibition).

**4.53 Effect of new molecular target agents on Ph+ leukemic stem cells**

We have been investigating the effects of new molecular targeted agents on Ph+ leukemic cell lines both in vitro and in vivo. Primary focus of our investigations were on the combined BCR-ABL and pan-Aurora kinase inhibitor PHA739358 (now Danusertib). Studying this compound, we could demonstrate both significant activity of the compound on Imatinib resistance conferring BCR-ABL mutations (incl. T315I) as well as a synergistic effect of combination treatment with Imatinib and Danusertib in vitro (1). Furthermore, a mechanism of resistance involving epigenetic upregulation of a drug transporter potentially allowing the cell to reduce intracellular drug levels of Danusertib was postulated to play a role at least in vitro (2 manuscripts in preparation). Consequently, data on in vivo feasibility and pharmacokinetics as well as first hints towards efficacy of the compound in multi kinase-inhibitor resistant patients were demonstrated recently (3).
Furthermore, by studying defined resistance conferring BCR-ABL mutations expressed in murine pro B cells BAF3 and using a proteomics-based approach, we could identify novel potential biomarkers for treatment with defined TKIs (3).

**4.54 Role of telomere shortening for resistance-confering mutations and disease progression in CML**

To investigate the therapeutic potential of telomerase inhibition in CML, we used a small molecule telomerase inhibitor, BIBR1532 as well as the expression of a dominant-negative mutant of hTERT (DNhTERT-IRES-GFP) in the p53-negative CML blast crisis cell line K562 and characterized the effects in long-term culture. BIBR1532-treated bulk cultures did not show altered growth kinetics despite of significant telomere shortening to a critical length of approximately 5 kb. In comparison, DNhTERT-expressing clones either lost telomere length leading to a significant but transient slow down in proliferation, but eventually escaped from senescence/crisis or, alternatively, remained virtually unaffected despite of measurable telomerase inhibition. Further analyses of affected sub-clones revealed impaired DNA damage response and altered expression of genes involved in DNA repair. However, upon restoration of p53 in telomerase-negative K562 clones with critically short telomeres, immediate re-induction of apoptosis was observed whereas vector control cells continued to

escape from crisis. These results suggest that the success of strategies aimed at telomerase inhibition in CML is highly dependent on the presence of functional p53 and should thus preferentially be explored in chronic phase CML. Retrospective analysis on the prognostic relevance of telomere shortening for development of resistance to TKIs in CML patients in vivo will show whether this parameter should be further explored in prospective clinical trials (see Annex Section 3, WP4-83, manuscript submitted for publication).

*Others*

**4.39b Definitions and standardization of relevant diagnostic and therapeutic procedures. A follow up position paper from an expert panel**

The updated and revised version of the ELN recommendations have been published in the Journal of Clinical Oncology (see Annex Section 3, WP4-2).

A prospective study of the evaluation of complete cytogenetic response (CCgR) with chromosome banding analysis of marrow cell metaphases and with fluorescence-in-situ-hybridization (FISH) of interphase marrow cells has been completed and published in Blood (see Annex Section 3, WP4-20). The study has shown that interphase FISH may be used to assess and to monitor CCgR, and is even more specific than chromosome banding analysis.

The final analysis of a study investigating the prognostic value of the deletions of the long arm of chromosome 9 (del 9q+) has been reported (see Annex Section 3, WP4-84) and published (see Annex Section 3, WP4-4), reporting that the cytogenetic and molecular response to Imatinib is not influenced by del9q+.

A prognostic evaluation of age and risk, based on 560 patients treated front-line with Imatinib in Italy, is being performed, and preliminary data were presented at the EHA and ASH 2009 meetings (see Annex Section 3, WP4-81, -84, -88).

A prognostic evaluation of more than 1500 patients who were treated front-line with Imatinib and are registered at the ELN registry, has been initiated (see Annex Section 3, WP4-91).

A comprehensive review of CML treatment and monitoring recommendations has been completed and published (see Annex Section 3, WP4-1). J. Guilhot is preparing a manuscript on “Relevant definitions for future trials”.

**4.43 Dasatinib and immunomodulation**

**Background**

Targeted inhibition of the oncogenic BCR-ABL tyrosine kinase by small-molecule inhibitors (TKIs) has profoundly changed the therapy of CML. Imatinib mesylate was the first drug approved for clinical use and currently is the standard first-line therapy for all CML patients. Imatinib is well tolerated and has few significant side-effects, as it predominantly only targets cells with the mutated

kinase. However, the inhibition profile of many 2nd generation TKIs is much broader. This may be therapeutically advantageous, but as long-term effects on normal cells are largely unknown, significant side-effects may emerge.

We have recently observed a massive clonal expansion of cytotoxic LGL (large granular lymphocyte)-cells in blood of several CML and acute lymphoblastic leukemia patients during dasatinib (2nd generation TKI) therapy. The aim of this project has been to characterize the clinical features of the phenomenon and to study background mechanism.

**Current status of the project (January 2010)**

We have collected a case series of patients with LGL expansion during dasatinib therapy (n>25) from different centers in Europe and US. Several clinical and basic research investigators (from Finland, Norway, Sweden, Germany, France, Spain and US) have participated in the project. We have found that the expansion of immune effector cells is linked to autoimmune reactivity, such as severe diarrhea and lung toxicity, as accumulation of clonal T -cells was also observed in these organs. Furthermore, several patients with advanced, poor-prognosis leukemia achieved long-lasting complete responses to dasatinib, thus strongly suggesting an antitumor effect of the expanded cytotoxic cells. We postulate that by inhibiting kinases in immune effector cells, dasatinib induces a reversible state of autoimmune reactivity resulting in host organ damage and in enhanced anti-leukemic control, both driven by cytotoxic T/NK LGL cells. These results have now been published in *Leukemia* journal (see Annex Section 3, WP4-64).

In our follow-up projects, we discovered that the expanding lymphocyte clones exist already before start of dasatinib therapy and remarkably, they can be detected at low levels already at the diagnostic phase of CML. Therefore our current working hypothesis is that clonal lymphocytes present at CML diagnosis are anergic/exhausted anti-leukemic lymphocytes and part of the immune escape mechanisms inherent to leukemogenesis. Dasatinib therapy may break this immune tolerance and revert anti-leukemic potential of pre-existing cytotoxic lymphocytes. Results from these experiments were preented at the ASH meeting in December 2009 and have now been submitted to *Blood* journal (see Annex Section 3, WP4-102).

**Further aims and future activities**

Currently we are studying *in vitro* the effects of TKIs on immune effector cells and we aim to isolate target kinase(s), which, when inhibited by dasatinib, cause a clonal expansion of cytotoxic T/NK cells. We also aim to identify the antigen targets of the activated cytotoxic cells on both normal and malignant cells and to assess the role of these cytotoxic cells in autoimmune/anti-leukemia manifestations in patients treated with TKI therapy. Further, we try to find the genetic factors which determine weather the patients develop lymphocytosis during dasatinib therapy and have therefore better therapy response. We hypothesize that KIR/HLA mismatch could be one of the mechanism and we are currently collecting samples from different centers in order to have big enough patient material.

Collaboration with international investigators continues actively as we try to use patient samples in *in vitro* studies to be able to draw direct conclusions to patient care.

**Importance of the study**

The aim of this project is to uncover the cellular and molecular mechanisms of TKI-induced anti-leukemia immune response in order to develop a novel, specific immunotargeting drug.

If successful, this project will introduce a significant addendum to the armament of treating leukemia: use of a molecularly targeted drug to induce a potent, durable anti-leukemia immune response.

### 4.48 Quality of life during imatinib treatment

Monitoring the quality of life should be an essential part of treatment of patients with CML. Validated testing methods enable us to monitor the physical, mental and social state together with spiritual aspects of patients. There exists a wide range of validated questionnaires which assess how patients feel about their quality of life in different stages of treatment and which compare the achieved quality of life when introducing new medicaments and medical methods. The aim of all testings is to know the needs of patients and to improve the quality of their lives during and after the treatment. The achieved results of the quality of life measurements need to be statistically processed and evaluated in short studies and both semi-longitudinal and longitudinal research. Instruments: Generic questionnaires: SF 36 (Short Form 36 Health Subject Questionnaire), EuroQolEQ-5D (European Duality of Life Questionnaire Version EQ-5D). Specific questionnaires: EORTC QLQ-C30, QHOQOL 100, FACT). Work done: Extensive questionnaire testing of 50 imatinib treated patients at least 1 year on treatment. Plans for the year 2010: The project is now finalized, what happened in 2009, and we expect some presentation this year.

### 4.55 Immunosuppressive mechanisms in CML

We have found that the Treg levels in patients with CML are increased compared to healthy controls. Further, the CML patients have increased levels of immunosuppressive proteins such as soluble IL-2Ra and IL10 in plasma and we have shown that these molecules can inhibit T-cell proliferation in vitro. The pro-inflammatory and Th1 stimulatory cytokines IL1b and IL12, respectively, are not detectable or expressed at low levels.

Furthermore, we have shown that the circulating CML stem cells (CD34+) express the receptor PDL1. PDL1 is the ligand to PD1 expressed on activated T cells. Upon binding, the T cell becomes anergic. By performing a mixed lymphocyte reaction using CML PBMCs and healthy donor T-cells we have shown that the presence of tumor cells completely block the proliferative response otherwise seen upon allogeneic T-cell cultures. The addition of antibodies that block PDL1 could reverse the tumor cell suppression of allogeneic T-cells.

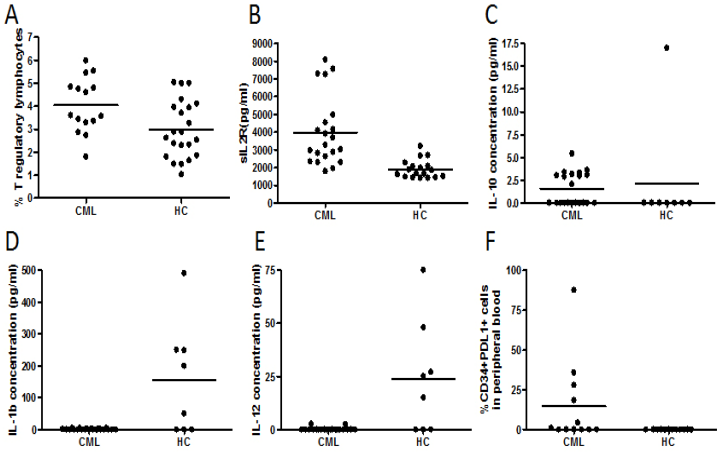
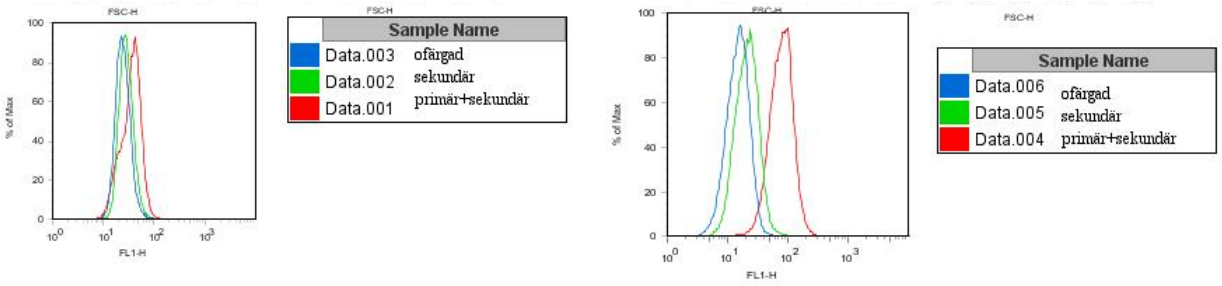



**Figure 4.4:** The Treg levels (CD4+Fox P3+CD127-) were evaluated using multicolor flow cytometry in CML patients and healthy controls (HC)(A). Suppressive and activation proteins (B: IL2R, C: IL10, D: IL1b, E: IL12) in blood were analyzed in plasma by ELISA and cytometric bead array. PDL1 expression on CD34+ stem cells in blood was evaluated by flow cytometry (F).

Currently, there are no methods for evaluating the total tumor cell population by flow cytometry because of the lack of specific markers. CD34 is used as a surrogate marker since most CD34+ cells in blood are malignant in CML patients. We are currently evaluating a flow-based protocol where we label bcr-abl proteins using intracellular staining protocols. By this method we hope to evaluate the phenotype of all malignant cells including the differentiated cells in blood.




The cell lines K562 and CML-T1 are both positive for bcr-abl translocation. However, K562 is positiv for b3a2 while CML-T1 express b2a2. Antibodies against b2a2 do not bind K562 cells (left) but selectively bind to the CML-T1 cells (right) as shown by our flow cytometry protocol.

**Significance**

Immunological evaluation of CML patients pre- and post treatment with tyrosinase kinase inhibitors is important to understand the mechanisms and possible differences of these inhibitors. If the inhibitors block suppressor cell function, these drugs may be important for the treatment of all cancers associated to increased frequency of suppressor cells.

### 4.56 Update ELN management recommendations

See **4.39**

**Table 4.2** List of deliverables WP 4, 2009

| Deliv. No. | Deliverable Name | Date due | Actual/Forecast delivery date | Estimated indicative person months*) | Used indicative person months*) | Lead contractor |
|---|---|---|---|---|---|---|
| **WP 4** | **CML** | | | | | |
| **Management** | | | | | | |
| **4.5** | Regular WP meetings | 62,66,72 | 62,66,72 | 0 | 4 | Simonsson, Guilhot, Hehlmann, Hochhaus |
| **4.6** | LP reports to NMC regarding structure, trial activities and integration of national leukemia trial groups (1 page, bullet point style) | 63,66,69,72 | 72 | 0 | 0,5 | Simonsson |
| **Registry** | | | | | | |
| **4.14d** | Report of study patients to registries (n > 400 per year) | 61-78 | 69 | 0 | 5 | Baccarani, Cervantes, Guilhot, Hasford, Hehlmann O'Brien, Simonsson, Thaler, Steegmann, Cornelissen, Ossenkoppele |
| **Studies** | | | | | | |
| **4.19e** | Study imatinib + IFN or AraC, progress reports | 61-78 | 69 | 0 | 2,5 | Hehlmann Guilhot, O'Brien Simonsson, Thaler |
| **4.20e** | Study consecutive vs. parallel imatinib/IFN combination (German CML IV), progress report | 66,72,78 | 70 | 0 | 5 | Hehlmann |
| **4.21e** | Study high dose imatinib in high-risk chronic phase CML, final report | 66 | 64 | 0 | 2 | Baccarani Haznedaroglu Simonsson |
| **4.22c** | Study high dose imatinib vs imatinib in standard dose (CML-Study IV), progress report | 72 | 69 | 0 | 5 | Hehlmann |
| **4.27c** | Optimization of imatinib based therapies (high dose imatinib, imatinib+lonafarnib, imatinib+RAD001), final report | 66 | 66 | 0 | 0 | Hochhaus Fischer |
| **4.28d** | Optimization of imatinib/IFN combination therapies in CML, manuscript in preparation | 72 | 72 | 0 | 2 | Hochhaus Neubauer |
| **4.30d** | Preclinical and phase 1 – 2 clinical studies of tyrosine kinase and Src inhibitors | 66,72 | 66 | 0 | 4 | Baccarani |
| **4.36c** | Phase II study of peptide vaccine to potentiate and stabilize imatinib effect in CP | 72,78 | 70 | 0 | 5 | Bocchia Baccarani |
| **4.38c** | Nilotinib upfront in CP | 66,72 | 66 | 0 | 5 | Baccarani |
| **4.40** | Long term effects of imatinib therapy | 78 | 69 | 0 | 4 | Gambacorti |
| **4.41** | Allo-SCT after second generation TKI | 72 | ongoing | 0 | 2 | Guilhot |
| **4.44** | Imatinib +/- hydroxyurea | 66,72 | 78 | 0 | 5 | Lange Niederwieser |

| Deliv. No. | Deliverable Name | Date due | Actual/Forecast delivery date | Estimated indicative person months*) | Used indicative person months*) | Lead contractor |
|---|---|---|---|---|---|---|
| **4.45** | Allo-HSCT in low risk patients | 66,78 | 69 | 0 | 4 | Gratwohl Niederwieser |
| **4.46** | European study on imatinib withdrawal | 66,72,78 | 78 | 0 | 3 | Gratwohl Cornelissen |
| **4.49** | Imatinib D/C in patients with CMolR (STIM) | 66 | 69 | 0 | 5 | Mahon |
| **4.50** | IFN to patients in MMolR after 2 years imatinib (INTERIM) | 78 | ongoing | 0 | 0,5 | Roy Guilhot |
| **4.51** | Optimization of imatinib treatment based on plasma imatinib level (OPTIM) | 66,78 | ongoing | 0 | 2 | Guilhot |
| **4.52** | Auto-SCT in CML | 66,78 | 64 | 0 | 1 | Hein Gratwohlt |
| **Lab** | | | | | | |
| **4.29d** | Dynamics of response and resistance in CML patients treated with tyrosine kinase inhibitors beyond imatinib (AMN 107, BMS 354825). Progress reports. | 66 | 66 | 0 | 5 | Hochhaus Saglio |
| **4.34c** | European control round for BCR-ABL mRNA quantify-cation (overlap with WP 12), progress report | 72 | 69 | 0 | 5 | Hochhaus Saglio |
| **4.35** | Mutated bcr-abl clones - In vivo sensitivity on a trans-criptional level | 66 | 66 | 0 | 5 | Müller Gruber Lange |
| **4.47** | DNA microassays in CD34+ CML cells | 72 | 78 | 0 | 2 | Mayer |
| **4.53** | Effect of new molecular target agents on Ph+ leukemic stem cells | 66 | 66 | 0 | 4 | Brümmendort Holyoake |
| **4.54** | Role of telomere shortening for resistance-confering mutations and disease progression in CML | 66 | 66 | 0 | 4 | Brümmendorf Hochhaus |
| **Others** | | | | | | |
| **4.39b** | Definitions and standardization of relevant diagnostic and therapeutic procedures. A follow up position paper from an expert panel | 66 | 66 | 0 | 3 | Baccarani |
| **4.43** | Dasatinib and immunomodulation | 72 | 72 | 0 | 2 | Porkka |
| **4.48** | Quality of life during imatinib treatment | 72 | 78 | 0 | 3 | Mayer |
| **4.55** | Immunosuppressive mechanisms in CML | 78 | 72 | 0 | 2 | Simonsson |
| **4.56** | Update ELN management recommendations | 78 | 66 | 0 | 5 | Baccarani, Guilhot, Simonsson, Hehlmann, Hochhaus |

*) if available

**Table 4.3** List of milestones WP 4, 2009

| Milestone No. | Milestone Name | Date due | Actual/Forecast delivery date | Lead contractor |
|---|---|---|---|---|
| **WP 4** | **CML** | | | |
| **4.51** | Optimization of imatinib treatment based on plasma imatinib level (OPTIM) | 66,78 | ongoing | Guilhot |
| **4.14d** | Report of study patients to registries (n > 400 per year) | 61-78 | 69 | Baccarani, Guilhot, Hasford Hehlmann, O'Brien Simonsson, Thaler Cervantes, Steegmann Cornelissen, Ossenkoppele |
| **4.21e** | Study high dose imatinib in high-risk chronic phase CML, final report | 66 | 66 | Baccarani, Haznedaroglu Simonsson |
| **4.34c** | European control round for BCR-ABL mRNA quantification (overlap with WP 12), progress report | 72 | 69 | Hochhaus Saglio |
| **4.39b** | Definitions and standardization of relevant diagnostic and therapeutic procedures. A follow up position paper from an expert panel | 66 | 66 | Baccarani |
| **4.46** | European study on imatinib withdrawal | 66,72,78 | To be launched month 76 | Gratwohl Cornelissen |

**Section 3: Consortium management**

WP4 in conjunction with the group of European Investigators on CML (EICML) has been a successful group of scientists, which is well recognized internationally. This group represents a solid basis for setting standards and for the rapid investigation of new drugs.

WP4 is managed by five lead participants with the help of the NMC in Mannheim. Three successful WP meetings (and one EICML meeting) demonstrate the active work in this group.

Communication between participants and with the NMC is running well.

**Section 4: Other Issues**

Ethical issues - none

Competitive calls - none

**Section 5: WP-Performance**

**Please update red marked rows**

| Performance indicators | Status |
|---|---|
| Number of clinical trials started and/or completed | 6 |
| Number of patients included into registries | approx. 3500 |
| Improved predictive, prognostic or quality of life assessments | Guidelines of diagnostic and therapeutic procedures updated for submission, interlaboratory control rounds continue |
| Degree of harmonization of trials | 4 collaborative trials on an European level |
| Number of SOPs and consensus papers | 2 |
| Number of publications | 85 |
| Number of meetings | 6 |
| Number of meta-analyses | 0 |
| Number of accredited trials | see website |

**AML (WP 05)**

*Objectives and starting point of work at beginning of the reporting period*

At the beginning of 2009 the situation was characterized by further progress and experience in the field of molecular markers (see Annex section 3, WP 5-37, 5-80). Besides their role as risk factors, the genetic and metabolic peculiarities of AML cells increasingly appeared as targets for new drugs (see Annex section 3, WP 5-50, 5-51). Promising therapeutic results were confirmed mainly in promyelocytic leukemia. (see Annex section 3, WP 5-54). First updates suggested a successful cooperation of trials in the AML Intergroup in younger patients (see Annex section 3, WP 5-92), while data and experiences in older age AML increased Europe wide (see Annex section 3, WP 5-43). An increasing availability of data on allogeneic SCT suggested the use in high-risk disease even in older patients (see Annex section 3, WP 5-6).

*Progress towards objectives – tasks worked on and achievements made with reference to planned objectives*

During 2009 further progress has been achieved in the European AML network (WP5). At the annual Reisensburg Symposium new data on gene mutations (CEBPA, RUNX1) and overexpressions (ERG, BAALC, MN1) have been presented and C. Bloomfield (Ohio State University) gave a comprehensive overview of the new WHO classification (minutes see Annex section 3, WP 5-1). New drugs and targets were updated at the Hematologic Malignancies conference in Brussels and by a survey see Annex section 3, WP 5-50). Epigenetic changes in AML related to age became the subject of a DFG funded research project (see application summary) and also a therapeutic target (see Krug et al. in Annex section 3, WP 5-1). The AML Intergroup as an ELN pilot study has now recruited more than 3000 patients. The latest update allows reliable projections to 5 years, and a publication is in progress. As another ELN pilot study main aspects of older age AML were elaborated in a large multicenter trial (see Annex section 3, WP 5-2). Uniform European recommendations on all clinical aspects of AML were published for both general AML (see Annex section 3, WP 5-4) and APL (see Annex section 3, WP 5-14). APL relapse, data and treatment, were contributed in an own publication (see Annex section 3, WP 5-7). Multiple approaches and experiences were reported on the field of allogeneic SCT. The role of growth factor priming in AML could be elucidated in a large multicenter trial as an ELN pilot project (see Annex section 3, WP 5-2).

*Deviations from the workprogram and corrective actions taken: identify the nature and the reasons for the problem, identify contractors involved*

No substantial deviations of the workprogram.

**5.5 Regular WP meetings**

WP5 Meeting at ELN Symposium Mannheim, 03.02.2009

AML Intergroup Meeting, Frankfurt, 11.05.2009

WP5 Meeting at EHA Berlin, 04.06.2009

AML Intergroup Meeting, at ASH, 06.12.2009

**5.6 LP Reports to NMC**

AML Intergroup Symposium Reisensburg, 06.02.2009 (see minutes)

WP5 meetings (see 5.5b).

**5.12f Current trials on novel therapies in Europe**

Report at International Symposium Hematological Malignancies, Brussels 01.10.2009

(See Annex section 3, WP 5-23, -93, -94).

**5.13e Pilot study treatment in subgroups, defined by genetic markers, up-front randomized, intention-to-treat**

(See Annex section 3, WP 5-2, -92, 93, 94).

**5.15e Pilot study AML Intergroup and a European AML network**

New update from the AML Intergroup: Participation of 5 trial groups, recruitment of 3602 patients age 16 to 60 years, median observation time between 2.0 and 4.8years, 358 patients (10% from all groups) in the common standard arm, overall survival probability at 5 years standard arm 0,41, all 5 participating trials within the 95% CI. Publication in preparation.

See Büchner T et al. in Annex section 3, WP 2-1 "Prospective Assessment of Outcome Determinants in AML: An ELN Pilot Project.", and in WP 5-64).

**5.16e Establishing a European network on management of Acute Promyelocytic Leukemia**

(See Annex section 3, WP 5-9, -14.).

**5.17e Establishing a European network on management of AML in older patients**

Pilot study in patients 60+ years of age in the German AML Intergroup underway (see Annex section 3, WP 5-2 Büchner T et al., 5-50 Krug UO et al., 5-96 Röllig C et al., 5-55 Löwenberg B et al., 5-72 Prébet T et al.).

**5.18e Develop frailty index for Leukemia in older patients, continuation**

A novel risk score that predicts the likelihood of a complete remission after intensive induction therapy in older patients has been published in 2009. A publication on the frailty index in older patients is in preparation (see Annex section 3, WP 5-94).

A publication by Lübbert M. et al. concerning the frailty index in older patients with AML has been prepared.

**5.21d Harmonizing the criteria of biologic subgroups, risk categories and treatment strategies for patients with AML in Europe**

**5.24b European AML Guidelines**

Recommendations for the diagnosis and management of AML in adults have been published in 2009 (See Annex section 3, WP 5-4).

**5.25 Epigenetic pattern of AML with respect to patients age and risk profile**

The project "Die Bedeutung altersabhängiger genomweiter DNA-Methylierungsmuster bei der Akuten Myeloischen Leukämie/ Kennwort: Biologie der AML im Alter", submitted by C. Müller-Tidow and T. Büchner, has been accepted for funding by the DFG/German Research Community.

**5.26 Growth factor priming in AML: Long-term results**

Long-term results in patients with acute myeloid leukemia (AML) and data of the AMLCG 1999 trial were published in Blood 2009 and in ASH Highlights (see Annex section 3, WP 5-92).

There was a contribution of WP5 to the current ELN Information Letter concerning the prospective assessment of outcome determinants in AML (see Annex section 3, WP 2-1).

**5.27 European cooperation of trialists on the evaluation of allogeneic and autologous stem cell transplantation**

WP5 maintained several fruitful cooperations with European trialists, resulting in 5 publications in 2009 (see Annex section 3, WP 5-6, -13, -54, -92, and WP 2-1).

**Table 5.1** List of Deliverables WP 5, 2009

| Deliv. No. | Deliverable Name | Date due | Actual/Forecast delivery date | Estimated indicative person months*) | Used indicative person months*) | Lead contractor |
|---|---|---|---|---|---|---|
| **WP 5** | **AML** | | | | | |
| **5.5** | Regular WP meetings | **65, 71,78** | 86 and beyond | 0 | 3 | Büchner Ossenkoppele |
| **5.6** | LP reports to NMC regarding structure, trial activities and integration of national leukemia trial groups (1 page, bullet point style) | **65, 71** | 86 and beyond | 0 | 4 | Büchner Ossenkoppele Sanz |
| **5.12f** | Current trials on novel therapies in Europe (new drugs new targets) | **78** | 86 and beyond | 0 | 2 | Berdel Müller-Tidow Serve Holowiecki Lübbert |
| **5.13e** | Pilot study, treatment in subgroups defined by genetic markers, up-front randomized, intention-to-treat | **72-78** | 86 and beyond | 0 | 3 | Büchner Berdel Kienast, Heinecke Serve |
| **5.15 e** | Pilot study AML Intergroup and a European AML network | **72-78** | 86 and beyond | 0 | 3 | Büchner Döhner Ehninger Ganser Niederwieser Pfirrmann Gratwohl |
| **5.16 e** | Establishing a European network on management of acute promyelocytic leukemia, continued | **72-78** | 86 and beyond | 0 | 3 | Sanz Lengfelder |
| **5.17 e** | Establishing a European network on management of AML in older patients, continued | **72-78** | 86 and beyond | 0 | 3 | Büchner Burnett Niederwieser Lübbert |
| **5.18 e** | Develop frailty index for leukemia in older patients | **72** | 86 and beyond | 0 | 2 | Lübbert Büchner |
| **5.21 d** | Harmonizing the criteria of biologic subgroups, risk categories and treatment strategies for patients with AML in Europe. | **72-78** | 86 and beyond | 0 | 4 | Ossenkoppele Sierra Büchner Lübbert |
| **5.24 b** | European AML Guidelines | **72** | 72 | 0 | 5 | Döhner Dombret Grimwade Ossenkoppele Büchner |
| **5.25** | Epigenetic pattern of AML with respect to patients age and risk profile | **72-78** | 86 and beyond | 0 | 3 | Müller-Tidow Haferlach Löwenberg |
| **5.26** | Growth factor priming in AML: Long-term results | **72-78** | 78 | 0 | 3 | Löwenberg, Amadori Büchner |
| **5.27** | European cooperation of trialists on the evaluation of allogeneic and autologous stem cell transplantation | **72-78** | 86 and beyond | 0 | 4 | Kienast Gratwohl Wheatley Krug Löwenberg Ehninger Niedewieser |

**Table 5.2:** List of milestones WP 5, 2009

| Milestone No. | Milestone Name | Date due | Actual/Forecast delivery date | Lead contractor |
|---|---|---|---|---|
| **WP 5** | **AML** | | | |
| **5.15e** | Pilotstudy, AML Intergroup and a European AML network | **72-78** | 86 and beyond | Büchner<br>Döhner<br>Ehninger<br>Ganser<br>Niederwieser<br>Pfirrmann<br>Gratwohl |
| **5.16e** | Establishing a European network on management of acute promyelocytic leukemia, continued | **72-78** | 86 and beyond | Sanz<br>Lengfelder |
| **5.24b** | European AML Guidelines | **72** | 72 | Döhner<br>Dombret<br>Grimwade<br>Ossenkoppele<br>Büchner |
| **5.27** | European cooperation of trialists on the evaluation of allogeneic and autologous stem cell transplantation | **72-78** | 86 and beyond | Kienast<br>Gratwohl<br>Wheatley<br>Krug<br>Löwenberg<br>Ehninger<br>Niederwieser |

## Section 4: Other Issues

Ethical issues - none

Competitive calls – none

## Section 5: WP-Performance

No major changes since 03/07

## Section 5: WP-Performance

| Performance indicators | Status |
|---|---|
| Number of clinical trials started and/or completed | 3 |
| Number of patients recruited into clinical trials | approx. 1300 |
| Number of patients included into registries | approx. 1000 |
| Improved predictive, prognostic or quality of life assessments | New AML European guidelines published (Blood 2009) |
| Degree of harmonization of trials | see publication (Blood 2009) |
| Number of SOPs and consensus papers | 4 |
| Number of publications | 100 |
| Number of meetings | 6 |
| Number of meta-analyses | 1 |
| Number of accredited trials | 16 |

**ALL (WP 06)**

The successful national European study groups for ALL aim to combine their efforts in order to create a world-wide leading research group for adult ALL. Thus the essential aims of WP6 remained the same since the beginning of the funding. Major aim is to strengthen collaboration between the national European ALL study groups, to initiate new national study groups, to provide a platform for trustfull discussion of data and future plans and to encourage and initiate collaborative projects.

Integrating activities

- Maintenance of central management structures
- Development of standardized laboratory procedures for diagnostic confirmation
- Overview on prognostic factors used in the different trials
- Overview on ongoing European studies in ALL with a study registry
- Discussion of results and future plans of the national ALL study groups

Jointly executed research activities

- Combination and standardization of methods, definitions and clinical application of MRD
- Phase I-III intergroup studies

Spread of excellence

- Internet-based information on adult ALL
- Evidence-based guidelines for diagnosis and treatment of ALL
- Presentation of the network at national and international meetings
- Extension of network

## Integrating activities

Management and structure of the working group:

The collaboration within EWALL was further extended **(D 6.5, 6.20)**. According to a defined meeting plan three meetings were organised by EWALL alone or in collaboration with other groups. The communication between the participants is based on regular e-mail exchange.

New members in 2008

In 2009 the newly founded Austrian working group for adult ALL joined the EWALL (see below) (**D 6.24d**)

Meetings in 2009

Two meetings were organised in the context of other international meetings (Heidelberg, Network Symposium; informal come-together at ASH, San Francisco). Beyond this the EWALL organised two separate 1 day internal meetings. One of these traditionally takes place in Frankfurt and the other by rotation in different member countries. The collaboration with the ESG-MRD group and joint meetings for standardisation of bcr-abl diagnostics continued (**6.5**).

- EWALL Meeting Heidelberg, January 2009: A new project on pharmacogenomics with the option for international participation was presented. One major topic was Ph+ ALL with updates on the

Dasatinib trial in Elderly, MRD and mutation analysis and two planned studies were presented. Several EWALL members reported their experience with treatment of relapsed ALL as the basis for future collaborative trials. Two proposals were presented for Clofarabine and erythrocyte encapsulated asparaginase. Planned meetings for 2008 were discussed and topics identified.

- EWALL Meeting Krakow, June 2009: The meeting was organised in collaboration with S.Giebel who is coordinating the Polish ALL study group (PALG) and covered 5 major topics. (1) New drugs in ALL: The company Micromet was invited to present their plans for European trials with Blinatumomab to be organised in close collaboration with EWALL. With the company Mundipharma options for the collaboration with trials with Bendamustine and Forodesine were discussed. (2) EWALL recommendations: The EWALL recommendation for adult ALL was presented and mainly the summary statements were discussed in detail. (3) Management of relapsed ALL: In extension from the meeting in Mannheim the new trials for relapsed ALL were discussed. Also intensive discussion regarding the creation of an EWALL backbone for relapsed ALL took place. The realisation is hampered by the effect that strategies are different in the European ALL study groups and that complicated algorithms have to be considered. Therefore the initiation of joint trials with new drugs and company support was considered more realistic. (4) Ph+ ALL: For Ph+ ALL updates of the EWALL dasatinib trial and the GIMEMA dasatinib trials were given. (5) Ongoing and planned projects: Finally suggestions for a planned UKALL analysis of T-ALL results, a joint analysis of G-CSF during chemotherapy and the outcome of ALL with the Romanian protocol were presented.
- EWALL meeting Frankfurt, November 2009:
- The meeting had two major parts. One part was a joint meeting of EWALL with the German Multicenter Study Group for Adult ALL (GMALL). The aim was to inform the German study group members about the EWALL activities and to initiate/intensify potential collaborations. The 2nd part was dedicated to internal EWALL discussions and covered 5 major topics. (1) Planned trials: Updates were given on planned trials with Blinatumomab, Forodesine and Clofarabine. (2) Supportive treatment: A new collaborative project on antifungal prophylaxis during ALL induction was presented. (3) EWALL recommendation: An update was discussed. (4) T-lymphoblastic lymphoma: The results of the Northern Italian group were presented with the aim to initiate a collaboration. This is the basis for a potential collaboration between the two national Italian study groups. (5) Ph+ ALL: Overall results of the NILG studies and on studies with Imatinib after SCT were presented.
- EWALL meeting, ASH New Orleans, December 2009: The group presented in the plenary session major achievements and future plans to the other network members. Thereafter an informal come-together took place.

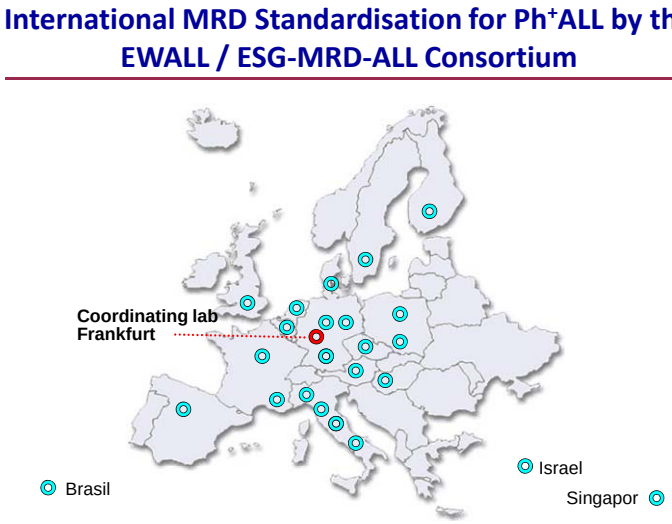
Web presentation

Further website contents were entered by WP2 **(D 6.21c)**.

Laboratory standardization

One essential aim of the EWALL was the development of standards for laboratory diagnostics in ALL. Mínimal Residual Disease (MRD) was in 2009 again one major focus of EWALL discussions. The joint publication with the ESG-MRD was prepared and discussions with regulatory authorities, particularly EMEA took place in order to introduce MRD as an accepted indication and endpoint for clinical trials with new drugs, even pivotal studies (**6.39**, see Annex Section 3, WP 6-1).

In Ph/BCR-ABL-positive ALL the standardisation process continued and the 3rd lab round took place (Leadership: H.Pfeifer). These rounds were organised in collaboration with the European MRD collaborative group (ESG), WP4 (CML) and WP 12 (MRD). The participating labs included those from pediatric study groups.




Study registry

The registry with ongoing European studies on adult ALL was maintained and extended (**D 6.25d**).

## Jointly executed research activities

Relapse treatment

The EWALL has identified the treatment optimisation in relapsed ALL as a major topic for collaboration. Several publications from EWALL member (Fielding et al, 2007; Tavernier et al, 2007 and Vives et al, 2008) have demonstrated extremely unfavourable results in relapsed adult ALL with a survival rate of only 6%. Therefore intensive exchange regarding results and strategies in the different European countries took place. A discussion on a backbone chemotherapy in order to test new drugs in relapsed ALL took place. However it was decided that subgroup adjusted treatments would be more promising e.g. MT103 in MRD positive ALL, Clofarabine in B-precursor ALL, Forodesine in relapse after SCT, Erythrocyte-encapsulated asparaginase in combination with chemotherapy, several Nelarabine combination trials.

Collaborative trials (**6.27d**)

The initiation of international joint European trials still is in practice extremely difficult and time-consuming – actually nearly impossible without large funds.

**The following studies are ongoing or in preparation:**

- GMALL B-ALL/NHL 2002

  The study conducted by the German ALL Study Group (GMALL) is ongoing in the Northern Italian Leukemia Group (NILG), the Polish Leukemia Group and the Spanish PETHEMA group. Since 2007 the Swedish group uses the protocol.

- EWALL Depocyte Trials

  The NILG study with Depocyte in prophylaxis was started. In the GMALL elderly study the planned patient number was achieved and follow-up is awaited.

- EWALL Chemotherapy Backbone for Elderly ALL

  The trial with Dasatinib for elderly Ph+ ALL was extended in order to achieve a sufficient number of Dasatinib treated patients. The trial with Forodesine in elderly Ph-negative ALL was postponed since new data on the oral formulation had to be awaited.

- Clofarabine in relapsed ALL

  A new study with a clofarabine combination in relapsed ALL was proposed by R.Bassan.

- Blinatumomab

  A joint European trial with Blinatumomab was proposed and will be conducted as a company sponsored trial

- Antifungal prophylaxis

  Intensive discussion including a questionnaire on preconditions for antifungal prophylaxis during induction therapy of ALL took place. A study may be started as company sponsored trial.

## Spread of excellence

With the website of the project a basis for internet-based information exchange and creation of a virtual center of excellence on adult ALL was maintained.

Members of the WP were also active speakers of educational sessions on national and international meetings and made contributions to textbooks (**6.24d**).

Hoelzer D: Allogeneic Stem Cell Transplant in Acute Lymphoblastic Leukemia: Who and When? (ASCO Education Session 2009)

Hunault M : Acute Lymphoblastic Leukemia in Adolescents and Young Adults: Is the Treatment Paradigm Changing? ( ASCO Education Session 2009)

Ottmann O.G.: Treatment of Ph+ ALL (ASH Education Session 2009)

Recommendations and guidelines

The chapters were submitted and edited. The printing of the book had to be postponed due to the difficulties with the regulatory realisation of a planned educational grant for printing of the book. The problem will most probably be solved in collaboration with the newly founded European Leukemia Foundation which can accept the grant.

Foundation of a EHA-EWALL Working Group

In order to integrate the EWALL in the work of the European Haematology Association the EWALL applied for acceptance as a EHA working group which was granted in 2009. This increases the sustainability of the group and will offer the opportunity to organise working group meetings during the annual EHA congress and thereby present the EWALL work to a broader audience of the EHA members.

Extension of the network

Another important goal was the extension of network by inclusion of additional network participants from other European countries. The aim is to integrate countries which have national study groups dedicated to ALL but not individual hospitals. The EWALL supported the foundation of an Austrian study group for adult ALL. This group was founded in 2009 and joined the EWALL with Ulrich Jäger and Alexander Hauswirth. (**D 6.24d)**. Negotiations with several Slovenian centers took place with the am to initiate foundation of a Slovenian ALL study group.

Publications

The members of the workpackage have developed a large number of national and international publications and were international opinion-leaders in many respects although these publications were not directly initiated by the network. The development of joint publications was not a primary aim of the workpackage. In 2009 a publication of a joint analysis of autologous SCT according to MRD appeared (see Annex Section 3, WP 6-1).

*Deviation from the workprogram and corrective actions taken: identify the nature and the reasons for the problem, identify contractors involved*

In 2009 the work of the European Working Group for Adult ALL (EWALL) was continued although – despite travel expenses for one working group meeting - no funding was available.

## List of Deliverables WP 6, 2009

| Deliv. No. | Deliverable Name | Date due | Actual/Forecast delivery date | Estimated indicative person months | Used indicative person months*) | Lead contractor |
|---|---|---|---|---|---|---|
| **WP 6** | **ALL** | | | | | |
| **6.5** | Regular WP meetings and symposiums (during international meetings) | **67-78** | 2009 | 0 | 12 | Gökbuget, Hoelzer |
| **6.20** | WP Management including reports | **67-78** | 2009 | 0 | 2 | Gökbuget, Hoelzer |
| **6.21c** | Extension of web-based information and communication services on ALL, continued | **67-78** | 2009 | 0 | 5 | Gökbuget, Hoelzer |
| **6.24d** | Support of newly funded European study groups and education | **67-78** | 2009 | 0 | 5 | Gökbuget, Hoelzer |
| **6.25d** | Extension of registry of ongoing European ALL studies | **67-78** | 2009 | 0 | 5 | Gökbuget, Hoelzer, Bassan, Ribera, Dombret, Foa, Meloni, Martinelli, Ottmann, Giebel |
| **6.27d** | Activation of further joint European studies | **67-78** | 2009 | 0 | 20 | Gökbuget, Hoelzer, Dombret, Bassan, Ribera, Rousselot, Ottmann, Foa, Meloni, Fielding, Giebel, Doubek |
| **6.39** | Joint publication with European Working Group for MRD analysis and Pediatric study groups on standards in MRD analysis | **66** | 2009 | 0 | 2 | Gökbuget Hoelzer, Dombret, Bassan, Ribera, Ottmann, Foa, Fielding, Giebel, Doubek |

## List of milestones WP 6, 2009

| Milestone No. | Milestone Name | Date due | Actual/Forecast delivery date | Lead contractor |
|---|---|---|---|---|
| **WP 6** | **ALL** | | | |
| **6.39** | Joint publication with European Working Group for MRD analysis and Pediatric study groups on standards in MRD analysis | **66+** | 2009 | Gökbuget Hoelzer |

**Section 3: Consortium management**

Regarding previous participants of the WP the following changes occurred

New participants of the WP6:

The Austrian ALL study group with the following representatives joined the EWALL: U.Jäger, A.Hauswirth

**Section 4: Other Issues**

Ethical issues: none, Competitive calls: none

**Section 5: WP-Performance**

| **Performance indicators** | **Status** |
|---|---|
| Number of clinical trials started and/or completed | European joint studies: 5 (4 planned) |
| Improved predictive, prognostic or quality of life assessments | Analysis of prognostic factors in European ALL trials, Joint proposal for a geriatric score, Consensus for MRD-analysis (BCR-ABL, gene rearrangements) |
| Degree of harmonization of trials | Ongoing |
| Number of SOPs and consensus papers | 2 consensus paper prepared for website<br>Patient info.,prepared for website (8 languages |
| Number of publications | 1 paper, 1 submitted, 38 additional papers |
| Number of meetings | 5 |
| Number of meta-analyses | 0 |
| Number of accredited trials | >20 |

**CLL (WP 07)**

*Objectives and starting point of work at beginning of report period:*

The European Research Initiative on Chronic Lymphocytic Leukemia (ERIC/WP7) comprises a well established association of more than 250 European/international clinicians and/or scientists, dedicated to creating a translational platform for clinical and basic research activities in the field of chronic lymphocytic leukemia (CLL). Over the past 8 years, ERIC has established an excellently working information- and communication structure and a notable core of world-wide recognized CLL specialists. With the election of a new board of directors, including Professor Emili Montserrat (Barcelona/Spain) as the executive chairman of ERIC in December 2008, ERIC has entered a new era of further development, restructuring and activities. During 2009, the main ERIC Secretariat office was transferred to Barcelona. However, parts of the ELN related administration and representation of ERIC are still carried out in Germany by former chairman and co-founder Professor Michael Hallek and the Cologne office (University of Cologne, Department of Internal Medicine I). 2009 was the first year that ERIC has successfully performed as a Scientific Working Group (SWG) within the European Hematology Association (EHA). As per the deliverables of WP7/ERIC, the following activities have been carried out during the past 12 months:

*Progress towards objectives – tasks worked on and achievements made with reference to planned objectives*

**7.5 Regular WP meetings**

1. As every year, 3 business meetings and one scientific workshop were held by ERIC/WP7 in 2009:

   19th ERIC Meeting at the 6th Annual Symposium of the ELN, Wednesday, February 03, 2009
   Attendance: Approximately 45 participants from EU and non EU countries
   The major goal of this ERIC/WP7 meeting, shortly after the general assembly in December 2008, was

   - to introduce Professor Montserrat to European members, who had not been able to attend the ASH-based ERIC meeting,
   - to summarize the status quo of all ongoing project activities and
   - to perform "brainstorming" for future structural and project news within ERIC. The meeting was kept informal for open discussion.

