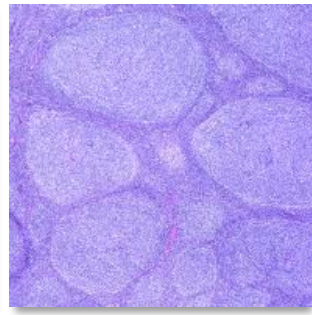
LMU KLINIKUM DER UNIVERSITÄT MÜNCHEN
MEDIZINISCHE KLINIK UND POLIKLINIK III
CAMPUS GROSSHADERN
DIREKTOR PROF. DR. W. HIDDEMANN

Introduction to Malignant Non-Hodgkin Lymphomas

SFB 1243 Fundamental Seminar Series

Oliver Weigert



The top 10 cancers

Top 10 Cancer Sites: 2010, Male, United States—All Races