2. ERIC/EHA Scientific Meeting/Workshop at the European Hematology Association (EHA) Congress, Berlin, June 04

   Attendance: Approximately 120 participants from EU and non EU countries
   As mentioned in recent reports, for the past years the annual EHA congress has become a fixed meeting venue for a series of very successful Scientific Workshops/Meetings, carried

out by ERIC/WP7. In 2009, the tradition was continued by ERIC, now additionally representing a Scientific Working Group of EHA, with a series of invited top speakers from Europe and the U.S. (see agenda attached). As an overall topic of the meeting "The role of the microenvironment in CLL" had been selected by the Scientific Committees of ERIC, reflecting one of the current hot topics and fields with most progress in CLL research. The scientific workshop was well anticipated and visited by members and other EHA congress attendees.

3. 20th General Meeting of ERIC Members, Berlin, June 04, 2009
   Attendance: Approximately 80 participants from EU and non-EU countries
   Prior to the official scientific workshop in Berlin (see 2.), a separate "business meeting", open to members and any newly interested EHA visitors, was held, focusing on comprehensive updates of ongoing and potential new project activities of ERIC (see agenda attached). Slides presented at the meeting were published on the ERIC webpage (www.ericll.org).
4. 21st General Meeting of ERIC Members, New Orleans, December 07, 2009
   Attendance: Approximately 50 participants from EU and non EU countries
   As every year, the ERIC/WP7 community was gathering in context of the "ASH Breakfast Meeting" carried out by the ELN at the annual congress of the American Society of Hematology (ASH, New Orleans, USA). According to the agenda, one major topic of interest was the current and future funding situation of ERIC/WP7. Besides usual short updates to current/new project activities, mainly strategies to launch future funding options from private and industrial sources were discussed.

The next ERIC assembly is going to place in Mannheim/Germany during the 7th Annual Symposium of the European LeukemiaNet (Feb 2, 2010).

**7.6 LP reports to NMC regarding structure, trial activities and integration of national leukemia trial groups**

See schedules for the ERIC/WP07 meetings in Mannheim, Berlin and New Orleans 2009.

**7.8e Treatment of early stage, high risk CLL with FCR continued**

The evaluation of early treatment with fludarabine/cyclophosphamide/rituximab (FCR) versus watch and wait in early stage high risk CLL is one main focus of transnational clinical trial activities of WP7/ERIC, carried out by German and French CLL study groups as previously described.

In 2009, Germany and France as the trial sponsoring countries finished trial recruitment with approximately 850 patients, registered by participating centers in 4 countries (deliverable D7.8 fulfilled). Unfortunately, legal and administrative requirements could not be fulfilled timely in the Czech Republic in order to allow Czech investigators to register patients (despite fulfilling ethical requirements and ethical approval). Over-recruitment of patients over the presumed number of 600

patients was required due to the unexpected lower number of high risk patients according to protocol definitions. In addition to completed trial recruitment, both sponsoring countries, Germany and France, have meanwhile established congruent data bases, which are currently undergoing quality testing activities. Data entry and management has been commenced in France and Germany. Data collection and continuous data cleaning, including medical review and data querying are currently ongoing and comprise a long-lasting and elaborate process. The harmonization of data documentation and data management including handling of queries, adverse events, SOPs etc. between the study groups in Germany and France is also an ongoing important prerequisite within this project. It is more difficult, time and man power consuming than originally assumed and is continued within deliverable D7.16.

**7.9e Exchange of study protocols of open clinical trials, information on structure and trial activity of national CLL trial groups**

The development of new potential curative treatment modalities for CLL and related diseases is one long-term goal of WP7/ERIC. Therefore, one ERIC objective is to support phase I/II/III trials with new agents alone or in combination with established therapies (purine anaologues, alkylating agents) in CLL and/or related entities. According to previous reports, the following protocol exchanges have been active within ERIC:

- Protocol on chemoimmuntherapy with FCR versus watch and wait in early CLL; German/French study group (GCLLSG/FCGCLL)
- Protocol on recommendations for stem cell transplantation in T prolymphocytic leukemia (T-PLL) and development of a national registry documentation for transplant cases in T-PLL (responsible: P. Dreger, Heidelberg/Germany, see D7.16c)

CLL cases with p53-abnormalities are continuously collected on a molecular and clinical basis (including sequence characteristics but also clinical routine data) by the p53 working group (responsible: Stephan Stilgenbauer, Ulm, Germany), as previously described. Deliverable D7.9 belongs to the long-term efforts of WP7/ERIC and fulfilment will last up to and exceed month 78.

**7.10c Common data safety monitoring boards in clinical trial on CLL in Europe**

The first exemplary Data Safety Monitoring Board (DSMB) within ERIC was constituted for the ERIC supported clinical trial protocol on early stage CLL patients, which is part of deliverable 7.8. Eva Kimby (Stockholm/Schweden) and Peter Hillmen (Leeds/UK) have been selected as independent reviewers of data acquired within this transnational study for any interim, final or follow up analysis in future. The DSMB has been instituted by the German and French CLL study groups to review the clinical plausibility and safety of data collected during the study, as previously described. With finished patient recruitment for deliverable 7.8e, data for a first interim analysis are expected to be available in fall 2010, and represent the first peak of activity of the DSMB. With respect to ongoing

and presumably long lasting trial follow up in deliverable 7.8 (due to included early stage CLL patients with long times to progression), the ERIC based DSMB will be a continuously working and developing institution beyond month 78 of funding.

**7.11e Web-based information- and communication services on CLL refined and up-dated**

One of the major goals of deliverable 7.11 is to maintain and spread updated information on the mission, goals and activities of ERIC/WP7 to clinicians/scientists, who are interested and/or active in the field of CLL. During the past 12 months the content of the ERIC core webpage (http://www.ericll.org) has been maintained and updated on a regular basis. Upcoming meetings, meeting agendas and minutes have been announced on the web page regularly. In addition to the core web page, the concordance of project specific web pages for "the harmonization of MRD analysis in CLL" (deliverable 7.24, www.mrd-cll.org) and the "ERIC consensus and review board on IGHV-analysis in CLL" (deliverable 7.23, www.ericll.org/projects/IGVHMutationalAnalysis.php) require additional web skills and high maintenance efforts: Continuous improvements and further development of the webpage setup, programming, structure and contents are ongoing. This task will be continued as deliverable 7.11. of WP7 beyond month 78.

**7.12d Assess and create new guidelines for diagnostic and therapeutic management of CLL**

Deliverable D7.12. is fulfilled, as previously reported.

**7.16e Harmonisation of clinical study protocols and trial accessories between national CLL study groups**

The harmonization of clinical study protocols and trial accessories between national CLL study groups has been exemplary initiated within deliverable D7.8 (treatment of early stage, high risk CLL with FCR versus watch and wait). In this pilot trial, the harmonization of the complete data management process including data documentation, handling of queries, adverse events, SOPs etc. between the cooperating study groups in Germany, France and other participating countries has been difficult, and by far more time and man power consuming than originally assumed. It also exceeded the input and operating expenses provided by each country for the "regular" trial conduction. As one successful step within the past 12 months, two data bases with an agreed framework consensus of patient data items have been established between German and French study groups in collaboration with the company WISP (Wissenschaftlicher Service Pharma GmbH, Langenfeld, Germany). While quality control and assurance activities by data base programmers on both sides are ongoing, both countries continue to collect completed CRFs and continue to perform continuous medical review, query processing and monitoring of participating study sites. The goal of deliverable 7.16 is to create exemplary harmonized trial accessories required to ensure high data quality in transnationally performed clinical trials. Setup of a completely harmonized and audit-withstanding clinical trial between several countries continues

to stay a big challenge for established study groups. According to our experience it is not accomplishable for public study groups without industrial support and funding. Further progress of this deliverable will take at least further months up to month 78 and requires more person-months.

**7.17c First proposal of definition, standardization and harmonization of cytogenetic analysis in CLL**

The deliverable is fulfilled, as previously described. Ongoing activities on p53 mutational and functional analysis are continued with deliverable D7.26.

**7.18c First proposal of definition, standardization and harmonization of ZAP70 analysis in CLL**

The deliverable has been fulfilled, as previously described. Follow-up project activities are continued as deliverable D7.25.

**7.19d Evaluation and follow-up of patients with advanced CLL treated with FCR/FC – progress report**

The treatment of advanced CLL with fludarabine, cyclophosphamide with or without addition of rituximab (FC versus FCR) has been investigated as multinational open-label randomized phase III trial on behalf of the GCLLSG and multiple European and international centres, also represented within ERIC. In addition to the first analysis of trial data in 2008, a follow up evaluation of available data was performed and presented at the recent ASH congress in New Orleans in December 2009 (see Hallek et al., ASH 2009): In updated analyses, treatment with FCR chemoimmunotherapy did not only improve response rates and progression-free survival (PFS, as reported previously) but also overall survival, when compared to the FC chemotherapy: The overall survival rate at 37.7 months was 84.1% in the FCR arm versus 79.0 % in the FC arm (p=0.01). In both arms, the median overall survival (OS) had not been reached. Further subgroup analysis showed, that only patients in Binet stages A and B showed a superior OS after FCR treatment (Binet A: HR 0.19, CI 95%, 0.023-1.613 p=0.09; Binet B: HR 0.45, CI 95%, 0.296-0.689, p<0.001; Binet C HR1.4, CI 95%, 0.843-2.620, p=0.168). Treatment related mortality was reported in 8 (2.0%) pts in each arm. Of these, 7 FC-treated pts and 5 FCR-treated patients had died from infections related to treatment. Further multivariate analysis was performed to evaluate factors predicting outcome. Age, sex, FCR-treatment, response, number of cycles (0-3), 17p-deletion, increased serum levels of thymidine kinase and ß2-microglobulin and unmutated IGVH genes were shown to be independent prognostic factors predicting OS or PFS.

In conclusion the deliverable confirmed that treatment with FCR chemoimmunotherapy is more effective than FC chemotherapy in previously untreated CLL patients. Furthermore, for the first time a survival benefit was demonstrated in a randomized setting for first-line treatment in CLL. The partial failure to demonstrate a benefit for FCR treatment in Binet stage C patients was discussed as potentially related to the higher tumor load in such patients. However, the results corroborate the

recommendation to use FCR as standard treatment in physically fit patients with CLL and in need of therapy. Future work for the deliverable includes a continuous follow up, data cleaning and management of continuously incoming data for long-term evaluation of patients and update trial outcomes. Data of the first analysis have been submitted for full publication. Thus, deliverable D7.19 is fulfilled, however, long-term follow-up requires ongoing action, which comprises a new ERIC/WP7 deliverable.

**7.20d European platform for phase I/II trials**

In the past funding periods the difficult aspects of performing clinical trials in rare disease entities have been discussed intensively in our activity reports at the examples of the following ERIC-supported trial protocols (deliverable 7.26):

- Protocol of primary or advanced T-PLL (Phase II trial of combined immunochemotherapy with fludarabine, mitoxantrone, cyclophosphamide and alemtuzumab (FMC-alemtuzumab) in patients with previously treated or untreated T-prolymphocytic leukemia T-PLL2, responsible: Georg Hopfinger, Vienna/Austria)
- Protocol of primary or advanced B-PLL (Phase II trial of combined immunochemotherapy with fludarabine, cyclophosphamide and rituximab in previously treated or untreated B-prolymphocytic leukemia, B-PLL, responsible: Michael Herold, Erfurt, Germany.

Despite tremendous efforts by local and European wide study groups, the spread of trial information via ERIC and negotiations with companies and application for public funding, as previously described, it was not possible to overcome financial and regulatory requirements to launch these trials in the sponsoring countries so far. This has been disappointing for responsible investigators, the ERIC community and patients. Current rescue strategies are considering re-application to public funding opportunities and design of a register trial. Further ideas and strategies are currently discussed among ERIC investigators and will be topic of future ERIC meetings. Thus deliverable will be a continuous task of ERIC/WP beyond month 78.

**7.21d European survey on treatment modalities in CLL patients**

Under guidance of Vincent Levy (Paris), ERIC is performing a prospective multicenter international internet-based survey on clinical CLL practice. Aim of the project is the evaluation of treatment modalities and behaviour of clinicians in selecting diagnostic and treatment regimens for CLL patients in different situations of clinical disease presentation. As an assessment tool, 7 CLL specific case vignettes are used, which have been shown to be valid tools to assess the quality of clinical practice. The study is conducted among hematologists within Europe, Israel, South America and Australia, actively engaged in treating CLL patients, participating or not in clinical trials and from all types of medical structures (from private practice to large tertiary centres). Within the past 12 months the following steps have been accomplished:

After an initial phase of vignette quality assessment and control the study is currently running in second phase and evaluated as a large-scale European and International survey. Contacts to European and other countries interested in participation have been partially established via ERIC.
Responsible contact person for the project is Vincent Lévy (Centre d'Investigations Cliniques, Hôpital Saint Louis, Paris, France). This interesting and innovative deliverable is not yet fulfilled and will last until month 78 for being fully accomplished.

**7.22 Notarial institution/foundation of the ERIC association**

The notarial/legal foundation of the ERIC association according to German law has been a long lasting process, which has been complicated by legal requirements and the international structure of the ERIC board and association, which put additional challenges on the legal prerequisites and approval process. The goal of this deliverable is to give ERIC a legally acceptable structure and to introduce ERIC as an incorporated society in the German register of associations. This aim is accomplished in cooperation with a notary office, G. Brambring/M. Hermans in Cologne and in collaboration with the German local court in Cologne. After several revisions of the bylaws according to requests from the German court, adoption of the revised bylaws by the ERIC assembly in December 2008 in San Francisco and election of Professor Michael Hallek as the administrative officer of ERIC within Germany, the processing of the ERIC paperwork by the German court is ongoing. The German court has required additional notary-confirmed signatures from the ERIC board members Eva Kimby and Emili Montserrat, which are currently collected by the Cologne office. This step is expected to complete legal requirements to finally register ERIC as an association (e.V.) according to German law. Deliverable D7.22 is close to be fulfilled.

**7.23c Harmonization, consensus, online support for interpretation and collection of "problematic cases" in IGHV gene mutational analysis**

The "IGHV"-working group is dedicated to standardize, harmonize and teach the correct way of mutation-analysis of rearranged immunoglobulin heavy chain variable (IGHV) region genes in patients with CLL. In several trials the IgHV mutation status has been proven to be one of the most potent prognostic factors for treatment and long-term outcome in CLL patients. Therefore, the creation of consensus guidelines for IGHV mutational analysis in clinical practice and trials has been one of the major focuses of the IGHV working group. In some patients, the analysis or interpretation of IGHV sequences is very difficult and not immediately conclusive. The IGHV group has established a very successful online system, offering online consultation/support for centers having difficulties in interpreting IGHV sequences and collecting IGHV sequences from participating centers throughout Europe (see previous activity reports). In 2009 the IGHV group had the following activities:

1. Continuous web-based/online support for trouble-shooting in IGHV sequence analyses: Over the year 80 queries from several countries throughout Europe and the US were received.

Most frequently, "troubled" sequences included insertions and/or deletions or single unproductive rearrangements, which hindered complete alignment with IGHV germline sequences.

2. The IGHV group was collaborating with IMGT (International Immunogenetics Information System) in order to refine the programmed analytical tools for the automated IGHV sequence analysis and alignment with germline sequences offered by www.imgt.org (IMGT/V-Quest). With the implementation of new bioinformatic/programmed tools, the detection and denomination of insertions, duplications and deletions with the IMGT/V-Quest system has been improved tremendously. Clinicians/scientists using IMGT/V-Quest can now retrieve more comprehensive and detailed information about inserted/deleted or duplicated nucleotides, when analyzing an affected IGHV sequence case.
3. According to last year the "IGHV group" performed a very successful teaching workshop on IGHV mutational analysis in Thessaloniki (Greece) in September 24/25 2009, sponsored by the ELN/ERIC and industrial support. Again 60 physicians/scientists (25 applications had to be turned down!) from more than 15 countries participated in the two-day course about the methodology, sequencing, interpretation and reporting of IGHV analyses. The next educational workshop of the IGHV group for 2011 is planned to be carried out in Italy.
4. Following the very successful first book release (title: "Immunoglobulin gene analysis in chronic lymphocytic leukemia"), which was also supported by the ELN/ERIC, the IGHV working group is currently preparing another book about "biological diagnostic markers in CLL". It will include modern diagnostic tools, like the immunoglobuline analysis, MBL diagnostics, flow cytometry, microRNA analysis etc. and focus on the future clinical application and potential of such diagnostic parameters.

Other scientific activities of the group in future include the work on bioinformatic tools to improve the analysis of incomplete immunoglobuline VDJ rearrangements and the creation of an user alerting system for troubled immunoglobuline sequences in the IMGT/V-Quest system. Overall, the accomplishments of this prospering working group within ERIC provide long-term benefits and output for the general scientific community and will last beyond month 78.

**7.24c Harmonization and quality control of MRD diagnostics**

The MRD (minimal residual disease) working group under guidance of Andy Rawstron (Leeds, UK) focuses on continuous improvements and standardization of MRD analysis techniques in CLL, as described in earlier activity reports. Besides the ongoing online support provided by the management and maintenance of an ERIC-connected MRD web page (www.mrd-cll.org), the working group continues to work on the following goals:

- To develop a quality control system for MRD analysis which simplifies a sort of "screening" assay for routine MRD assessment in CLL

- To develop a standardized 6-colour flow cytometric assay running under the quality control aspects developed above.

Compared to 2008, ongoing activities of the working group in 2009 have not changed and concentrate on the following aspects.

- To determine optimal antibody combinations by investigating electronically manipulated data in 4/5/6-color formats
- To conduct dilution studies between European wide participating centers: representative data files were sent to Milano, Kiel & Barcelona and are under investigation
- To establish/re-develop a "rapid screening approach" of MRD by flow cytometry using the minimally required antibody combination for the highest number of correct MRD estimations (500 cases are tested so far, further tests are ongoing, this approach may be highly effective during treatment but response assessment usually requires a full MRD panel)
- To establish, evaluate and improve an MRD quality control data analysis scheme: First e-trial-results have been collected from 16 centres (of 31 registered, each centre has to process a given CLL case with a certain amount of residual CLL cells and denominate the number/percentage of detected CLL cells).
- Collection and review of difficult MRD cases, discussion and continuous online support.

The accomplishment of these tasks has to be continued under the auspices of ERIC beyond month 78. First results will be presented and discussed in the ERIC community in 2010.

**7.25c Harmonization and quality control of ZAP70 analysis in CLL**

ERIC/WP7 has initiated a "ZAP70-network" which is coordinated by Florence Cymbalista and Remi Letestu (both Paris/France). Overall goal is the development of a harmonized system of ZAP70 analysis and quality control tools, which can be recommended as a standardized approach for routine application. Several scientists from 10 different countries including Europe and Canada are collaborating in this network. Recent working steps of the ZAP70-network were based on the validation of previously established (electronic) flow data (first e-trial) and included the evaluation of established e-protocols by circulating "real" fresh patient blood samples between participating centers (second practical trial). As described in the last year activity report the deliverable has been fulfilled and reached the following goals:

- To develop a validated standardized method for ZAP70 analysis applicable to whole blood
- To optimize the control of fluorescent background and other parameters influencing data quality
- To optimize the method using newly available antibody reagents (i.e. ZAP70-antibody of the SBZAP clone)

Results were presented to the ERIC community in 2008. However, the publication of results is pending. Future work will be focussed on the comparison of current results to other ZAP70-assessing techniques like polymerase-chain reaction and the further evaluation for routine assessment strategies.

**7.26c Collection & investigation of functional aspects of p53 mutation**

The "p53 working group" within ERIC comprises a very active subgroup of scientists/clinicians from 9 European countries interested in p53 (a tumor suppressor inactivated in several tumor subtypes, also in a subgroup of CLL patients with very poor prognosis) related translational and basic research.

Within the past year the following activities have been accomplished:

- A large series of 268 different p53 mutations in 254 patients has been collected and characterized. Mutations have been identified as mostly missense mutations (74%), followed by deletions/insertions (20%), nonsense mutations (4%) and affecting splice sites (2%). The most frequent amino acid positions of mutations have been determined (i.e. AA 175, 179, 248, 273). Detailed results were published by the p53 working group in several journals or at ASH (see Annex Section 3, WP 7-2).
- Further focus of the p53 working group is to retrieve clinical correlations between p53 mutations and treatment outcome and longterm prognosis in clinical trials. Therefore, the group is promoting "p53 trials", where refractory CLL patients with or without affected p53 gene loci can be included. One example is the CLL2O trial by the German CLL study group (phase II study of subcutaneous alemtuzumab combined with oral dexamethasone, followed by alemtuzumab maintenance or allogeneic stem-cell transplantation, in CLL associated with 17p deletion or refractory to fludarabine) or the meanwhile closed CLL206 NCRI trial (phase II study investigating the role of alemtuzumab (iv or sc) plus methylprednisolone in CLL patients with p53 deletion)
- A "p53 workshop" for ERIC members and interested non-members to encourage scientific exchange and discussion on p53-related topics in CLL was performed in context of the ERIC meeting at the EHA congress in Berlin, June 4, 2009. The workshop was very well anticipated and visited by ca. 50 participants. Due to its success, the working group is planning to set up p53-workshops on an annual basis, if respective funding is available.

The deliverable has been successfully established and produced publishable results. However, due to the biological and clinical high relevance of p53-aberrations for CLL treatment outcome and prognosis, the deliverable will be an ongoing and long-lasting "task-force" of ERIC.

**7.27c Phase I/II trial platform for the treatment of rare subentities T-PLL and B-PLL**

With the phase I/II trial platform launched in deliverable 7.20 focusing on the so far NOT successfully activated studies on

- the reatment of primary or advanced T-PLL (Phase II trial of combined immunochemotherapy with fludarabine, mitoxantrone, cyclophosphamide and alemtuzumab (FMC-alemtuzumab) in patients with previously treated or untreated T-prolymphocytic leukemia T-PLL2, responsible: Georg Hopfinger, Vienna/Austria),
- the treatment or advanced B-PLL (Phase II trial of combined immunochemotherapy with fludarabine, cyclophosphamide and rituximab in previously treated or untreated B-prolymphocytic leukemia, B-PLL, responsible: Michael Herold, Erfurt, Germany,

Deliverable 7.20 covers contents of 7.27, please see there for details. The creation of a common diagnostic platform on prolymphocytic diseases in Germany with a new central reference laboratory in Cologne (responsible: Dr. Marco Herling, University of Cologne) has been one step forward within the past year. First diagnostic samples have been received and processed by the Cologne laboratory. Other European diagnostic laboratories interested in PLL-diagnostics have shown their interest and willingness to collaborate for future European wide trials on PLL-related diseases. Deliverable D7.27 is ongoing beyond month 78.

**7.28 Recommendations for (allogeneic) stem cell transplantation (SCT) in T prolymphocytic leukemia (T-PLL)**

About 2 years ago WP 7/ERIC and WP14 ("Stem Cell Transplantation") established a European platform for transplantation studies as a joint effort via ERIC in cooperation with the CLL subcommittee of the EBMT (European group for blood and bone marrow transplant, responsible subcommittee chairman: Peter Dreger, Heidelberg/Germany). Both groups have been collaborating to define "recommendations for (allgeneic) stem cell transplantation (SCT) in T prolymphocytic leukemia (T-PLL)". The final edition of the recommendations has been published on the ERIC webpage (www.ericll.org), as previously described (deliverable partially fulfilled). Since it has been impossible under the current regulatory framework to perform an international prospective trial on stem cell transplantation in T-PLL (see deliverable 7.27), the EBMT has established a register trial, were transplanted T-PLL patients can be registered and be evaluated retrospectively. In addition to retrospective patient registration and analysis, 23 European centers have agreed to register T-PLL patients prospectively, prior performance of their transplantation, to allow early data collection and evaluation. The trial is supported by ERIC and first data status and results of 13 autologous transplanted patients, 52 allogeneic transplanted patients and 27 prospectively registered patients were discussed at the latest ERIC meeting in New Orleans. Deliverable 7.28 will stay a long-lasting activity of ERIC/WP7 with fulfillment beyond month 78. Main goal of the activity is to intensify networking between WP7 and WP14 as well as the exchange and spread of expertise and trial efforts on stem cell transplantation in CLL.

### 7.29 Improvement of long-term follow-up of CLL patients in European trials

One of the recently launched ERIC projects is the implementation of a new trial system to collect long-term follow-up data in randomized phase III trials within Europe. Previously published phase III trials in CLL show median observation times ranging from 22 to 41 months, most of the trials exhibit only around 2 years of observation time. One reason for the unacceptable availability of long-term follow up data in clinical trials is the limited affordability for non-commercial study groups to accomplish long-term follow up data collection, management and evaluation. The ERIC trial system is planned to be conducted as a web-based repository, further details have been described in the last activity report. The project is aiming to collect long-term data including the following items: the date of the annual follow-up, status of the patient (alive/dead), disease status (CR, PR, SD or PD), incidence of secondary diseases, further therapies and responses and death related informations. Responsible leaders of this project are Peter Hillmen (Leeds, UK) and Barbara Eichhorst (Cologne, Germany). Within the past year negotiations with companies have been carried out to set up legal, ethical and practical requirements for the project. In collaboration with a CRO company, ICON, first steps to realize the follow up trial system have been undertaken and were presented and discussed at the last ERIC meeting in New Orleans. Currently, the group is working on solutions for the complex ethical situation regarding approval to acquire long-term follow up data on a European level, the setup of the remote trial system available for multiple countries, the governance of data flow, management and the overall system, and the maintenance of long-term confidence of investigators participating in the long-term follow-up system. Deliverable 7.28 is ongoing beyond month 78.

### 7.30 Promotion of ERIC for the sustainability of WP7

The main goal of ERIC is to promote the development and sustainability of clinical, translational and basic research activities on CLL. To accomplish this goal on a long-term basis and sustain ERIC as a European and world-wide recognized platform for CLL research, in 2010 the ERIC Board and Subcommittees are focusing on the following topics:

- to consolidate a professional secretariat office in Barcelona which allows further improvement of the structure and administrative organisation of ERIC.
- to consolidate the different working groups/subcommittees by facilitating the organization of specific scientific meetings and
- to facilitate effective transversal collaboration between the different working groups.
- to set up an annual retreat commencing in 2010 where leaders of the working groups/subcommittees together with the Board can establish long-term strategies/goals plus set a strategic research agenda for the coming year.
- to promote new projects in different research areas of interest in CLL.

- to improve the website by creating a slide bank consisting of powerpoint presentations or other scientific material provided by the different working groups and speakers during ERIC meetings.
- to create an educational link through the website (ie, publications of difficult clinical cases)
- to raise future funding sources from European institutions and pharmaceutical companies.
- to establish permanent communication with different professional societies (European Hematology Association, European Bone Marrow Transplantation) and to disseminate information to them.
- to encourage publications aimed at the above mentioned aims.

Deliverable 7.28 is ongoing long-term effort beyond month 78.

*Deviations from the work program and corrective actions taken: identify the nature and the reasons for the problem, identify contractors involved*

None

**Deliverable List WP7, 2009**

| Deliv. No. | Deliverable Name | Date due | Actual/Forecast delivery date | Estimated indicative person months | Used indicative person months*) | Lead contractor |
|---|---|---|---|---|---|---|
| **WP7** | **CLL** | | | | | |
| **7.5** | Regular WP meetings | 54,59,66 | 67, 73, 80 | 0 | 2 | Hallek |
| **7.6** | LP reports to NMC regarding structure, trial activities and integration of national leukemia trial groups (1 page, bullet point style) | 54,66 | 84 and beyond | 0 | 2 | Hallek |
| **7.8e** | Treatment of early stage, high risk CLL with FCR -continued | 72 and beyond | 78 and beyond | 0 | 6 | Hallek |
| **7.9e** | Exchange of study protocols of open clinical trials, information on structure and trial activity of national CLL trial groups | 72 and beyond | 78 and beyond | 0 | 4 | Hallek |
| **7.10c** | Common data safety monitoring boards in clinical trial on CLL in Europe | 72 and beyond | 78 and beyond | 0 | 1 | Hallek |
| **7.11e** | Web-based information- and communication services on CLL refined and up-dated | 72 and beyond | 78 and beyond | 0 | 5 | Hallek |
| **7.12d** | Assess and create new guidelines for diagnostic and therapeutic management of CLL | 60 | 68 | 0 | 0 | Hallek |
| **7.16e** | Harmonisation of clinical study protocols and trial accessories between national CLL study groups | 72 and beyond | 78 and beyond | 0 | 4 | Hallek |
| **7 17c** | First proposal of definition, standardization and harmonization of cytogenetic analysis in CLL | 66 | 66 | 0 | 2 | Stilgenbauer |
| **7.18c** | First proposal of definition, standardization and harmonization of ZAP 70 analysis in CLL | 66 | 66 | 0 | 2 | Hallek |

| | | | | | | |
|---|---|---|---|---|---|---|
| **7.19d** | Evaluation and follow-up of patients with advanced CLL treated with FCR/FC – progress report | **66** | 66 | 0 | 5 | Hallek |
| **7.20d** | European platform for phase I/II trials | 72 and beyond | 78 and beyond | 0 | 3 | Levy |
| **7.21d** | European survey on treatment modalities in CLL patients | 72 and beyond | 78 and beyond | 0 | 3 | Levy |
| **7.22** | Notarial institution/foundation of the ERIC association | 60 | 68 | 0 | 2 | Hallek |
| **7.23c** | Harmonization, consensus, online support for interpretation and collection of "problematic cases" in IGHV gene mutational analysis | 72 and beyond | 78 and beyond | 0 | 5 | Ghia |
| **7.24c** | Harmonization and quality control of MRD diagnostics | 72 and beyond | 78 and beyond | 0 | 4 | Hallek |
| **7.25c** | Harmonization and quality control of ZAP 70 analysis in CLL | 66 | 72 | 0 | 3 | Cymbalista |
| **7.26c** | Collection & investigation of functional aspects of p53 mutation | 72 and beyond | 78 and beyond | 0 | 5 | Stilgenbauer |
| **7.27c** | Phase I/II trial platform for the treatment of rare subentities T-PLL and B-PLL | 72 and beyond | 78 and beyond | 0 | 4 | Hallek |
| **7.28** | Recommendations for (allogeneic) stem cell transplantation (SCT) in T prolymphocytic leukemia (T-PLL) | 72 and beyond | 78 and beyond | 0 | 4 | Dreger |
| **7.29** | Improvement of long-term follow-up of CLL patients in European trials | 72 and beyond | 78 and beyond | 0 | 4 | Hallek |
| **7.30** | Promotion of ERIC for sustainability of WP7 | 72 and beyond | 78 and beyond | 0 | 2 | Montserrat |

*) if available

## List of milestones WP 7, 2009

| Milestone No. | Milestone Name | Date due | Actual/Forecast delivery date | Lead contractor |
|---|---|---|---|---|
| **WP 7** | **CLL** | | | |
| **7.5 and 7.23 c** | Spread of excellence throughout by high-quality scientific meetings, educational workshops and an ERIC lauched educational book release | 54,59,66 | 78 and beyond (ongoing) | Hallek |
| **7.12** | Final release and publication of new guidelines for diagnostic and therapeutic management of CLL | 60 | 60 | Hallek |
| **7.16** | Harmonization of the CLL7 trial between the German and French CLL study groups as example for future harmonization activities | 72 and beyond | 78 and beyond (ongoing) | Hallek |
| **7.17c** | First proposal of definition, standardization and harmonization of cytogenetic analysis in CLL | 66 | 66 | Stilgenbauer |
| **7.19d** | First Evaluation and successful report of patients with advanced CLL treated with FCR/FC | 66 | 71 | Hallek |
| **7.21d** | European survey on treatment modalities in CLL patients successfully launched and test vignettes validated | 72 and beyond | 78 and beyond (ongoing) | Levy |
| **7.22** | Notarial institution/foundation of the ERIC association | 60 | 68 | Hallek |
| **7.23c** | Continued and improved online support for interpretation and collection of “problematic cases” in IGHV gene mutational analysis | 72 and beyond | 78 and beyond (ongoing) | Ghia |

| Milestone No. | Milestone Name | Date due | Actual/Forecast delivery date | Lead contractor |
|---|---|---|---|---|
| **7.22** | Notarial institution/foundation of the ERIC association | 60 | 68 | Stilgenbauer |
| **7.28** | Successful accomplishment of recommendations for (allogeneic) stem cell transplantation (SCT) in T prolymphocytic leukemia (T-PLL) | 72 and beyond | 66 (first part), 78 and beyond (prospective part) | Dreger |

**Section 3: Consortium management**

The European Research Initiative on CLL (ERIC/WP7) is a continuously growing institution, which is more and more anticipated and recognized in Europe and world wide. 2009 was the prime time for ERIC as a Scientific Working Group of the European Society of Hematology (EHA): The Scientific Workshop offered by ERIC at the annual EHA congress was attracting increasing numbers of clinicians and scientists and stood out through high-ranked and up-to date speakers and presentations. ERIC/WP7 is continuously active in the education/spread of excellence on clinical and scientific topics in CLL, predominantly by the p53- and IGHV-working groups. Besides the harmonization of important diagnostic procedures in CLL (ZAP70 and MRD), evaluation of first clinical trial data on FCR first-line treatment and the p53 mutation analyses have been most successful in 2009. With the notarial registration of ERIC, the association is currently gaining legal format in Germany.

With the new chairman Professor Emili Montserrat and complete transfer of the ERIC office to Barcelona in 2010, fundraising activities and infrastructural improvements will be an important focus in the upcoming months. Overall ERIC/WP7 continuous to be a strivingly active and well prospering group within the ELN and EHA, dedicated to the improvement of clinical and basic science and treatment of CLL patients in- and outside of Europe.

**Section 4: Other Issues**

Ethical issues - none

Competitive calls - none

**Section 5: WP-Performance**

| Performance indicators | Status |
|---|---|
| Number of clinical trials started and/or completed | 5 |
| Number of patients recruited into clinical trials | >1500 |
| Number of patients included into registries | n.a. |
| Improved predictive, prognostic or quality of life assessments | ~1500 |
| Degree of harmonization of trials | Well established |
| Number of SOPs and consensus papers | 5 |
| Number of publications | 39 |
| Number of meetings | 3 (+1) |
| Number of meta-analyses | 0 |
| Number of accredited trials | 2 |

**MDS (WP 08)**

*Objectives and starting point of work at beginning of reporting period*

The collaborators of this network established a European platform for integration of MDS trial groups and their interdisciplinary partners. This infrastructure prevents European fragmentation and augments scientific interaction and collaboration. The platform communicates and decides about diagnostic standards, prognostic tools, new molecular targets for new treatment modalities, and guidelines for various treatment approaches. Clinical trials are prepared and perform on a European scale. In addition, a MDS registry has been developed to determine incidence and disease patterns.

The starting point of work at beginning of the reporting period was as follows.

We had interacted with many different Workpackages of European LeukemiaNet for integrated activities: e.g. Diagnostics WP10 (immunophenotyping in diagnostic guidelines in MDS), Cytogenetics WP11 (cytogenetics in diagnostic guidelines in MDS), AML WP5 (development of a common prognostic score), Minimal Residual Disease WP12 and Gene Profiling WP13, for translational studies. WP-MDS interacted actively internationally with the EORTC Leukemia Group, with the international MDS Foundation (several members of the steering committee are board members of the MDS Foundation), with the European Hematology Association (EHA), with European School of Hematology (ESH), and with numerous pharmaceutical companies which actively support the MDS registry and other clinical or translational projects. Knowledge like new treatment modalities and diagnostic and therapeutic guidelines were disseminated by meetings and presentation on the ELN website.

Close cooperation with numerous European MDS study groups resulted in much progress on the development of a European MDS Registry Study. All planned deliverables for this project have been fulfilled and patient inclusion started in April 2008. The first interim analysis of the EUMDS registry has been performed on the first 400 registered patients and these data have been presented at the 2009 ASH meeting.

Furthermore, new initiatives were taken like the study entitled “Prognostic significance and longitudinal assessment of patient-reported quality of life and symptoms in intermediate II and high risk myelodysplastic syndromes (MDS). An international multicenter observational study”. The aim of this study is to obtain additional key data to further facilitate clinical decision-making in MDS patients. This initiative fits very well in our deliverables on developing a frailty index for treatment decision-making for older patients with MDS or AML. Therefore, this study proposal is incorporated in our LeukemiaNet activities.

*Progress towards objectives – tasks worked on and achievements made with reference to planned objectives*

**8.5 Regular WP meetings**

- Annual ELN Symposium, MDS WP meeting, Mannheim, 3 Feb. 2009; 95 participants from EU
- European MDS Registry project, Steering Committee meeting, Mannheim, Feb. 3, 2009; 16 participants
- MDS symposium in Patras, 6th May, 2009: steering committee meeting of European low risk MDS Registry" project: 16 participants
- MDS symposium in Patras, 7th May, 2009: ELN MDS meeting on therapeutic guidelines; attendance steering committee WP8; 16 participants
- MDS Iron Chelation Think Tank during annual EHA meeting, Berlin 3 June 2009: 120 participants
- Operational team meeting of European MDS Registry" project ,Amsterdam-Airport – July 01, 2009, 15 participants
- European MDS Registry" project, Steering Committee and operational team meeting, London, September 25, 2009; 26 participants
- Eugesma Cost Action (BM 0801) second Workshop meeting "European Genetic and Epigenetic studies in MDS and AML in collaboration with 5th ELN Workshop "Genetics in MDS", 12-13 October 2009, Hannover, Germany, 45 participants
- MDS Work Package 8 steering committee meeting during the ESH-MDS postgraduate training course Mandelieu, October 24, 2009; 18 participants
- The second Workshop on flow cytometry in MDS, 30-31 Oct 2009 in Munich, Germany (host: Dr. W. Kern; chair: AA van de Loosdrecht); 70 participants
- ELN Workshop at the Annual ASH meeting New Orleans: presentation of progress of projects within MDS WP8

**8.6 LP reports to NMC regarding structure, trial activities and integration of national trial groups (1 page, bullet point style)**

LP reports have been sent to NMC as requested.

**8.49b Maintenance of the MDS WP8 section of ELN website**

The MDS WP8 section of ELN website has been updated on a regular basis. A considerable number of documents have been prepared and are presented on the LeukemiaNet website. In e-mails towards participants, links to the website pages have been included.

**Diagnostic Guidelines**

**8.25b Yearly update of the guidelines for diagnostic standards in MDS and presentation on the ELN website**

The MDS guidelines were revised on the basis of the new WHO classification, 4th edition 2008 and presented on the ELN website.

E. Hellström Lindberg and A. Porwit prepared a revised version of the guidelines: updated according to WHO and revised regarding flowcytometry, according to minutes from the previous meeting. The document was sent to all participants of the MDS WP. Many comments were received by email and E. Hellström Lindberg summarized the major comments during the Mannheim ELN MDS WP 8 meeting. The guidelines should include a work-up of suspected MDS or mixed MDS/MPNs. It was proposed and agreed to keep the MDS and AML guidelines separated because of the new WHO classification. Both IPSS and WPSS will be included in the guidelines (WPSS is less validated compared to IPSS). It was proposed and agreed to remove the WHO classification 2001. E. Hellstrom-Lindberg prepared a new version of the guidelines using the comments of the MDS WP participants. This new version will be published on the ELN website and evaluated after one year. It was suggested to add a section on the website were participants may comment on the guidelines. In addition, it was proposed to add a summarized version of these guidelines to the therapeutic guidelines which is in preparation for publication.

The proposals for an ELN standardization protocol of Flow Cytometry in MDS have been presented during the ELN MDS WP 8 meeting in Mannheim, February 3, 2009

The following proposals were presented:

- Potential impact of flow cytometry in MDS.
- Proposed antigens of major importance in flow cytometry in MDS.
- Proposed marker combinations for flow cytometry in MDS.
- Proposed Concensus [%] on aberrant antigen expression in MDS.
- Number of aberrancies in the myeloid lineage as assessed by flow cytometry.
- Pathological control samples for flow cytometry: defining specificity towards MDS.

The working group on flow cytometry in myelodysplastic syndromes convened twice in 2009; in May in Patras and in October in Munich 2009. After its start in Amsterdam in 2008 the WP focussed on minimal flow cytometric criteria in the diagnosis of MDS. The group defined in its first publication (see Annex Section 3 WP 8-2) the role of flow cytometry not only in the diagnosis but also its contribution in classification and prognostification of MDS. This report describes in detail a standard flowcytometric method dealing with sampling handling, use of antibodies as well as defining antigens involved in dyspoiesis primarily concerning the erythroid, granulocytic and monocytic cell lineages. In 2009, the second workshop (MLL Munich Lab; chair: AA van de Loosdrecht; co-chair: W. Kern) discussed in more detail the immature and maturing granulocytic and monocytic cell lineages to define those antigens expressed during differentiation which might be of relevance to distinguish normal from dysplastic hematopoietic cells. This critical multidimensional approach is needed to translate potential aberrant profiles to a numerical scoring system. A newly defined scoring system could be instrumental for diagnostic and prognostic purposes. The latter will be the focus of the third international flow cytometry meeting of the WP8 on flow and MDS which will be held in London late

2010 (co-chair: R. Ireland). The results of the second meeting are being processed in a document which will be submitted to a journal in 2010. WP10 will be involved in the planned meetings.

**8.25c Incorporation of Cytogenetics in diagnostic guidelines in MDS/AML**

In the diagnostic guidelines a comment is included on the independent predictive value of IPSS cytogenetics. In addition, in October 2008 the 4th workshop "Genetics of MDS " took place together with Cytogenetics WP11.

The joint meetings of ELN WPs 8–MDS and 11–Cytogenetics are dedicated to the mutual presentation of the most recent data on genetic mechanisms underlying MDS on the one hand and on therapeutic developments based on genetic findings on the other.

After more than 30 years from its discovery the molecular background of 5q- is unravelled and it is now targeted by specific treatment. Arrays technologies are expected to provide us with new insights in the biology, and hopefully clinical management of MDS, including refinement of prognostic scoring. Specific polymorphisms of genes encoding DNA repair proteins and/or enzymes for detoxification may clarify mechanisms of origin of MDS. Constitutional genetic conditions, such as trisomy 8, neurofibromatosis 1, dyskeratosis congenita are helpful to understand development of MDS.

During the workshop a session took place in which joint research programs were discussed. Results of the workshop are relevant for further updating the guidelines.

**8.26b Integration of diagnostic guidelines in MDS and secondary AML and subsequent annual updates**

It has been decided not to integrate the diagnostic guidelines in MDS and sAML (see: 8.25b).

**Therapeutic Guidelines**

**8.27b Yearly update of the guidelines for therapeutic procedures in MDS and presentation on the ELN website**

The steering committee discussed the issue of the indication of lenalidomide for 5q- MDS. We reached a consensus that this indication can be recommended with a clear paragraph on the potential risk for progression of low risk MDS to more advanced stages and secondary AML, a clear statement that the EMEA has not approved this indication and a statement that the patient should be informed about this risk. The final version of the manuscript entitled "Evidence- and consensus-based guidelines for the therapy of adult primary myelodysplastic syndromes - A statement from the European LeukemiaNet" is in its final stage The draft will be circulated as soon as possible and everybody will pay special attention to the lenalidomide paragraph. The manuscript will be submitted to Blood in 2010. The therapeutic guidelines are presented on the ELN website.

**8.27c Web based scenario analysis by the experts for development of evidence and consensus based guidelines for therapy of MDS**

See attachment 8.13 with background and the aims of the project.

**8.29 Development of a web-based training program using virtual patients to exercise the therapeutic guidelines and supervised by experts and European clinicians**

The website for the training program on the therapeutic guidelines for MDS is ready. http://mds.haematologica.org**.**

A report of the web based training program is foreseen in 2010.

**Trials**

**8.31b Yearly update of a list of all trials by MDS study groups in Europe**

We updated the list of MDS trials presented on the LeukemiaNet website.

We asked all participants of the MDS WP to inform us about new studies on MDS,

and to indicate which studies are closed. The updated list will be sent to all participants of the MDS WP and is presented on http://www.leukemia-net.org/content/e58/e3956/e3957.

**New List of trials and studies**

(Note : Ongoing studies listed in the old list are integrated in the new list)

**Interventional studies**

- MDS AlloSCT-Clofarabine (active) : Allogenic stem cell transplantantion with Clofarabine, Busulfan and ATG
- MDS Amifostine (temporary halt) : Treatment with or without Epoetin Alfa
- MDS Antithymocyte Globulin-Cyclosporine (temporary halt) : A randomized trial comparing ATG + CSA with best supportive care
- MDS Azacitidine-Epoetin Beta (active) : Azacitidine combined to Epoetin Beta in low-risk and intermediate-1 MDS patients
- MDS Azacitidine-Epoetin Beta II (active) : Efficacy and safety of the treatment in MDS patients
- MDS Azacitidine (active) : Maintenance with Azacitidine in patients achieving complete or partial remission after chemotherapy
- MDS Bevacizumab (active) : A trial of Bevacizumab in patients with excess of marrow blasts
- MDS Clofarabine (active) : Clofarabine in combination with a remission induction regimen
- MDS Combi-Chemo-Idarubicin (temporary halt) : Combination chemotherapy with or without Idarubucin in patients with MDS
- MDS Combi-Chemo (active) : Combination chemotherapy with or without Gemtuzumab or Tipifarnib in high-risk MDS
- MDS Cytarabine-Daunorubicin (temporary halt) : A combination therapy in treating children with newly diagnosed MDS
- MDS Darbepoetin Alpha I (Active) : Darbepoetin in low- and intermediate-1 risk MDS patients with anemia
- MDS Darbepoetin Alpha II (active) : A phase II study of Darbopoetin Alpha in MDS
- MDS Decitabine (active): A phase II study in patients with chronic MDS
- MDS Eltrombopag (active): Treatment of thrombocytopenia in patients with advanced MDS
- MDS Erlotinib (active): A phase I/II trial of Erlotinib in high risk MDS
- MDS Erythropoetin (active): Comparison between Erythropoietin and therapy containing Acid 13-Cis-Retinoic and vit. D3, in patients without excess of blasts

- MDS Lenalidomide I (active): Lenalidomide vs Placebo in RBC-dependent patients with low- or intermediate-1 risk MDS with 5q-
- MDS Lenalidomide II (pending): A phase II tial to assess the efficacy Lenalidomide with or without Erythropoietin and GSC factor in low- and intermediate-1 MDS
- MDS Lenalidomide III (active): A study of efficacy and safety of Lenalidomide combined to escalating doses of chemotherapy in intermediate-2 or high risk MDS
- MDS Lintuzumab (temporary halt): Monoclonal antibody therapy in treating patients with primary MDS
- MDS Romiplostim I (active): A study evaluating the safety and long term dosing of Romiplostim in thrombocytopenic patients with MDS
- MDS Romiplostim II (active): A study evaluating the efficacy and safety of Romiplostim in patients with low or intermediate-1 MDS
- MDS Stem Cell Transplant I (temporary halt): Donor stem cell transplant with or without chemotherapy in children with primary MDS
- MDS Stem Cell Transplant II (active): A study of reduced stem cell transplantation in poor risk MDS with Fludarabine, Busulphan and Thymoglobulin
- MDS Valproic-Lenalidomide (pending): Determination of efficacy and tolerability of the combination of Valproic acid and lenalidomide
- MDS Velcade (active): Phase II study of PS341 (Velcade) in MDS
- MDS Velcade-Zarnestra (Active) : Bortezomib and Tipifarnib in MDS
- MDS Vorinostat (active): Vorinostat in combination with low dose Ara-C in patients with intermediate-2 or high risk MDS

**Observational Studies**

- MDS Biomarkers: Molecular and functional characterization of bone marrow function in patients with MDS and secondary disorders of hematopoiesis
- MDS Cytogenic Analysis: A study for epidemiology and characterization of MDS and juvenile myelomonocytic leukemia
- MDS European Registry: A prospective registry for newly diagnosed patients with MDS of low and intermediate-1 IPSS
- MDS Quality of life I (active): Effects of anemia in elderly MDS patients, regarding quality of life and cardiac function
- MDS Quality of life II (active): Assessment of patient-reported quality of life and symptoms in patients with high risk MDS

**8.32 Update list of new drugs (phase I, II, III)/treatment modalities potentially interesting for treatment of MDS patients, with involved groups/scientists/pharmaceutical companies/potential translational activities**

Every year an inventory on new drugs/treatments is made, by asking all partcipants of the MDS WP for input regarding this issue. Furthermore, new drugs/treatments is discussed at several MDS WP8 meetings. If necessary an investigator meeting on a particular new drug/treatment is organized.

**8.51d Frailty index for treatment decision-making for older patients with MDS or AML. Full evaluation based on the 140 pts that are planned (=3 groups: go- go/induction, slow-go/low-dose DAC, no-go/sole BSC)**

The comprehensive geriatric assessment was performed in 195 patients in Freiburg, Düsseldorf and Dresden aiming at exploring prognostically important assessment instruments and eventually defining a frailty index. Multicenter evaluation was feasible. After a median of 40 days after initial diagnosis, 75 patients receiving induction chemotherapy, 73 patients treated within decitabine studies and 47

receiving best supportive care only, were assessed. After a median of 6 months a second assessment was realizable in 89% of survivors (n=134). Multivariate analysis revealed "Activities of daily living" (ADL) and fatigue measured with the QLQ C30 questionnaire as highly prognostic for survival in the entire patient cohort. Follow-up assessments revealed that no severe deterioration in geriatric and QOL (quality of life) domains occurred within 6 months under treatment. Statistical calculations are currently being performed to define a risk score. Final publication of data is planned for 2009.

**8.52 Define shared criteria of response for AML and MDS, including the Cheson criteria, and present on ELN website**

High grade MDS is usually treated with intensive chemotherapy in study protocols for acute myeloid leukemia. Therefore these patients follow the same response criteria as in AML. The remaining patients follow the response criteria as defined by Cheson.

**8.55 Define common core data set in AML and MDS in cooperation with EBMT, and present on ELN website**

The Med A/B forms of the EBMT have been harmonized according to consensus criteria developed within the respective EBMT Working Parties.

**MDS registries**

**8.54 Prospective, non-interventional multicenter European MDS Registry (IPSS low and intermediate-1)**

Summary from the investigators meeting in London, September 25, 2009. The statistician, Dr Alex Smith, presented the planned interim analysis on the first 400 registered patients during this meeting. It is clear that the quality of the data is very high and informative. The registry is collecting a unique data set which will prove to be very valuable for future questions and studies as well. The abstract of this analysis has been accepted for presentation at ASH 2009. The results of the first interim analysis will be used to propagate the enthusiasm of the collaborators and sites by national meetings. The effect is already clear because the accrual has risen again to a monthly accrual of almost 50 patients, leading to an accrual of 560 patients in September 2009 (650 per 31 December). This means that the future and extension of the registry has to be discussed in 2010. The first step is to extend the follow-up time from 2 to 5 years; the second step will be to increase the number of patients to 2,000 as originally planned. Negotiations with Novartis will start as soon as we will have reached 700 patients (February/March 2010). We should consider extending the support to a consortium support. We should also seriously consider to merge the low risk MDS- registry with the high risk registry if the support will come from a consortium or other funding (outreach programs, FP-EU programs).

**8.73-8.79 A prospective, non-interventional multicenter European high-risk MDS Registry**

The steering committee discussed the progress of the development of this registry during the ELN annual meeting in Mannheim 2010. The study protocol has been developed and agreed upon during the meeting (will be available on the website in 2010). A consortium of sponsors are being invited to support the study. The CRFs and the web-based reporting will be adapted from the low risk registry system developed by the University of York. Merging of the low risk and high risk registries is foreseen after completion of the low risk MDS registry project as described in 8.54. The twelve registries of the low risk MDS study are expected to participate and 6 additonal countries have expressed their interest in this study (Portugal, Poland, Belgium, Russia, Israel and Switzerland). Canada will join as a nonEuropean partner as well.

**Translational research**

**8.57 Identification of genetic lesions in MDS using high resolution SNP-arrays**

Dr J. Jansen presented the progress of the project: "Novel genetic lesions in myelodysplastic syndromes (MDS) and myeloproliferative syndromes MPS) and MDS/MPS" in the steering committee meeting during the ESH MDS postgraduate course in Mandelieu (see: meetings)

Several novel mutations have been identified in MDS and MPS such as TET-2 mutations in MDS and JAK-2 mutations in MPS. These mutations are not mutually exclusive: TET2 mutations were also reported by Delhommeau & Vainchenker et al in JAK2 positive MPD. Both mutations are early events in the pathogenesis of myeloid malignancies. Mutations are acquired during development of disease. The group agreed to prepare a grant application on this topic to HEALTH-2010-2.4.1-8: Predicting individual response and resistance to cancer therapy.

**8.64 Development of a mouse MDS model**

The results from this research are described in the attached publication entitled "BCL-2 and Mutant NRAS Interact Physically and Functionally in a Mouse Model of Progressive Myelodysplasia" (see Annex Section 3, WP 8-25).

**8.61a/b Cooperation with WP13. An International Multi-Center Microarray Study for the Molecular Classification of Leukemia. Definition of functional sub-classes and define implications for future diagnostic guidelines MDS/AML**

The so called "MILE study"is a collaboration with WP13. The central morphology review was completed and a manuscript, acknowledged to LeukemiaNet, is submitted for publication. The manuscript is entitled "Microarray classification of myelodysplastic syndrome (MDS) identifies subgroups with distinct clinical outcomes and identifies patients with high risk of AML transformation". More samples will be accumulated for expression studies and these will contribute to a validation set.

**8.80 and 8.80a: Iron Pathophysiology and imaging of iron overload: side studies of the low risk MDS registry study.**

The protocol has been finalized after discussions in the steering committee in May 2009. The contract of the sponsor has been signed in October 2009. Collection of necessary samples has already been performed in m ore than 150 patients (total goal: 300 patients). The imaging protocol has been finalized and it has been sent to the sponsor for approval.

**8.81: Cytomorphology side study of the low risk MDS registry study.**

It has been decided to review 10% of the cytology of histology samples by a central commission (chair: Dr Ulrich Germing from Düsseldorf) consisting of 5 experts and 5 general (nonacademic) cytologists/pathologists). A two-day central review meeting is planned in 2010. The protocol of this study has been discussed and approved in the steering committee.

**8.82: Geriatric assessment side study of the low risk MDS registry study.**

The CRFs of the low risk MDS registry study contain data on quality of life (Euro QoL questionnaire or EQ5D) Karnofsky score, Body mass index, and co-morbidity which allow to calculate the Sorror co-morbidity index. The EQ5D has been reported in 322 of the 400 patients of the first interim analysis. Dr Reinhard Stauder from Innsbruck, Austria, the project leader of the geriatric assessment substudy, presented the data at the Mannheim ELN meeting 2010. An abstract with the assessment at registration will be submitted for EHA 2010 and a second abstract is foreseen after the second interim analysis which will provide information on QoL and co-morbidity during follow-up. This analysis will be submitted to ASH 2010.

**Table 8.1**: List of deliverables WP 8: **New deliverables list covering months 61 – 78**

| **WP 8** | **MDS** | | | | | |
|---|---|---|---|---|---|---|
| **Deliv. No.** | **Deliverable Name** | **Estimated indicative person months** | **Responsible lead participant/ investigator** | **Nature** | **Dissemi-nation level** | **Delivery/ Achieve date,** *Month* |
| **8.5** | Regular WP meetings | 2,5 | De Witte | R | PP | 65, 72,74 |
| **8.6** | LP reports to NMC regarding structure, trial activities and integration of national trial groups (1 page, bullet point style) | 1,5 | De Witte | R | RE | 66, 78 |
| **8.49b** | Maintenance of the MDS WP8 section of ELN website | 1 | De Witte | www. R | PU | 66, 78 |
| | **Diagnostic Guidelines** | | | | | |
| **8.25a** | Yearly update of the guidelines for diagnostic standards in MDS and presentation on the ELN website | 2 | Hellström-Lindberg | O | PU | 73 |
| **8.25b** | Integration of immunophenotyping in diagnostic guidelines in MDS | 2 | Hellström-Lindberg Van de Loosdrecht | O | PU | 73 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **8.25d** | Workshop at 7th May, 2009 in Patras: Implementation of consensus protocol on Immunophenotyping in MDS | 2 | Van de Loosdrecht | R | PP | 65 |
| **8.25e** | The second Workshop on flow cytometry in MDS- will be held on 30-31 Oct 2009 in Munich, Germany (host: Dr. W. Kern; chair: AA van de Loosdrecht) | 2 | Van de Loosdrecht | R | PP | 70 |
| | **Therapeutic Guidelines** | | | | | |
| **8.27a** | Yearly update of the guidelines for therapeutic procedures in MDS and presentation on the ELN website | 1 | Malcovati/ Cazzola | O | PU | 66, 78 |
| **8.27c** | Webbased scenario analysis by the experts for development of evidence and consensus based guidelines for therapy of MDS | 1 | Malcovati/ Cazzola | O | PP | 73 |
| **8.27d** | Report of web based training program based on scenario analysis and consensus based guidelines for therapy of MDS developed by experts in this field | 1 | Malcovati/ Cazzola | R | PP | 78 |
| **8.29** | Development of a web-based training program using virtual patients to exercise the therapeutic guidelines and supervised by experts and European clinicians | 1 | Malcovati/ Cazzola | O | PP | 66 |
| **8.29a** | Evaluation of web-based scenario analysis experts versus trainees. | 2 | Malcovati/ Cazzola | R | PP | 78 |
| | **Trials** | | | | | |
| **8.31** | Yearly update of a list of all trials by MDS study groups in Europe | 2 | de Witte | O | PU | 66 |
| **8.51d** | Impact of frailty index on various therapeutic approaches, supportive care, hypomethylating agents, intensive anti-leukemic therapy. | 2 | Lübbert / Deschler | O | PP | 78 |
| **8.57** | GIMEMA-ELN QoL - MDS 0108 study Prognostic significance and longitudinal assessment of patient-reported quality of life and symptoms in high risk myelodysplastic syndromes. Obtain additional key data to further facilitate clinical decision-making in MDS patients. | 2 | Efficace | R | PU | 78 |
| | **MDS registry** | | | | | |
| **8.54** | Monthly progress reports of the prospective, non-interventional multi-center European MDS Registry (IPSS Low and Intermediate-1) project | 2 | De Witte | R | PP | 61-78 |
| **8.54f** | Presentation of the prospective, non-interventional multi-center European MDS Registry (IPSS Low and Intermediate-1) project at the MDS symposium in Patras, May 2009 | 2 | De Witte | R | PP | 65 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **8.54g** | First interim analysis (400 patients) entered in the prospective, non-interventional multi-center European MDS Registry (IPSS Low and Intermediate-1). | 2 | De Witte | R | PP | 66 |
| **8.54h** | Inclusion of next 600 patients | 2 | De Witte | O | PP | 76 |
| **8.54i** | Extension of follow-up, 2-5 years. | 16 | De Witte/Bowen | O | PP | Planned in 2010 |
| **8.54j** | Extension to more registries (new countries):<br><br>Denmark in 2009 | 4 | De Witte | O | PP | 76 |
| **8.54k** | Extension of registry to 2000 patients | 16 | De Witte/Bowen | O | PP | Planned in 2010 |
| **8.73** | A prospective, non-interventional multicenter European high-risk MDS Registry. Finalize protocol | 4 | De Witte | R | PP | 73 |
| **8.74** | Building up of high risk European MDS registry: Support from pharmaceutical companies. | 4 | De Witte/Bowen | O | PP | 73 |
| **8.75** | Establishment of a high-risk European MDS registry: Setting up central IT structure | 2 | Bowen | O | PP | 78 |
| **8.76** | High-risk European MDS registry: Implementation of organisational structure | 3 | De Witte | O | PP | 77 |
| **8.77** | High-risk European MDS registry: Detailed workingplan for datamanagement and statistical unit, including CRF | 4 | De Witte/ Bowen | O | PP | 78 |
| **8.78** | High-risk European MDS registry: Feasibility study | 3 | De Witte | R | PP | 76 |
| **8.79** | High-risk European MDS registry: Start inclusion | 3 | De Witte | O | PP | Planned in 2010 |
| | **Translational research** | | | | | |
| **8.80** | Side study of Low Risk MDS Registry: Iron pathophysiology. | 2 | M McKenzie | R | PU | 78 |
| **8.80a** | Side study of Low Risk MDS Registry: Imaging of iron overload. | 6 | T. de Witte | R | PU | Planned in 2010 |
| **8.81** | Side study of Low Risk MDS Registry: Cytomorphologic sub-study. | 2 | U Germing | R | PU | 78 |
| **8.82** | Side study of Low Risk MDS Registry: Geriatric Assessment. | 6 | R. Stauder | R | PU | 78 |
| **8.83** | Evaluation of the prognostic value of TET-2 mutations in MDS. | 2 | Jansen | R | PU | 76 |
| **8.84** | Evaluation of the prognostic value of TET-2 mutations in AML. | 2 | Jansen | R | PU | 76 |
| **8.59** | ESH-EHA Scientific Workshop on Experimental Haematopoiesis and Therapeutics 2010. (MRD, Gene Profiling, Immunophenotyping, Cytogenetics, in AML and MDS) | 2 | Padua | R | PU | 78 |

**Section 3: Consortium management**

In general, we speculate that MDS WP8 has been an active and productive WP within the European LeukemiaNet, as indicated by this report and the website content of WP8. We have interacted with many different Workpackages of European LeukemiaNet for integrated activities: e.g. Diagnostics WP10 (immunophenotyping in diagnostic guidelines in MDS), Cytogenetics WP11, (cytogenetics in diagnostic guidelines in MDS), AML WP5 (integration of diagnostic guidelines in AML and MDS, shared criteria of response for AML and MDS) and Gene Profiling WP13 (Multi-Center Microarray Study for the Molecular Classification of Leukemia).

The cooperation with WP 11 and WP13 is coordinated within the COST action (coordinator: Dr Ken Mills) and Eugesma (coordinated by Dr Rose-Ann Padua) They organised two Working group meetings each attended by ~95 participants from 20 countries. Cost (Action) and Eugesma participants organized two major FP7 applications:

- MATRIX involving participants from WG's 1,2, 3 & 4
  - ✓ Resistance in AML and MDS
  - ✓ Selected from 460 Stage I applications for Stage II
- DCDVACL, a one-stage application, from WG4
  - ✓ Innovative Therapeutic Approaches and Interventions (DNA Vaccines)
  - ✓ One-stage application – currently in EU review

Close cooperation of many European MDS study groups resulted in much progress on the European MDS Registry Study (see Annex Section 3, WP 8 (del. 8.53e). The inclusion started April 1st 2008. At the end of December 2009, the overall recruitment was 650 patients in 12 countries.

The study entitled "Prognostic significance and longitudinal assessment of patient-reported quality of life and symptoms in high risk myelodysplastic syndromes (MDS) is progressing well. This international multicenter observational study" GIMEMA-ELN QoL - MDS 0108 aims to obtain additional key data to further facilitate clinical decision-making in MDS patients. This initiative fits very well in our deliverables on developing a frailty index for treatment decision-making for older patients with MDS or AML. Therefore, this study is incorporated in our LeukemiaNet activities. Finally, much progress was made for the translational studies: Using SNP-arrays 40 novel recurrent genetic loci in MDS were identified (del.8.57). Development of a mouse MDS model resulted in a paper entitled "BCL-2 and Mutant NRAS Interact Physically and Functionally in a Mouse Model of Progressive Myelodysplasia" (del.8.64, see Annex Section 3, WP 8).

The present steering committee of our workpackage has been in office for more than 6 years. The steering committee felt it important to continue and to extend its activities through active participation of "junior experts" in our field. The steering committee discussed the extension of the steering committee with young investigators during the ESH-EHA MDS postgraduate course, in Mandelieu France. Uwe Platzbecker Dresden), Lionel Ades (Avicenne), Arjan van de Loosdrecht (Amsterdam), Luca Malcovati (Pavia), Wolf-Karsten Hofmann (Mannheim) and Martin Jadersten (Huddinge) have been invited as steering committee members. We shall identify the topics which the junior steering committee members will coordinate.

**Section 4: Other Issues**

Ethical issues – none, Competitive calls -none

## Section 5: WP-Performance

| Performance indicators | Status |
|---|---|
| Number of clinical trials started and/or completed | 8 |
| Number of patients re-cruited into clinical trials | Not reported |
| Number of patients included into registries | The inclusion started April 1st 2008. At the end of December 2009, the overall recruitment was 650 patients in 12 countries. |
| Improved predictive, prognostic or quality of life assessments | See del. 8.25b Yearly update of the guidelines for diagnostic standards in MDS and presentation on the ELN website. The MDS guidelines were adapted on the basis of the new WHO classification, 4th edition 2008 and presented on the ELN website.<br>See del. 8.25b Addition of information on Immunophenotyping in diagnostic guidelines in MDS/AML. This concerns a cooperation of WP8 and WP10 (Diagnostics). The second International ELN Workshop on standardization of flow cytometry in MDS in Munich, October 2009 was very successful. A general consensus protocol developed during the first Workshop has been published and became operational in the beginning of 2009.<br>See del. 8.51d Frailty index for treatment decision-making for older patients with MDS or AML. The comprehensive geriatric assessment was performed in 195 patients in Freiburg, Düsseldorf and Dresden aiming at exploring prognostically important assessment instruments and eventually defining a frailty index. This index has been validated in a group of patients with myeloid malignancies candidates for allogeneic stem cell transplantation.<br>In addition, this model is tested prospectively in the study entitled "Prognostic significance and longitudinal assessment of patient-reported quality of life and symptoms in high risk myelodysplastic syndromes (MDS). An international multicenter observational study" GIMEMA-ELN QoL - MDS 0108 which has started in 2008. |
| Degree of harmonization of trials | Multiple deliverables regarding harmonization of trials have been fulfilled and the results are presented on the ELN website:<br>See del. 8.25b Guidelines for diagnostic standards.<br>See del. 8.25b Immunophenotyping in diagnostic guidelines, a cooperation of WP8 and WP10 (Diagnostics). A general consensus protocol developed during the first Workshop has been published (see pdf 8.5) and became operational in the beginning of 2009. See del. 8.27c Webbased scenario analysis by the experts for development of evidence and consensus based guidelines for therapy of MDS (see attachment 8.13)<br>See del. 8.29 Development of a web-based training program using virtual patients to exercise the therapeutic guidelines and supervised by experts and European clinicians http://mds.haematologica.org<br>See del. 8.31b We updated the list of all trials by MDS study groups in Europe.<br>See del. 8.32 Every year an inventory on new drugs/treatments is made, by asking all partcipants of the MDS WP for input regarding this issue. Furthermore, new drugs/treatments is discussed at several MDS WP8 meetings. If necessary an investigator meeting on a particular new drug/treatment is organized. |
| Number of SOPs and consensus papers | 4 |
| Number of publications | 56 |
| Number of meetings | 11 |
| Number of accredited trials | See 8.31b |

**CMPD (WP 09)**

*Progress towards objectives – tasks worked on and achievements made with reference to planned objectives*

**9.5. Regular WP meetings**

WP9 participants met 3 times in 2009 during International congresses: in Mannheim on February, in Berlin on June 4 (EHA meeting), and in New Orleans on December 6 (ASH meeting). Written minutes of those meetings were provided to WP9 members, and are available upon request.

**9.6. LP reports to NMC regarding structure, trial activities and integration of national leukemia trial group**

Minutes of meetings were sent to the NMC.

**9.26d Phase II study of Imatinib therapy in polycythemia vera PV patients – (last patient recruited in June 2009)**

**End of the study June 2009**

The recruitment was completed in June 2009

Primary objective: To determine the antiproliferative effects of imatinib on the major parameters of the increased myeloproliferation in patients with PV, utilizing a dose escalation schedule. The main endpoint of the study is the response rate to the therapy (reduction of the phlebotomy rate, of platelet count, of white blood cell count, of spleen size) after one year of treatment.

Secondary objectives: To determine the rate and severity of side effects of the therapy; to determine the PV-related complications and symptoms (thrombosis, bleeding, microvascular disturbances, pruritus) under therapy with imatinib.

Main inclusion criteria: Newly diagnosed or pretreated patients with PV according to the WHO criteria. Patients ≥18 years of age no upper age limit.

Main exclusion criteria: Postpolycythemic myelofibrosis. Secondary acute leukemia. Pretreatment with $^{32}P$. Other malignant disease requiring therapy or with life expectancy of less than one year.

**Treatment:** Imatinib starting dose of 400mg daily. During follow up, the dose will be adapted to response and tolerability (stepwise dose escalation to 600mg and 800mg or reduction to 300mg in adaptation to blood counts, spleen size and side effects).

**Results:**

Included patients: 34 patients (17f / 17 m) from 9 German centers

Median age (64 (44 – 84) years

Previous therapy: phlebotomy (n = 17), cytoreductive therapy (n = 13)

Median duration of imatinib therapy: 13 (0,1 – 35) months

Response rate of at least one parameter (erythrocytosis, leukocytosis, thrombocytosis , splenomegaly): observed in approximately 60% of patients.

**9.28dAdvancement in a registry of pregnancies in ET (ongoing)**

There is an ongoing registry of pregnancies in MPD patients, with forms available on the ELN web site, chaired by M. Griesshammer (Minden). At last evaluation, 130 pregnancies were reported in 63 patients, implemented by hematologists from 6 different EU countries. The majority of patients had ET (50/63), but several pregnancies in PV and PMF patients were also reported. Pregnancy outcome could be evaluated in 117 pregnancies. Live birth rate was 72%, including 64% of full term normal deliveries, a rate significantly higher than previously reported (about 50% in the literature). Spontaneous abortions remained the main complication, occurring in 28% of pregnancies. Maternal complications were low, but clearly higher than in "normal" pregnancies: preeclampsia (3%), major bleeding (5%), venous thromboembolism (3%). Implementation of this registry will allow better knowledge and recommendation for management of pregnancies in MPD patients.

**9.30d Advancement in a randomized clinical trial of 2 phlebotomy regimens in low-risk PV start of trial (still recruiting patients)**

**Patients:** PV diagnosed according to WHO criteria, age > 18 years.

**Randomization:** between standard target hematocrit at less than 45%, and the experimental arm with a target hematocrit between 45 and 50%. The study aim is to recruit 500 PV patients in each arm.

**Primary endpoint:** To demonstrate that, in patients with PV and treated at the best of recommended therapies (i.e., low-dose aspirin when indicated and adequate control of standard cardiovascular risk factors), long term, aggressive cytoreductive therapy aimed at maintaining HCT < 45% (either with phlebotomy and/or HU) is more effective than cytoreductive therapy aimed at maintaining HCT in the range 45-50% (either with phlebotomy and/or HU) in reduction of:

CV deaths plus thrombotic events (stroke, acute coronary syndrome [**ACS**], transient ischemic attack [**TIA**], pulmonary embolism [**PE**], abdominal thrombosis, deep vein thrombosis [**DVT**], and peripheral arterial thrombosis).

**Secondary endpoints:** The events included in the PEP, arterial and venous thrombosis, major and minor thrombosis as well as hospitalization for any reason, hospitalization for CV reason, malignancy, and PV-related malignancy (progression to myelofibrosis, myelodysplastic or leukemic transformation) will be analyzed separately to assess the full benefit/risk profile of experimental treatments.

Recruitment has started in May 2008. As of January 2010, 263 patients were registered and 246 were randomized. The study is still recruiting patients.

**9.31d Advancement in a registration study of high-risk ET patients treated with Anagrelide (last patient enrolled in April 2009)**

The Exels study is a non-interventional, multicenter, European observational study of a large cohort of at-risk ET patients on cytoreductive therapy. The study was a prerequisite for the registration of Xagrid® (anagrelide) as an orphan drug by EMEA. 125 centres in Europe have now completed the recruitment of 3600 patients. The inclusion was closed in April 2009. The patients will be followed for 5 years, and the first patient to complete the study will do so in March 2010.

The patients are followed with 6-monthly data collections regarding disease complications, toxicity, drug use, efficacy of therapy, death and pregnancy. Reports to the DSMB every 6 months have not shown any new safety concerns.

The analysis of collected data shows that the treatment pattern is rather homogenous throughout Europe with a couple of exceptions. Hydroxyurea is first line treatment except in patients under 50 years of age, where anagrelide is more common.

The cohort consists of two large treatment groups, hydroxyurea (around 2000 patients), anagrelide (around 900 patients) as well as more than 150 patients with combination therapy and about 150 treated with interferon. Pipobroman is used only in a couple of countries in Europe.

The number of events is still too low to allow statistical comparison of various treatment groups. A total of 101 thrombohemorrhagic events were reported at the latest data-cut in September 2009.

This study, which is sponsored by Shire, the manufacturer of Xagrid, now encompasses a large cohort of ET patients, and results are expected to include frequency of thrombosis, bleeding, transformation to myelofibrosis and leukaemia as well as safety data.

Final reports will be due after the completion of the last patient in 2014, but interim reports will be possible when a larger number of events have been collected.

**9.34d Protocol for a multicenter study of vorinostat in CMPDs (started in 2009)**

> The COSMYD protocol "Safety and Efficacy of Vorinostat in the Treatment of Polycythemia Vera and Essential Thrombocythemia" - a multicenter study enrolling patients from centers within the COSMYD-group ( UK,Holland, Sweden and Denmark).

This is an investigator-driven study in several countries within the EuLeuNet. H.C. Hasselbalch is the representative of the Sponsor for this Study – University of Copenhagen , Department of Hematology, Herlev Hospital – and Professor Mary Frances McMullin, Belfast City Hospital, is the representative for the UK –sites in the study. The study has now enrolled 20 patients. H.C. Hasselbalch is currently involved in monitoring timely enrolment of patients and several News Letters have been forwarded to the participating centres. Preliminary data are extremely encouraging. In the large majority of patients the leukocyte and platelet counts normalize within a few weeks in concert with a decline in the need of phlebotomies and an improvement in well-being. Side effects are modest including diarrhoe, hair thinning and in a few patients an increase in plasma creatinine – in most within the normal range. Slightly elevated blood glucose levels have been recorded in a few patients. Since vorinostat seems to

have a striking effect, including a melting away of huge splenomegaly in one of the patients HCH has taken the initiative to forward an application for enrolment of additional 20 patients with myelofibrosis and large splenomegaly. Furthermore, an application has been forwarded to Merck, US to extend the study period in order to obtain long-term efficacy and safety data on vorinostat in the treatment of patients with Ph-negative chronic myeloproliferative neoplasms.

**9.35 Definition of response criteria in ET and PV**

European experts were convened to develop a definition of response to treatment in polycythemia vera (PV) and essential thrombocythemia (ET). Clinico-hematological (CH), molecular and histological response categories were selected. In ET, CH complete response (CR) was: platelet count ≤ 400 x109/L, no disease related symptoms, normal spleen size, and WBC count ≤ 10 x 109/L. Platelet count ≤ 600 x109/L or a decrease greater than 50% was partial response (PR). In PV, CH-CR was: hematocrit < 45% without phlebotomy, platelet count ≤ 400 x109/L, WBC count ≤ 10 x 109/L, and no disease related symptoms. A hematocrit < 45% without phlebotomy, or response in three or more of the other criteria was defined as PR. In both ET and in PV, molecular CR was a reduction of any molecular abnormality to undetectable levels. Molecular PR was defined as a reduction ≥ 50% in patients with < 50% mutant allele burden, or a reduction ≥ 25% in patients with > 50% mutant allele burden. Bone marrow histological response in ET was judged on megakaryocyte hyperplasia, while on cellularity and reticulin fibrosis in PV. The combined use of these response definitions should help standardize the design and reporting of clinical studies (see Annex Section 3, WP 9-3).

**9.36 Survey and harmonization of assay methods for JAK2-V617F**

This deliverable refers to a project in common with WP 12, MRD. In this year, we have performed additional experiments to characterize different published quantitative assays for JAK2V617F mutation, and we have now resolved that three of the initial 8 assays present acceptable characteristics of reproducibility and specificity. These are being used in current experiments. In collaboration with Ipsogen, that is involved in WP12, we have also performed a RQ assay using different plasmid preparations of JAK2 wild-type and V617F-mutated, as well as progressive dilutions of JAK2V617F mutated HEL cells. The data have been centrally collected and analyzed, and they have been discussed at the WP12 meeting held in New Orleans, December 2009. Furthermore, our laboratory has prepared and distributed to all participant laboratories progressive dilutions of a different JAK2V617F-mutated cell line, UKE-1, both as cell dilutions in normal mononuclear cells and as dilutions of purified DNA. Analysis of these preparations has been accomplished by most of involved laboratories, and overall results are planned to be presented in Mannheim, February 2010. Finally, this WP has interacted with the new born COST Action, coordinated by Dr Sylvie Hermouet, that aims at the standardization and dissemination in Europe of molecular techniques for the study of MPN.

**9.37 Registry of IFN-treated MPD patients**

Last year, H.C. Hasselbalch forwarded a proposal for a deliverable "A Registry of Patients with Polycythemia Vera, Essential Thrombocythemia and Primary Myelofibrosis Treated with Alpha-Interferon within EuropeanLeuNet". This will be further discussed on the coming meeting in Mannheim .

"The Nordic Long-Term IFN-Efficacy Study in Patients with Polycythaemia Vera and Essential Thrombocythemia"

On the initiative of H.C. Hasselbalch this study was initiated in October 2008 aiming at collecting a large cohort of patients with ET and PV being treated long term with pegylated Interferon-alpha2. The impetus for this study is the observation in several Danish Patients that long term treatment with IFN-alpha is able to induce a state of "minimal residual disease " with normalisation of the bone marrow and "complete molecular remission" with JAK2V617F mutation load below 1 %, even after discontinuation of IFN-alpha2 for up to 24 months (operational cure ?). A total of 35 Danish patients has been enrolled and additional patients are expected to be included in the study within this year. An interim analysis will hopefully be presented at ASH 2010.

**9.38 A pilot study of efficacy and safety of erlotinib in PV and ET (to be started in 2010)**

"Erlotonib in the Treatment of Polycythemia Vera and Essential Thrombocythemia. A Pilot Study of Efficacy and Safety"

The study has been delayed owing to lack of financial support in the Clinical Research Unit. The protocol is expected to be activated at the Department of Oncology-Hematology , Roskilde Hospital, University of Copenhagen, within the next 6 months. It is a Pilot Study which will include a total of 10 patients. Based upon the experience in the pilot study it will be decided whether to extend the study to other centres.

**Study of MPD leukemic transformations**

Transformation to acute myeloid leukemia (AML) is a known complication of myeloproliferative neoplasia (MPN). Recent studies have reported the high incidence (53%) of JAK2 negative blasts from transformed *JAK2*V617F-MPN. We collected, by cell sorting, blast cells and mature cells (GRA) from total bone marrow (BM) of 34 patients newly diagnosed of secondary AML. At MPN diagnosis (PMF n = 18; PV n = 9; ET n = 7), *JAK2* was mutated in 22 of 34 patients. Twenty of 22 *JAK2*V617F-MPN (91%) maintained the mutation in blasts and GRA after leukemic switch, while in 2 of 22 patients the selected compartments lost the mutation. Surprisingly we also found the first case of *JAK2*V617F-AML from a wild type (WT)-MPN. In contrast to the previous works, we conclude that *JAK2*V617F-MPN yields rarely (9%) a *JAK2*WT-AML.

**New project achieved in 2009: Definition of resistance / intolerance to hydroxyurea in PV and PMF**

A consensus conference was performed in 2009 to define resistance / intolerance to hydroxyurea in PV and PMF. Experts from the ELN WP9 and invited experts convened in 2 conferences, and provided their expertise through questionnaires sent by email, to produce a consensual definition. The project was completed and the results were published in the *British Journal of Haematology* in 2009.

**List of deliverables WP 9, 2009**

| Deliv. No. | Deliverable Name | Date due | Actual/Forecast delivery date | Estimated indicative person months*) | Used indicative person months*) | Lead contractor |
|---|---|---|---|---|---|---|
| **WP 8** | **MDS** | | | | | |
| **9.5** | Regular WP meetings | **54,66** | 62,66,72 | 0 | 2 | Barbui Barosi |
| **9.6** | LP reports to NMC regarding structure, trial activities and integration of national leukemia trial group (1 page, bullet point syle) | **54,66** | 62,66 | 0 | 0,5 | Kiladjian |
| **9.26d** | Phase II study of Imatinib therapy in Pv patients – (still recruiting patients) | **66** | 66 | 0 | 2 | Lengfelder |
| **9.28d** | Advancement in a registry of pregnancies in ET (ongoing) | **49-66** | 61-72 | 0 | 2 | Griesshammer |
| **9.30d** | Advancement in a randomized clinical trial of 2 phlebotomy regimens in low-risk PV start of trial (still recruiting patients) | **49-66** | ongoing | 0 | 4 | Barbui, Finazzi |
| **9.31d** | Advancement in a registration study of high-risk ET patients treated with Anagrelide (still recruiting patients) | **54,66** | ongoing | 0 | 3 | Birgegard |
| **9.34d** | Protocol for a multicenter study of vorinostat in CMPDs (to be started in 2009) | **49-66** | 66 | 0 | 4 | Hasselbalch |
| **9.35** | Definition of response criteria in ET and PV (ongoing) | **49-66** | 66 | 0 | 3 | Barbui Barosi |
| **9.36** | Survey and harmonization of assay methods for JAK2-V617F (ongoing) | **49-66** | ongoing | 0 | 5 | Vannucchi |
| **9.37** | Registry of IFN-treated MPD patients | **49-66** | ongoing | 0 | 3 | Kiladjian + Hasselbalch |
| **9.38** | A pilot study of efficacy and safety of erlotinib in PV and ET (to be started in 2009) | **49-66** | ongoing | 0 | 4 | Hasselbalch |

**List of milestones WP 9, 2009**

| Milestone No. | Milestone Name | Date due | Actual/Forecast delivery date | Lead contractor |
|---|---|---|---|---|
| **WP 9** | **CMPD** | | | |
| **9.35** | Definition of response criteria in ET and PV | 49-66 | Completed, and published in 2009 | Barbui Barosi |
| **9.36** | Survey and harmonization of assay methods for JAK2-V617F | 49-66 | ongoing | Vannucchi |

## Section 3: Consortium management

### Section 4: Other Issues

Ethical issues - none

Competitive calls - none

### Section 5: WP-Performance:

| Performance indicators | Status |
|---|---|
| Number of clinical trials started and/or completed | 4 |
| Number of patients recruited into clinical trials | About 1500 |
| Number of patients included into registries | About 500 |
| Improved predictive, prognostic or quality of life assessments | 2 |
| Degree of harmonization of trials | 0 |
| Number of SOPs and consensus papers | 1 |
| Number of publications | 48 |
| Number of meetings | 5 |
| Number of meta-analyses | 0 |
| Number of accredited trials | 0 |

**Diagnostic platform (WP 10)**

*Objectives and starting point of work at beginning of reporting period*

The major goals this year were to develop the field of morphology, publish flow information on normal bone marrow flow cytometry and further interact with other work packages. It was planned to keep contributing to the dissemination of knowledge. It was also expected that publications from WP10 would become effective, which was indeed the case.

*Progress towards objectives – tasks worked on and achievements made with reference to planned objectives*

**10.1 Web-based information- and communication services on WP available**

More documents produced by the WP have been posted on the ELN website this year. The links provided towards other web-based facilities remain posted, especially towards Onkodin. The project of having some of the Onkodin cases translated in English has not met much success. The atlas for acute myeloblastic leukemias from the French image bank from the Goelams trial LAM2001 is progressing. Two meetings allowed to finalize the format and some cases have been selected.

**10.2 European platform for leukemia diagnostics**

The platform is a free group and has again changed during the year. Current members on the mailing list are:

Alonso Luis Garcia, Aventin Anna, Bassan Renato, Basso Giuseppe, Bellos Frauke, Béné Marie Christine, Bettelheim Peter, Binder Thomas, Buldini Barbara, Bumbea Horia, Cermak Jaroslav, Cuneo Antonio, Delgiudice Ilria, Dengler Jolanta, Dugas Martin, Dumitrescu Adriana, Engels Marianne, Faber Edgar, Fioretos Thomas, Franke Sabine, Frickhofen Norbert, Ganepola Suzanne , Gassmann Winfried, Gerhardt Anke, Grüneisen Andreas, Grymki Z, Haferlach Torsten, Hastha Jan, Heiden Martin, Horst Hans, Hubner Bernd, Intermesoli Tamara, Jost Emil, Jotterand Martine, Karow Jochen, Keisponeit Dietz, Kern Wolfgang, König Josef, Koskenvesa Perttu, Lanza Francesco, Lemez Petr, Link Hartmut, Ludwig Wolf Dieter, Marinov Yuri, Matutes Estella, Mikalenkova Dana, Nebe Thomas, Nitu Georgeta, Ölschlägel Ute, Orfao Alberto, Pickl Winfried, Popov Viola, Porwit Anna, Reith Albrecht, Richter Susanne, Rothe Gregor, Rymkewitz Gregorz, Salvi A, Sambani Constantina, Sambani Cristina, Schabath Richard, Schabath Richard, Schäckel Ulrike, Schatz Michael, Schmalzl Franz, Schmitt Armelle, Schuler Martin, Schuurhuis Gerrit, Schwartzmann Peter, Shazi Nayla, Sokler Martin, Solenthaler Max, Stamminger Gudrun, Strobl Herbert, Subklewe Marion, Te Kronnie Truus, Tomin Dragila, Topaly Julian, Troussard Xavier, Tschurtschenthaler Gertrud, Van't Veer Mars, Vanura Katrina, Verbeek Walter, Verbeek Walter, Vladareanu Anna Maria, Von Beinere Alexandra, Weiss Tamara, Werner Martin, Willenbade Wolfgang, Zini Gina.

Besides these participants to WP10 meetings and/or recipients of information via Internet, Pr Gina Zini has gathered a faculty for the morphology project described below. Members of this faculty are:

Bain Barbara, Bettelheim Peter, Browne Paul , Brusselmans Caroline, Castoldi Gianluigi, Cortez José, d'Onofrio Giuseppe, Faber Edgar, Haferlach Torsten, Kacirkova Petra, Laub Petersen Bodil, Lewandowski Krzysztof, Liso Vincenzo, Matutes Estella, Maynadie Marc, Meletis John, Porwit Anna, Terpos Evangelos , Tichelli André, Urbanska-Rys Halina, Vallespi Teresa, Van't Veer Mars, Woessner Soledad, Zini Gina,

**10.3 Regular WP meetings**

WP10 participants met at the ELN annual meeting in Mannheim. Some of the team met also at the EGIL meeting in Vienna in April, at the MDS meeting in München in October and at the EHA European School in Vienna in November.

**10.4 LP reports to NMC regarding structure, activities and integration of national groups**

Reports have been forwarded to the ELN management as requested.

**10.5 Set up telemicroscopical system**

**10.6 Create DVDs of microscopical videos on leukemia diagnostics**

**10.7 Internet forum for interdisciplinary discussion of challenging cases**

The Morphology Faculty of the ELN WP10 has continued its harmonized nomenclature of now over 600 cells displayed on the ELN Website with a table of names. This can be used for training. The group is pursuing its activities by expanding the series of pathological cells and preparing cases. A manuscript has been submitted for publication depicting the work achieved.

**10.8 Create European recommendations for multiparameter flow cytometry in immunophenotyping leukemias**

The documents produced by ELN WP10 and posted on the website provide guidelines for antibody panels, preanalytical precautions, flow cytometry performance and suggested combinations. It was decided early in 2009 to produce a manuscript of the first document, explicating the choices made for mandatory panels and explaining the utility of the optional markers proposed in these documents. This manuscript has been written and is currently completing a Delphi round before being submitted for publication. Its final form will be discussed at the Mannheim meeting in February 2010.

Besides, in order to accompany the flow cytometry atlas posted on the website, a manuscript describing how if was achieved and describing precisely the strategies used to generate it has been published (see Annex Section 3, WP 10-3). This paper also refers to an approach for establishing chemosensitivity in acute myeloblastic leukemia by a simple recurrent examination of peripehra blood un flow cytometry, presented at ELN meetings, and also published in 2009 (see Annex Section 3, WP 10-9).

**10.9 Create European recommendations for the detection of minimal residual disease in flow cytometry**

Several meetings with WP12 over the years have allowed to better understand the strategies used in various European countries and for different types of leukemias. The review paper that had been planned to be prepared between these two workpackages has been completed and published this year (see Annex Section 3, WP 10-3). The manuscript was submitted for comments to a panel of members from both workpackages before being sent for publication.

**10.10 Development and improvement of teaching facilities**

**10.11 Create an internet library of powerpoint presentations on leukemia diagnostics**

**10.12 Create an internet library of microscopical videos on leukemia diagnostics**

All of the activities of WP10 that are posted on the website of the ELN are potentially useful for self-training or as teaching material. The participation of WP10 to educational sessions especially within the European School of Hematology should also be mentioned.

The internet library of powerpoint presentations on leukemia diagnostics that was established (www.leukemia-diagnostics.org**).**

**10.13 Continuous training courses on leukemia diagnostics on the European level,** MC Béné participated at as to the meeting of the Bone Marrow Pathology group in May in Geneva on Mixed Lineage Acute Leukemias immunophenotyping. Several members of WP10 (Anna Porwit, Estella Matutes and Marie Chrisitine Béné notably) have contributed to the updating of the WHO definition of leukemia now published.

**10.14 Establish regular consensus conferences on leukemia diagnostics on the European level,** This part has been achieved by WP10 and it will be discussed at the Mannheim meeting in 2010 whether such an activity should now be extended to the potentially new strategies emerging from recent developments in both instruments and software.

**Other activities,** The cooperation between WP13 and WP11 around the MILE project initiated by WP13 in collaboration with Roche continues, even though the industrial partner withdrew. A manuscript is in press describing the whole project and its outcome on more than 3000 leukemias. The database is available to participants and will be used for further projects, including some related to leukemia immunophenotyping.

**Further activities and milestones**

Developments are expected in the coming years about the use of flow cytometry for minimal residual disease monitoring, and following the outcome of several large ongoing studies, specific meetings will likely be organized by WP10.

Moreover, as two meetings have already been organized around the immunophenotype of myelodysplasia by WP8, this work will be pursued. The Amsterdam meeting led to a publication (see Annex Section 3, WP 10-4). At the Munich meeting, a minimal panel was devised that will be tested in the various labs and data will be collegially reviewed at a further meeting.

**List of Deliverables WP 10 2009**

**Table 10.2:** List of Deliverables WP 10, 2009

| Deliv. No. | Deliverable Name | Delivery/ Achieve date | Actual/Forecast delivery date | Estimated indicative person months | Used indicative person months*) | Respon-sible lead participant/ investigator |
|---|---|---|---|---|---|---|
| **WP 10** | **Diagnostics** | | | | | |
| **10.5** | Regular WP meetings, Telephone conferences | **66,78** | 62,,66,72 | (2) | 4 | Béné |
| **10.6** | LP reports to NMC regarding structure, activities and integration of national groups (1 page, bullet point style) | **66,72** | achieved | 0 | 0,5 | Béné |
| **10.11e** | Ongoing European quality control rounds on (morphological) leukemia diagnostics on the 'reference center level' | **66-78** | 61-72 | 0 | 5 | Zini |
| **10.18d** | Ongoing extension of internet library of microscopical pictures (incl. immuncytology), case reports, leukemia diagnostics | **66-78** | 61-72 | 0 | 4 | Link Hastka |
| **10.20d** | European recommendations on Minimal Residual Disease strategies in immunophenotyping - paper ready | **66** | 69 | 0 | 4 | Béné |
| **10.22d** | Interaction with other groups in diagnostic for design of algorithms | **66-78** | 61-72 | 0 | 4 | Béné |
| **10.24d** | Specific project on microarray for preDC leukemia with WP13-continued | **66-78** | 61-72 | 0 | 3 | Béné |

**Table 10. 3:** List of milestones WP 10, 2009

| Milestone No. | Milestone Name | Date due | Actual/Forecast delivery date | Lead contractor |
|---|---|---|---|---|
| **WP 10** | **Diagnostics** | | | |
| **10.18d** | Ongoing extension of internet library of microscopical pictures (incl. immuncytology), case reports, leukemia diagnostics | **66-78** | 61-72 | Link Hastka |
| **10.20d** | European recommendations on Minimal Residual Disease strategies in immunophenotyping - paper ready | **66** | 69 | Béné |
| **10.24d** | Specific project on microarray for preDC leukemia with WP13-continued | **66-78** | 61-72 | Béné |

**Section 3: Consortium management,** Management of the WP10 is going smoothly, with a lot of electronic communication. New members are joining. It is sometimes required to renew call for papers revision or documentation but the electronic way chosen costs only time. Cooperation with other programs is effective with WP8, WP13 and WP12. Contacts have been made with the clinical WP and will be reinforced.

## Section 4: Other Issues

Ethical issues - none,

## Section 5: WP10-Performance

| Performance indicators | Status |
|---|---|
| Establishment of European reference panels | done |
| Organization of interdisciplinary consensus conferences | done |
| Development of consensus protocols for the diagnostic work up of all types of leukemia and related syndromes | done |
| Organization of quality control rounds | Done, new round in progress |
| Establishment of European telemicroscopical networks | ongoing |
| Set up of internet forum | done |
| Training courses and improvement of teaching facilities with new technologies | done |
| Number and quality of publications within the network | 12 |

**Cytogenetics (WP 11)**

*Objectives and starting point of work at beginning of reporting period*

- Intensify harmonization of cytogenetic techniques between laboratories based on consensus protocols and practical training in other laboratories.
- Establish working groups on distinct cytogenetic questions
- Improve analysis of large and complex cytogenetic data sets

*Progress towards objectives – tasks worked on and achievements made with reference to planned objectives*

**11.5 Regular WP meetings**

- WP meeting at annual network symposion in Mannheim in February 2009
- WP meeting at 7th ECA conference in Stockholm in July 2009
- WP meeting in Hannover together with COST initiative in October 2009.

**11.6 LP reports to NMC regarding structure, activities and integration of national cytogenetics groups:**

LP reports were prepared in time.

**11.10e Further presentation of difficult cases**

For questions regarding, cytogenetic methods, nomenclature, FISH-probes, and help in difficult cases technical support was continuously offered in the WP11 website and an email address to contact experts of the field was presented.

**11.14e Data exchange with other subgroups of the network**

Additional data of ALL cases were collected for the evaluation of the prognostic impact of chromosome aberrations in collaboration with WP6.

**11.15e Influence of genomic imbalances on gene expression: an integrated analysis of SNP-array and gene expression array data**

In cooperation with WP 13 25 AML cases with complex aberrant karyotype were analysed by SNP arrays and gene expression analysis. An algorithm was developed to find DNA regions of consistent abnormality between gene expression andcopy number (e.g. underexpressed genes together with a loss of DNA material. This new algorithm has been published in 2009 (see Annex Section 3, WP 11-33).

**11.16e Further identification of new recurring chromosome aberrations by analyzing large cytogenetic databases**

The online Cytogenetic Data Analysis System (CyDAS.org) was continued for the analysis of large cytogenetic data sets.

**11.17e Continuation of data collection on rare abnormalities**

New cases with rare chromosome aberrations were collected in collaboration with the Atlas of Genetics and Cytogenetics in Oncology and Hematology which is edited by Dr. Huret.

**11.18e Continuation of identification and analysis of cryptic and complex chromosome aberrations by using new cytogenetic methods**

SNP microarray analysis revealed cytogenetically cryptic 17q11 deletion encompassing the NF1 gene in 6 out 37 AML with CBFB-MYH11 positive AML. Based on this finding a new project on the identification of NF1 deletions using interphase FISH in other myeloid malignancies was started.

**11.20e Continuous development and provision of additional methods**

An additional interlaboratory test of the chromosome banding analysis procedure using viable leukemia cells involving 37 laboratories was performed. A CML cell line carrying typical chromosome aberrations was used. All five target aberrations were detected by 70% of the laboratories.

**11.23c Collection of cytogenetic and clinical data of MDS patients from Germany, Austria, Great Britain and USA**

A publication on cytogenetic findings of 2124 MDS patients of Germany and Austria appeared in December 2007 in BLOOD (Haase et al., Bood, 2007). The data collection and merging of the databases are still in progress:

Up to date, 3856 cases of primary and secondary MDS were collected of whom 2901 patients received no disease-altering therapy. The patients included are coalesced from the IMRAW- (Greenberg et al.; n=816), the German-Austrian- (n=2011), and the Spanish- (Solé et al.; n=975) databases. Additionally, 53 patients from an ICWG-cooperative project, supported by the MDS-Foundation, were included. Based on the 2901 primary, untreated patients mentioned above, a new cytogenetic scoring system was designed. Dr. Schanz from Prof. Haases group wrote the manuscript regarding this project, which is under review of the statistician (Heinz Tüchler, Vienna) at the moment. It will be submitted within the next weeks.

Dr. Schanz from Prof. Haases group also has performed a multicentric analysis on 2855 MDS patients that indicates an underestimation of poor risk cytogenetics in the IPSS. The manuscript has been submitted and is under review up to now.

The data collection and merging of the databases is still in progress.

**11.24c Specific translocations in T-ALL**

No additional cases with specific translocations in T-ALL could be collected.

### 11.25c Cytogenetically unrelated clones in MDS

68 cases with MDS cytogenetically unrelated clones were collected from different national and international laboratories. The incidence, based on the international database described in 11.23c, is 0.7%. The most frequent combination was a clone with 5q deletion and a clone with trisomy 8. Overall, trisomy 8 is overrepresented in independent clones. The prognostic impact of independent clones was calculated as intermediate (median overall survival 18.5 months, median AML-free survival 84.3 months). The manuscript concerning this project will be written and submitted in the first half of 2010.

### 11.26 Provide data for the establishment of a European external quality assessment to EUROGENTEST

Two participants of the ELN WP11 continued to participate in the development of the pilot Cytogenetic External Quality Assessment (CEQA) Scheme in Hematology of the EUROGENTEST.

### 11.27 Administration of WP11 website and spreading of excellence by promotion of webbased information

The contents of the WP11 site were kept up to date by the WP11. E.g., the minutes of the annual Symposion were integrated.

## List of Deliverables WP11, 2009

| Deliv. No. | Deliverable Name | Delivery/ Achieve date | Actual/Forecast delivery date | Estimated indicative person months | Used indicative person months*) | Respon-sible lead participant/ investigator |
|---|---|---|---|---|---|---|
| **WP 11** | **Cytogenetics** | | | | | |
| **11.5** | Regular WP meetings | **54,66,78** | 54,66, 78 | 10 | 10 | Fonatsch, Haferlach C. |
| **11.6** | LP reports to NMC regarding structure, activities and integration of national cytogenetics groups | **49,52,55** | achieved | 4 | 4 | Fonatsch |
| **11.10e** | Further presentation of difficult cases | **78** | 78 | 4 | 4 | Rieder Haferlach C |
| **11.14e** | Data exchange with other subgroups of the network | **78** | 78 | 4 | 4 | Rieder |
| **11.15e** | Influence of genomic imbalances on gene expression: an integrated analysis of SNP-array and gene expression array data in cooperation with WP13 | **78** | 78 | 4 | 4 | Haferlach C |
| **11.16e** | Further identification of new recurring chromosome aberrations by analyzing large cytogenetic databases | **78** | 78 | 6 | 6 | Rieder |
| **11.17e** | Continuation of data collection on rare abnormalities | **78** | 78 | 5 | 5 | Haferlach C, Rieder, Fonatsch |
| **11.18e** | Continuation of identification and analysis of cryptic and complex chromosome aberrations by using new cytogenetic methods | **78** | 78 | 12 | 12 | Rieder Haferlach C Fonatsch |
| **11.20e** | Continuous development and provision of additional methods | **78** | 78 | 6 | 6 | Fonatsch Rieder |
| **11.23c** | Continuous collection of cytogenetic and clinical data of MDS patients from Germany, Austria and Great Britain | **78** | 78 | 6 | 6 | Haase |
| **11.24c** | Specific translocations in T-ALL | **50** | ongoing | 0 | 0 | Johansson Beverloo Storlazzi |
| **11.25c** | Cytogenetically unrelated clones in MDS | **78** | 78 | 4 | 4 | Haase Haferlach C. Fonatsch |
| **11.26** | Provide data for the establishment of a European external quality assessment to EUROGENTEST | **78** | 78 | 6 | 6 | Rieder, Dastugue |
| **11.27** | Administration of the WP11 website and spreading of excellence by promotion of web-based information | **78** | 78 | 6 | 6 | Rieder |

List of milestones WP 11, 2009

| Milestone No. | Milestone Name | Date due | Actual/Forecast delivery date | Lead contractor |
|---|---|---|---|---|
| **WP 11** | **Cytogenetics** | | | |
| **11.15e** | Influence of genomic imbalances on gene expression: an integrated analysis of SNP-array and gene expression array data in cooperation with WP13 | **78** | 78 | Haferlach C |
| **11.23c** | Continuous collection of cytogenetic and clinical data of MDS patients from Germany, Austria and Great Britain | **78** | 78 | Haase |
| **11.26** | Provide data for the establishment of a European external quality assessment to EUROGENTEST | **78** | 78 | Rieder, Dastugue |

**Section 3: Consortium management**

Cooperation with other Workpackages is effective especially with WP6, WP8, WP9 and WP13.

**Section 4: Other Issues**

Ethical issues-none

Competitive calls-none

**Section 5: WP-Performance**

| Performance indicators | Status |
|---|---|
| Establishment of European reference panels | in progress |
| Organization of interdisciplinary consensus conferences | COST meeting in cooperation with WP 8 (MDS) took place |
| Development of consensus protocols for the diagnostic work up of all types of leukemia and related syndromes | first consensus protocol published in Genes Chromosomes Cancer (see Section 3, 11.1) |
| Set up of internet forum | done |
| Number of rare abnormalities for which the prognostic impact could be clarified | 1 |
| Number of new recurrent abnormalities identified | 2 |
| Number and quality of publications within the network 2009 | 35 |
| Implementation of technology transfer | in progress |
| Improved techniques with better results | in progress |

**Minimal residual disease (WP 12)**

*Objectives and starting point of work at beginning of reporting period*

A coordinated and integrated working group has been established to develop new assays to increase the proportion of patients with myeloid leukemias/myeloproliferative disorders (MPDs) who could potentially benefit from minimal residual disease (MRD) monitoring using real-time quantitative PCR (RQ-PCR) approaches. Key objectives over the last year have been to continue to improve standardization of established assays (i.e. BCR-ABL, JAK2 V617F in collaboration with WP4 and WP9, respectively), the evaluation of novel RQ-PCR assays (i.e. Wilms' Tumor gene (WT1) and nucleophosmin (NPM1) mutation) and the validation and implementation of a computer software reporting package to improve standards of reporting of RQ-PCR data to clinicians, which also serves to facilitate comparison of results between laboratories.

While development of RQ-PCR assays for fusion genes associated with myeloproliferative disorders enables sequential MRD assessment to guide therapy with tyrosine kinase inhibitors (Jovanovic et al, Blood 2007; and see Annex Section 3, WP 12-7, -8, -13), in acute myeloid leukemia (AML) we have been exploring a number of approaches whereby MRD detection could lead to improved management and clinical outcome. For leukemia-specific markers that afford relatively high levels of assay sensitivity (i.e. leukemic fusion genes e.g. PML-RARA, NPM1 mutation) it is possible to use MRD monitoring to pinpoint those patients destined to fail first-line therapy, thereby allowing the administration of additional treatment in first remission – this approach has been evaluated initially in acute promyelocytic leukemia (APL) (see Annex Section 3, WP12-25). For AML cases lacking a leukemia-specific molecular marker, MRD monitoring relies upon flow cytometry to detect a leukemia-associated aberrant phenotype or RQ-PCR analysis of genes that are highly expressed in the blast population (e.g. WT1). In this situation, evidence to date suggests that MRD assessment is best suited to investigate the degree of leukemic blast reduction during early phases of therapy and its relationship to subsequent risk of relapse (reviewed Freeman et al, Semin Oncol 2008; see Annex Section 3, WP12-1). We have recently shown that determination of depth of response to induction chemotherapy using an optimized ELN WT1 assay provides an independent prognostic factor in AML suggesting that it could be used to enhance risk stratification (see Annex Section 3, WP12-3, -24). Development of optimized protocols for flow cytometric detection of MRD has been a focus of attention for the "Diagnostic Platform" workpackage (WP10) and we have established a joint program to investigate the optimal approach for MRD-directed therapy in AML cases lacking a leukemia-specific molecular target. Prospective parallel analysis of flow cytometry and optimized RQ-PCR assays is now being evaluated by ELN MRD laboratories within the context of large scale clinical trials. These studies will establish the extent to which MRD assessment affords additional prognostic information as compared to conventional risk factors, facilitating the development of enhanced risk stratified treatment approaches to AML and providing more insights into the role of autologous or allogeneic transplantation in first remission.

*Progress towards objectives – tasks worked on and achievements made with reference to planned objectives:*

**12.5 Regular WP meetings**

Instrumental to the progression and development of the experimental program for WP12 over the course of the last year has been the provision for regular meetings. WP12 meetings were linked to international hematology meetings: LeukemiaNet Annual Symposium, Mannheim (3rd February); European Hematology Association (EHA), Berlin (4th June) and American Society of Hematology (ASH), New Orleans (4th December). In addition, two meetings linked to WP12 were held as part of the international effort to achieve standardized approaches to RQ-PCR detection and reporting of BCR-ABL MRD results in chronic myeloid leukemia (CML); these were held in Berlin (7th June) and New Orleans (4th December), coinciding with EHA and ASH meetings, respectively.

**12.6 LP reports to NMC regarding structure, activities and integration of national groups**

Minutes from each WP12 meeting are drawn up by the lead participant and submitted to ELN NMC following approval by the membership of WP12. Updates from international BCR-ABL standardization meetings chaired by Prof Cross are fed back to the relevant national groups, such as the UK network of molecular diagnostic laboratories (meeting 29th July, 2009), the German Kompetenznetz "Akute und chronische Leukämien", the Italian and the Nordic networks.

**12.10c Evaluation of expression levels of target genes in diagnostic material**

Prior to this reporting period, WP12 projects had established through application of optimized RQ-PCR assays that leukemic fusion genes e.g. FIP1L1-PDGFRA in hypereosinophilic syndrome (Jovanovic et al, Blood 2007; Reiter et al, Haematologica 2007) and PML-RARA in acute promyelocytic leukemia (see Annex Section 3, WP12-25) exhibit significant variation in expression in diagnostic samples (~ 3-log range), which impacts significantly upon sensitivity of assays to detect MRD. Over the course of this year WP12 has continued to focus on the analysis of NPM1 mutations and WT1, which afford the opportunity to evaluate response to therapy using a molecular marker in a substantial proportion of AML cases.

NPM1: RQ-PCR assays have been developed for the commonest NPM1 mutations (types A, B & D) by Prof Saglio's group (Gorello et al, Leukemia 2006) and evaluated more widely within WP12. Analysis of diagnostic samples has shown that the NPM1 mutant allele is highly expressed, typically affording assay sensitivities of between 1 in 104 and 106 (see Figure12.1).

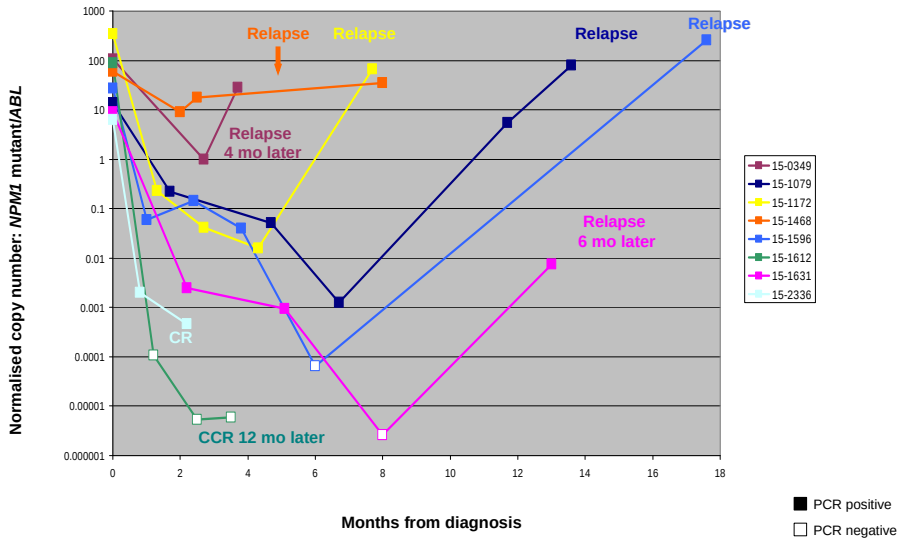



**Figure 12.1**

**RQ-PCR monitoring of MRD in AML by detection of NPM1 mutation:**
Sequential monitoring of *NPM1* mutation by real-time quantitative PCR in patients treated in UK MRC AML15 trial. AML cases found to have *NPM1* type A or B mutation were subject to retrospective quantification of *NPM1* mutant allele relative to expression of the *ABL* control gene in stored follow-up samples. The *NPM1* mutant allele was expressed 6-350 fold higher than *ABL*, affording assay sensitivities of between 1 in $10^4$ and $10^6$. In patients subject to relapse, *NPM1* mutant was detected at a persistently high level throughout treatment or relapse was preceded by rising transcript numbers. Cases 15-0349 and 15-2336 had type B mutation, the rest were type A.
Abbreviations: Ct, Cycle threshold; CR, complete remission; CCR, continuing complete remission (Freeman *et al*, *Semin Oncol* 2008).

WT1: This is an interesting potential target for MRD detection in that it has been reported to be over-expressed in approximately 70% of AML and is being investigated as a target for immunotherapy in this disease. In a project led by Daniela Cilloni and Giuseppe Saglio involving 11 WP12 laboratories, 9 published or "in-house" WT1 assays were systematically analyzed in parallel prior to this reporting year, leading to the selection of an assay located within exons 1 and 2, which was confirmed to be RNA specific and afforded greatest sensitivity. The selected "ELN WT1" assay also has the distinct advantage that it is located in a region of the gene that is rarely subject to mutation in AML. Indeed WT1 mutations which occur in ~10% of normal karyotype AML typically involve exons 7 and 9, where many published WT1 RQ-PCR assays are located thereby giving rise to the potential for "false negative" results. A full length WT1 plasmid was developed in conjunction with Ipsogen, Marseille and included in an "ELN WT1 kit" including primers and probe for the ELN WT1 assay, ABL control gene assay (Europe Against Cancer) and respective plasmid standards. ELN WT1 kits were centrally distributed to participating laboratories for evaluation in large numbers of AML and non-leukemic samples (620 pre-treatment AML samples and 204 control PB, BM and PBSC samples). This allowed us to establish thresholds for background levels of expression of WT1 in normal PB and BM (upper limit 50 and 250 copies/ 104 ABL copies, respectively). This relatively high background level of expression limits the sensitivity of WT1 RQ-PCR assays to detect residual disease as compared to use

of leukemia-specific markers (e.g. mutant NPM1, PML-RARA), suggesting that WT1 is most appropriately used to measure kinetics of disease response during early phases of therapy rather than for serial MRD monitoring to track impending relapse. Based upon the differential expression of WT1 in AML blasts and normal PB and BM, PB was considered to provide the preferred sample source allowing at least a 2-log reduction in transcripts to be discriminated in approximately half of AML patients.

No significant difference in WT1 expression level as determined by the ELN assay was observed in AML cases harboring mutations in exons 7 and 9 of the gene as compared to those with wild type WT1 (p=0.2). However, sequence analysis of a series of 32 cases of AML in which the ELN assay suggested a low level of WT1 transcript expression (<250 copies/ 104 ABL copies), showed that they were enriched for mutations in exons 1 and 2 that disrupted primer and/or probe binding sites. During this reporting year, all data from the ELN WT1 study were collated and subsequently published (see Annex Section 3, WP12-3). The optimized ELN WT1 assay has now been taken forward to assess MRD in multicenter clinical trials including the UK NCRI AML17 trial as a tool to enhance risk stratification and the forthcoming Epicept study (EPC2008-02) evaluating histamine dihydrochloride and IL-2 as maintenance therapy in AML (12.15d).

**12.11d Establish the additional proportion of leukemic patients that can be monitored using novel targets**

The major focus of this work has been the development of optimized RQ-PCR assays for detection of WT1 and the commonest NPM1 mutations, thereby substantially extending the proportion of AML patients that can be monitored for disease response beyond the range of fusion gene assays developed in the Europe Against Cancer program, which are applicable to only ~25% of AML.

*NPM1*

Over the course of the last year significant progress has been made, with the Munich, Ulm and Lille groups providing strong evidence that NPM1 mutations provide highly promising MRD targets that could allow the development of individualized treatment approaches in a significant proportion of AML patients. The Munich laboratory have developed assays for 17 different NPM1 mutation types based on the Lightcycler platform to analyze 252 AML cases (Schnittger et al, Blood 2009). Relapses were predicted by failure to reduce NPM1 mutant level by more than 3 logs or by more than a 1 log rise in the mutant level. In this study NPM1 mutant level was the most important predictor of relapse in multivariable analysis considering age and FLT3-ITD status. In a study led by Jan Krönke, the Ulm group has undertaken MRD detection in over 1000 samples from 212 AML patients with Type A, B and D mutations using the Gorello assays. MRD positivity following the second induction and at the post-consolidation timepoint were both predictive of subsequent risk of relapse. On longitudinal monitoring, median time from PCR positivity to relapse was 3 months; in some patients the time from molecular conversion to relapse was very prolonged, while others showed intermittent PCR positivity

without relapse. Intermittent detection of NPM1 mutant transcripts could potentially relate to non-leukaemic cells or leukemic stem cells and the Lille group (Aline Renneville & Claude Preudhomme, unpublished data) has shown that very late relapses (up to 12 years from diagnosis) with stability of the NPM1 mutation can occur.

Since it is anticipated that NPM1 MRD monitoring data will increasingly be used to guide patient therapy, a major focus of WP12 over the last year has been to establish predictive thresholds, evaluate the optimal sample type for monitoring (PB vs BM), investigate the kinetics of disease relapse, and consider the stability of the NPM1 mutation as an MRD target. Based on analysis of the Ulm data, a threshold of 0.1 NPMmut/ABL has been proposed for diagnosis of molecular relapse (equivalent to 3-4 logs below diagnostic level). Detailed mathematical modelling of the raw data provided from the Munich study, performed by Hans Ommen (Aarhus, Denmark), has suggested that NPM1 mutant levels above a threshold of 5 x 10-5 relative to ABL are indicative of MRD (see Annex Section 3, WP12-10). To investigate the optimal sample source for MRD monitoring 174 paired PB and BM follow-up samples have been analyzed using the Gorello assays for Type A, B and D mutations by the Lille group. Good concordance was observed in NPM1 MRD results obtained with the two sample sources, with bone marrow typically affording ~0.5log greater sensitivity. Kinetics of disease relapse have been investigated in the Munich data set, showing that speed of relapse is significantly more rapid in the group with coexistant FLT3-ITD mutations than in NPM1mut cases with wild type FLT3 (see Annex Section 3, WP12-10, 37).

A key aim of WP12 is to establish optimal MRD monitoring schedules to predict disease recurrence and allow time for pre-emptive therapy to be delivered to prevent clinical relapse. Applying the mathematical model which is independent of assay sensitivity, the relationship between sampling interval and likelihood of relapse detection in NPM1 mutant AML in relation to other molecular subsets was defined. Thus, taking a 3 month bone marrow sampling interval as an example, the median time from molecular positivity to hematological relapse was 120 days for NPM1mut AML as compared to 200 days for CBFB-MYH11+ patients, 90 days in RUNX1-RUNX1T1+ cases, but as short as 45 days in PML-RARA+ patients (Ommen et al, Blood 2009). Application of the mathematical model to the Munich data set showed that 6 monthly and 4 monthly BM examinations are required to achieve a relapse detection frequency of at least 90% with a window of at least 60 days to hematological relapse in NPM1c+/FLT3-ITD- and NPM1c+/FLT3-ITD+ AML, respectively. Optimal MRD sampling frequencies are currently being prospectively validated in multi-center clinical trials such as the UK NCRI AML17 trial.

The stability of the NPM1 mutation as an MRD marker has also been considered. The Munich group reported stability of the NPM1 mutation in 84 of 84 paired diagnostic and relapse samples (see Annex Section 3, WP12-37). The Lille group have also found that the NPM1 mutation is stable based on an analysis of 55 paired diagnostic and relapse samples (Aline Renneville, Claude Preudhomme unpublished data). However, the Ulm group have observed occasional cases in which the NPM1 mutation is lost at “relapse”, including one with acquisition of trisomy 8 and RUNX1 mutation, which

most likely reflects development of t-AML rather than relapse of the original clone. These studies support the notion that NPM1 mutation is a primary lesion in the pathogenesis of AML, but also serve to highlight the importance of comprehensive molecular and cytogenetic characterization of patients with "relapsed" AML.

The Munich NPM1mut assays involve use of a mutation-specific forward primer and common reverse primer, which do not amplify the mutation-specific plasmid standards originally developed by Ipsogen to be used in conjunction with the Gorello assays. Therefore, over the course of this reporting year in collaboration with Ipsogen, Marseille a set of universal plasmid standards for the commonest mutation types (A, B & D), accounting for ~90% of cases that can be used in conjunction with all RNA- and genomic DNA-based assays has been developed. These have been evaluated within WP12, showing good performance profile and will allow for standardized reporting of NPM1 MRD data across different RQ-PCR platforms.

*WT1:*

During the course of this year we have continued the investigation of the prognostic value of MRD detection using the optimized ELN WT1 assay considering a cohort of 142 AML patients with high level WT1 expression at diagnosis (>20,000 WT1 copies/ 104 ABL copies) treated with standard

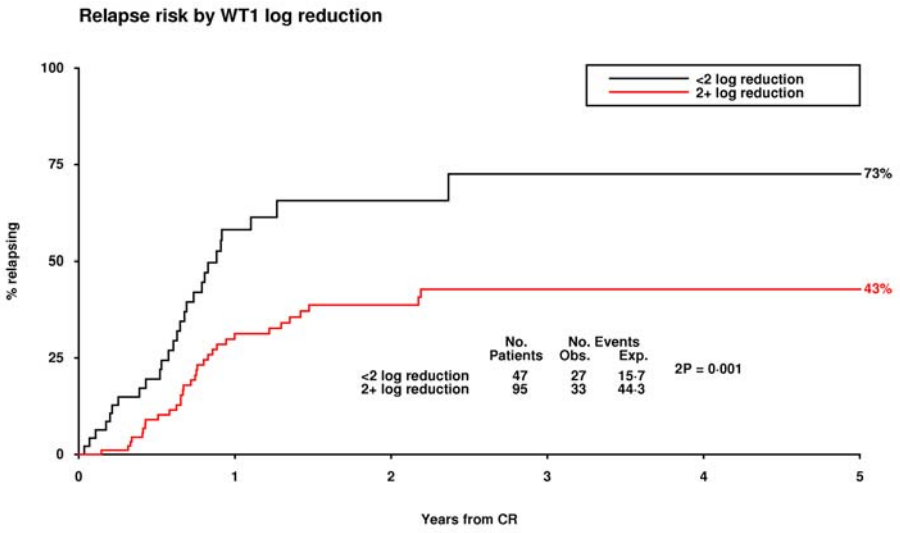



**Figure 12.2: Kinetics of minimal residual disease response following induction therapy are predictive of subsequent relapse risk in AML**

The predictive value of MRD assessment by standardized ELN WT1 RQ-PCR assay was determined in a cohort of 142 AML patients treated with conventional anthracycline and cytarabine based treatment. Analysis was undertaken in AML cases with WT1 expression exceeding 2 x104 copies/ 104 ABL copies in pre-treatment samples, allowing the detection of at least a 2-log reduction in WT1 transcripts following induction, taking into account the background level of expression observed in normal hematopoietic tissues. The patient cohort included 91 cases reported previously (Cilloni et al, J Clin Oncol 2009) combined with a further 51 cases treated in the MRC AML15 trial (samples kindly provided by John Yin and Michelle Sale, Manchester Royal Infirmary and analyzed at Guy's Hospital, London, UK).

anthracycline and cytarabine-based therapy (Grimwade & Hills, Hematology Am Soc Hematol Educ Program 2009). In this informative group, greater WT1 transcript reduction after induction predicted reduced relapse risk (hazard ratio, 0.54 per log reduction; 95% CI, 0.36 to 0.83; P =0.004) that remained significant when adjusted for age, WBC count, and cytogenetics (Figure 12.2). Failure to reduce WT1 transcripts below the threshold limits defined in normal controls by the end of consolidation also predicted increased relapse risk (P= 0.004).

*Integrated approaches to MRD detection:*

This aim is being addressed in conjunction with WP10, with current data indicating that virtually all AML patients can be subject to assessment of MRD using flow cytometry- and/or RQ-PCR- based approaches (see Annex Section 3, WP 12-1). A major aim of WP10 is to achieve greater collaboration between groups performing flow cytometry within the context of national clinical trials. In an ongoing study, Vincent van der Velden (Rotterdam) is making direct comparisons between RQ-PCR and flow cytometric approaches for MRD detection in pediatric AML. Moreover, Gerrit Schuurhuis has led a national Dutch study prospectively evaluating flow cytometry-based MRD detection to predict outcome in AML and which will compare flow data with molecular approaches to MRD detection using RQ-PCR. This theme is being further developed in the UK NCRI AML17 trial which commenced in April 2009 in which RQ-PCR (using EAC and ELN standardized assays) and flow-cytometry are being evaluated prospectively in parallel to establish whether early MRD assessment provides greater discriminatory power than current conventional criteria to identify those patients most and least likely to benefit from allogeneic transplantation in first remission.

*FIP1L1-PDGFRA:*

A further focus of WP12 has been to develop RQ-PCR assays to direct molecularly targeted therapies in myeloproliferative disorders, in collaboration with WP9. Indeed the structure of WP12 has enabled our group to continue to collect clinical material from patients with relatively rare conditions such as *FIP1L1-PDGFRA*+ hypereosinophilic syndrome which we have found to account for ~10% cases of persistent unexplained eosinophilia (Jovanovic et al, Blood 2007), enabling us to gain further biological insights into this subset of disorders, complementing the work of WP9 (see Annex Section 3, WP12-14 and Burgstaller et al, Leukemia 2007; Reiter et al, Haematologica 2007; Metzgeroth et al, Br J Haematol 2008). Indeed, in a study led by Prof Nick Cross, we also showed that genomic DNA based RQ-PCR assays for the FIP1L1-PDGFRA fusion can detect MRD following imatinib therapy with significantly greater sensitivity than RNA-based assays (see Annex Section 3, WP12-13). The ELN is ideally suited to the conduct of such studies, which would not have been feasible at the national level.

**12.13c Development of standardized protocols for MRD assessment using RNA-based targets (from bedside to clinical report)**

*BCR-ABL:*

In order to achieve this aim, WP12 has linked up with the international standardization efforts for RQ-PCR analysis and reporting of BCR-ABL results in chronic myeloid leukemia (CML), led by Prof Nick Cross. This ongoing effort will establish key principles that will be relevant to development of standardized protocols for other MRD targets. The BCR-ABL related work within WP12 has focused on the development of accredited reference (IS) reagents as a means to facilitate the promulgation of the International Scale for MRD determination in CML. Following a series of successful pilot experiments and control rounds we commissioned ECACC (European Collection of Cell Cultures) to grow 40 litres of HL60 cells in Autumn 2008, from which we made four mixtures of K562/HL60 to approximate 10%, 1%, 0.1% and 0.01% on the IS. These mixtures were prepared as rapidly as possible and transported to the National Institute of Biological Standards and Control (NIBSC) for aliquoting into ampoules and freeze drying, yielding approximately 3000 vials per dilution.

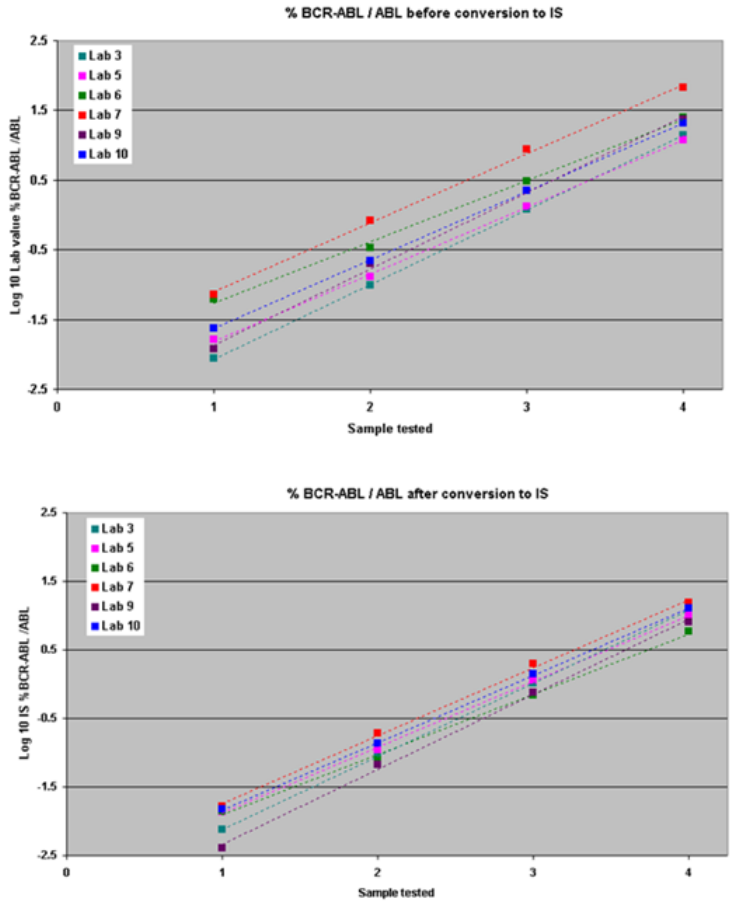



**Figure 12.3: BCR-ABL QC results of freeze dried cell dilution analysis for the 6 laboratories that used ABL as the control gene.** Top panel: before conversion; bottom panel: after conversion using local CFs. The mean of the converted values were assigned as IS values to each dilution.

Following initial successful in house evaluation of the freeze dried material we performed a field trial in January-March 2009 that aimed to establish IS values for each dilution. Laboratories were selected that had validated conversion factors (CF), with at least three laboratories for each of the three internationally accepted control genes: ABL, BCR and GUSB. A total of 10 laboratories were involved (6 from the EU) using 4 different protocols and 8 different RQ-PCR platforms. Each lab received 3 vials at each of the four dilution levels. RNA was extracted from each vial and reverse transcribed twice on different days yielding 24 datapoints/lab. The amounts of RNA extracted, absolute copy numbers of control gene, BCR-ABL/control gene before and after conversion were calculated and the mean for the laboratories used to calculate the IS values for each dilution (Figure 3). In addition, the performance of the freeze dried materials was evaluated by homogeneity and stability testing. The coefficients of variation of 17 randomly selected freeze dried vials for each dilution were similar to the variation seen in 17 aliquots of non-freeze dried material and also patient replicates, confirming batch homogeneity. In accelerated degradation studies, the amounts of extractable RNA fell significantly when the vials were maintained at >20°C for 10 months, but the BCR-ABL/ABL ratios were distorted only in samples that had been maintained at 45 degrees or higher (see Figure 12.4).

The documentation describing these experiments was submitted by NIBSC to the World Health Organisation (WHO) in July 2009 and following assessment of the evidence the materials were approved as primary reference reagents in November 2009. The supply of these reagents will be limited to companies and reference laboratories that are able to generate the secondary reference materials that will actually be used by testing laboratories. Facilitating the process of developing these secondary reagents and their validation will form our major focus for 2010.

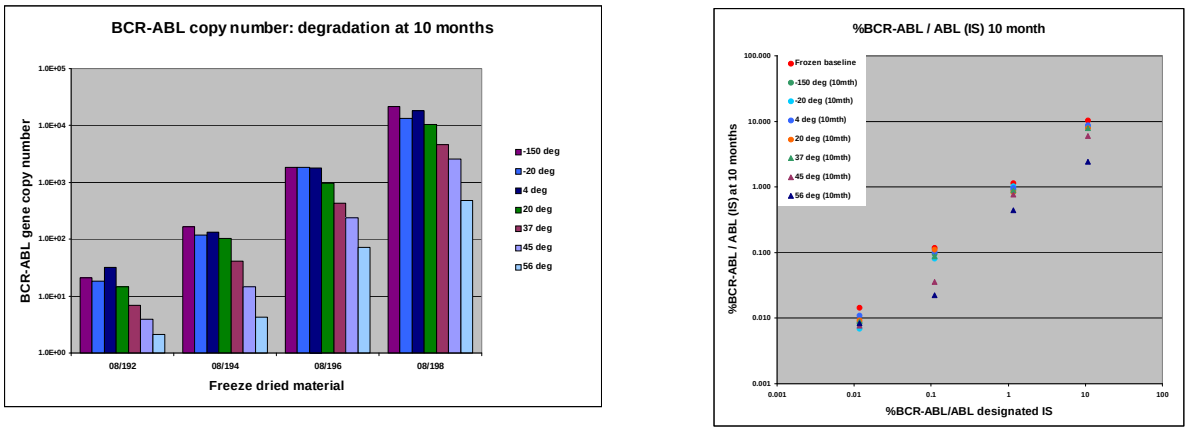



**Figure 12.4. Stability of BCR-ABL transcripts in freeze dried cells in accelerated degradation studies.** Left panel: absolute copy numbers for each of the four dilutions extracted from vials of freeze dried cells that had been maintained at 7 different temperatures for 10 months. Right panel: Values plotted as BCR-ABL/ABL ratios.

In addition to the work above, the EUTOS group has focused very productively on the establishment of conversion factors (CFs) for at least one laboratory per country or region following the protocol developed by the Adelaide laboratory. A control round to assess the ability of laboratories to detect

resistance-associated mutations is underway, with samples distributed in November 2009 and data analysis scheduled for February 2010.

*JAK2-V617F (12.25-12.28):*

With the development of JAK2 inhibitors, the establishment of reliable DNA-based quantitative PCR assays to detect the V617F JAK2 mutation to assess disease response in myeloproliferative disorders will become relevant. Therefore, WP12 has been instrumental in the systematic evaluation of published and "in house" JAK2 assays in a multi-laboratory setting, conducted in collaboration with WP9 (Prof Barbui/Vannucchi/Kiladjian). Over the course of the last year the number of participating laboratories has increased from three (Florence [Vannucchi], London [Nickless/Tobal/Grimwade] and Paris [Cassinat/Chomienne/Kiladjian] to include Nantes (Sylvie Hermouet), Bordeaux (Eric Lippert), Freiburg (Heike Pahl), Bern (Elisabeth Oppliger) and Cambridge (Anthony Bench), with Belfast (Melanie Percy/Mary Frances McMullin) and Nijmegen (Bert van der Reijden) scheduled for inclusion in 2010. Two QC rounds were conducted during the course of this reporting year. The first involved distribution of dilutions of HEL and K562 cells, which harbor JAK2-V617F and wild type JAK2 alleles respectively, which were tested in 4 laboratories using the three best-performing published wild type and mutant assays (Larsen, Lippert & Nussenzveig), that were taken forward from previous QC rounds conducted within WP12 (that led to the elimination of 3 published assays, with suboptimal performance). The Larsen mutant assay was found to be the most efficient and afforded greater sensitivity, as compared to the Lippert and Nussenzveig assays. There was limited crossover of the Larsen mutant assay when tested on K562 cells (100% wild type JAK2), but much more crossover with the Lippert assay. The wild type JAK2 assays showed significant crossover as evidenced by amplification of the mutant allele in HEL cells, which was less marked with the Nussenzveig and Lippert assays than with the Larsen assay.

The second QC round involved 8 laboratories (Florence, Freiburg, Cambridge, Paris, Bern, London, Nantes, Bordeaux) and investigated 8 JAK2 assays (4 V617F mutant assays [Larsen, Lippert, Nussenzveig & Bern (Oppliger) "in house" assay]; 3 wild type assays [Larsen, Lippert & Nussenzveig]; total JAK2 [Oppliger "in house" assay]) and parallel amplification of independent control gene assays (albumin [BIOMED] and cyclophilin A [Pallisgaard "in house"]) to control for variations in template in each reaction. Plasmid standards for the wild type JAK2, mutant JAK2 and control gene assays were developed by Ipsogen, Marseille on behalf of WP12 and were found to perform well (Figure 12.5 and Table 12.1). Genomic DNA extracted from serial dilutions of HEL in K562 cells and K562 dilutions in HEL cells, reaction mixes for each RQ-PCR assay and plasmid standards for wild type and mutant JAK2 and the independent control genes were prepared and centrally distributed by Nicolas Maroc, Ipsogen Marseille. A standardized format for performing the QC exercise was distributed to the participating laboratories and data were returned to Nicolas Maroc and David Grimwade/Jelena Jovanovic (Guy's Hospital, London) during November 2009 for centralized analysis. The identities of the JAK2 mutant and wild type assays were blinded to all

participants by Ipsogen, and which were not revealed until after the results of the analyses had been completed. The design of the QC exercise that included HEL and K562 cells which harbor only mutant and wild type JAK2 alleles respectively allowed the specificity of the wild type assays to be assessed, in conjunction with assessment of the specificity and sensitivity of the mutant assays. Despite the different platforms (ABI7300, ABI7000, ABI7500 n=2, ABI7900 n=2, LC480, RG6000) and consequent differences in run conditions, marked concordance in the results obtained with all of the respective assays between the laboratories was observed, highlighting the validity of the exercise to draw firm conclusions.

In accordance with previous QC rounds, both the wild type and mutant Nussenzveig assays exhibited poor amplification plots and markedly inferior efficiency (median slopes -3.69 & -3.77, respectively). The Lippert wild type assay exhibited greater specificity than the Larsen wild type assay, in accordance with previous QC rounds. The Oppliger and Larsen mutant assays were found to be the most specific yielding Ct values >40 when applied to neat K562 cells in the majority of laboratories, irrespective of platform. Taking into account the detection limit of RQ-PCR assays (taken as Ct value of 40 according to the Europe Against Cancer [EAC] program consensus) and the level of background amplification observed for the mutant assays in neat K562 cells, the level of sensitivity of the mutant assays was determined in serial dilutions of HEL in K562 cells (taking detection limit as ⩽1 Ct below background amplification).

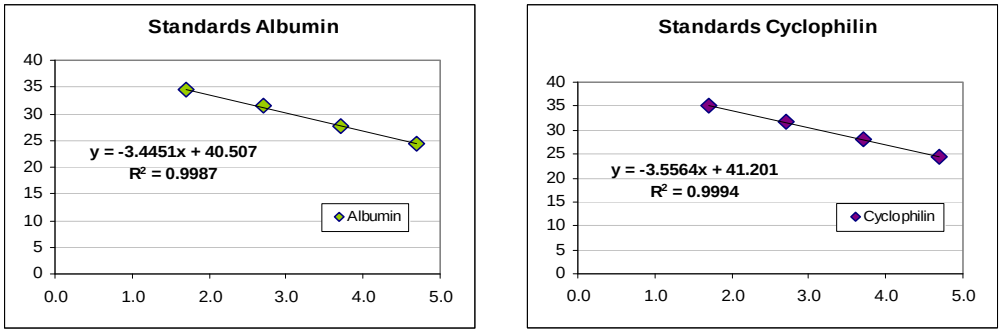



**Figure 12.5:** Development of plasmid standards for independent control genes to normalize MRD data for DNA-based Q-PCR assays

The mutant assays differed in their sensitivities (Table 12.2), with the Oppliger assay capable of detecting an estimated 0.008% mutant JAK2, the Larsen assay detected 0.08-008%, the Lippert assay was consistently less sensitive – 0.08% and the Nussenzveig assay the least sensitive due to inferior efficiency (0.8%). These data are in accordance with those of previous QC rounds which showed that the Larsen assay exhibited better performance than the Lippert assay, with both assays being superior to the Nussenzveig assay. Based upon these and previous data, the Nussenzveig assay will be dropped from the next QC round that is planned for early 2010 and will involve evaluation of the assays in UKE-1 cells which harbor the JAK2-V617F mutant allele. This cell line may be preferable to the use

of HEL cells, which contains multiple copies of mutant JAK2. Work in 2010 will focus on completing the optimization process and development of standardized protocols suitable for analysis of pre-treatment and follow-up samples from the next phase of clinical trials in JAK2-V617F positive MPDs, including evaluation of JAK2 inhibitors.

**Table 12.1. Comparison of performance of wild type (WT) and mutant (MUT) JAK2 assays in QC exercise conducted in 8 laboratories.**
The values provided are slopes reported for plasmid standard curves generated with centrally distributed reagents; assays with maximal efficiency exhibit a slope value of -3.3. Data for the independent control gene assays Albumin (ALB) and Cyclophilin (CYC) are also shown.
Design A: Lippert assay
Design B: Bern (Oppliger) "in house" assay. For this assay the "WT" data relate to total JAK2 (i.e. wild type and mutant)
Design C: Nussenzveig assay
Design D: Larsen assay

| | | Vannucchi (ABI 7300) | Pahl (ABI 7000) | Bench (ABI 7500) | Cassinat (ABI 7500 fast) | Oppliger (ABI 7900) | Tobal (ABI 7900HT) | Lippert (LC480) | Hermouet (RG 6000) |
|---|---|---|---|---|---|---|---|---|---|
| Design A | WT | -3.54 | -3.36 | -3.61 | -3.91 | -3.44 | -3.45 | -3.46 | -3.55 |
| | MUT | -3.86 | -3.56 | -3.71 | -3.72 | -3.55 | -3.29 | -3.60 | -3.61 |
| Design B | WT | -3.44 | -3.29 | -3.79 | -3.18 | -3.34 | -3.43 | -3.27 | -3.50 |
| | MUT | -3.53 | -3.36 | -3.53 | -3.47 | -3.47 | -3.35 | -3.52 | -3.67 |
| Design C | WT | -3.73 | -3.38 | -3.71 | -3.66 | -3.01 | -3.56 | -3.98 | -3.76 |
| | MUT | -3.72 | -3.48 | -3.81 | -4.06 | -3.83 | -3.72 | -4.21 | -3.68 |
| Design D | WT | -3.32 | -3.35 | -3.38 | -3.34 | -3.44 | -3.24 | -3.43 | -3.55 |
| | MUT | -3.49 | -3.49 | -3.75 | -3.66 | -3.55 | -3.71 | -3.50 | -3.61 |
| | ALB (avg) | -3.37 | -3.43 | -3.63 | -3.56 | -3.30 | -3.45 | -3.61 | -3.65 |
| | CYC (avg) | -3.49 | -3.45 | -3.73 | -3.73 | -3.24 | -3.36 | -3.65 | -3.80 |

**Table 12.2. Determination of relative sensitivity of 4 assays to detect JAK2-V617F mutant allele in serial dilution of HEL cells in K562 cells in QC exercise conducted in 8 laboratories.**
The sensitivity quoted for each assay (0.8%-0.008%) by each laboratory takes into account the detection limit of RQ-PCR assays (taken as Ct value of 40 according to EAC) and the level of background amplification observed for the mutant assays in neat K562 cells (taking detection limit as □1 Ct below background amplification).
Design A: Lippert assay
Design B: Bern (Oppliger) "in house" assay
Design C: Nussenzveig assay
Design D: Larsen assay

| | Vannucchi (ABI 7300) | Pahl (ABI 7000) | Bench (ABI 7500) | Cassinat (ABI 7500 fast) | Oppliger (ABI 7900) | Tobal (ABI 7900HT) | Lippert (LC480) | Hermouet (RG 6000) | Max |
|---|---|---|---|---|---|---|---|---|---|
| Design A | 0.08 | 0.8 | 0.08 | 0.08 | 0.8 | 0.8 | 0.08 | 0.08 | 0.08 |
| Design B | 0.008 | 0.008 | 47.1 | 0.008 | 0.08 | 0.08 | 0.008 | 0.008 | 0.008 |
| Design C | 0.8 | 0.8 | 0.8 | 0.8 | 0.8 | 0.8 | 7.5 | 0.8 | 0.8 |
| Design D | 0.08-0.008 | 0.08 | 0.08 | 0.08 | 0.08 | 0.08 | 0.08 | 0.08 | 0.08-0.008 |

The development of novel RQ-PCR assays requires confirmation that they are RNA-specific and determination of background levels of amplification due to non-leukemic cells. RNA-specificity was previously confirmed in novel assays designed to amplify FIP1L1-PDGFRA fusion transcripts in chronic eosinophilic leukemia (Jovanovic et al, Blood 2007). In AML we have shown that levels of

background amplification in NPM1 Type A, B and D mutation assays due to the wild type allele are too low to compromise assay sensitivity.

Since WT1 is expressed in normal hematopoietic progenitors and is therefore not a leukemia-specific target we have previously undertaken extensive analyses using centrally distributed ELN WT1 kits to establish reference ranges for levels of expression of WT1 transcripts in normal blood (n=118, median 0.01 WT1 copies/104 ABL copies, 0.01-47.6), marrow (n=61, median 19.8, 0-213), and peripheral blood stem cells (n=25, median 6.1, 0-39) (Figure 6, left panel). Sequential analysis of PB and BM samples from 15 AML cases with low WT1 expression (<250 copies) showed no significant modulation in transcript level on regeneration after chemotherapy (Figure 12.6, right panel), indicating that in WT1+ AML, transcript levels detected in follow-up samples reliably reflect disease status.

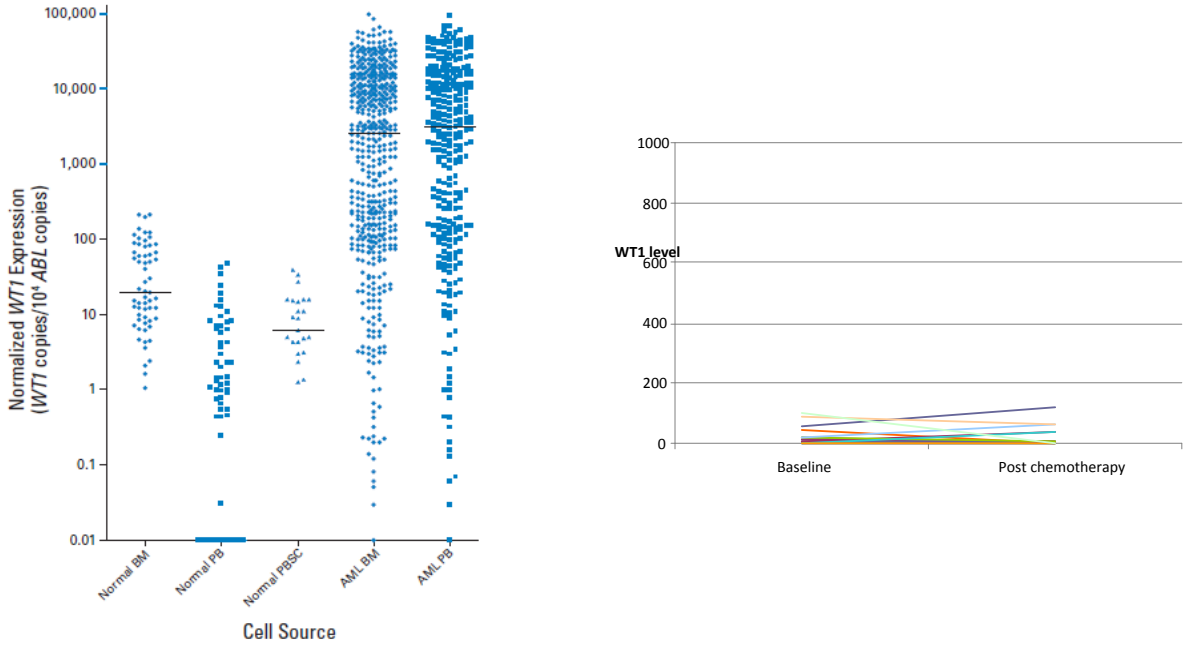



**Figure 12.6. Evaluation of standardized ELN WT1 assay for MRD detection in AML**
Left panel: Relative expression of WT1 (WT1 copies/104 ABL copies) in pre-treatment PB and BM samples from AML patients relative to control PB, BM and peripheral blood stem cell (PBSC) samples derived from normal volunteers. Median values denoted by a horizontal bar
Right panel: Comparison of WT1 transcripts between diagnosis and follow-up samples taken on regeneration following intensive chemotherapy in patients lacking over-expression of WT1 in leukemic blasts. These data provide evidence that WT1 expression is not modulated on regeneration following chemotherapy, supporting its use as a valid MRD target.

### 12.15d Evaluation of validated RQ-PCR assays in national clinical trials

Prospective detection of *PML-RARA* transcripts to direct treatment of APL patients:

A key premise is that molecular detection of MRD using RQ-PCR can reliably predict relapse, thereby allowing early treatment intervention which could potentially avert full-blown relapse and improve overall chances of cure. There is preliminary evidence from the GIMEMA and PETHEMA groups to

support this notion in acute promyelocytic leukemia (APL), although this had not been evaluated prospectively in multi-center clinical trials using RQ-PCR. In a project led by David Grimwade, this has been addressed in collaboration with Alan Burnett and Francesco Lo Coco in WP5 (AML) in the UK Medical Research Council (MRC) AML15 trial. First-line treatment involved ATRA and anthracycline-based chemotherapy, with RQ-PCR used to identify patients with persistent disease or molecular relapse to direct pre-emptive therapy with arsenic trioxide prior to transplantation, with type of transplant (autologous vs allogeneic) being dependent upon molecular response as well as donor availability. Over 6,000 samples were prospectively analyzed by RQ-PCR from 303 patients, including over 2,000 paired BM and PB samples. The majority of samples were analyzed by Jelena Jovanovic, who is jointly supported by ELN WP12 and charitable funding (Leukaemia Research). MRD monitoring according to the recommended schedule (3 monthly BM examination – based upon the data acquired concerning maximal assay sensitivity and kinetics of disease relapse) successfully identified the majority of patients subject to relapse and provided the most powerful predictor of relapse free survival (RFS) in multivariable analysis (HR 17.87, 95% CI 6.88-46.41,$p<0.0001$), far superior to presenting WBC (HR 1.02, CI 1.00-1.03,$p=0.02$) which is currently widely used to guide therapy. In patients who were predicted to experience relapse on the basis of MRD monitoring, early treatment intervention with arsenic trioxide prevented progression to overt relapse in the majority, associated with 73% relapse free survival at 1 year (see Annex Section 3, WP12-25).

Applying the strategy of sequential MRD monitoring to direct pre-emptive therapy within AML15 was associated with a cumulative incidence of clinical relapse (CIR) of only 5% at 3 years. This was lower than the 12% rate of CIR ($p=0.02$) observed in the previous MRC AML12 trial involving patients treated with combination MRC chemotherapy with extended ATRA, but in which MRD monitoring was not performed (Figure 12.7). While it is recognized that AML12 represents a historical control group, treatment was less intensive in half the patients in AML15 who were randomized to receive the PETHEMA schedule. The lower relapse rate in AML15 could not be accounted for by differences in the distribution of Sanz risk groups, the rate or relative timing of relapses between MRC and PETHEMA treatment schedules. Indeed analyses adjusted for any differences in age, performance status or WBC gave a consistent hazard ratio of 0.51 (0.26-1.03) $p=0.06$.

Based on comparison of survival of patients treated with MRC chemotherapy in the successive trials, with RQ-PCR assays costing an average of $5,370 per patient and assuming a life expectancy of 25 years for patients successfully salvaged, MRD monitoring was found to be most cost-effective in high risk patients (WBC >10) with a 10% survival benefit at 5 years giving $2,415/quality adjusted life year (QALY) compared to those with WBC<10 (1% survival benefit at 5 years giving $25,600/QALY). This prospective multi-center study has been very helpful in establishing the most appropriate MRD monitoring schedules in APL, that have been taken into account in the British Committee for Standards in Haematology (BCSH) AML guidelines (Milligan et al, Br J. Haematol

2006) and International APL guidelines developed by an expert working group convened by ELN and led by Prof Miguel Sanz on behalf of WP5 (see Annex Section 3, WP12-12).

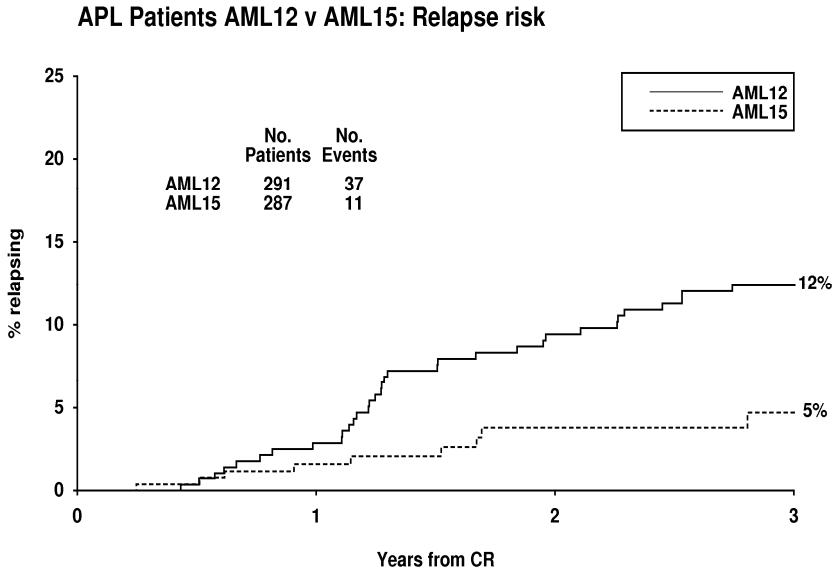



**Fig 12.7. Evaluation of minimal residual disease (MRD) monitoring and pre-emptive therapy to reduce rates of frank relapse in PML-RARA+ acute promyelocytic leukemia (APL) in the Medical Research Council Acute Myeloid Leukaemia 15 (MRC AML15) trial.**
Cumulative incidence of clinical relapse was compared between patients with APL treated with extended all-transretinoic acid (ATRA) and anthracycline-based chemotherapy in the MRC AML12 trial, in which MRD monitoring and pre-emptive therapy were not routinely undertaken, and the MRC AML15 trial, in which this was performed. The ADE/ADE/MACE/MiDAC schedule from AML12 was given to half the patients in MRC AML15, and the remaining patients were randomized to receive the less intensive PETHEMA schedule involving ATRA and anthracycline monochemotherapy. A significant reduction in relapse rate was observed in AML15, which was apparent across risk groups defined by presenting white blood count (WBC) (10 v 10 x 109/L) or Sanz risk group.

Analysis of RQ-PCR profiles in APL has served to highlight important principles that enable the development of optimized schedules for MRD detection, suitable for guiding therapy according to the needs of the individual patient. This is becoming increasingly relevant with interest in investigation of de-intensified treatment protocols for APL, placing greater reliance on MRD monitoring to identify patients who need additional therapy to secure cure of their disease. RQ-PCR using the standardized assay is being used prospectively to guide the management of APL patients in a number of multi-center European studies being conducted by the GIMEMA, DSIL and UK NCRI groups evaluating the use of chemotherapy-free schedules comprised solely of molecular-targeted therapies (i.e. arsenic + ATRA) as compared to conventional ATRA+anthracycline-based therapy. The results of the MRC AML15 trial have also helped inform the International Pediatric APL trial (ICC-APL01) in which treatment reduction will be investigated in low-risk disease and which will use MRD monitoring to guide treatment approach.

### 12.23 Development and enhancement of computerized RQ-PCR reporting systems:

This project has been led by Peter Hokland (Aarhus) in collaboration with a Danish software house – Langtved Data, with the aim of developing a program to report RQ-PCR results from any platform in a standardized manner (see Figure 8), since this could have a major benefit in management of patients. A beta version of the program was generated in Spring 2005. Further modifications to the program were made following a users' group meeting and intermittent system review. The software program was installed in September 2006 for evaluation in two laboratories in London (Guy's Hospital and King's College Hospital) using ABI platforms (ABI7700/7900) and in the Munich Leukemia Laboratory which employs Lightcycler technology. Installation was successful; however, a number of minor operational issues were identified regarding the display of sensitivity values for follow-up samples, selection of a reference standard and export of data from the Lightcycler platform. These prompted further modifications to the program and an installation guide and "User manual" were prepared by Mette Østergaard and Charlotte Guldborg Nyvold.

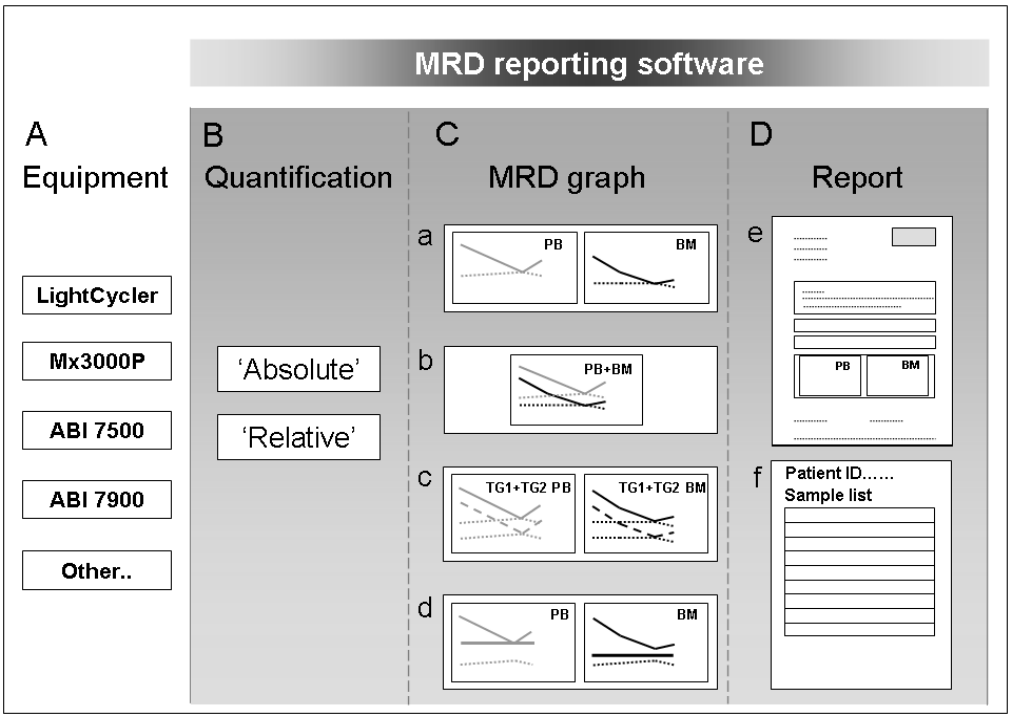



**Figure 12.8. MRD reporting program software overview**
A) The software accommodates raw data from a broad range of qPCR hardware (carousel/plate/microplate principle). B) Two standard modes of MRD calculation, 'absolute' and 'relative' quantification, as well as two different ways of assessing assay sensitivity can be employed – based on control gene copy number or ΔCt as reported (Grimwade et al, J Clin Oncol 2009). C) A number of different MRD graphs (solid lines) and sensitivity graphs (hatched lines) can be produced, e.g. a) peripheral blood (PB) and bone marrow (BM) in either separate or b) combined graphs, c) with up to three different target genes (TG) in one graph, and d) inclusion of a fixed threshold line (in bold), e.g. for illustration of the normal expression level for WT1 assessments. Graph colors and styles are editable. D) A premade report template allows for fast and easy completion and printing of e) a PDF report to the referring department, or f) a list of all results from a given patient (exportable to Excel).

During the course of this reporting year, use of the reporting program was rolled out to 8 WP12 laboratories (Aarhus, Copenhagen, Frankfurt, Istanbul, London [King's College & Guy's Hospital], Turku & Vejle). The capacity of the program to allow reporting of MRD data in a standardized fashion irrespective of RQ-PCR platform was evaluated through a QC exercise that was coordinated by Charlotte Nyvold (Aarhus). This involved centralized distribution of leukemic cDNA samples

(provided by Aarhus), RQ-PCR primers/probes and plasmid standards (provided by Ipsogen, Marseille) to the 8 laboratories (3 labs with some experience of the MRD reporting program, 5 labs in which the program had just been installed and were testing it for the first time). Serial samples were provided from a CML patient (5 consecutive samples + cDNA from the K562 cell line as a reference) and also from an AML patient (5 consecutive samples), to be monitored by CBFB-MYH11 and WT1 assays in parallel (using the standardized EAC and ELN assays, respectively). Data were normalized to the ABL control gene. Between the participating laboratories, 4 platforms were used (ABI 7500/7900, Mx3000 & Lightcycler 480). Relative quantification based on ΔΔCt method (compared to diagnostic sample and K562 for the CML sample) and absolute quantification (comparison to plasmid standards) methods for RQ-PCR data reporting were evaluated.

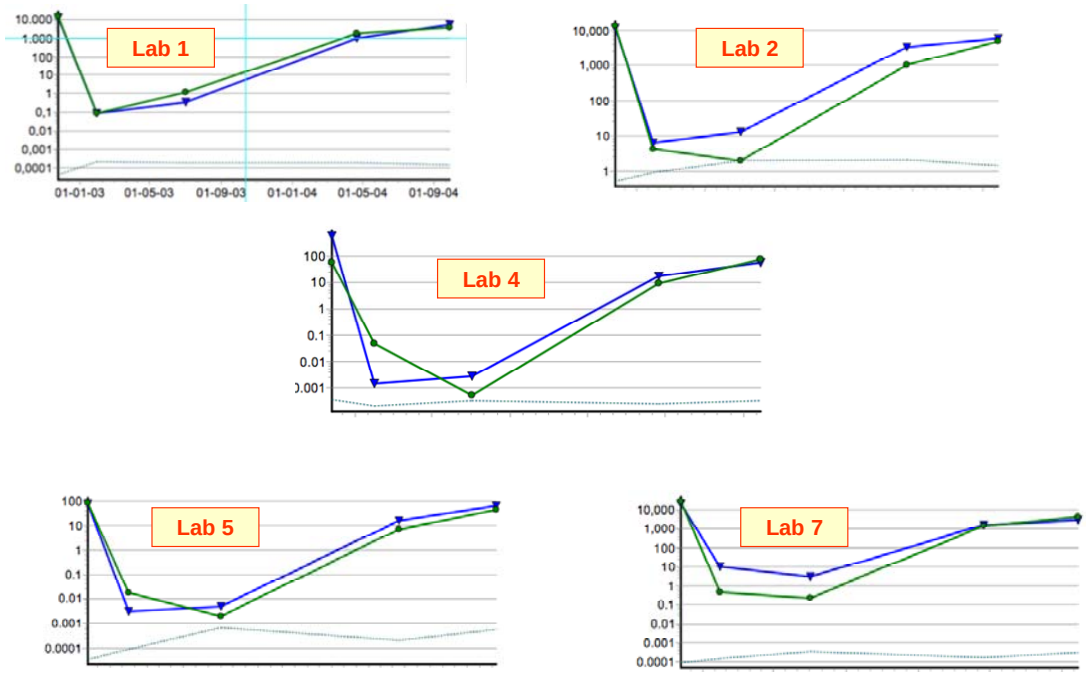



**Figure 12.9. Generation of standardized MRD reports using ELN Reporting Program**
Complementary DNAs derived from diagnostic and follow-up samples from (inv)16 related AML were dispatched to laboratories participating in the QC exercise, analyzed using centrally distributed assay reagents (CBFB-MYH11, WT1, ABL) and reported in a standardized fashion using the ELN MRD reporting program. Good concordance was observed between normalized MRD results obtained using the Europe Against Cancer CBFB-MYH11 (green line – labs 2, 4 & 5; blue line – labs 1 & 7) and ELN WT1 (blue line – labs 2, 4 & 5; green line – labs 1 & 7) assays. Good concordance was also observed in the reports generated with the program, although differences in the scale of the y-axis reflect normalization to 100 or 10e4 ABL copies.

For the BCR-ABL samples, remarkable intra- and inter-laboratory concordance was observed in the results irrespective of whether data were reported relative to the diagnostic sample, to the K562 cell line, or whether absolute quantification based on plasmid standards was used. A high degree of concordance was also observed between laboratories in the reporting of WT1 and CBFB-MYH11 data, when using diagnostic levels as reference or absolute quantification (Figure 12.9). Moreover, very close concordance was observed between the WT1 and CBFB-MYH11 MRD profiles in each laboratory; although, there were some discrepancies where particular labs had adopted different cut-off

thresholds to define samples as PCR positive (e.g Ct <41 and Ct <45) or had normalized target gene expression to different numbers of ABL copies (e.g. per 100 or per 10e4 copies).
The QC exercise usefully revealed some minor teething problems in the installation and use of the program; these included difficulties in uploading data to the program, generating certain report types and failure of some labs to use recommended settings. These issues were easily rectified following advice provided by Aarhus or Langtved Data. The QC exercise clearly highlighted the potential of the program to facilitate greater standardization in reporting of MRD data between laboratories and the revised program is now used routinely for reporting of all MRD results by the APL reference laboratory at Guy's Hospital, London, including all samples from the UK NCRI AML17 trial.

During the forthcoming year, it is planned to complete the evaluation of the program through a further QC study that will involve reporting of BCR-ABL data according to the International Scale. Over the course of 2010 we anticipate that the MRD reporting program, which is available free of charge to all ELN members, will be disseminated even more widely. Measures are being put in place for Langtved Data to provide a user help desk to support the program, covered by a service charge (~€2,200 per annum). The legal agreement regarding the future of the program, service agreement, escrow and intellectual property issues has been drawn up between Langtved Data and the ELN Management Center.

**12.21c Spreading of excellence by promotion of web-based information, exchange of researchers, training courses and promotion of guidelines**

In previous years WP12 members have contributed to practice guidelines and recommendations on the use of MRD monitoring by RQ-PCR approaches to guide therapy in patients with CML and APL (Hughes *et al, Blood* 2006; Baccarani *et al, Blood* 2006; Milligan *et al, Br J Haematol* 2006). Over the course of the last year, ELN guidelines on the management of APL (led by Miguel Sanz) and AML (led by Hartmut Döhner) have been finalized and published (see Annex Section 3, WP 12-5, -12), which both include guidance on the role of MRD monitoring, contributed by David Grimwade on behalf of WP12.

**12.22c Analysis of gender specific issues**

A major source of interest to the group is the male preponderance of *FIP1L1-PDGFRA* associated leukemia. Andreas Reiter is leading the project to define the genomic anatomy of the chromosomal rearrangement underlying this condition which may provide some insights into the sex bias associated with this disease and which could be pertinent to the pathogenesis of other subsets of leukemia. Recently, his group analyzed *FIP1L1-PDGFRA* junction sequences from 113 patients at the mRNA (n=113) and genomic DNA (n=85) levels (see Annex Section 3, WP 12-14). Transcript types could be assigned in 109 patients as type A (n=50, 46%) and type B (n=47, 43%), which were created by cryptic acceptor splice sites in different introns of *FIP1L1* (type A) or within *PDGFRA* exon 12 (type

B). A new transcript type was identified – type C (n=12, 11%) in which both genomic breakpoints fell within coding sequences creating a hybrid exon without use of a cryptic acceptor splice site. The location of genomic breakpoints within *PDGFRA* and the availability of AG splice sites determine the transcript type and restrict the *FIP1L1* exons used for the creation of the fusion. Stretches of overlapping sequences were identified at the genomic junction site, suggesting that the *FIP1L1-PDGFRA* fusion is created by illegitimate non-homologous end-joining. Statistical analyses provided evidence for clustering of breakpoints within *FIP1L1* that may be related to DNA- or chromatin-related structural features. The variability in the anatomy of the *FIP1L1-PDGFRA* fusion has important implications for strategies to detect the fusion at diagnosis or for monitoring response to treatment.

In a related study current detection methods for *FIP1L1-PDGFRA* were evaluated by developing a means to rapidly amplify genomic breakpoints (Score et al, Leukemia 2009). Two hundred and two cases were screened and genomic junctions detected in all samples previously identified as RT-PCR positive (n=43). Genomic fusions were amplified by single step PCR in all cases, whereas only 22 (51%) were single step RT-PCR positive. Importantly, *FIP1L1-PDGFRA* was detected in two cases that initially tested negative by RT-PCR or fluorescence in situ hybridization. Absolute quantification of the fusion by real-time PCR from genomic DNA (gDNA) using patient-specific primer/probe combinations at presentation (n=13) revealed a 40-fold variation between patients (range, 0.027-1.1 *FIP1L1-PDGFRA* copies/haploid genome). In follow up samples, quantitative analysis of gDNA gave 1-2 log greater sensitivity than RQ-PCR of cDNA. Minimal residual disease assessment using gDNA showed that 11 of 13 patients achieved complete molecular response to imatinib within a median of 9 months (range, 3-17) of starting treatment, with a sensitivity of detection of up to 1 in 105. One case relapsed with an acquired D842V mutation. Detection of *FIP1L1-PDGFRA* from gDNA is thus a useful adjunct to standard diagnostic procedures and enables more sensitive follow up of positive cases after treatment.

*Deviations from the workprogram and corrective actions taken: identify the nature and the reasons for the problem, identify contractors involved.*

Not applicable

## List of deliverables WP 12, 2009

| Deliv. No. | Deliverable Name | Date due | Actual/Forecast delivery date | Estimated indicative person months*) | Used indicative person months*) | Lead contractor |
|---|---|---|---|---|---|---|
| **WP 12** | **MRD** | | | | | |
| **12.5** | Regular WP meetings | 61,66,72 | done | 0 | 15 | Grimwade, Hochhaus, Reiter |
| **12.6** | LP reports to NMC regarding structure, activities and integration of national groups | 61,64, 67,70 | ongoing | 0 | 3 | Grimwade |
| **12.11d** | Establish the additional proportion of leukemic patients that can be monitored using novel targets | 66 | done | 0 | 8 | Grimwade Saglio Preudhomme |
| **12.15d** | Evaluation of validated RQ-PCR assays in national clinical trials | 78 | ongoing | 0 | 10 | Grimwade |
| **12.21c** | Spreading of excellence by promotion of web-based information, exchange of researchers, training courses and promotion of guidelines | 78 | ongoing | 0 | 1 | Grimwade |
| **12.22c** | Analysis of gender specific issues | 66 | done | 0 | 2 | Reiter |
| **12.23** | Installation and implementation of Q-PCR reporting program within ELN member laboratories | 66 | done | 0 | 4 | Grimwade Hokland |
| **12.24** | Evaluation of MRD monitoring to predict relapse and direct donor leucocyte administration following allogeneic transplant | 78 | ongoing | 0 | 2 | Grimwade |
| **12.25** | Conduct of QC exercises for mutation targets | 66 | done | 0 | 2 | Grimwade |
| **12.26** | Compare sensitivity and specificity of published JAK2 V617F Q-PCR assays to establish best-performing assay | 72 | ongoing | 0 | 3 | Grimwade |
| **12.27** | Compare performance of reference gene assays for JAK2 V617F quantification | 72 | done | 0 | 2 | Grimwade |
| **12.28** | Develop plasmid standards for JAK2 V617F and selected reference gene assay | 72 | done | 0 | 2 | Hermitte |
| **12.29** | Comparison of RNA- and DNA-based Q-PCR assays for NPM1 mutations | 72 | ongoing | 0 | 1 | Grimwade |

*) if available

## List of milestones WP 12, 2009

| Milestone No. | Milestone Name | Date due | Actual/Forecast delivery date | Lead contractor |
|---|---|---|---|---|
| **WP 12** | **MRD** | | | |
| **12.13c** | Development of standardized protocols for MRD assessment using RNA-based targets (from bedside to clinical report) | 66 | 66 | Grimwade Hochhaus Cross Hokland |
| **12.15d** | Establish prognostic significance of validated Q-PCR assays in national clinical trials | 66 | 66 | Grimwade Saglio |
| **12.23** | Service implementation of ELN MRD reporting program | 66 | 66 | Grimwade |
| **12.26-8** | Establish optimal assay for quantification of JAK2 V617F mutant allele load | 72 | 72 | Grimwade |

## Section 4: Other Issues

Ethical issues - none

Competitive calls - none

## Section 5: WP-Performance

| Performance indicators | Status |
|---|---|
| Organization of interdisciplinary consensus conferences | Done |
| Development of consensus protocols for the diagnostic work up to identify MRD targets in leukemia | In progress |
| Organization of quality control rounds | On-going |
| Set up of internet forum | In progress |
| Number and quality of publications within the network | 42<br>17 abstracts (6 oral, 11 poster) |
| Number of researchers in exchange programs | 0 |
| Implementation of technology transfer | In progress |
| RQ-PCR assays for rare fusion gene transcripts, leukemia associated mutations and for novel overexpressed genes | 4 |
| Evaluation of validated RQ-PCR assays in national clinical trials | In progress |
| Development of standardized protocols for MRD assessment using RNA-based targets (from bedside to clinical report) | Done |
| Development of optimized sensitive validated assays for MRD detection | Done |

**Gene profiling (WP 13)**

*Objectives and work within reporting period*

WP 13 is an established working group of MDs and PhDs interested in using gene expression profiling both for investigating basic research topics and the application of microarrays in a clinical setting. These tasks were strongly supported by biostatisticians. Microarray data was collected within the ELN network and involved respective subgroups in WP 13 as well as other WPs in close collaborations.

Thus, general interactions with other groups (WPs 5, 8, 10, 11 and 12) improved and now more benefited from data available: As the MILE (Microarray Innovations in LEukemia) project – funded in part by ROCHE Molecular Systems (RMS) – ended in 2/2008 the data is now in press (JCO) and available for all (see below). Yet, during 2009 data from MILE study still was successfully driven by members of the ELN WP 13 and also resulted in several publications in 2009 and also 2010. In many aspects, major expert knowledge of WP participants (WPs 10, 11, 12) was provided to the MILE project that helped to integrate data from morphology, cytogenetics, molecular genetics and immunophenotyping and is now given back to the other WP (see new deliverables). In particular, expert recommendations were required to analyze and validate the "Gold Standard" diagnoses for more than 3500 samples tested ultimately in both MILE and DACH studies and can now be used for new projects in 2010 (see detailed information below).

The DACH study (already delivered 2008) involved new ELN centers in Linz (Dr. Haschke-Becher), Austria, and Basel (Dr. Meyer-Monard) and Geneva (Dr. Matthes), Switzerland. In 2009/2010 a new project started with Dr. Matthes in Geneva to use genes from the MILE data set to test the new so called nanostring technique in cooperation with WP13 and founded by the Swiss Cancer league.

In parallel, all biostatistical platforms have been upgraded: one for the MILE publication (ROCHE in-house), and a second one – GAP – lead by Prof. Dugas (Münster) for ELN members. GAP is freely available for all ELN members, and not restricted to the MILE subgroups. In the ELN GAP database, data can easily be stored, exchanged and analyzed within the participating WPs (see below). Microarray raw data from the MILE study are submitted to the GEO database at the NCBI in 12/2008 and are now made publicly available to the world-wide scientific community after acceptance of the paper (since 12/2009, see information below).

Several other publications were published in 2009 using parts of the MILE data set and more are upcoming and started to be performed in WP13, especially together with WP8, WP10 and WP11.

*Progress towards objectives – tasks worked on and achievements made with reference to planned objectives*

**13.1d Expand of WP information and communication structures**

The GAP database in Münster was further improved and includes now much more multiple statistical packages for analysis of gene expression microarray data (for details see http://imiblinux05.uni-muenster.de/). This is all only possible due to the strong support of this outstanding statistic group (Head Prof. Dugas) within and through the WP13.

Still all data from MILE prephase paper by Kohlmann et al. (Br J Haematol. 2008 Sep;142(5):802-7) can be accessed in GEO database: http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE11135. Corresponding data from the DACH study can still be accessed in the supplement of the respective paper (Kohlmann et al. Clin Chem. 2008 Oct;54(10):1705-15.)

The data from the MILE study is publically available at the GEO database at the NCBI since 12/2009. The manuscript is in press in the JCO (see proofs below):

## MILE Study: Current Status

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Clinical Utility of Microarray-Based Gene Expression Profiling in the Diagnosis and Subclassification of Leukemia: Report From the International Microarray Innovations in Leukemia Study Group

Torsten Haferlach, Alexander Kohlmann, Lothar Wieczorek, Giuseppe Basso, Geertruyte Kronnie, Marie-Christine Bené, John De Vos, Jesus M. Hernández, Wolf-Karsten Hofmann, Kin J. Mills, Amanda Gilkes, Sabina Chiaretti, Sheila A. Shurtleff, Thomas J. Kipps, Laura Z. Rassenti, Allen E. Yeoh, Peter R. Papenhausen, Wei-min Liu, P. Mickey Williams, and Robin Foà

ABSTRACT

Purpose
The Microarray Innovations in Leukemia study assessed the clinical utility of gene expression profiling as a single test to subtype leukemias into conventional categories of myeloid and lymphoid malignancies.

Methods
The investigation was performed in 11 laboratories across three continents and included 3,334 patients. An exploratory retrospective stage I study was designed for biomarker discovery and generated whole-genome expression profiles from 2,143 patients with leukemias and myelodysplastic syndromes. The gene expression profiling–based diagnostic accuracy was further validated in a prospective second study stage of an independent cohort of 1,191 patients.

Results
On the basis of 2,096 samples, the stage I study achieved 92.2% classification accuracy for all 18 distinct classes investigated (median specificity of 99.7%). In a second cohort of 1,152 prospectively collected patients, a classification scheme reached 95.6% median sensitivity and 99.8% median specificity for 14 standard subtypes of acute leukemia (eight acute lymphoblastic leukemia and six acute myeloid leukemia classes); in 29 (67%) of 51 discrepant cases, the microarray results had outperformed routine diagnostic methods.

Conclusion
Gene expression profiling is a robust technology for the diagnosis of hematologic malignancies with high accuracy. It may complement current diagnostic algorithms and could offer a reliable platform for patients who lack access to today's state-of-the-art diagnostic work-up. Our comprehensive gene expression data set will be submitted to the public domain to foster research focusing on the molecular understanding of leukemias.

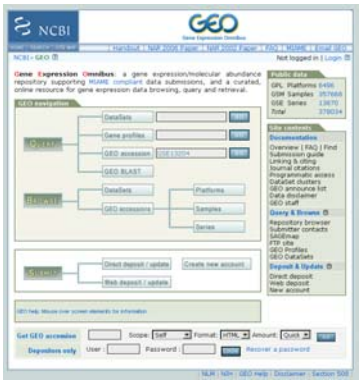
J Clin Oncol 28. © 2010 by American Society of Clinical Oncology

Haferlach T et al., JCO in press

## MILE Study: Current Status

**Complete study database uploaded to GEO repository**

**All CEL files available now! (n = 3248)**




GSE13204

Haferlach T et al., JCO in press

Data from the MDS study (Prof. Mills, Belfast) were submitted to GEO. The MDS manuscript is performed as a sub-cohort of the MILE study and its data set is available here:

## MILE Study: MDS Subgroup Analysis

MYELOID NEOPLASIA

Microarray-based classifiers and prognosis models identify subgroups with distinct clinical outcomes and high risk of AML transformation of myelodysplastic syndrome

Introduction

Mills et al., Blood. 2009 Jul 30;114(5):1063-72.

## MILE Study: MDS Subgroup Analysis

**Complete study cohort uploaded to GEO repository**

**All CEL files available (n = 435)**


Mills et al., Blood. 2009 Jul 30;114(5):1063-72.

Together with the group of Prof. Ehninger/Thiede in Dresden and Prof. Döhner/Dr. Bullinger in Ulm the Munich Leukemia Laboratory as part of the ELN performed another new and independent study on GEP in AML-NK focusing on molecular markers. This paper as part of ELN WP13 was accepted in Leukemia (in press), data is available in GEO also for further spreading of information:

## MILE Study Extension into AML-NK

**Gene expression profiling in AML with normal karyotype can predict mutations for molecular markers and allows novel insights into perturbed biological pathways**

Alexander Kohlmann[1], Lars Bullinger[2], Christian Thiede[3], Markus Schaich[3], Susanne Schnittger[1], Konstanze Döhner[2], Martin Dugas[4], Hans-Ulrich Klein[4], Hartmut Döhner[2], Gerhard Ehninger[3], and Torsten Haferlach[1]

[1]MLL Munich Leukemia Laboratory, Munich, Germany; [2]Internal Medicine III, University of Ulm, Ulm, Germany; [3]Medical Clinic I, University Hospital, Dresden, Germany; [4]Department of Medical Informatics and Biomathematics, University of Münster, Münster, Germany

Kohlmann et al., Leukemia 2010, in press

## MILE Study Extension into AML-NK

**Complete study cohort uploaded to GEO repository**

**All CEL files available (n = 251)**


GSE15434

Kohlmann et al., Leukemia 2010, in press

Some MILE data were also including in the paper shown below (data set also available in GEO):

## MILE Study Data: AML (*NPM1*)

MYELOID NEOPLASIA

AML with mutated *NPM1* carrying a normal or aberrant karyotype show overlapping biologic, pathologic, immunophenotypic, and prognostic features

Introduction

Haferlach C et al., Blood. 2009 Oct 1;114(14):3024-32.

## MILE Study Data: AML (*NPM1*)

**Complete study cohort uploaded to GEO repository**

**All CEL files available (n = 107)**


Haferlach C et al., Blood. 2009 Oct 1;114(14):3024-32.

To further use data from ELN WP13 and the Munich Leukemia Laboratory (in part combined with Dresden and Ulm group) the group of Prof. Dugas in Münster and the MLL together established new statistic tools that were published in 2 high rated biostatistic journals in 2009, these methods are now available for the ELN and are also made public due to these papers for the whole scientific community:

## Leukemia Database Effort

BMC Bioinformatics

Research article — Open Access

**Quantitative comparison of microarray experiments with published leukemia related gene expression signatures**

Hans-Ulrich Klein*[1], Christian Ruckert[1], Alexander Kohlmann[2], Lars Bullinger[3], Christian Thiede[4], Torsten Haferlach[2] and Martin Dugas[1]

Abstract

Background: Multiple gene expression signatures derived from microarray experiments have been published in the field of leukemia research. A comparison of these signatures with results from new experiments is useful for verification as well as for interpretation of the results obtained. Currently, the percentage of overlapping genes is frequently used to compare published gene signatures against a signature derived from a new experiment. However, it has been shown that the percentage of overlapping genes is of limited use for comparing two experiments due to the variability of gene signatures caused by different array platforms or assay-specific influencing parameters. Here, we present a robust approach for a systematic and quantitative comparison of published gene expression signatures with an exemplary query dataset.

Results: A database storing 138 leukemia-related published gene signatures was designed. Each gene signature was manually annotated with terms according to a leukemia-specific taxonomy. Two analysis steps are implemented to compare a new microarray dataset with the results from previous experiments stored and curated in the database. First, the global test method is applied to assess gene signatures and to constitute a ranking among them. In a subsequent analysis step, the focus is shifted from single gene signatures to chromosomal aberrations or molecular mutations as modeled in the taxonomy. Potentially interesting disease characteristics are detected based on the ranking of gene signatures associated with these aberrations stored in the database. Two example analyses are presented. An implementation of the approach is freely available as web-based application.

Conclusions: The presented approach helps researchers to systematically integrate the knowledge derived from numerous microarray experiments into the analysis of a new dataset. By means of example leukemia datasets we demonstrate that this approach detects related experiments as well as related molecular mutations and may help to interpret new microarray data.

Page 1 of 11

**Klein et al., BMC Bioinformatics. 2009 Dec 15;10:422.**

## Integrated Genomics Data Analysis

BIOINFORMATICS ORIGINAL PAPER

Genome analysis

**Integrated analysis of copy number alterations and gene expression: a bivariate assessment of equally directed abnormalities**

Martin Schäfer[1,2,*], Holger Schwender[1,3], Sylvia Merk[4], Claudia Haferlach[5], Katja Ickstadt[1,2] and Martin Dugas[6]

[1]Collaborative Research Center 475, [2]Department of Statistics, TU Dortmund University, Dortmund, Germany, [3]Department of Biostatistics, Johns Hopkins University, Baltimore, USA, [4]Galenus-G.H. AG, Basel, Switzerland, [5]MLL Munich Leukemia Laboratory, Munich and [6]Department of Medical Informatics and Biomathematics, University of Münster, Münster, Germany

Received on April 23, 2009; revised on October 9, 2009; accepted on October 12, 2009

Advance Access publication October 14, 2009

Associate Editor: Ivo Hofacker

ABSTRACT

1 INTRODUCTION

**Schäfer M et al., Bioinformatics. 2009 Dec 15;25(24):3228-35.**

Several other papers were published in 2009 from members of the WP13, using in part data from the MILE study cohort to support own findings or to create hypotheses for new investigations, the next slide gives an overview:

## Further MILES Contributions

**Two independent gene signatures in pediatric t(4;11) acute lymphoblastic leukemia patients.**
Trentin L, Giordan M, Dingermann T, Basso G, Te Kronnie G, Marschalek R.
Eur J Haematol. 2009 Nov;83(5):406-19.

**MLL rearrangements in pediatric acute lymphoblastic and myeloblastic leukemias: MLL specific and lineage specific signatures.**
Zangrando A, Dell'orto MC, Te Kronnie G, Basso G.
BMC Med Genomics. 2009 Jun 23;2:36.

**Gene expression profile of protein kinases reveals a distinctive signature in chronic lymphocytic leukemia and in vitro experiments support a role of second generation protein kinase inhibitors.**
Tavolaro S, Chiaretti S, Messina M, Peragine N, Del Giudice I, Marinelli M, Santangelo S, Mauro FR, Guarini A, Foà R.
Leuk Res. 2009 Dec 23.

**High BAALC expression predicts chemoresistance in adult B-precursor acute lymphoblastic leukemia.**
Kuehnl A, Goekbuget N, Stroux A, Burmeister T, Neumann M, Heesch S, Haferlach T, Hoelzer D, Hofmann WK, Thiel E, Baldus CD.
Blood. 2010 Jan 11.

New collaborations were initiated between the Munich Leukemia Laboratory (ELN center 127, SME) and Prof. Müller-Tidow (Münster) now with more than 350 samples of AML (all uniformly treated in AMLCG-99 study) that have been measured on a chip-on chip platform. Data collection will end in 3/2010 and will be available in Q3/2010. Statistics will be performed by Prof. Dugas group.

Two new investigations started in cooperation with WP10 (Prof. Béné) and WP11 in 2009 and will be ongoing in more depth in 2010 by using GEP data from WP13 groups, especially from MILE study and an independent data set from MLL, Munich: 1) Investigation of ALLs with knowledge of the lineage, CD20 expression and asparagine synthetase (or synthase) in line with the resistance of CD20+ ALL with hyperleucocytosis to chemotherapy. 2) Investigation of 104 patients with B-lineage ALL from MILE and Munich Leukemia Laboratory with known CD10 status. It is intended to focus on those with CD10+ *versus* those being CD10- on the array and to compare biology (all cytogenetics are available) and outcome.

### 13.4e Optimize European gene profiling platform

See D13.1d

Due to strong efforts from members of WP13 (**Mills**, Dugas, Haferlach) the EU funded a new project:

## Activities at the European Level

- **EuGESMA**
  European Genomics and Epigenomics Study on MDS and AML
  (coordinator: Ken Mills, Belfast)
- Workgroup Informatics
  Spain (Javier Des las Rivas, Lara Nonell)
  Italy (Silvio Bicciato, Cesare Furlanello)
  France (Chimène Moreilhon)
  Finland (Jaakko Hollmen)
  Poland (Lucjan Wyrwicz)
  Germany (Martin Dugas)

cost
EUROPEAN COOPERATION IN SCIENCE AND TECHNOLOGY

## EuGESMA Goals: Workgroup Informatics

- Central support for data analysis, management and interpretation
- Research into novel methods for integration of clinical and molecular data, initially with respect to the analysis of microarray data
- Development of data management and analysis systems for various chip platforms, such as gene expression profiling (Affymetrix), SNP arrays, array CGH, ChIP-on-chip, microRNA data, epigenetic profiling, proteomic data, high-throughput sequencing

cost
EUROPEAN COOPERATION IN SCIENCE AND TECHNOLOGY

This new group will closely cooperate with WP13 in the ELN to spread information in the upcoming years.

**13.5 Regular WP meetings**

One regular WP meeting for all WP13 members, combined in part with WP11, had been organized in Heidelberg in 2/09. One meeting with participants from Ulm, Dresden and Munich discussing side projects on NPM1 and CEBPA were held in Mannheim in 10/2009 (see paper on AML-NK).

Furthermore, some members of WP13, mostly representing members also of the European part of the MILE study, met together with WP10, MDS-flow-group in 10/2009 in the Munich Leukemia Laboratory to discuss flow in MDS, and to publish new standards in addition to the paper already available (see Annex Section 3, WP8-2). These investigations are supported also be WP13 as they are overlapping in part of data and in personnel.

**13.6 LP reports to NMC regarding structure, activities and integration of national GEP groups**

- Ongoing exchange of information regarding GEP data management and analysis strategies with ELN partners from Germany (Dresden, Freiburg, Munich, Ulm), Switzerland (Geneva), UK (Belfast, Cardiff), France (Montpellier, Nancy), Italy (Padua, Rome) and Spain (Salamanca)
- Regular updates to the European biostatistical data analysis platform (GAP) in Münster based on input from ELN participants available for all WP13 partners, also making new data sets public (see above)

**13.10d Develop new biostatistical approaches and expand the centralized database**

See in detail 13.1d above

**13.11d Detect further new subgroups of leukemia according to gene expression profiles**

As part of a collaboration between Dresden, Munich and Ulm on AML with normal karyotype over 250 cases predefined by NPM1, MLL-PTD, FLT3-ITD, CEPBA and WT1 status were analyzed with HG-U133 Plus 2.0 microarrays. Data are now in press, see in detail 13.1d above.

New investigations ongoing with Müller-Tiedow in AML (see 13.1d) and Béné in ALL (see 13.1d).

**13.12d Further evaluation of new genes for therapeutic and diagnostic purposes**

See studies by Müller-Tiedow and Béné more outlined in 13.1d.

**13.16c Further evaluation of new biostatistical methods**

Has been published or made publically available in 2009 (see 13.1d) and is still ongoing, now expanding to next-generation sequencing data.

**13.18d Find new diagnostic markers and MRD markers with WP 10, 11, 12**

See studies by Müller-Tiedow and Béné more outlined in 13.1d.

This aspect will be addressed in MILE study as being now publicly available through the GEO database. Parallel efforts of data mining are ongoing using the GAP resources in Münster.

In 2010 another new project will be performed with Dr. Matthes in Geneva to use genes from MILE data set to test the new so called nanostring technique in cooperation with WP13 and founded by the Swiss Cancer league.

**13.19d Define new entities in AML with WP5 with respect to prognosis in intermediate risk group**

Done, paper by Kohlmann et al. Leukemia in press (Annex Section 3, WP 13-30), for more information see 13.1d.

**13.21 Finalize ELN database for the public**

See for new tolls implemented in 2009: (`http://imiblinux05.uni-muenster.de/`).

*Deviations from the work program and corrective actions taken: identify the nature and the reasons for the problem, identify contractors involved*

Not applicable.

List of all deliverables WP 13, 2009

| Deliv. No. | Deliverable Name | Date due | Actual/Forecast delivery date | Estimated indicative person months*) | Used indicative person months*) | Lead contractor |
|---|---|---|---|---|---|---|
| **WP 13** | **Gene profiling** | | | | | |
| **13.1d** | Expand of WP information and communication structures | **61-78** | 12/2010 | 0 | 8 | Haferlach Dugas |
| **13.4e** | Optimize European gene profiling platform | **61-78** | 12/2010 | 0 | 6 | Haferlach Dugas |
| **13.5** | Regular WP meetings | **72** | 10/2010 | 0 | 1 | Haferlach |
| **13.6** | LP reports to NMC regarding structure, activities and integration of national GEP groups (1 page, bullet point style) | **72,78** | 12/2010 | 0 | 1 | Haferlach |
| **13.10d** | Develop new biostatistical approaches and expand the centralized data base | **61-78** | 2/2011 | 0 | 4 | Dugas |
| **13.11d** | Detect further new subgroups of leukemia according to gene expression profiles | **61-78** | 2/2011 | 0 | 4 | Haferlach Dugas |
| **13.12d** | Further evaluation of new genes for therapeutic and diagnostic purposes | **61-78** | 12/2010 | 0 | 4 | Haferlach, Béné, Müller-Tidow |
| **13.16c** | Further evaluation of new biostatistical methods | **61-78** | 12/2010 | 0 | 4 | Dugas |
| **13.18d** | Find new diagnostic markers and MRD markers with WP 10, 11, 12 | **61-78** | 2/2011 | 0 | 4 | Haferlach Grimwade Foa Bene |
| **13.19d** | Define new entities in AML with WP 5 with respect to prognosis in intermediate risk group | **61-78** | done | 0 | done | Haferlach Döhner, Thiede |
| **13.21** | Finalize ELN data base for the public | **64** | 2/2011 | 0 | 4 | Dugas Haferlach |

*) if available

**List of milestones WP13, 2009**

| Milestone No. | Milestone Name | Date due | Actual/Forecast delivery date | Lead contractor |
|---|---|---|---|---|
| **WP 13** | **Gene profiling** | | | |
| **13.16b** | Further evaluation of new biostatistical methods | 61-78 | Ongoing, in part published | Dugas |
| **13.18c** | Find new diagnostic markers and MRD markers with WP 10, 11, 12 | 61-78 | ongoing | Haferlach Grimwade Foà, Béné |
| **13.19c** | Define new entities in AML with WP 5 with respect to prognosis in intermediate risk group | 61-78 | Ongoing, in part published | Haferlach Döhner Thiede |
| **13.21** | Finalize ELN database for the public | 64 | Ongoing with new data sets | Dugas Haferlach |
| **13.22** | Include SNP data and further projects of WP13 members | 12/2010 | 12/2010 | Dugas, Haferlach, Müller-Tidow |

**Section 3: Consortium management**

Together with other workpackages, i.e. WPs 10, 11 and 12, a training course for microscopy was held in 11/2009 in Kiel (Prof. Kneba/Horst) for deeper insights in diagnostics and the biological relationship between morphology and other diagnostic techniques. This workshop also included talks on next-generation technologies for future investigations in the diagnostic field of leukemia.

A workshop together with WP10 and WP8 was held in Munich, see 13.5.

Participants of WP 13 further played a major role at important international and national conferences on microarray data and leukemia and chaired several sessions or presented their individual data in talks or as posters.

**Section 4: Other Issues**

Ethical issues - none

Competitive calls – none

**Section 5: WP13-Performance**

| Performance indicators | Status |
|---|---|
| Establishment of European reference panels | See published papers |
| Organization of interdisciplinary consensus conferences | See published papers |
| Development of consensus protocols for the diagnostic work up of all types of leukemia and related syndromes | See published papers |
| Organization of quality control rounds | done |
| Number and quality of publications within the network | See 13.1.d |
| Implementation of technology transfer | In further progress |
| Number of difficult cases presented in the expert forum | Done for MDS and GEP, and for all misclassifications in MILE study, ongoing in new study with Béné in ALL |
| Number of new cooperations between network participants | More than 10 within WP13, WP10, 11, 12, see above, including papers in 13.1d |

Papers: See all in 13.1d in detail, including GEO numbers.

**Stem cell transplantation (WP 14)**

*Objectives and starting point of work at beginning of reporting period*

The evident problem was again the directive for academic clinical studies. The majority of the scientific publications on the introduction of the directive report that the initial goal to simplify the burocracy is not met in the academic environment and that the number of Academic Sponsored Trails in Hematology and Oncology decreased considerably in several countries (see Hemminki et al. BMJ 332 501-2; see also Lancet publications). This is also the experience by the EBMT/ELN, which noted a reduction of new trials and an increase in trial costs including insurance costs. Even if the original idea to harmonize the procedure for clinical study in Europe was excellent, the results are quite disappointing and need immediate actions. The diagnosis for having failed reside in the generalization of clinical trials (industry sponsored, academic, observational etc.), in the different implementation in member states, in the increased and often redundant requests from national authorities and in vague definitions and descriptions within the directive. By fixing these points we might have a predominance of the positive effects of the directive. A meeting was also held under DG Research mit the title "Can we facilitate multinational investigator-driven trials?" Brussels, November 10, 2009 (see report).

Many important deliverables were achieved and milestones were reached in WP 14 during 2009. This was possible by performing regular working party meetings and continuing the important work started previously with the EBMT/ELN. As in previous years, the stem cell transplant activity was collected in Europe, but also the harmonization between the European Stem Cell transplant activity and the US was continued, providing valid information on changes in indications, frequencies among the different countries but also among diseases. In this regard a global survey was performed and information on more than 51.400/SCT collected in 2006.

The main aim consisted in connecting the activities of the different disease-oriented WP of the ELN with the WP hematopoetic cell transplantation (HCT) on one site but also to improve the procedure related questions. In one of the deliverables (high risk cytogenetic AML 14.67) it was realized that a considerable amount of patients are not reaching the transplant procedure even if they have a donor. The main reasons are relapse between consolidation cycles, early death from chemotherapy or discontinuation of therapy because of infections. This problem has now gained considerable attention and further studies will be designed in a way that transplant is considered an essential part of the treatment in high risk patients and donor search started as soon as possible. After many phase II studies the first randomized study comparing SCT with non-SCT procedures in patients with AML and a matched donor was started. These important achievements were possible only by performing frequent and regular meetings between WP14 and disease WP such as CML and AML. In this respect the European LeukemiaNet is the ideal platform for networking.

Disease related questions:

In AML the first randomized study comparing transplant vs. non-transplant treatment and involving the major AML study groups has started in January 2010 and 3 patients were already included. The

second study on reduced intensity conditioning for patients with related donors in comparison to non transplant treatment has included now more than 100 patients. Analysis on molecular risk factors and their role for patients with or without SCT were initiated in retrospective analysis. New prospective studies are now being developed and discussed within the WP. The possibility to use a common arm in Europe raised considerable discussions and has still to be developed in more detail. In MDS the significance of reduced intensity conditioning in comparison to conventional SCT is being studied in the RICMAC study.

In ALL, phase II protocols for older patients using allogeneic HCT after reduced intensity conditioning have been initiated. The results are very encouraging and justify a prospective protocol investigating the role of allogeneic HCT in high risk patients. Especially in high risk patients, an advantage of reduced intensity conditioning regimen seems apparent. Such protocols need further development and international participation.

In CML analyses on SCT outcome after second generation TKI are very important. In addition, indication for SCT has to be defined considering the improvements and definition of risk factors of the last years. Therefore outcome of patients with low risk Gratwohl score has been analyzed. A prospective study investigating the role of Dasatinib in patients relapsing after SCT has been finalized and the results of Donor Lymphocyte updated.

In T-PLL the survival of patients after autologous and allogenic SCT was updated and a prospective registration audit initiated.

In regard to multiple myeloma the NMMA 2000 study has been updated and a longer follow up is now available. The results have been presented at ASH in an oral presentation and will be communicated as a manuscript. For patients relapsing after autologous HCT a randomized study comparing Velcade, Thalidomide and steroids with Thalidomide and steroids has recruited already more than 240 patients.

Procedure related questions:

The indications and definitions for hematopoietic cell transplantation (HCT) in Europe will be updated and the first contacts established during this period. The paper appeared in Bone Marrow Transplantation in 2009.

A significant improvement in reducing complications after SCT was obtained in the pediatric randomized study for VOD prevention. Defibrotide was able to reduce VOD but also the incidence of GvHD. This work will receive the VanBekkum Award in March 2010.

In addition standardization and spreading of excellence was pursued by training courses and by standardizing indications for SCT. The DMSO prospective audit is proceeding as expected and complications registered. A standardization of DMSO concentration is urgently needed.

**14.5 Regular WP meetings:**

8 meetings were held during 2009 including joint WP meetings with WP 4 and WP5 (see Annex/Section 3 for details):

2009 01 EBMT/ELN Meeting, City Conference Center, Angers

2009 02 ELN/EBMT Meeting Mannheim,

2009 03 EBMT/ELN Room A6, Göteborg

2009 06 EHA/ELN/EBMT WP5/WP14 Berlin

2009 07 EBMT subcommittee chair meeting Leiden

2009 09 EBMT/ELN Meeting Milan

2009 11 EBMT subcommittee chair meeting Leiden

2009 12 ELN meeting WP5/WP14 New Orleans

**14.6 LP reports to NMC regarding structure, trial activities and integration of national leukemia trial groups (1 page, bullet point style)**

Reports have been sent to NMC.

**14.12 Implementation and Guidelines of reaccreditation**

The 4th edition of the Standards along with the Accreditation Manual and Inspection Checklist was released on 31 October 2008 and entered into force on 1 February 2009. Preparation of the 5th edition of the Standards has commenced and a kick-off meeting in Barcelona is in preparation for June 2010 with participation by both FACT and JACIE. Final release of the 5th edition is scheduled for the end of 2011.

At the 2009 EBMT Annual Meeting, a dedicated JACIE session featured on Monday with a full auditorium.

The 2009 Annual Meeting also included a pilot Quality Management Meeting as part of the congress programme. This proved very successful with 150 attendees enjoying a varied programme with opportunities to ask questions and share experience. The meeting will become a regular part of future Annual Meetings.

**Study: Retrospective and Prospective Study of Different Approaches to Inspection of Tissue Establishments and Associated Haemopoietic Progenitor Collection Facilities**

Based on a JACIE initiative, discussions have taken place with representatives of the following Competent Authorities: AGES PhamMed, Austria; CNT, Italy and IGZ, The Netherlands. The study is entitled 'Retrospective and Prospective Study of Different Approaches to Inspection of Tissue Establishments and Associated Haemopoietic Progenitor Collection Facilities'.

The retrospective study has commenced and is expected to be completed by March 2010. The retrospective study will compare the outcome of inspections of establishments visited by both JACIE and the competent authority. The prospective study will be commenced upon completion of the

retrospective study. The prospective study aims to look at outcome over the coming 24 months. The project is expected to conclude in 2011.

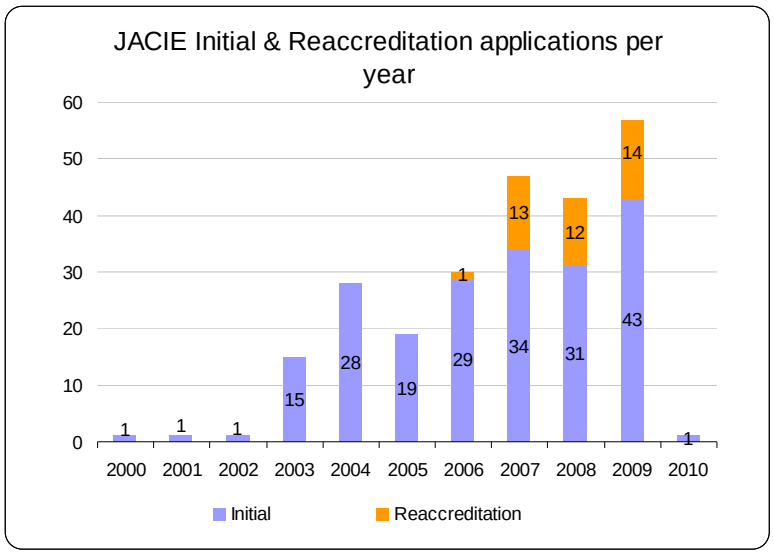
9 courses were run on the initiative of national societies or individuals with JACIE support. A total of 66 participants received training either as inspectors or in preparing their centre for accreditation.

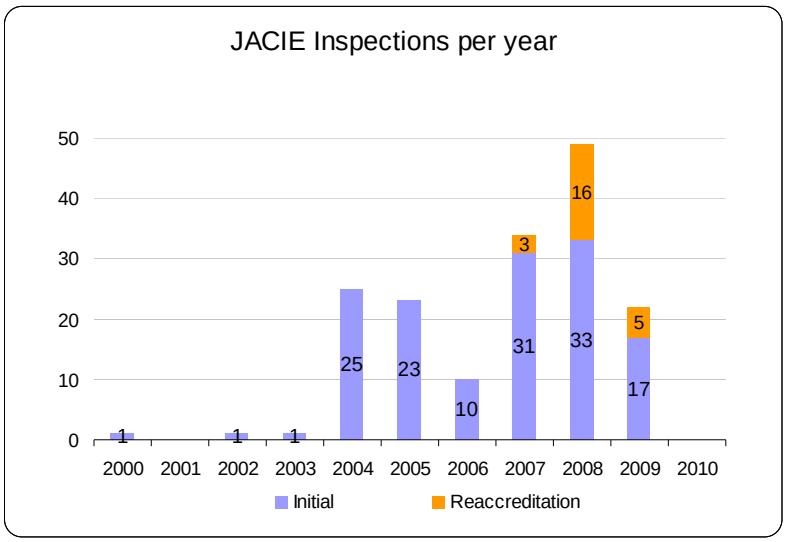
The number of trained inspectors continues to grow and now stands at over 200 from 19 countries.

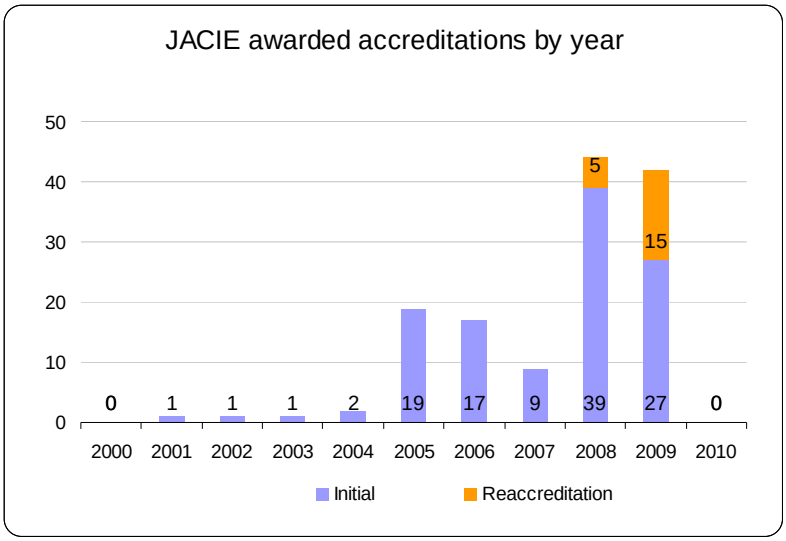
Publications see Annex section 3, WP 14-39, -90, -93.

**Accreditation Programme Status:**

43 new applications received and 14 applications for reaccreditation.
22 audits were performed in 2008 (17 first-time and 5 reaccreditation)
27 centres were accredited for the first time and 15 were reaccredited.
Total centres/facilities registered: 203
Centres in progress: 40
Centres inspected: 168
Accredited: 87
Countries: 16






**14.14e Report of study patients to registry**

Information on 352.605 SCT in 300.214 patients are now available in the EBMT Registry and describe patients with autologous and allogeneic SCT (222.285 and 129.914 respectively; 406 unknown type), transplants from related and unrelated donors (86.631 and 42.499 respectively; 784 unknown type), from cord blood, bone marrow and peripheral stem cell grafts (4.187, 93.156 and 257.004 respectively; of which 5.671 have more than one type of source and 3.243 are of unknown source).

The EBMT Registry also allows the registration of other type of cell therapy procedures such as mesenchymal cells, whether performed for similar or new indications, and whether performed by themselves or in association with haematopoietic stem cell transplantation. Currently there are 292 patients for which such procedures have been registered, including 257 mesenchymal cells therapy and 52 dendritic cells therapy.

**14.42c Randomized study in patients with AML over the age of 60 a studying the role of SCT with reduced intensity conditioning (EBMT study)**

After the Paul Ehrlich Institute (PEI) asked for an investigator brochure on stem cell transplantation, this was provided including animal models, toxicity, side effects and risk analysis, which delayed further the start of the study. After having received a catalogue of questions related to the procedure and mainly to the production of stem cells, the answers were sent to the Paul Ehrlich Institute and the protocol finally accepted also by the PEI. The correspondence is included as an addendum as well the investigator brochure, labelling of stem cell grafts and specifications of stem cell grafts, hoping that can be used by other PI for clinical studies involving SCT. The protocol was submitted also to the national authorities in Switzerland, Nederland and France. An application for founding was written to the Deutsche Krebshilfe, which was so kind to financially support the study. Further negotiations were started with the KKSL in Leipzig for randomisation and for data collection. After setting up all the required items the study was started on January 4$^{th}$ in Germany and 3 patients were included so far.

**14.45b Allogeneic reduced intensity conditioning transplantation versus conventional conditioning in MDS (RICMAC) Study start**

The RICMAC is an European EBMT-trial comparing a dose-reduced conditioning versus a standard myeloablative conditioning regimen followed by allogeneic SCT in patients with myelodysplastic syndome or secondary acute myeloid leukaemia. So far (1/2010) 50 patients have been included from 15 centers in 4 nations (Germany, Italy, Finnland, Russia). Finally, countries such as France and United Kingdom could be initiated in 12/2009 and will start recruitment in 2010.

**14.46c MMVAR Study to treat relapse in myeloma after autologous SCT**

TD regimen has provided significant results in relapsed MM. In attempts to further improve those results without significantly increasing toxicity, some investigators have included Velcade to the combination, the so called VTD regimen. In January 2006, the EBMT group initiated a prospective, randomized, parallel-group, open-label phase III, multicenter study, comparing VTD (arm A) with TD (arm B) for MM patients progressing or relapsing after autologous transplantation. Inclusion criteria were: patients in first relapse after at least one autologous transplantation, including those who may have received Velcade or Thalidomide before transplant. Exclusion criteria: subjects with severe neuropathy or non secretory MM. 340 patients will participate (170 in each arm). Primary study end point was time to progression. Secondary end points included toxicity, response rate, event-free survival and overall survival. Treatment was scheduled as follows: Velcade 1.3 mg/m2 will be given as an i.v bolus on Days 1, 4, 8 and 11 followed by a 10-Day rest period (days 12 to 21) for 8 cycles (6 months) and then on Days 1, 8, 15, 22 followed by a 20-Day rest period (days 23 to 42) for 4 cycles (6 months). In both arms, Thalidomide will be given at 200 mg/Day per os for one year and Dexamethasone 40 mg/Day per os four days every three weeks for one year. Thrombosis prophylaxis

is mandatory. Prophylaxis (in arm A) against reactivation of varicella zoster virus is highly recommended. Patients reaching remission could proceed to a new stem cell harvest. However, transplantation, either autologous or allogeneic, could only be performed after achieving the one year treatment. Response was assessed by EBMT criteria, with additional category of nCR. Adverse events are graded by the NCI-CTCAE, Version 3.0.

As of December 29, 2009, 241 patients entered the study. 129 in France (IFM 2005-04 study), 18 in Italy, 34 in Germany, 19 in Switzerland (SAKK), 18 in Belgium, 7 in Austria , 8 in the Czech republic, 6 in Hungary,1 in the UK and 1 in Israel. 241 are assessable: 152 males, 89 females; median age: 61.1 yrs (range 35-87), number of autologous transplant: one: 120, two: 121. Of these patients, 121 were randomly assigned to receive Velcade+Thalidomid+Dexamethason (VTD) and 120 to receive Thalidomid+Dexamethason (TD). Treatment was discontinued in 96 patients. An interim toxicity analysis was performed when the first hundred patients had been included. The safety committee agreed to resume the trial. An interim analysis is currently ongoing. Protocol EU-DRACT number: 2005-001628-35.

**14.47c Related allo-SCT after Reduced Intensity Conditioning versus Best Standard of Care in elderly patients with AML in CR1**

This is an academic study, comparing reduced intensity transplants (RICT) with standard of care in AML. Based on the availability of an HLA identical sibling, patients in their first remission are allocated to a RICT group or a control group. Primary endpoint is survival and the study is supported by the Canadian BMT Group and several funds. PI is Mats Brune Göteborg, Sweden.

At this point, 108 pts have been enrolled from centers in Canada, Norway, Finland, Germany, New Zealand and Sweden. An interim analysis of the first 100 pts revealed 12% non-relapse mortality. Kaplan-Meier estimates of 3 year OS and PFS in the whole study group (RICT+Control) were 50% and 45%, respectively.

**14.48c AlloSCT after tyrosine kinase inhibitors (TKI) in CML**

The retrospective study on second generation TKI use prior to allo-transplant is in its final analysis.
An abstract has been submitted for the EBMT meeting, the final manuscript should be ready within the first half of 2010.

Stem cell transplantation (SCT) will continue to be a treatment option for patients with CML despite the introduction of tyrosine kinase inhibitors (TKI). However, many patients will have received prior therapy with TKIs, including Nilotinib or Dasatinib at the time of allogeneic SCT. While the use of Imatinib prior to SCT seems to have no adverse impact on the outcome of allogeneic SCT little is known on the impact of prior use of second generation TKIs. Therefore we conducted a retrospective registry study and identified 56 patients with CML who received an allotransplant after having been treated with Nilotinib and/or Dasatinib. Best responses to second generation TKIs were major

molecular response in 11%, complete cytogenetic response in 7%, partial cytogenetic response in 18%, complete haematologic remission in 25% and no response in 34%, respectively. At SCT, 37% of the patients were in accelerated or in blast phase, 36% in CP2 or higher and 27% in first chronic phase. Graft failure occurred in two patients. The median follow-up for surviving patients is 19 months. At 24 months the estimated non-relapse mortality was 33% and the relapse incidence 15%. As expected, probability of survival is best in patients transplanted in CP1 with more than 85% at 2 years. In univariate analysis there was a non significant trend in favor for pretreatment with Nilotinib as compared to the other groups. However, in multivariate analysis only stage of the disease was a predictor for survival. With respect to overall survival no significant differences could be identified for the following variables: patient age, donor type, stem cell source, intensity of the conditioning, time diagnosis to transplant, in or ex vivo T-cell depletion, response to treatment with second generation TKIs. Patients transplanted in blast crisis had a significant higher risk of non relapse mortality. In summary, despite the shortcomings of a retrospective study the numbers reported are comparable to earlier studies on the impact of Imatinib on the outcome of SCT and it should be emphasised that the timing of allogeneic stem cell transplantation remains crucial to avoid unacceptable high treatment related mortality.
The prospective non interventional study (ONIS) is ready to start recruiting patients within the EBMT. For this audit the protocol has been finalised.

**14.50c Study investigating the role of Kepivance for treating Mucositis after autologous SCT**
This three arm phase III study is investigating the role of Kepivance in reducing the incidence and severity of oral mucositis in patients undergoing autologous stem cell transplantation for multiple myeloma. The multicenter and multinational study compares the efficacy of palifermin relative to placebo when given either pre- and post-high dose chemotherapy or pre-high dose chemotherapy only with regard to the severity of oral mucositis (WHO grades 0/1, 2, 3 or 4). The study was closed to enrolment in December 2008 after more than 350 patients were entered. The data were collected, the file locked and a first analysis planed by November/December 2009. The results will be communicated in the first quarter of 2010.

**14.55b Comprehensive survey outside Europe**
The WBMT has collected information from 1,350 transplant centers in 71 reporting countries over all continents on the numbers of HSCT by indication and donor type for 2006. There were a total of 51,421 first HSCT, 22,163 allogeneic (43%), 29,258 autologous (57%). Main indications were leukemias 17,553 (34%; 89% allogeneic), lymphomas 27,778 (54%; 87% autologous), solid tumors 2,954 (6%; 95% autologous) and non-malignant disorders 2,771 (5%; 93% allogeneic). There were significant differences between and within regions. In an analysis of macro-economic factors, more transplants were performed in countries with higher health care expenditures, higher GNI/capita and

higher team density. Hence, governmental support, access to a transplant center, disease prevalence and availability of resources are the key factors related to regional transplant activity.
Data were presented as oral presentation at the annual meeting of the American Society of Hematology in New Orleans, December 2009. A manuscript is submitted.

**14.56b Integration of risk factor profiling into risk adapted therapy pilot AML HOVON/SAKK < 60 years**

The basis for a correct integration of HSCT into the algorithm has been made by the publication of the EBMT risk score, which was shown to be applicable for AML as well as for CML. This forms now a basis for recommendations; a draft guidelines manuscript is in preparation (see Annex Section 3, WP 14-56).

**14.57b Autologous SCT for CML (30 patients reported to the EBMT) Heim**

Autologous HSCT has seen a rapid decline; a total of 5 autologous HSCT were performed in 2008. Hence, based on a discussion of the CLWP, no specific analysis was made of these very limited data. In the new revised CML treatment guidelines, autologous HSCT is not recommended (see Annex section 3, WP 14-4).

**14.58b Outcome of patients with low risk Gratwohl score CML**

Patients with CML and a low EBMT risk score have an excellent survival with a transplant related mortality of 10% only and a survival which was not different from a similar cohort of patients without a donor but treated within the prospective controlled German-Swiss CML IV study. Similar excellent survival was documented in a cohort of more than a 100 patients of the EBMT (see Annex section 3, WP 4-19).

**14.59b Guidelines for secondary allotransplantation after relapse (retrospective analysis)**

The manuscript is in preparation and an updated analysis done. In a retrospective analysis, all second allogeneic HSCT carried out for a relapse of malignant disease after the first transplantation at the centers of the EBMT between 1994 and 2005 and reported to the EBMT registry (n = 1633) were analysed for outcome and predictive factors. The principal aim was to evaluate transplantation-related problems. The age of the patients was 1-71 (median 35) years. 558 patients had primary AML, 366 ALL, 265 CML, 149 MDS, 73 lymphoma, 71 myeloproliferative disorder (including 41 MPS/MDS), 50 myeloma, 47 secondary acute leukemia, 28 CLL, and 26 other diagnosis. At the second transplantation, 23 % of the patients were in complete or partial remission or in chronic phase, 59% were in relapse or had resistant or progressive disease, and in 18% the data is missing. In the second transplantation the donor was HLA-identical sibling in 67 %, other related in 9 % and unrelated in 24 % of the cases. In 81 % the donor was the same as in the first transplantation. The conditioning was reported to be myeloablative (MAC) in 65 % and of reduced intensity (RIC) in 18 % of the

transplantations, in 17% this data is missing. The graft was blood stem cells in 75 %, bone marrow in 23 %, a combination of these in 1 %, and cord blood in 1 %. 22% of the patients had had grade II-IV acute GvHD and 15 % chronic GvHD after the first transplantation. The overall survival in the whole group of patients was 39% at one year, 29 % at 2 years and 21 % at 5 years. The respective figures for the cumulative incidence of relapse were 39, 44, and 49%, those for non-relapse death 31, 35 and 37 %, and those for RFS 30, 21, and 14 %. In multivariate analysis, factors highly significantly associated with better survival were disease (chronic leukemias vs. other diagnoses), longer interval between first and second transplantation (> 1year vs. < 1 year), younger age, and the state of the disease (CR, CP or partial remission vs. others). Factors showing no significant independent association with overall survival were the occurrence of grade II-IV acute GvHD or chronic GvHD after the first transplantation, duration of remission after the first transplantation, conditioning at the second transplantation or any combination of conditioning intensity in the two transplantations (MAC – RIC), the type or donor, and whether the donor was the same as in the first transplantation or not. The main cause of death was relapse or disease progression in 52 %, GvHD in 17 %, infection in 11 %, organ damage or failure in 12 % and other non-relapse cause in 8 %. There were no differences in non-relapse mortality between acute leukemias (AL), chronic leukemias (CL), myelodysplastic/ myeloproliferative syndromes (MDS/MPD), and plasma cell dyscrasias/ lymphomas/ solid tumours. At 5 years, the cumulative incidence of relapse was 53 % in AL, 44 % in MDS/MPD and 35 % in CL. The relapse-free survivals were 9, 15, and 27 % and overall survivals 15, 18, and 40 %, respectively. As examples, among patients with AL not in CR, transplanted within one year from the first transplantation, the survival at one year was 14 %, whereas 54 % of patients with CL in CR/CP/partial remission transplanted more than one year from the first transplantation survived at 5 years. In conclusion, retransplantation offers a reasonable option especially for younger patients with a time interval of > 1 year from the first transplantation and a disease responsive to reinduction.

**14.60b Prospective feasibility study phase II Dasatinib for relapse in CML after allo**

Regulatory approval has been obtained and the study is open for recruitment in four countries at the end of year 2009 (UK, Germany, Switzerland and France). Currently, no more country is planned in the contract but additional countries will potentially be added in the future (Hungary is expected).

This Phase II efficacy study analyzes the role of dasatinib in patients with chronic and accelerated phase chronic myeloid leukemia relapsing after allogeneic blood or bone marrow transplantation. Patients ≥ 18 years of age with Ph+ CML, whose disease is relapsed after transplant from an HLA-identical sibling or an HLA-matched unrelated donor (MUD) and have not responded to withdrawal of immunosuppressive treatment where this is possible, are entered. The primary objective is to assess the efficacy of dasatinib therapy in chronic and accelerated phase BCR-ABL (+) CML patients that undergo molecular, cytogenetic or hematological relapse following SCT. The secondary objectives determine the impact of dasatinib therapy on patient survival after relapse post-SCT and the incidence

of any subsequent need for ‘rescue’ DLI and the safety of dasatinib in this clinical context using this specific dose regimen.

**14.61b T-PLL after autologous and allogeneic SCT**

It is the largest group ever evaluated with this disease comprised of 54 patients. The analysis is completed and the first draft of the manuscript released. Within two months the manuscript will be finalized and submitted.

**14.62b Prospective registration audit for T-PLL**

This prospective observational study has been set up, has started and already included 32 patients of originally planned 50. It is also a novel approach to studies for very rare disease under situation of trial directive (the make virtually technically impossible normal prospective trials).

The first is called "EBMT prospective observational study on allogeneic and autologous transplant-tation in T-PLL" and means that transplant centers are encouraged to register their patients with T-PLL very timely with the EBMT, followed by mandatory submission of EBMT MedB and follow-up forms. The second is the "EBMT/ELN recommendations for allogeneic and autologous transplantation in T-PLL". Everybody has agreed on standard diagnostic criteria and standard treatment algorithm and a manuscript submitted to BMT..

**14.65 Long term outcome of CML patients treated with DLI after allogenic SCT from an HLA-identical sibling**

In this now updated analysis factors associated with GvL without GvHD are identified. New follow up is needed to complete the study and write a manuscript.

**14.66 Recommendation for allogeneic and autologous stem cell transplantation in T-PLL: An EBMT/ERIC proposal**

Its purpose is mainly to avoid transplants in situations where they are very unlikely to be successful and to avoid excess heterogeneity of eventual transplants performed, thereby facilitating scientific analysis. This expert opinion-based framework covers criteria for the diagnosis of T-PLL, transplant eligibility, pre-transplant remission induction strategies, remission requirements, timing of HSCT, donor compatibility criteria, conditioning, GVHD prophylaxis, and MRD monitoring. With these two complementary components it should be possible to largely improve the usual quality of registry-based data and to generate scientifically sound knowledge on HSCT in an orphan disease such as T-PLL. A manuscript is in preparation, however the results of the retrospective evaluation and the audit should be available before writing the recommendations.

**14.67 Cytogenetic high risk AML: results of a biological randomizated study in patients under the age of 60 a (Basara)**

The analysis was published in Leukemia 2009 and showed the important role of allogeneic SCT in high risk patients:

Early related or unrelated hematopoietic cell transplantation results in higher overall survival and leukaemia-free survival compared with conventional chemotherapy in high-risk acute myeloid leukemia patients in first complete remission (see Annex section 3, WP 14-21).

Between 1996 and 2004, a total of 708 patients were enrolled in the acute myeloid leukaemia (AML) '96 and '02 studies of the East German Study Group (OSHO). Of these, 138 patients (19.5%) had unfavourable cytogenetics defined as complex karyotype, del (5q)/-5, del (7q)/-7, abn (3q26) and abn (11q23). In all, 77 (56%) achieved complete remission 1 (CR1) after induction chemotherapy and were eligible for haematopoietic cell transplantation (HCT). HCT was performed after a median of two cycles of consolidation chemotherapy (CT) in the AML '96 and one cycle in the AML '02 study (P=0.03). After a median follow-up of 19 months, overall survival (OS) at two years was significantly better in the donor group (52±9%) versus the no-donor group (24±8%; P=0.005). Differences in outcomes were mainly because of a lower relapse incidence in patients after HCT (39±11%) compared with a higher relapse incidence in patients undergoing CT (77±10%; P=0.0005). Treatment-related mortality was low and not statistically significantly different between the two treatment groups (15±7 and 5±5% for HCT and chemotherapy, respectively; P=0.49).We conclude that early HCT from related or unrelated donors led to significantly better OS and leukaemia-free survival compared with chemotherapy in patients with unfavourable karyotype (see Annex section 3, WP 14-21).

**14.68 DMSO prospective audit**

The study is completed and recruitment closed at the end of last year. 69 centers participated and 1529 patients have been included. More reports are still being received. Most centers used a DMSO concentration of 10% for cryopreservation and only a minority used 5%. 43 centers used additional additives for cryopreservation (HSA, HES, heparin etc.). Side effects during reinfusion were common but usually mild and occurred in nearly 80% of the patients. More severe side effects were observed in 92 patients. A complete analysis is being prepared.

**14.69 ATG-depending outcome in MUD patients transplanted for CML**

The analysis has now sufficient follow up to be written in a manuscript and will be presented as an oral presentation at the EBMT meeting.

To reduce the incidence of acute and chronic graft versus host disease (GVHD) anti-T-cell globulins (ATG) have been incorporated into the preparative regimen for allogeneic stem cell transplantation (SCT) from alternate donors by many centers. Different ATG preparations are available and little is known about the optimal dosing. Therefore we conducted this retrospective registry study utilizing

specific questionnaires to participating centers. Chronic myelogenous leukemia (CML) in chronic phase has been selected as underlying disease in order to have a rather homogenous patient population. A total of 1359 patients (pts) have been analyzed. 534 pts had received no ATG, 288 ATG-Fresenius, 122 Thymoglobuline® (Genzyme), 261 other in vivo T-cell depletion, mainly Campath, and 154 had received in- and ex-vivo T-cell depletion, utilizing Thymoglobuline® for in-vivo depletion. A cumulative dose of less than 40 mg/kg ATG-Fresenius or less than 10 mg/kg Thymoglobuline® has been defined as low-dose. The median follow-up for surviving pts is 62 months (range: 1 – 187) with no statistically difference in the different pts groups. Only the use of ATG-Fresenius and Thymoglobuline® proved to be an independent positive prognostic factor for overall survival in multivariate analysis incorporating the EBMT risk score. This was due to decreased treatment related mortality. However, any of the analyzed T-cell depletion strategies increased the risk of relapse, which did not translate into overall survival, since relapse after allo SCT is manageable in CML pts. When also analyzing the dosing of ATG, the use of high dose ATG-Fresenius was associated with the best long-term overall survival of about 70%. When comparing high dose Fresenius versus all others the use of high dose Fresenius had the same impact on overall survival as the EBMT risk score, indicating that the use of high dose Fresenius is an independent positive prognostic factor. Similar effects were not seen with high-dose Thymoglobuline®. Interestingly, the positive effects of ATG only became obvious after 4 months after transplant suggesting no protection against acute GVHD but protection against mortality from chronic GVHD. Although unrelated allogeneic SCT in chronic phase CML is nowadays a rather rare indication these data nevertheless prove beneficial effects of in vivo T-cell depletion and also emphasize, that the different preparations are not interchangeable and that the dosing is of great importance.

**14.70 Prophylaxis and treatment of GvH-D: an EBMT survey**

This was extensively discussed at the last meeting. In Heidelberg there was no agreement in the general assembly whether such a survey should be performed or not. Meanwhile the interest in a new survey has increased. At the last meeting it was decided to perform a survey on GvHD prophylaxis and treatment. Tapani Ruutu provided a draft for the survey and the draft was extensively discussed. Especially between older and jounger patients interesting questions come up and many suggestions for modifications were made. After building in all the suggestions the questionnaire will be circulated again.

**14.71 Analysis of non-disease related complications after HCT (T. Ruutu)**

M. Stern is working on an analysis on GvHD as surrogate marker for GvL on relapse using the CLWP megafile. The following questions should be answer a.) How do different diseases compare? b.) How do different transplant settings compare c.) Are there differences between unrelated and related/ sibling transplantations d.) Are there differences between TCD and non-TCD grafts?

A further topic is the topical tacrolimus for chronic cutaneous GvHD**.** The recruitment will start in March 2010 and will end October 2011. The Follow-Up time of this study will be six months after recruitment. The target will be to recruit 100 patients to this study.
Finally the role of comorbidity on stem cell transplantation will be defined in detail. This study will be a prospective study, which is now in a very preliminary status.

**14.72 Randomized study on VOD in pediatric patients n=360**

The study has been closed and updated in 2009. The results were presented as an oral presentation at ASH and a manuscript is in preparation. The use of defibrotide prevents VOD but also reduces the incidence of GvHD.
Defibrotide (DF) for the Prevention of Hepatic Veno-Occlusive Disease (VOD) in Pediatric Stem Cell Transplantion: Results of a Prospective Phase II/III Randomized, Multicenter Study by Selim Corbacioglu, MD et al
Hepatic VOD is a life-threatening complication following SCT with a particularly high incidence in children. Development of VOD is one of the most common causes of early death after SCT. DF (Gentium SpA), a polydisperse oligonucleotide, demonstrates a protective effect on vascular endothelial cells in vitro. Small non-randomized trials to assess DF for the prophylaxis of VOD were promising without significant anticoagulant effects. Eligibility criteria included pts <18 years with myeloablative SCT and at least 1 of the following high risk criteria for VOD: conditioning with busulfan and melphalan, pre-existing liver disease, 2nd myeloablative transplant, allo-SCT for leukemia in 2nd relapse, macrophage activating syndromes, prior abdominal irradiation, prior gemtuzumab, osteopetrosis, and adrenoleukodystrophy. Pts were prospectively randomized to the control arm (no prophylactic DF) or to receive DF 25mg/kg/day IV from the start of conditioning until D+30 post SCT. All pts diagnosed with VOD received DF for treatment. Primary endpoint: incidence of hepatic VOD by D+30 using modified Seattle criteria (2 or more of the following: bilirubin > 2 mg/dL, hepatomegaly, ascites and/or unexplained weight gain > 5%). VOD was assessed by physical exam; hepatomegaly and ascites were confirmed by abdominal ultrasound. A blinded independent review committee of 3 expert hematologists confirmed the diagnosis of VOD. Although the study was not powered to assess mortality, a composite score was assessed as a secondary endpoint that incorporated VOD-associated toxicity (respiratory failure, renal failure, encephalopathy) and mortality. Incidence and severity of graft versus host disease (GvHD) was assessed. As the true incidence of VOD in this population was unknown, the trial incorporated a planned adaptive interim analysis to be reviewed by an independent DSMB. Based on the recommendations of the DSMB, 360 pts were enrolled between January 2006 and January 2009 by 28 centers in the EU and Israel. An Intent-to-Treat (ITT) analysis was performed on all randomized pts who signed informed consent (DF: 180; control: 176). Median age was 4.8 years; 24% infants, 52% children (ages 2-11 years) and 23% adolescents. 41% were female, 59% male. 68% were allo-, 31% auto-SCT. There were no significant differences between the two arms in disease types or risk factors. Ninety-three percent (93%) of the

patients completed the primary endpoint at day +30. In the ITT analysis, 12% (22/180) of the pts of the DF arm and 20% (35/176) of the control group developed VOD by D+30 (P=0.054); in the PP analysis, the VOD incidence was 12% (20/164) vs 21% (35/169) (P=0.037). VOD was experienced by 23% of the infants, 14% of the children and 13% of the adolescents. The composite score (assessing VOD morbidity and mortality) was significantly in favor of the DF arm (P=0.034). Significantly less acute GvHD by D+100 was reported in the DF pts (32% (57/180) vs 43% (75/176); P=0.023 by Wilcoxon test). Observation of VOD in either arm led to a higher mortality: mortality of pts with VOD equaled 24.6% (14/57) compared to 7% in pts without VOD (21/299). Renal failure was observed in 1% (2/180 pts) of DF pts vs 6% (10/176) of the control (P=0.017); respiratory failure was observed in 7% vs 9% (NS); and encephalopathy in 1% vs 2% (NS). SAEs were experienced by 58% of the DF pts vs 59% of the control, including infections (24% vs 27%) and respiratory disorders (12% vs 9%); 9 hemorrhagic events were seen in the DF arm compared to 21 in the control. This Phase II/III randomized study demonstrates the efficacy and safety of DF in preventing VOD in pediatric pts at high risk of VOD. Use of prophylactic DF results in a 40% reduction in the incidence of VOD. Consistent with the role of DF in endothelial protection, both renal failure and acute GvHD were significantly lower in the DF arm. Safety of DF was confirmed by lack of significant toxicity (including hemorrhage). DF can be recommended for the prevention of VOD in this high risk population.

### 14.73 Effect of Stem Cell Source on Transplant Outcomes in Adults with AL. A Comparison of Unrelated BM, PBSCT and CD

Umbilical cord blood (UCB) is increasingly considered as an alternative to peripheral blood progenitor cells (PBPC) or bone marrow (BM), especially when a HLA-matched unrelated donor is not available. In order to determine the appropriateness of current graft selection practices, we compared leukemia-free survival rates in adults with acute leukemia according to cell source. Data were available on 1525 patients aged >16 years with acute leukemia transplanted between 2002 and 2006 using UCB (n=165), PBPC (n=888) and BM (n=472). UCB units were matched at HLA-A and -B at antigen level and -DRB1 at allele level (n=10) or mismatched for one (n=40) or two antigens (n=115). PBPC and BM donors were matched to their recipients at HLA-A, -B, -C, DRB1 (n=632; n=332) or mismatched at one locus (n=256; n=140), respectively. Findings: Leukemia-free survival after UCB transplant was not statistically different to that observed in recipients of allele-matched PBPC or BM (matched at HLA-A, -B, -C, -DRB1). Treatment-related mortality, however was lower after transplantation allele-matched PBPC (HR 0.62, p=0.003) and BM (HR 0.59, p=0.003). Compared to UCB recipients, grade 2-4 acute (HR 1.76, p<0.001) and chronic graft-versus-host disease (HR 2.62, p<0.001) was higher in recipients of allele-matched PBPC transplants but not recipients of allele-matched BM transplants. Interpretation: Together, these data support the use of UCB as first line therapy for adults with acute leukemia, especially when transplant is urgently needed or when an HLA-matched unrelated adult donor is lacking.

*Deviations from the workprogram and corrective actions taken: identify the nature and the reasons for the problem, identify contractors involved*

**14.49c Role of unrelated allogeneic SCT after autologous SCT in comparison to second autologous SCT in multiple myeloma (NMMA 2005, start study)**

The study has been modified according to new drugs available and founding is still an issue. Application for funding has been submitted, but decisions are pending. As soon as the financial problems are resolved we can submit the study to the ethical committee and national authorities. Several meetings with Celgene and Orthobiotech were held. Induction treatment with Lenalidomide + Velcade + Dex is considered. In patients still immunofixation positive, Lenalidomide maintenance is planned.

In the mean time the study auto-allo related, which is the basis for this protocol, has been analyzed in detail and presented at ASH as oral presentation. Tandem Autologous(ASCT)/ Allogeneic Reduced Intensity Conditioning Transplantation (RIC) with Identical Sibling Donor Versus ASCT in Previously Untreated Multiple Myeloma (MM): Long Term Follow up of a Prospective Controlled Trial by the EBMT, by Gosta Gahrton, MD, PhD et al

Allogeneic hematopoietic stem cell transplantation with reduced intensity conditioning (RIC) is a controversial treatment in multiple myeloma. There are only few prospective studies and results are contradictory. The EBMT initiated a prospective study in the year 2000 comparing ASCT followed by RIC to ASCT. 358 myeloma patients from 26 European centres were included in a prospective study comparing ASCT-RIC versus ASCT based on the availability of an HLA identical sibling donor. Patients with an HLA-identical sibling were allocated to the ASCT-RIC-arm (n=107) and patients without a matched sibling donor to the ASCT (n=251). Study inclusion was at the time of conditioning for the first autologous transplant at the achievement of a response status of at least stable disease after VAD (vincristine, doxorubicine, dexamethasone)-like induction treatment of previously untreated patients. Single or tandem (n=122) autografting was optional in the ASCT arm. Conditioning for ASCT was melphalan 200 mg/m$^2$, and for RIC fludarabine 30 mg/m$^2$ x 3 plus TBI 2 Gy. The accrual period was from February 2001 to February 2005, and median follow-up time is 60 months. The two treatment groups were well matched for the standard prognostic parameters, karyotype (del(13) or not), and response status at ASCT. On an intention to treat basis the cumulative 24 months non-relapse-mortality (NRM) was 13 % in the ASCT-RIC- and 5 % in the ASCT arm (p=0.014) and the CR rate was 43 % (CI:35-54%) and 38% (CI:32-45%) respectively. At 60 months after trans-plantation Relapse/Progression rate was 49% (CI: 40-60%) and 75% (CI: 69-80%) (significant at 5% level), PFS 35% (CI: 27-45%) and 18% (CI:14-24%) (significant at 5% level) and OS 65% (CI:56-74 %) and 57% (CI:51-64%) (at 84 months 60% and 22%) for the ASCT-RIC- and ASCT -arms, respectively. A comparison between those patients who received a second allo (n=88) versus a second auto (n= 104) the corresponding figures were for CR rate 51 % in the ASCT-RIC-arm and 43 % in the ASCT-arm, Relapse/Progession rate 45% and 77%, PFS 39% and 19% and OS 63% and 60%

respectively. Information about the chromosome 13 deletion (del(13q14)) was present in 214 patients. In those with the deletion (n= 92) OS at 60 months was 70% and 53%, and PFS 30% and 11% for the ASCT-RIC- and ASCT-arms, respectively. The corresponding figures for patients without the deletion ( n=122) was for OS 70% vs 61% and PFS 44% vs 19%. Relapse rates were lower in the ASCT-RIC in both subgroups. The risk of myeloma relapse was significantly lower in the ASCT-RIC group as compared to ASCT group, both on an intention to treat analysis and when only those patients that received the correct treatment were analysed. NRM was significantly lower in the ASCT group, but still on an acceptable level in the ASCT-RIC group considering the significantly lower relapse/progression rate, improved PFS and a tendency for better long term OS. An improvement or tendency for improvement were seen in both poor (deletion 13) and good (no deletion 13) prognosis subgroups.

**List of deliverables WP 14, 2009**

| Deliv. No. | Deliverable Name | Date due | Actual/Forecast delivery date | Estimated indicative person months | Used indicative person months*) | Lead contractor |
|---|---|---|---|---|---|---|
| **WP 14** | **SCT** | | | | | |
| **14.5** | Regular WP meetings | 66,78 | 62,63,64,66,67,69,71,72 | 0 | 4 | Niederwieser |
| **14.6** | LP reports to NMC regarding structure, trial activities and integration of national leukemia trial groups (1 page, bullet point style) | 54,66,78 | achieved | 0 | 0,5 | Niederwieser |
| **14.12** | Implementation and Guidelines of reaccreditation | 72-86 | 63, ongoing | 0 | 5 | |
| **14.14e** | Report of study patients to registry | 78 | ongoing | 0 | 2 | Brand |
| **14.42c** | Randomized study in patients with AML over the age of 60 a studying the role of SCT with reduced intensity conditioning. Start study | 78 | 73, ongoing | 0 | 6 | Niederwieser, Löwenberg, Sierra, Dombret, Cornelissen, Verdonck, Gratwohl, Rocha |
| **14.45b** | Allogeneic reduced intensity conditioning transplantation versus conventional conditioning in MDS (RICMAC) Study start | 78 | 73, ongoing | 0 | 2 | Kröger deWitte |
| **14.46c** | MMVAR Study to treat relapse in myeloma after autologous SCT (40 patients) | 78 | 72, ongoing | 0 | 1 | Gahrton |
| **14.47c** | Related allo-SCT after Reduced Intensity Conditioning versus Best Standard of Care in elderly patients with AML in CR1 (Brune) | 78 | 72, ongoing | 0 | 1 | Brune |
| **14.48c** | AlloSCT after TKI in CML | 78 | 72, ongoing | 0 | 2 | Schleuning (2), Guilhot |
| **14.49c** | Role of unrelated allogeneic SCT after autologous SCT in comparison to second autologous SCT in multiple myeloma (NMMA 2005, start study). | 78 | ongoing | 0 | 4 | Niederwieser, Gahrton, Gratwohl, |
| **14.50c** | Study investigating the role of Kepivance for treating Mucositis after autologous SCT (350 patients). | 78 | 72, ongoing | 0 | 2 | Niederwieser, Blijlevens, deWitte, |

| Deliv. No. | Deliverable Name | Date due | Actual/Forecast delivery date | Estimated indicative person months | Used indicative person months*) | Lead contractor |
|---|---|---|---|---|---|---|
| **14.55b** | Comprehensive survey outside Europe (publication) | 78 | ongoing | 0 | 2 | Gratwohl, Niederwieser |
| **14.56b** | Integration of risk factor profiling into risk adapted therapy pilot AML HOVON/SAKK <60 years | 78 | ongoing | 0 | 1 | Gratwohl |
| **14.57b** | Autologous SCT for CML (30 patients reported to the EBMT). Evaluation | 78 | 73 | 0 | 2 | Heim, Gratwohl |
| **14.58b** | Outcome of patients with low risk Gratwohl score CML | 78 | 72 | 0 | 3 | Heim, Gratwohl |
| **14.59b** | Guidelines for secondary allotransplantation after relapse (retrospective analysis) | 78 | 72, ongoing | 0 | 4 | Ruutu |
| **14.60b** | Prospective feasibility study phase II Dasatinib for relapse in CML after allo | 78 | ongoing | 0 | 4 | Olavarria, Schleuning (2) |
| **14.61b** | T-PLL after autologous and allogeneic SCT (44 patients) | 78 | ongoing | 0 | 4 | Jedrzejczak |
| **14.62b** | Prospective registration audit for T-PLL | **78** | ongoing | 0 | 2 | Jedrzejczak |
| **14.65** | Long term outcome of CML patients treated with DLI after allogenic SCT from an HLA-identical sibling | **78** | ongoing | 0 | 4 | Guglielmi |
| **14.66** | Recommandation for allogeneic and autologous stem cell transplantation in T-PLL: An EBMT/ERIC proposal | **78** | ongoing | 0 | 2 | Jedrzejczak |
| **14.67** | Cytogenetic high risk AML: results of a biological randomizated study in patients under the age of 60 a | **78** | ongoing | 0 | 1 | Basara (Leipzig) |
| **14.68** | DMSO prospective audit | **78** | ongoing | 0 | 2 | Morris |
| **14.69** | ATG-depending outcome in MUD patients transplanted for CML | **78** | ongoing | 0 | 3 | Schleuning |
| **14.70** | Prophylaxis and treatment of GvH-D: an EBMT survey | **78** | ongoing | 0 | 4 | Hertenstein |
| **14.71** | Analysis of non-disease related complications after HCT | **78** | ongoing | 0 | 3 | Ruutu |
| **14.72** | Randomized study on VOD in pediatric patients n=360 | **78** | 72 | 0 | 2 | Corbaciouglou (Ulm) |
| **14.73** | Effect of Stem Cell Source on Transplant Outcomes in Adults with AL. A Comparison of Unrelated BM, PBSCT and CD | **78** | 72 | 0 | 2 | Rocha |

**List of milestones WP14, 2009**

| Milestone No. | Milestone Name | Date due | Actual/Forecast delivery date | Lead contractor |
|---|---|---|---|---|
| **WP 14** | **SCT** | | | |
| **14.42** | Randomized study in patients with AML over the age of 60 a studying the role of SCT with reduced intensity conditioning | 78 | Started recruitment , recruitment will last 2-3 years. | Niederwieser, Löwenberg, Sierra, Dombret, Cornelissen, Verdonck, Gratwohl, Rocha |
| **14.57** | Autologous SCT for CML (30 patients reported to the EBMT). Evaluation | 78 | 73 | Heim, Gratwohl |
| **14.58** | Outcome of patients with low risk Gratwohl score CML | 78 | 72 | Heim, Gratwohl |
| **14.61b** | T-PLL after autologous and allogeneic SCT (44 patients) | 78 | ongoing | Jedrzejczak |
| **14.65** | Long term outcome of CML patients treated with DLI after allogenic SCT from an HLA-identical sibling | 78 | ongoing | Guglielmi |
| **14.66** | Recommandation for allogeneic and autologous stem cell transplantation in T-PLL: An EBMT/ERIC proposal | 78 | ongoing | Jedrzejczak |
| **14.70** | Prophylaxis and treatment of GvH-D: an EBMT survey | 78 | ongoing | Hertenstein |
| **14.71** | Analysis of non-disease related complications after HCT | 78 | ongoing | Ruutu |
| **14.72** | Randomized study on VOD in pediatric patients n=360 | 78 | 72 | Corbaciouglou (Ulm) |
| **14.73** | Effect of Stem Cell Source on Transplant Outcomes in Adults with AL. A Comparison of Unrelated BM, PBSCT and CD (manuscript ready) | 78 | 72 | Rocha |

**Section 3: Consortium management**

**Section 4: Other Issues**

Ethical issues - none

Competitive calls - none

**Section 5: WP-Performance**

| Performance indicators | Status |
|---|---|
| Number of clinical trials | 10 |
| Number of patients registered in the survey | 40.000 |
| Number of metaanalyses | 5 |
| Development of standardization and guidelines | done |

**Supportive care/anti-infection prophylaxis and treatment (WP 15)**

*Project objectives and major achievements during the reporting period*

The work with guidelines has continued during the period. One paper were published during 2008 including a large international effort from many groups. In addition collaboration has been initiated with the Infectious Diseases Society of America regarding update of vaccination guidelines in patients with leukemia and other hematological malignancies.

*Progress towards objectives – tasks worked on and achievements made with reference to planned objectives*

**15.5 Regular WP meetings**

The WP has held meetings at the ELN meeting in Mannheim in February, at the EBMT meeting in Göteborg, March, in Juan-les-Pins September 25-26, and in Rome October 31.

**15.6 LP reports to NMC regarding structure, trial activities and integration of national leukemia trial groups**

No new activity

**15.22d Initiation of a protocol to use KGF immune reconstitution after allo-SCT: Use of the established platform for an actually performed prospective trial**

The protocol is finalized and the discussions ongoing with a potential sponsor. An additional study using, photodepleted DLI after haploidentical SCT has started recruitment.

**15.25 Develop European guidelines for management of respiratory virus and adenovirus infections in leukemia patients**

These were completed regarding stem cell transplant recipients and merged into the international effort described in 15.30.

**15.27c Develop common protocols for molecular diagnosis of fungal infections by PCR**

A multicenter study evaluating different PCR protocols has been completed and data have been published (see Annex Section 3, WP 15-29).

The protocol is finished and ready to start. Negotiations with the sponsor are ongoing. This topic was extensively reviewed during the ECIL meeting in Juan-les-Pins.

**15.29c Arrange courses in infectious diseases in stem cell transplant recipients**

A training course was held in Rome October 29-31 with approximately 30 participants

**15.30 Develop guidelines for prevention of infections in stem cell transplant recipients not covered in previous guidelines**

The work has been combined with a large international collaboration regarding infections in stem cell transplant patients with several organizations as partners both in Europe, in the US and Canada. The guidelines were published during 2009. In addition collaboration has been initiated with IDSA regarding guidelines for vaccination of patients with hematological malignancies and a 3:d European Conference regarding Infections in Leukemia has been held updating previous guidelines (slides not published on the ELN website), and covering new topics. A couple of manuscripts are in preparation.

**Table 15.1:** List of deliverables WP15, 2009

| Deliv. No. | Deliverable Name | Date due | Actual/Forecast delivery date | Estimated indicative person months | Used indicative person months*) | Respon-sible lead participant/ investigator |
|---|---|---|---|---|---|---|
| **WP 15** | **Supportive care, anti-infection prophylaxis and treatment** | | | | | |
| **15.5** | Regular WP meetings | **66,72, 78** | March 30<br>September 25-26<br>October 31 | 0 | 1 | Ljungman<br>Einsele |
| **15.6** | LP reports to NMC regarding structure, trial activities and integration of national leukemia trial groups (1 page, bullet point style) | 66, 72,78 | Delivered | 0 | 0.5 | Ljungman<br>Einsele |
| **15.22d** | Initiation of a protocol to use KGF immune reconstitution after allo-SCT: Use of the established platform for an actually performed prospective trial | **66** | Delivered | 0 | 1 | Einsele<br>Ljungman |
| **15.25** | Develop European guidelines for management of respiratory virus and adenovirus infections in leukemia patients | **66** | Delivered | 0 | 1 | Ljungman<br>Einsele |
| **15.27c** | Develop common protocols for molecular diagnosis of fungal infections by PCR | **72** | Delivered | 0 | 2 | Einsele<br>Maertens |
| **15.29c** | Arrange courses in infectious diseases in stem cell transplant recipients | **66, 78** | Delivered | 0 | 0.5 | Einsele<br>Ljungman<br>Cordonnier |
| **15.30** | Develop guidelines for prevention of infections in stem cell transplant recipients not covered in previous guidelines | **78** | Delivered | 0 | 3 | Einsele<br>Ljungman<br>Cordonnier |

List of milestones WP15, 2009

| Milestone No. | Milestone Name | Date due | Actual/Forecast delivery date | Lead contractor |
|---|---|---|---|---|
| **WP 15** | **SCT** | | | |
| **15.27c** | Develop common protocols for molecular diagnosis of fungal infections by PCR | **72** | Evaluation of PCR protocols completed. Evaluation in the clinic started | Einsele Maertens |
| **15.30** | Develop guidelines for prevention of infections in stem cell transplant recipients not covered in previous guidelines | **78** | Delivered | Einsele Ljungman Cordonnier |

**Section 3: Consortium management**

All deliverables and milestones that had to get revised timetables during previous years have now been achieved with the exception of the planned review for transfusion guidelines. It was decided in 2008 not to pursue this topic and instead concentrate on infectious complications. The two previously created subcommittees have continued to function. One subcommittee handles the specific topic of infections in stem cell transplant recipients. This subcommittee is lead by Hermann Einsele. The second subcommittee did the planning for the 3:d European Guidelines meeting and is now working on the publications. This group is chaired by Catherine Cordonnier and incorporates representatives for the ELN, the EBMT, the ICHS, and the EORTC.

**Section 4: Other Issues**

Ethical issues - none

Competitive calls -none

**Section 5: WP-Performance**

| Performance indicators | Status |
|---|---|
| European guidelines for anti-infection prophylaxis and therapy in neutropenic patients | Finalized and expanded |

**Biometry of Registry, Epidemiology, Metaanalyses and Prognosis (WP 17)**

With regard to the major objectives as stated in the original grant application many years ago, most of them have been achieved in the field of CML. This is partly due to the fact that there had been already a close collaboration among the premier European CML study groups since 1992. But a major reason why comparable achievements were missing for a long time for the other leukemia entities was lack of funds. Initially a considerably higher funding (actually 4 times as much as finally awarded) was expected and planned for. To establish a registry requires considerable and enduring activities over a long time without the hope of immediate rewards like presentations and publications. This in combination with lack of funds is certainly not a good starting point. Over time and certainly influenced by the constant flow of presentations of the CML Registry, the situation has changed. Thus an ELN-MDS-Registry has been initiated with the support of Novartis which will become productive once a sufficiently sized sample has been recruited and observed for an adequate period of time.

Quite recently similar first activities have been started for AML, too. Guided by the German AML Study Groups and U. Mansmann (IBE, University of Munich) planning and design activities have started. A decisive factor for the outcome of these activities is of course the access to funding.

Considering that the establishment of European Leukemia Registries is pioneer work there are considerable achievements. In this context one should not forget that the legal situation with regard to registries, clinical eand epidemiological research and data confidentiality issues differs from country to country and is thus rather complicated, and difficult to overcome.

*Objectives and starting point of work at beginning of reporting period*

There were two major objectives for the current reporting period (01.01.2009-31.12.2009):

1) to do a comparative analysis of Imatinib-treated patients from the IRIS trial with the genetically randomised SCT-patients from the German CML III studies.
2) to expand and update the European CML-registry which collects data about the epidemiology and the clinical management of patients with CML in the various member states of the EU.

Considerable progress has been achieved with regards to both objectives.

**Comparative Analysis SCT vs. Imatinib**

Early allogeneic stem cell transplantation has been considered the only curative treatment for CML. The advent of imatinib provided a new chance to suppress long-lastingly the disease without risk of early deaths. As there is no randomized trial comparing transplantation with imatinib therapy, we compared the outcome between transplanted and imatinib-treated patients of two randomized trials. We used the survival data of patients randomly allocated to imatinib in the IRIS trial (Druker et al. N

Engl J Med 2006; 355:2408) and compared them with the genetically randomized transplanted (matched related donors) patients of the German CML III and IIIA studies (Hehlmann et al. Blood 2007; 109:4686).

Applying uniform inclusion criteria for age (18–55 yrs at diagnosis) to generate comparable samples, survival time was determined according to the intention-to-treat principle and after stratification for the Euro and EBMT scores using Kaplan-Meier curves. Information about Sokal and Euro score was missing for 123 and 128 patients from the IRIS trial and for 4 resp. 6 patients from the German CML III/IIIA studies.

377 CML patients in chronic phase treated with Imatinib and 285 patients with early allogeneic SCT were analyzed. In the Imatinib arm of the IRIS trial, 42 patients had been transplanted and 12 patients have died subsequently. Five-year-survival in this subgroup of 377 younger patients of the IRIS trial was 94.7%. The patients' characteristics of the two groups were comparable (CML III/IIIA vs IRIS), median age: 38 vs. 44 yrs., female sex: 40% vs. 39%, Sokal Score low 49.8% vs. 58.3%, intermediate 30.2% vs. 25.2%, high risk 19.9% vs. 16.5%; Euro Score low 62.7% vs. 58.6%, intermediate 31.5% vs. 34.9%, high risk 5.7% vs. 6.4%. Median observation time was 75 months for transplanted patients and 61 months for Imatinib-treated patients. Patients of both groups have not yet reached median survival times. Five-year survival rates were 94.7 % (all Imatinib treated patients) and 71.1 % (all transplanted patients). In all prognostic strata, irrespective of the prognostic score used, five-year-survival with Imatinib was evidently superior compared to transplantation: Euro score: low risk 97.8% vs. 78.3%, intermediate risk 93.6% vs. 58.9%, EBMT score 0-2: 94.7% vs. 78.8%, EBMT score 3-4: 94.7% vs. 52.2%. There were just 5 transplanted patients with an EBMT score >4. Neither the censoring of the 42 transplanted patients of the IRIS trial affected the results nor the in- or exclusion of the 12 subsequent deaths.

We could not identify any subgroup of patients with CML who clearly showed a benefit from early transplantation compared to treatment with Imatinib, given an observation time of 5–6 years.

**European CML-registry**

With the additional funds provided by Novartis within the EUTOS program considerable progress has been achieved, both with regard to centers contributing data and to getting follow up data.

Research plans for registering patients included in studies (In-Study-Patients) and for patients not included in studies (Out-Study-Patients) have been written and finalized.

In between data from Czech Republic, France, Germany, Italy, Poland, Romania, Russia, Slovakia, Spain, Switzerland, and the Nordic countries have been collected. It is comparatively easy to get the baseline data. The real challenge is the follow-up. At the end of the reporting period there were baseline data of 2595 patients and follow-up data of 1989 patients in the registry. Median follow-up time is 24 months.

*Progress towards objectives – tasks worked on and achievements made with reference to planned objectives*

**17.5 Regular WP meetings**

WP meetings took place at the annual ELN meeting in Mannheim (1/2009), Berlin (EHA 6/2009), Mannheim (CML 7/2009), Barcelona (10/2009). Most often these WP meetings were joint meetings of WP17 and WP4.

**17.6 LP reports to NMC regarding structure, activities and integration**

There were regular reports to the NMC regarding structure, activities and integration.

**17.13c Collect data for prognostic model analyses and meta-analyses (European CML registry)**

Data of about 2595 patients from Austria, Czech Republic, Denmark, Finland, France, Germany, Israel, Italy, Norway, Poland, Romania, Russia, Spain , Sweden and Switzerland have been checked and included in the registry.

**17.14c Quality control of incoming data**

Quality control of incoming data is a prerequisite of any data evaluation. There are plausibility checks of each variable, concerning completeness, minimum and maximum, valid numbers, valid dates etc. Furthermore there are two-dimensional plausibility checks concerning more than one variable. Finally comparisons between centres are being conducted to find outliers, which can be due to misinterpretations or erroneous documentation.

There will be send queries to the centres to complete the documentation and improve the quality of the data. The results of the quality control of incoming data are being presented to all participants. This activity has to continue as long as the registry collects data.

There were considerable problems due to many languages used to describe and explain the variables and items, and the ‘translation´ to English took some extra time. But we are confident now that we have solved this problem. It is very helpful for us to get the documentation in the Excel template sheets that are provided by us, the participants can cross-check their documentation by filling in them so the number of queries can be reduced.

**17.15d Spreading of Excellence by promotion of web-based information, educational training courses etc.**

- A major point of basically all presentations was to encourage the physicians in the audience to treat elderly patients with modern treatments like Imatinib.
- In May, Joerg Hasford and Markus Pfirrmann participated in the “European investigators in CML” meeting. in Crete. Hasford and Pfirrmann met most European coordinators of studies in CML. The occasion was used to promote the CML registry. In addition results of our analyses were presented and discussed.

- In July Joerg Hasford presented results at the annual CML-Symposium in Mannheim and in October at the DGHO-Congress in Mannheim.

**17.16d Update of the CML registry**

As already mentioned in 2008, we tried hard to update the information in the registry. In the last quarter, many study groups provided updates so that we can present new results at the next ELN-meeting beginning of February 2010 in Mannheim.

**17.17b Gender specific issues**

- To analyse the influence of gender is an obligate issue in each analysis. Gender and age are considered as potential prognostic variables in each standard evaluation of leukaemia studies and therefore compulsory. But it is planned to check for sex-specific disease-, treatment-, and outcome characteristics, too. Due to the fact that most data provided by the study groups consisted of baseline data, our plans of first analyses could not yet be fulfilled with the registry.
- To overcome these problems we established a cooperation with the social health insurance accredited physicians of Bavaria. Their data-base covers 85% of the Bavarian population (~ 10,4 millions of people). Analysing the treatment data of more than 800 patients with CML in 2006 we could not find any relevant differences between the sexes (for more data see 17.22).

**17.21bAnalysis and Validation of prognostic models**

Due to the delays in updating the data and the comparable few events (e.g. death, relapse) seen under Imatinib, we could not yet analyse prognostic factors. We hope to progress in 2009.

**17.22b Estimates of incidence of CML and treatment survey.**

We have updated the treatment survey as far as prescription data were already available.

Considering the first 9 months of 2007 patients with CML were treated as follows, based on a population of more than 800 CML patients in Bavaria:

| | |
|---|---|
| Imatinib | 59,2% |
| Imatinib in combination | 67,8% |
| Hydroxyurea | 27,6% |
| IFN alfa | 3,7% |

There were no relevant differences seen between the sexes, but elderly patients had less chances to get treated with Imatinib. Analysing the comorbidity profiles of the CML patients, we could not find any relevant associations between comorbidity and the prescribing of imatinib or hydroxyurea.

**17.24 Decision aid for SCT vs. Imatinib**

As we could not identify a single subgroup of CML patients which experienced a clear benefit from SCT there was no need to develop a specific decision aid.

However SCT is still an option for patients who do not tolerate or respond to TKIs, who prefer SCT, and for very young patients.

**Table 17.6:** Deliverables of WP 17 in 2008

| Deliv. No. | Deliverable Name | Date due | Actual/Forecast delivery date | Estimated indicative person months | Used indicative person months*) | Respon-sible lead participant/ investigator |
|---|---|---|---|---|---|---|
| **WP 17** | **Biometry of Registry, Epidemiology, Metaanalyses and Prognosis** | | | | | |
| **17.5** | Regular WP meetings | 66 | As scheduled | 2 | 2 | Hasford |
| **17.6** | LP reports to NMC regarding structure, activities and integration (1 page, bullet point style) | 66 | 78 | 1 | 1 | Hasford |
| **17.13d** | Collect data for prognostic model analyses and meta-analyses-continues | 66 | 72 | 1 | 1 | Hasford |
| **17.14d** | Quality control of incoming data-continued | 66 | 72 | 3 | 3 | Hasford. Müller |
| **17.15e** | Spreading of excellence by promotion of web-based information, educational training courses etc | 66 | 49-60 | 4 | 4 | Simonsson Hasford J Guilhot Baccarani |
| **17.16e** | Update of CML-Registry | 55 | 72 | 0 | 2 | Hasford J. Guilhot Baccarani Simonsson |
| **17.21c** | Analysis and Validation of prognostic models | 66 | ongoing | 0 | 2 | Hasford |
| **17.22c** | Estimates of incidence of CML and treatment survey | 66 | 60 | 0 | 2 | Hasford |
| **17.23** | Comparison of the outcomes of SCT vs Imatinib | 55 | 58 | 4 | 4 | Hasford |
| **17.24** | Decision aid for SCT vs Imatinib treatment | 66 | ongoing | 5 | 5 | Hasford |

List of milestones WP17, 2008

| Milestone No. | Milestone Name | Date due | Actual/Forecast delivery date | Lead contractor |
|---|---|---|---|---|
| **17.21c** | Analysis and Validation of prognostic models | 66 | ongoing | Hasford |
| **17.22c** | Estimates of incidence of CML and treatment survey | 66 | 72 | Hasford |
| **17.24** | Decision aid for SCT vs Imatinib treatment | 66 | ongoing | Hasford |

**Section 3: Consortium management**

**Section 4: Other Issues**

Ethical issues – none, Competitive calls - none

**Section 5: WP-Performance**

| Performance indicators | Status |
|---|---|
| Development of core data sets | done (for CML, MDS) |
| Number of clinical trials performed with standardized common data sets | CML trials |
| Number of involved countries | 11 |
| Number of involved/registered patients | 1870 |
| Number and quality of publications of joined research activities | 6 |

# Annex - Plan for using and disseminating the knowledge

## Section 1: Exploitable knowledge and its use

Is not yet relevant and not the primary aim of the network.

## Section 2: Dissemination of knowledge: WP-Meetings

WP-Meetings WP 1

- Annual ELN Symposium, Mannheim, February 3rd

Attendance: Approximately 420 participants from EU and non EU countries

- WP-meetings, EHA, Berlin, June 4

Attendance: Approximately 235 participants from EU countries

- ELN ASH Breakfast Meeting 2009, New Orleans, December 06 th, 2009

Attendance: Approximately 160 participants from European countries

WP-Meetings WP 2

- Annual ELN Symposium, Mannheim, February 3rd.

Attendance : Approximately 60 participants

WP-Meetings WP 3

- Annual ELN Symposium, Mannheim, February 3rd

Attendance: Approximately 40 participants from EU and non EU countries

- Workshop for statistics-specialists, "Advances in Statistical Modeling of High Dimensional Data: Variable selection and Challenges in Image Analysis", Munich, September 17-18, 2009

Attendance: 48

WP-Meetings WP 4

- Annual ELN Symposium, Mannheim, February 3rd

Attendance: Approximately 100 participants from EU and non EU countries

- Annual ELN Symposium, EUTOS Meeting, Mannheim, February 3rd

Attendance: Approximately 75 participants from EU and non EU countries

- International EI-CML symposium, Salzburg May 2009

Attendance: Approximately 40 participants from EU

- WP meeting, EHA, Berlin, June 4

Attendance: Approximately 50 participants from EU

- CML symposium, Mannheim June 27

Attendance: Approximately 120 participants from EU and non-EU

- ELN Fromtiers meeting, Barcelona, September 2009

Attendance: 400 participants from EU

- ESH-ELN joined CML meeting, Bordeaux, September 2009

Attendance: 300 participants from EU

- ELN Breakfast meeting at ASH, New Orleans, December 6

Attendance: Approximately 55 participants from European countries

- EUTOS registry meeting WP4, ASH, New Orleans, New Orleans December 05

Attendance: Approximately 10 participants from EU countries

WP-Meetings WP 5

- Annual ELN Symposium, Mannheim, February 3rd

Attendance: Approximately 60 participants from EU and non EU countries

- AML Intergroup meeting, Reisensburg February 09

Attendance: Approximately 70 participants from EU and non EU countries

- WP meeting, EHA, Berlin, June 4

Attendance: Approximately 50 participants from EU

- AML Intergroup Meeting, Frankfurt, 11.05.2009

Attendance: Approximately 20 participants from EU countries

- AML Intergroup Meeting, Frankfurt, 28.09.2009

Attendance: Approximately 20 participants from EU countries

- ELN Breakfast meeting at ASH, New Orleans, December 6

Attendance: Approximately 20 participants from European countries

WP-Meetings WP 6

- Annual ELN Symposium, Heidelberg

Attendance : Approximately 45participants from EU and non EU countries

- EWALL, Krakow June 2009

Attendance: Approximately 20 participants; EWALL internal meeting

- EWALL-GMALL, Frankfurt, November 2009

Attendance: Approximately 50 participants; GMALL-EWALL joint meetings

- ASH, New Orleans, December 2009

Informal meeting during the ELN breakfast meeting; approximately 10 EWALL members

WP-Meetings WP 7

- 19th ERIC Meeting at the 6th Annual Symposium of the ELN, Mannheim, Wednesday, February 03, 2009

Attendance: Approximately 45 participants from EU and non EU countries

- ERIC/EHA Scientific Meeting/Workshop at the European Hematology Association (EHA) Congress, Berlin, June 04th

Attendance: Approximately 120 participants from EU and non EU countries

- 20th General Meeting of ERIC Members, Berlin, June 04, 2009

Attendance: Approximately 80 participants from EU and non EU countries

- 21st General Meeting of ERIC Members, New Orleans, December 07th, 2009 (ELN ASH Breakfast Meeting 2009)

Attendance: Approximately 50 participants from EU and non EU countries

WP-Meetings WP 8

- Annual ELN Symposium, MDS WP meeting, Mannheim, 3 Febuary 2009;

Attendance: 95 participants from EU

- European MDS Registry" project, Steering Committee meeting, Mannheim, February 3, 2009

Attendance: 16 participants

- MDS symposium in Patras, 6th May, 2009: steering committee meeting of European low risk MDS Registry" project

Attendance: 16 participants

- MDS symposium in Patras, 7th May, 2009: ELN MDS meeting on therapeutic guidelines; attendance steering committee WP8

Attendance: 16 participants

- MDS Iron Chelation Think Tank during annual EHA meeting, Berlin 3 June 2009

Attendance: 120 participants

- Operational team meeting of European MDS Registry, Amsterdam-Airport – July 01, 2009

Attendance: 15 participants

- European MDS Registry" project, Steering Committee and operational team meeting, London, September 25, 2009

Attendance: 26 participants

- Eugesma Cost Action (BM 0801) second Workshop meeting "European Genetic and Epigenetic studies in MDS and AML in collaboration with 5th ELN Workshop "Genetics in MDS", 12-13 October 2009, Hannover, Germany

Attendance: 45 participants

- MDS WP 8 steering committee meeting during the ESH-MDS postgraduate training course Mandelieu, October 24, 2009

Attendance: 18 participants

- The second Workshop on flow cytometry in MDS, 30-31 Oct 2009 in Munich, Germany (host: Dr. W. Kern; chair: AA van de Loosdrecht)

Attendance: 70 participants

- ELN Workshop at the Annual ASH meeting New Orleans: presentation of progress of projects within MDS WP8

Attendance: 70 participants

WP-Meetings WP 9

- Annual ELN Symposium, Mannheim, February 3rd

Attendance: Approximately 60 participants from EU and non EU countries

- European Hematology Association (EHA) Congress, Berlin, June 04th

Attendance: 15 participants from European countries

- ECA conference, Stockholm 2009

Attendance: 15 participants from European countries

- ELN Breakfast meeting, ASH, New Orleans, December 6th

Attendance: 20 participants from European countries

WP-Meetings WP 10

- Annual ELN Symposium, Mannheim, February 3rd

Attendance: Approximately 60 participants from EU and non EU countries

- EGIL meeting in Vienna, April

Attendance: Approximately 10 participants from EU and non EU countries

- MDS meeting, Munich, October

Attendance: Approximately 15 participants from EU and non EU countries

- EHA European School in Vienna, November

Attendance: Approximately 15 participants from EU countries

WP-Meetings WP 11

- Annual ELN Symposium, Mannheim, February 3rd

Attendance: Approximately 60 participants from EU and non EU countries

- EHA, Berlin, June 2009

Attendance: Approximately 30 participants from EU countries

- WP meeting in Hannover together with COST initiative in October 2009.

Attendance: Approximately 40 participants from EU countries

WP-Meetings WP 12 (2008)

- Annual ELN Symposium, Mannheim, February 3rd

Attendance: Approximately 60 participants from EU and non EU countries

- EHA, Berlin, June 2009

Attendance: Approximately 60 participants from EU countries

- EUTOS Mol. Meeting (after EHA), Berlin, June 2009

Attendance: Approximately 50 participants from EU countries

- ELN BCR-ABL meeting, ASH, New Orleans

Attendance: Approximately 50 participants from EU countries

- ELN WP12 meeting, ASH, New Orleans

Attendance: Approximately 70 participants from EU countries

WP-Meetings WP 13

- Annual ELN Symposium, Mannheim, February 3rd

Attendance: Approximately 60 participants from EU and non-EU countries

WP-Meetings WP 14

- EBMT CLWP/ELN; City Conference Center, Angers, January 30-31, 2009

Attendance: n.a.

- Annual ELN Symposium, Mannheim, February 3rd

Attendance: Approximately 80 participants from EU and non-EU countries

- EBMT CLWP/ELN; City Conference Center, Angers, January 30-31, 2009

Attendance: Approximately 60 participants from EU and non-EU countries

- EBMT annual meeting, Göteborg, March 29, 2009

Attendance: Approximately 70 participants from EU and non-EU countries

- WP5/WP14 meeting at EHA/ELN, Berlin, June 4, 2009

Attendance: Approximately 50 participants from EU and non-EU countries

- Subcommittee meeting in Leiden July 03, 2009

Attendance: Approximately 30 participants from EU and non-EU countries

- EBMT CLWP/ELN; Milan, September 11- 12, 2009

Attendance: Approximately 70 participants from EU and non-EU countries

- CLWP Subcommittee chair meeting in Leiden 13/11/09

Attendance: Approximately 30 participants from EU and non-EU countries

- ELN Breakfast meeting, ASH, New Orleans, WP5/WP14 New Orleans December 06

Attendance: Approximately 40 participants from EU and non-EU countries

WP-Meetings WP 15

- Annual ELN Symposium, Mannheim, February 2nd

Attendance: Approximately 10 participants from EU and non EU countries

- EBMT meeting in Göteborg March 29

Attendance: Approximately 30 participants from EU and non-EU countries

- EBMT meeting in Juan-les-Pins September 25-26

Attendance: Approximately 30 participants from EU and non-EU countries

- EBMT meeting in Rome October 31

Attendance: Approximately 30 participants from EU and non-EU countries

WP-Meetings WP 17

- Annual ELN Symposium together with WP4 and WP5, Mannheim, February 3rd

Attendance: Approximately 100 participants from EU and non EU countries

- EICML Meeting, May 2009, Salzburg

Attendance: Approximately 40 participants from EU countries

- 17th International CML Workshop, Juny 2009, Mannheim

Attendance: Approximately 120 participants from EU and non EU countries

- ELN-Frontiers meeting, CML Educational, September 2009, Barcelona

Attendance: Approximately 400 participants from EU and non EU countries

- ELN Breakfast meeting tohether with WP4, ASH, New Orleans, New Orleans December 06

Attendance: Approximately 40 participants from EU and non-EU countries

- EUTOS registry meeting WP4, ASH, New Orleans, New Orleans December 05

Attendance: Approximately 10 participants from EU countries

**Presentations / Spread of excellence**

**Table Annex 1:** (Press release (PR), oral presentations (OP), organization (O), Exhibition (E), Congress/ Symposium (CS), Poster (PO), email, Website (www), Workshop (WS))

| WP | Planned/actual Dates | Type | Event | Type of audience | Countries addressed | Size of audience | Partner(s) responsible/involved |
|---|---|---|---|---|---|---|---|
| All | permanent | www | Website www.leukemia-net.org | Network members & General public | all | See ELIC report | ELIC |
| 1/2 | 10-09 | E | DGHO Wien, Germany | Researcher | Germany Austria, Siwtzerland | not applicable | NMC,ELIC |
| 1/2 | 12-09 | PR | Information Letter | All | all | not applicable | NMC |
| 1/4 | 19.01.09 | OP | Tannheimer Tal, Vortrag: "Klinik und Prognose der P. vera" | Researcher | European | 50 | Hehlmann |
| 1 | 21.01.09 | OP | Hannover, Vortrag: „Leukämieforschung in Europa" | Clinicians and Scientists | Germany | 100 | Hehlmann |
| 1/4 | 22.01.09 | OP | Tannheimer Tal, Vortrag: „Aktuelle Richtlinien des ELN für die Diagnose und Therapie der CML" | Clinicians | European | 60 | Hehlmann |
| 1 | 03.02.09 | CS | Mannheim, ELN/KNL-Symposium „Welcome to the ELN-Symposium 2009" | Research | European | 350 | NMC, Hehlmann |
| 1 | 02-2009 | CS | Assembly, European LeukemiaNet meeting Mannheim | Research | European | 350 | NMC, Saußele |
| 1 | 02.02.09 | O | Future of IACRLRD | Research | International | 15 | Hehlmann |
| 1 | 06.02.2009 | CS | AML Intergroup, Reisensburg, Germany | Physicians and Scientists | Germany | 50 | Hehlmann |
| 1/4 | 07.02.09 | OP | Rom, Vortrag: „La storia dello svelupo degli inibi-tori delle tirosino-chinasi" | Clinicians and Scientists | International | not available | Hehlmann |
| 1 | 12.-14.02. 2009 | OP | Asian Hematology Association, Kobe: "The Paradigm CML and the Integration of Leukemia Research in Europe" | Physicians and Scientists | International | not available | Hehlmann |
| 1 | 17.02.09 | OP | Onkologieforum, Mainz: "Krebsforschung – zukunftsfähig durch Vernetzung" | All | Germany | 50 | NMC, Hehlmann |
| 1/4 | 20.02.2009 | OP | St. Gallen, ESO, Vortrag: „Chronische myeloische Leukämie: State of the art 2009" | Physicians and Scientists | International | | Hehlmann |
| 1 | 02.03.09 | WS | Frankfurt, Carreras-Beirat | Physicians and Scientists | Germany | | Hehlmann |
| 1/4 | 08.03.09 | OP | Paris, Vortrag: „Are we on the path to curing CML?", Global Opinion Leader Summit (GOLS) | Physicians and Scientists | International | | Hehlmann |

| WP | Planned/actual Dates | Type | Event | Type of audience | Countries addressed | Size of audience | Partner(s) responsible/involved |
|---|---|---|---|---|---|---|---|
| 1 | 23.-24.03. 2010 | OP | Polish Society of Hematology, Warszwa: "Imatinib – standards of first line therapy. Essential conclusions from the IRIS study and other clinical trials". | Research | Germany | 50 | Hehlmann |
| 1/4 | 28.03.2009 | OP | Turin, „BMT for CML in Germany today: which outcome can we expect?" | Physicians and Scientists | International | 200 | Hehlmann |
| 1/4 | 29.03.2009 | | Turin: „The importance of a European coordinated approach: the example and the experience of the European Investigators on CML" | Physicians and Scientists | International | 200 | Hehlmann |
| 1 | 01.-03.04. 2009 | O | EHA 2009 final Meeting | Research | Germany | 20 | NMC, Hehlmann |
| 1/4 | 17.04.09 | OP | ÖGHO Frühjahrstagung, Salzburg, "Therapie-optimierung und Kombinationstherapien mit Imatinib" | Physicians and Scientists | International | 100 | Hehlmann |
| 1 | 18.04.09 | OP | Polish School of Hematology, Wisla, „Are we on the right way to cure CML without HSC-allo transplantation?" | Physicians and Scientists | International | 140 | Hehlmann |
| 1 | 19.-22. 04. 2009 | E | Tagung Ges. für Innere Medizin, 3x Chairman | Physicians and Scientists | Germany | 50-400 | Hehlmann |
| 1 | 22.04.09 | O | ELN Foundation Kickoff Meeting, Frankfurt Airport | Physicians and Scientists | International | 12 | NMC, Hehlmann |
| 4 | 7.-10.05. 2009 | OP | Salzburg, EI-CML-Meeting „Updates CML Study IV" | Physicians and Scientists | European | 50 | Hehlmann |
| 1 | 11.05.2009 | O | Frankfurt, Leukämienetz Vorstandssitzung | Physicians and Scientists | European | 20 | Hehlmann |
| 1/4 | 18.-19.05. 2009 | | Neapel, EUTOS-Educational, Vortrag: "EUTOS - a public private partnership to improve quality controlled outcome in CML" | Physicians and Scientists | European | 35 | Hehlmann |
| 1/4 | 22.-23.05. 2009 | | St. Petersburg, Vortrag: „Are we on the path to curing CML?" | Physicians and Scientists | European | 150 | Hehlmann |
| 1 | 03.06. 2009 | WS | Report to EHA-Board | Physicians and Scientists | International | 10 | Hehlmann |
| 1 | 05.06.2009 | OP | Opening address, EHA Berlin 2009 | Physicians and Scientists | International | 3000 | Hehlmann |
| 1 | 05.06.2009 | OP | Dinner Speech, Opern-Palais, EHA Referentenabend | Physicians and Scientists | International | 250 | Hehlmann |
| 1 | 06.06.2009 | OP | Welcome, social evening (Gemäldegalerie) | Physicians and Scientists | International | 700 | Hehlmann |
| 1 | 25.06.2009 | | EUTOS – Executive Committee Meeting Heidelberg | Physicians and Scientists | European | 6 | NMC |

| WP | Planned/actual Dates | Type | Event | Type of audience | Countries addressed | Size of audience | Partner(s) responsible/involved |
|---|---|---|---|---|---|---|---|
| 1/4 | 10.-13.09. 2009 | CS | Bordeaux, ESH-Education: Chair/Co-Organisation | Physicians and Scientists | European | 300 | Hehlmann Hochhaus Saußele Mahon Goldman |
| 1 | 23.09.2009 | OP | ELN and EUTOS | Physicians and Scientists | European | 15 | Hehlmann Simonsson |
| 1/4 | 2.-8.12. 2009 | OP | New Orleans, ASH | Physicians and Scientists | International | 3000-10.000 | Hehlmann Saußele Pletsch Kossak-Roth |
| 1 | 06.12.2009 | | New Orleans, ELN-Breakfast meeting. Overview ELN 2009 | Physicians and Scientists | International | 150 | Hehlmann |
| 1 | 03.02.09 | OP | ELN Symposium Update ELN-Foundation | Physicians and Scientists | International | 300 | P.Schrotz-King |
| 1 | 04.12.09 | OP | ELN Breakfast Meeting Update ELN-Foundation | Physicians and Scientists | International | 150 | C. Bradley |
| 2 | 18.03.09 | OP | IIT Workshop: Der oftmals steinige Weg von der Studienidee zum Einschluß des ersten Patienten: Strategien für das risikoadaptierte Monitoring | Expert | National | 40 | Gökbuget |
| 2 | 26.06.09 | OP | CML-Studientreffen: GCP-Fortbildung: Safety-Management in IITs: | Expert | National | 50 | Gökbuget |
| 2 | 2.2.-4.2.09 | OP | European Leukemia Net und Netzwerksymposium Kompetenznetz Leukämien: GCP-Fortbildung: Safety-Management | Expert | Englisch | 40 | Gökbuget |
| 2 | 30.9.09 | OP | Arbeitstagung der Überwachungsbeamten | Expert | Deutsch | 30 | Gökbuget |
| 3 | 02-09 | CS | GCP Workshop, ELN Symposium Heidelberg | Physicians and Scientists | European | 45 | NMC, ELIC, CICS |
| 3 | September 17-18, 2009 in Munich | WS | Advances in Statistical Modeling of High Dimensional Data: Variable selection and Challenges in Image Analysis | Physicians and Scientists | International | 48 | IBE, ELN |
| 4 | 06.06.2009 | OP | EHA: "Randomized clinical trial for the optimization of imatinib therapy by combination, dose escalation and trans-plantation. Designed first interim analysis of the German CML Study IV" | Physicians and Scientists | International | 2000 | Hehlmann |
| 4 | 06.06.2009 | OP | EHA: "Results of transplanted pts. in the CML Study IV" | Physicians and Scientists | International | 2000 | Saußele |
| 4 | 18.06.2009 | OP | Breslau: „On the path to curing CML – the new ELN-recommen-dations", Polish Society of Hematology and Blood Transfusion | Physicians and Scientists | European | 150 | Hehlmann |

| WP | Planned/actual Dates | Type | Event | Type of audience | Countries addressed | Size of audience | Partner(s) responsible/involved |
|---|---|---|---|---|---|---|---|
| 4 | 25.06.2009 | OP | international CML-Workshop, EUTOS Meeting: CML Study IV | Physicians and Scientists | International | 120 | Hehlmann |
| 4 | 02.09.2009 | OP | Bonn, Vortrag: „Chronische myeloische Leukämie, Update 2009 | Physicians and Scientists | International | 100 | Hehlmann |
| 4 | 18.-20.09.09 | CS | Barcelona, ELN-Symposium, Vortrag, Chair, Organizer | Physicians and Scientists | European | 500 | Hehlmann Baccarani Cervantes Saußele |
| 4 | 05.10.2009 | OP | DGHO, Mannheim, Vortrag: CML IV | Physicians and Scientists | Germany | 300 | Hehlmann |
| 4 | 05.10.2009 | OP | DGHO, Mannheim, Vortrag: CML IV | Physicians and Scientists | Germany | 300 | Saußele Müller |
| 4 | 15.10.2009 | OP | Columbus (Ohio), IACRLRD, Vortrag: "Beyond life-long administration of tyrosine kinase inhibitors: what is next for CML patients?" | Physicians and Scientists | International | 500 | Hehlmann |
| 4 | 04.11.2009 | OP | Atlanta: "Can we cure CML? New developments in CML" | Physicians and Scientists | America | 50 | Hehlmann |
| 4 | 07.11.2009 | OP | New York: "Treatment of accelerated and blast phase disease update" | Physicians and Scientists | America | 500 | Hehlmann |
| 4 | 13.11.2009 | OP | Taschkent: "How can we improve survival? CML treatment options in 2009" | Physicians and Scientists | Russia | 250 | Hehlmann |
| 4 | 2.-3.12.09 | | New Orleans, 3rd Global Workshop on CML | Physicians and Scientists | International | 100 | Hehlmann |
| 4 | 06.12.2009 | | New Orleans, ASH, Vortrag: The German CML-Study IV | Physicians and Scientists | International | 2000 | Hehlmann |
| 4 | 06.12.2009 | | New Orleans, ASH, Vortrag: The German CML-Study IV | Physicians and Scientists | International | 2000 | Pletsch |
| 4 | 01.09 | OP | Post-ASH Symposium Mannheim,: Chair | Physicians and Scientists | International | 150 | Hochhaus, Müller |
| 4 | 2.02.09 | OP | ELN Symposium Heidelberg, "Studies" | Physicians and Scientists | International | 70 | Hochhaus |
| 4 | 03.02.09, | OP | ELN Symposium Heidelberg, "Standardization of BCR-ABL RQ-PCR" | Physicians and Scientists | International | 70 | Müller |
| 4 | 18.-19.5.08 | WS | EUTOS Educational meeting for young fellows, Naples | Physicians and Scientists | International | 40 | Hehlmann, Saußele, Hochhaus, Pane, Baccarani,Saglio, Martinelli, Soverini |
| 4 | 07.-10.05.08 | WS | EI-CML Workshop Salzburg, Austria | Physicians and Scientists | European | 50 | Hehlmann/ Hochhaus/ Saußele/Müller |
| 4 | 28.05.-02.06.2009 | OP | CML-Symposium, ASCO, Orlando | Physicians and Scientists | International | 500 | Hochhaus/ Müller |
| 4 | 26.-27.06.09 | WS | „The German CML-study IV", 18. International CML-Workshop, Mannh. | Physicians and Scientists | Germany | 120 | Hehlmann |

| WP | Planned/actual Dates | Type | Event | Type of audience | Countries addressed | Size of audience | Partner(s) responsible/involved |
|---|---|---|---|---|---|---|---|
| 4 | 26.-27.06.09 | WS | „The German CML-study IV“, 18. International CML-Workshop, Mannh. | Physicians and Scientists | Germany | 120 | Saußele, Müller Hochhaus, Erben |
| 4 | 02.09.2009 | OP | “Chronische myeloische Leukämie”, Bonn | Physicians and Scientists | Germany | 100 | Hehlmann |
| 4 | 02.-06.10. 2009 | OP | CML-Symposium, DGHO, Mannheim | Physicians and Scientists | Europe | 430 | Hehlmann, Hochhaus, Müller, Saußele |
| 4 | 02.-06.10. 2009 | OP | DGHO-Jahrestagung, Mannheim | Clinicians & Researchers | Germany, Switzerland, Austria | 430 | Härtel, La Rosée |
| 4 | 27.11.09 | OP | “Zwischenauswertung der Pilotphase der CML-Studie IV“, CML-Studientreffen, Frankfurt | Physicians and Scientists | Germany | 50 | Hehlmann, Saußele, Proetel, Jung-Munkwitz, Pletsch |
| 4 | 27.11.08 | OP | “CML-Studie 5“, CML-Studientreffen, Frankfurt | Physicians and Scientists | Germany | 50 | Hochhaus, |
| 4 | 27.11.08 | OP | “Molekulares Monitoring CML-Studie IV“, CML-Studientreffen, Frankfurt | Physicians and Scientists | Germany | 50 | Müller |
| 4 | 6.12.2009 | OP | 3rd annual global CML-workshop, Post-ASH, Natchez | Physicians and Scientists | International | 150 | Hehlmann, |
| 5 | 02.02.-03.02.09 | OP | European LeukemiaNet Symposium, Mannheim, Germany | Physicians and Scientists | International | 439 | Büchner |
| 5 | 06.02.09 | OP | AML Intergroup Meeting, Reisensburg, Germany | Physicians and Scientists | International | 40 | Büchner |
| 5 | 11.05.09 | OP | AML Intergroup Meeting, Frankfurt, Germany | Physicians and Scientists | Germany | 20 | Büchner |
| 5 | 22.-23.05.09 | OP | HAM & CHOPS Symposium München, Germany | Physicians and Scientists | International | 50 | Büchner |
| 5 | 03.-05.06.09 | OP | European LeukemiaNet Meeting at EHA, Berlin, Germany | Physicians and Scientists | “ | 40 | Büchner |
| 5 | 28.09.09 | OP | AML Intergroup Meeting, Frankfurt, Germany | Physicians and Scientists | Germany | 20 | Büchner |
| 5 | 17.-21.09.09 | OP | Raissa Gorbacheva Memorial Lecture, St. Petersburg, Russia | Physicians and Scientists | International | 100 | Büchner |
| 5 | 29.09-01.10.09 | OP | Hematologic Malignancies, Brüssel, Belgium | Physicians and Scientists | ,, | 100 | Büchner |
| 5 | 18.11.09 | OP | Advisory Board Meeting, Amsterdam, Netherlands | Physicians and Scientists | International | 20 | Büchner |
| 5 | 04.12.09 | OP | ELN Breakfast Meeting at ASH, New Orleans, USA | Physicians and Scientists | International | 25 | Büchner |
| 5 | 06.12.09 | OP | ASH Annual Meeting, New Orleans, USA | Physicians and Scientists | “ | 100 | Büchner |
| 6 | 07.06.09 | OP | 14th Congress of the European Hematology Association | Expert | Englisch | 100 | Gökbuget |
| 6 | 2.2.-4.2.09 | OP | European Leukemia Net und Netzwerksymposium Kompetenznetz Leukämien | Expert | UK | 40-100 | Gökbuget |
| 6 | 19.-20.6.09 | OP | 16th Meeting of the EWALL | Expert | UK | 25 | Gökbuget |

| WP | Planned/actual Dates | Type | Event | Type of audience | Countries addressed | Size of audience | Partner(s) responsible/involved |
|---|---|---|---|---|---|---|---|
| 6 | 28.05.-02.06..2009 | OP | "Acute lymphoblastic leukemia in adolescents and young adults: is the treatment paradigm changing? | Physicians and Scientists | International | 500 | Hunault |
| 6 | 28.05.-02.06..2009 | OP | "Treatment of Ph+ ALL" | Physicians and Scientists | International | 500 | Ottmann |
| 6 | 28.05.-02.06..2009 | OP | "Allogeneic stem cell transplant in ALL: Who and when?" | Physicians and Scientists | International | 500 | Hoelzer |
| 6 | 22.6.09 | OP | Advances in Hematology | Expert | UK | 70 | Gökbuget |
| 6 | 7.2.09 | OP | 88.ALL-Studientreffen Frankfurt | Expert | Germany | 60 | Gökbuget |
| 6 | 13.11.09 | OP | 89.ALL-Studientreffen | Expert | Germany | 50 | Frankfurt |
| 6 | 14.11.09 | OP | 17th Meeting of the EWALL | Expert | UK | 25 | Gökbuget |
| 6 | 12.5.09 | OP | Paul-Martini-Stiftung: Arzneimitteltherapie seltene Krankheiten – Heraus-forderungen und Chancen | Expert | Germany | 100 | Gökbuget |
| 6 | 4.10.09 | OP | Symposium Onkologikum: Molecular Targeting in Oncology | Expert | Germany | 100 | Gökbuget |
| 6 | 10.09.09 | OP | Wilsede-Schule: Hämatologie-Kompakt | Expert | Germany | 60 | Gökbuget |
| 6 | 16.09.09 | OP | Tumorzentrum Frankfurt: Update Hämatologie | Expert | Germany | 50 | Gökbuget |
| 6 | 29.9.09 | OP | Akute Leukämien: Update 2009 | Expert | Germany | 30 | Gökbuget |
| 6 | 6.10.09 | OP | DGHO-Jahrestagung KN-Leukämien: Neue Konzepte in der Leukämietherapie | Expert | Germany | 60 | Gökbuget |
| 6 | 3.10.09 | OP | Hematologic Malignancies 2009 | Expert | UK | 50 | Gökbuget |
| 6 | 21.11.09 | OP | Hämatologie-Kurs Stuttagart | Expert | Germany | 70 | Gökbuget |
| 6 | 5-8.12.09 | OP | ASH, New Orleans December 5-8 | Expert | UK | 100 | Gökbuget |
| 6 | 5-8.12.09 | OP | ASH New Orleans December 5-8 | Expert | UK | 250 | Gökbuget |
| 6 | 5-8.12.09 | OP | ASH, New Orleans December 5-8 | Expert | UK | 100 | Gökbuget |
| 7 | 03.02.09 | CS | 19th ERIC Meeting Annual Symposium of the European LeukemiaNet, Mannheim | clinical + basic researchers | International | 45 | Hallek |
| 7 | 04.06.09 | CS, WS | ERIC/EHA Scientific Meeting/Workshop, Berlin | clinical + basic researchers | International | 120 | Hallek |
| 7 | 04.06.09 | CS, WS | 20th General Meeting of ERIC Members, Berlin | clinical + basic researchers | International | 80 | Hallek |
| 7 | 06.12.09 | CS, WS, OP, PO | ERIC/ELN Breakfast Meeting at the 51th Annual Congress of the American Society of Hematolgy, New Orleans, USA | clinical + basic researchers | International | 50 | Hallek |
| 8 | 03.02.09 | CS | Annual ELN Symposium, MDS WP meeting, Mannh. | clinical + basic researchers | European | 95 | De Witte |

| WP | Planned/actual Dates | Type | Event | Type of audience | Countries addressed | Size of audience | Partner(s) responsible/involved |
|---|---|---|---|---|---|---|---|
| 8 | 03.02.09 | CS | ELN MDS Steering committee meeting together with Novartis Oncology on EUMDS Registry, MA | Clinical and basic researchers | European | 16 | De Witte |
| 8 | 06.05.09 | | MDS symposium in Patras, Steering Comm-ittee Meeting, European MDS, low risk registry | Clinical and basic researchers | European | 16 | De Witte |
| 8 | 07.05.09 | | MDS symposium in Patras, ELN MDS meeting on therapeutic guidelines; attendance steering committee WP8 | Clinical and basic researchers | European | 16 | De Witte |
| 8 | 03.06.09 | | MDS Iron Chelation Think Tank, EHA Meeting, Berlin | clinical + basic researchers | European | 120 | De Witte |
| 8 | 01.07.09 | CS | Operational team meeting of European MDS Registry" project, Amsterdam airport | clinical + basic researchers | European | 15 | De Witte |
| 8 | 25.09.09 | CS | European MDS Registry" project, Steering Committee and operatio-nal team meeting, London | clinical + basic researchers | European | 26 | De Witte |
| 8 | 12-13.10.09 | CS | Eugesma Cost Action (BM 0801) second Workshop meeting "European Genetic and Epigenetic studies in MDS and AML in collaboration with 5th ELN Workshop "Genetics in MDS, Hannover, Germany | clinical + basic researchers | European | 45 | De Witte |
| 8 | 24.10.09 | | MDS Work Package 8 steering committee meeting during the ESH-MDS postgraduate training course Mandelieu, France | clinical + basic researchers | European | 18 | De Witte |
| 8 | 30-31.10.09 | | The second Workshop on flow cytometry in MDS, Munich, Germany | clinical + basic researchers | European | 70 | De Witte |
| 8 | 06.12.09 | | ELN Workshop at the Annual ASH meeting New Orleans: presenta-tion of progress of proj-ects within MDS WP8 | Clinical and basic researchers | European | 20 | De Witte |
| 9 | 03.02.09 | | Annual ELN Symposium | clinical + basic researchers | European | 30 | Barbui |
| 9 | 03.02.09 | | WP meeting at the EHA Congress in Berlin, Germany | clinical + basic researchers | European | 35 | Barbui |
| 9 | 06.12.09 | | WP meeting at the ASH in New Orleans, US | clinical + basic researchers | International | 20 | Barbui |
| 10 | 03.02.09 | CS | Annual ELN Symposium | clinical + basic researchers | European | 20 | Béné |
| 10 | 04.09 | CS | EGIL meeting in Vienna in April, | clinical + basic researchers | European | 35 | Béné |
| 10 | 30-31.10.09 | CS | The second Workshop on flow cytometry in MDS, Munich, Germany | clinical + basic researchers | European | 70 | Béné |
| 10 | 6-8.11.09 | CS | EHA European School in Vienna in November | clinical + basic researchers | European | 30 | Béné |
| 12 | 04.02.09 | | WP 12 meeting, ASH, New Orleans, December | clinical + basic researchers | European | 30 | Grimwade |
| 12 | 04.06.09 | | EHA, Berlin June 7th | Research + Clinical | International | 30 | Grimwade |

| WP | Planned/actual Dates | Type | Event | Type of audience | Countries addressed | Size of audience | Partner(s) responsible/involved |
|---|---|---|---|---|---|---|---|
| 12 | 07.06.09 | | BCR-ABL Standardization meeting, Berlin June 7th | Research + Clinical | International | 80 | Cross |
| 12 | 04.12.09 | WS/OP | BCR-ABL stándar-dization meeting, New Orleans | Research + Clinical | International | 80 | Cross |
| 13 | 03.02.09 | WS | WP meeting for all WP13 members, combined in part with WP11, in Heidelberg, Germany | Research + Clinical | International | 30 | Haferlach |
| 13 | 10.09 | WS | NPM1 and CEBPA (Participants from Ulm, Dresden and Munich) Mannheim, Germany 10/2009 | Research + Clinical | Germany | 20 | Haferlach |
| 13 | 10.09 | WS | WP 13 members representing the European part of the MILE study, met together with WP10, MDS-flow-group in the Munich Leukemia Laboratory to discuss flow in MDS, and to publish new standards in addition to the paper already available: | Research + Clinical | International | 25 | Haferlach |
| 14 | 01.09 | CS | EBMT/ELN Meeting, City Conference Center, Angers | Research + Clinical | International | 60 | Niederwieser |
| 14 | 02.09 | CS | ELN/EBMT Meeting Mannheim, Germany | Research + Clinical | International | 40 | Niederwieser |
| 14 | 03.09 | CS | EBMT/ELN Room A6, Göteborg | Research + Clinical | International | 40 | Niederwieser |
| 14 | 06.09 | CS | EHA/ELN/EBMT WP5/WP14 Berlin, Germany | Research + Clinical | International | 50 | Niederwieser |
| 14 | 07.09 | CS | EBMT subcommittee chair meeting Leiden | Research + Clinical | International | | Niederwieser |
| 14 | 09.09 | CS | EBMT/ELN Meeting Milan | Research + Clinical | International | | Niederwieser |
| 14 | 11.09 | CS | EBMT subcommittee chair meeting Leiden | Research + Clinical | International | | Niederwieser |
| 14 | 12.09 | CS | ELN meeting WP5/WP14 New Orleans | Research + Clinical | International | | Niederwieser |
| 15 | 02.09 | | WP meeting at the ELN symposium in Mannheim, Germany, and in Rome October 31. | Clinicians and basic researchers | international | | Ljungmann |
| 15 | 03.09 | | WP meeting at the EBMT meeting in Göteborg, | Clinicians and basic researchers | international | | Ljungmann |
| 15 | 09.09 | | WP meeting at the EBMT meeting in Juan-les-Pins | Clinicians and basic researchers | international | | Ljungmann |
| 15 | 10.09 | | WP meeting at the EBMT meeting in Rome | Clinicians and basic researchers | international | | Ljungmann |
| 17 | 2-2009 | OP | 7th Annual Symposium of the ELN, Mannheim | Hematologists | European | 100 | J. Hasford |

## Section 3: Publishable results

WP 1 (NMC) and WP 2 (ELIC)

1-1 N. Gökbuget, D. Hoelzer, S. Saussele, R. Hehlmann (Editors). WP2 in cooperation with WP 1, 01/2010: 6th ELN Information Letter.

1-2 ELN Booth, Mannheim, 10/2009

1-3 ELN Booth, Barcelona, 10/2009

1-4 ELN Booth, ASH, New Orleans, 12/2009

1-5 Steering Committee 2009, Minutes

1-6 Steering Committee 2010, Minutes

1-7 ELN Assembly minutes 2009

WP 3 (CICS) Publications:

*International publications that are the direct result of the European LeukemiaNet (**without** a reference to the European LeukemiaNet)*

3-1 R. Strobl, G. Stucki, E. Grill, M. Muller and U. Mansmann. Graphical models illustrated complex associations between variables describing human functioning. J Clin Epidemiol 2009;62(9):922-933.

3-2 K. H. Metzeler, A. Dufour, T. Benthaus, M. Hummel, M. C. Sauerland, A. Heinecke, W. E. Berdel, T. Buchner, B. Wormann, U. Mansmann, J. Braess, K. Spiekermann, W. Hiddemann, C. Buske and S. K. Bohlander. ERG expression is an independent prognostic factor and allows refined risk stratification in cytogenetically normal acute myeloid leukemia: a comprehensive analysis of ERG, MN1, and BAALC transcript levels using oligonucleotide microarrays. J Clin Oncol 2009;27(30):5031-5038.

3-3 V. Henschel, J. Engel, D. Holzel and U. Mansmann. A semiparametric Bayesian proportional hazards model for interval censored data with frailty effects. BMC Med Res Methodol 2009;99.

3-4 M. Eravci, U. Mansmann, O. Broedel, S. Weist, S. Buetow, J. Wittke, C. Brunkau, M. Hummel, S. Eravci and A. Baumgartner. Strategies for a reliable biostatistical analysis of differentially expressed spots from two-dimensional electrophoresis gels. J Proteome Res 2009;8(5):2601-2607.

WP 4 (CML)

*International publications that are the direct result of the European LeukemiaNet (**with** a reference to the European LeukemiaNet)*

4-1 M. Baccarani, F. Castagnetti, G. Gugliotta, F. Palandri and S. Soverini. Response definitions and European Leukemianet Management recommendations. Best Pract Res Clin Haematol 2009;22(3):331-341.

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*International publications that are the direct result of the European LeukemiaNet*
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## WP 5 (AML)

*International publications that are the direct result of the European LeukemiaNet (**with** a reference to the European LeukemiaNet)*

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## WP 8 (MDS)

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WP 9 (CMPD)

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## WP 10 (Diagnostics)

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### *International publications that are the direct result of the European LeukemiaNet(**without** a reference to the European LeukemiaNet)*

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## WP 11 (Cytogenetics)

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WP 12 (MRD)

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## WP 13 (Gene profiling)

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14-117 J. Zaia, L. Baden, M. J. Boeckh, S. Chakrabarti, H. Einsele, P. Ljungman, G. B. McDonald and H. Hirsch. Viral disease prevention after hematopoietic cell transplantation. Bone Marrow Transplant 2009;44(8):471-482.

**Attachments + Abstracts**

14-118 Meetings, Minutes and Agendas of WP 14 in 2009.

14-119 A. Gratwohl, H. Baldomero, M. Aljurf, M. Pasquini, F. Bouzas, A. Yoshimi, J. Szer, J. Lipton, A. Schwendener, M. Gratwohl, K. Frauendorfer, D. Niederwieser, M. Horowitz and Y. Kodera. Hematopoietic Stem Cell Transplantation: a Global Perspective From the Worldwide Network of Blood and Marrow Transplantation. in press 2010.

WP 15 (Supportive care/anti-infection prophylaxis and treatment)

*International publications that are the direct result of the European leukemia Network (**with** a reference to the European leukemia Network)*


15-1 J. Styczynski, P. Reusser, H. Einsele, R. de la Camara, C. Cordonnier, K. N. Ward, P. Ljungman and D. Engelhard. Management of HSV, VZV and EBV infections in patients with hematological malignancies and after SCT: guidelines from the Second European Conference on Infections in Leukemia. Bone Marrow Transplant 2009;43(10):757-770.


*International publications that are the direct result of the European LeukemiaNet (**without** a reference to the European LeukemiaNet)*


15-2 G. Avetisyan, J. Mattsson, E. Sparrelid and P. Ljungman. Respiratory syncytial virus infection in recipients of allogeneic stem-cell transplantation: a retrospective study of the incidence, clinical features, and outcome. Transplantation 2009;88(10):1222-1226.

15-3 M. Boeckh and P. Ljungman. How we treat cytomegalovirus in hematopoietic cell transplant recipients. Blood 2009;113(23):5711-5719.

15-4 A. Bohme, M. Ruhnke, D. Buchheidt, O. A. Cornely, H. Einsele, R. Enzensberger, H. Hebart, W. Heinz, C. Junghanss, M. Karthaus, W. Kruger, U. Krug, T. Kubin, O. Penack, D. Reichert, S. Reuter, G. Silling, T. Sudhoff, A. J. Ullmann and G. Maschmeyer. Treatment of invasive fungal infections in cancer patients--recommendations of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO). Ann Hematol 2009;88(2):97-110.

15-5 R. D. Camara, I. Jarque, M. A. Sanz, S. Grau, M. A. Casado, F. J. Sabater and E. Carreras. Economic evaluation of posaconazole vs fluconazole in the prevention of invasive fungal infections in patients with GVHD following haematopoietic SCT. Bone Marrow Transplant 2009.

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15-7 C. Cartoni, P. Niscola, M. Breccia, G. Brunetti, G. M. D'Elia, M. Giovannini, C. Romani, L. Scaramucci, A. Tendas, L. Cupelli, P. de Fabritiis, R. Foa and F. Mandelli. Hemorrhagic complications in patients with advanced hematological malignancies followed at home: an Italian experience. Leuk Lymphoma 2009;50(3):387-391.

15-8 S. Cesaro, H. H. Hirsch, M. Faraci, J. Owoc-Lempach, A. Beltrame, A. Tendas, I. Baltadakis, J. H. Dalle, Y. Koc, J. Toporski, J. Styczynski, M. A. Yesilipek, W. Heinz, M. Caniglia, J. Rascon, A. A. Fauser, M. Michallet, L. Lopez-Corral, S. Neuburger, G. Tridello and H. Einsele. Cidofovir for BK virus-associated hemorrhagic cystitis: a retrospective study. Clin Infect Dis 2009;49(2):233-240.

15-9 C. Cordonnier, M. Labopin, V. Chesnel, P. Ribaud, R. De La Camara, R. Martino, A. J. Ullmann, T. Parkkali, A. Locasciulli, K. Yakouben, K. Pauksens, H. Einsele, D. Niederwieser, J. Apperley and P. Ljungman. Randomized study of early versus late immunization with pneumococcal conjugate vaccine after allogeneic stem cell transplantation. Clin Infect Dis 2009;48(10):1392-1401.

15-10 C. Cordonnier, M. Labopin, K. U. Jansen, M. Pride, V. Chesnel, E. Bonnet, H. Einsele and P. Ljungman. Relationship between IgG titers and opsonocytophagocytic activity of anti-pneumococcal antibodies after immunization with the 7-valent conjugate vaccine in allogeneic stem cell transplant. Bone Marrow Transplant 2009.

15-11 O. A. Cornely, A. Bohme, D. Buchheidt, H. Einsele, W. J. Heinz, M. Karthaus, S. W. Krause, W. Kruger, G. Maschmeyer, O. Penack, J. Ritter, M. Ruhnke, M. Sandherr, M. Sieniawski, J. J. Vehreschild, H. H. Wolf and A. J. Ullmann. Primary prophylaxis of invasive fungal infections in patients with hematologic malignancies. Recommendations of the Infectious Diseases Working Party of the German Society for Haematology and Oncology. Haematologica 2009;94(1):113-122.

15-12 J. de la Rubia, P. Montesinos, R. Martino, I. Jarque, M. Rovira, L. Vazquez, J. Lopez, M. Batlle, R. de la Camara, A. Julia, J. J. Lahuerta, G. Deben, J. Diaz, R. Garcia and M. A. Sanz. Imipenem/cilastatin with or without glycopeptide as initial antibiotic therapy for recipients of autologous stem cell transplantation: results of a Spanish multicenter study. Biol Blood Marrow Transplant 2009;15(4):512-516.

15-13 J. Diekmann, E. Adamopoulou, O. Beck, G. Rauser, S. Lurati, S. Tenzer, H. Einsele, H. G. Rammensee, H. Schild and M. S. Topp. Processing of two latent membrane protein 1 MHC class I epitopes requires tripeptidyl peptidase II involvement. J Immunol 2009;183(3):1587-1597.

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15-17 M. Hummel, C. Warga, H. Hof, R. Hehlmann and D. Buchheidt. Diagnostic yield of blood cultures from antibiotic-naive and antibiotically treated patients with haematological malignancies and high-risk neutropenia. Scand J Infect Dis 2009;41(9):650-655.

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15-30 J. Mensa, R. De La Camara, E. Carreras, M. Cuenca Estrella, J. A. Garcia Rodriguez, M. Gobernado, J. Picazo, J. M. Aguado and M. A. Sanz. [Treatment of fungal infections in patients with hematologic neoplasia]. Med Clin (Barc) 2009;132(13):507-521.

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15-34 K. Spinnler, M. Mezger, M. Steffens, H. Sennefelder, O. Kurzai, H. Einsele and J. Loeffler. Role of Glycogen Synthase Kinase 3 (GSK-3) in innate immune response of human immature dendritic cells to Aspergillus fumigatus. Med Mycol 2010.

15-35 C. Stuehler, S. Mielke, M. Chatterjee, J. Duell, S. Lurati, F. Rueckert, H. Einsele, R. C. Bargou and M. S. Topp. Selective depletion of alloreactive T cells by targeted therapy of heat shock protein 90: a novel strategy for control of graft-versus-host disease. Blood 2009;114(13):2829-2836.

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15-38 S. Varani, M. Stanzani, M. Paolucci, F. Melchionda, G. Castellani, L. Nardi, M. P. Landini, M. Baccarani, A. Pession and V. Sambri. Diagnosis of bloodstream infections in immunocompromised patients by real-time PCR. J Infect 2009;58(5):346-351.

15-39 C. Viscoli, R. Herbrecht, H. Akan, L. Baila, A. Sonet, A. Gallamini, A. Giagounidis, O. Marchetti, R. Martino, L. Meert, M. Paesmans, L. Ameye, M. Shivaprakash, A. J. Ullmann and J. Maertens. An EORTC Phase II study of caspofungin as first-line therapy of invasive aspergillosis in haematological patients. J Antimicrob Chemother 2009;64(6):1274-1281.

15-40 J. Zaia, L. Baden, M. J. Boeckh, S. Chakrabarti, H. Einsele, P. Ljungman, G. B. McDonald and H. Hirsch. Viral disease prevention after hematopoietic cell transplantation. Bone Marrow Transplant 2009;44(8):471-482.

## WP 17 (Biometry of Registry, Epidemiology, Metaanalyses and Prognosis)

### *International publications that are the direct result of the European LeukemiaNet (**with** a reference to the European LeukemiaNet)*

17-1 M. Baccarani, B. Simonsson, D. Lindorfer, G. Rosti, A. M. Almeida, A. Bogdanovic, R. E. Clark, A. Colita, P. A. Costeas, L. Griskevicius, J. Guilhot, A. Hellmann, K. Indrak, E. Laane, B. Labar, T. Masszi, S. Lejniece, J. Mayer, G. Ossenkoppele, P. Panayiotidis, K. Porkka, S. Saussele, A. Hochhaus, J. L. Steegmann, J. Thaler, A. Turkina, G. Verhoef, A. Zaritskey, I. P. Zupan, F. Rancati, L. Montrucchio, R. Hehlmann and J. Hasford. The European Treatment and Outcome Study (EUTOS) for Chronic Myeloid Leukemia (CML). A Prospective, Population-Based European Registry. ASH Annual Meeting Abstracts 2009;114(22):4272.

17-2 T. Ernst, F. X. Gruber, O. Pelz-Ackermann, J. Maier, M. Pfirrmann, M. C. Muller, I. Mikkola, K. Porkka, D. Niederwieser, A. Hochhaus and T. Lange. A co-operative evaluation of different methods of detecting BCR-ABL kinase domain mutations in patients with chronic myeloid leukemia on second-line dasatinib or nilotinib therapy after failure of imatinib. Haematologica 2009;94(9):1227-1235.

### *International publications that are the direct result of the European LeukemiaNet (without a reference to the European LeukemiaNet)*

17-3 M. Rohrbacher, U. Berger, A. Hochhaus, G. Metzgeroth, K. Adam, T. Lahaye, S. Saussele, M. C. Muller, J. Hasford, H. Heimpel and R. Hehlmann. Clinical trials underestimate the age of chronic myeloid leukemia (CML) patients. Incidence and median age of Ph/BCR-ABL-positive CML and other chronic myeloproliferative disorders in a representative area in Germany. Leukemia 2009;23(3):602-604.

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17-5 M. Schaich, L. Kestel, M. Pfirrmann, K. Robel, T. Illmer, M. Kramer, C. Dill, G. Ehninger, G. Schackert and D. Krex. A MDR1 (ABCB1) gene single nucleotide polymorphism predicts outcome of temozolomide treatment in glioblastoma patients. Ann Oncol 2009;20(1):175-181.

**Abstracts:**

17-6 J. Hasford, G. Rosti, D. Lindoerfer, M. Baccarani, J. Guilhot, L. Montrucchio, F. Rancati, B. Simonsson, F. E. Nicolini, G. Ossenkoppele and R. Hehlmann. Outcome and Prognosis of 1955 Patients with Chronic Myeloid Leukemia: First Results of the CML-Registry of the European Treatment and Outcome Study EUTOS. ASH Annual Meeting Abstracts 2009;114(22):1109.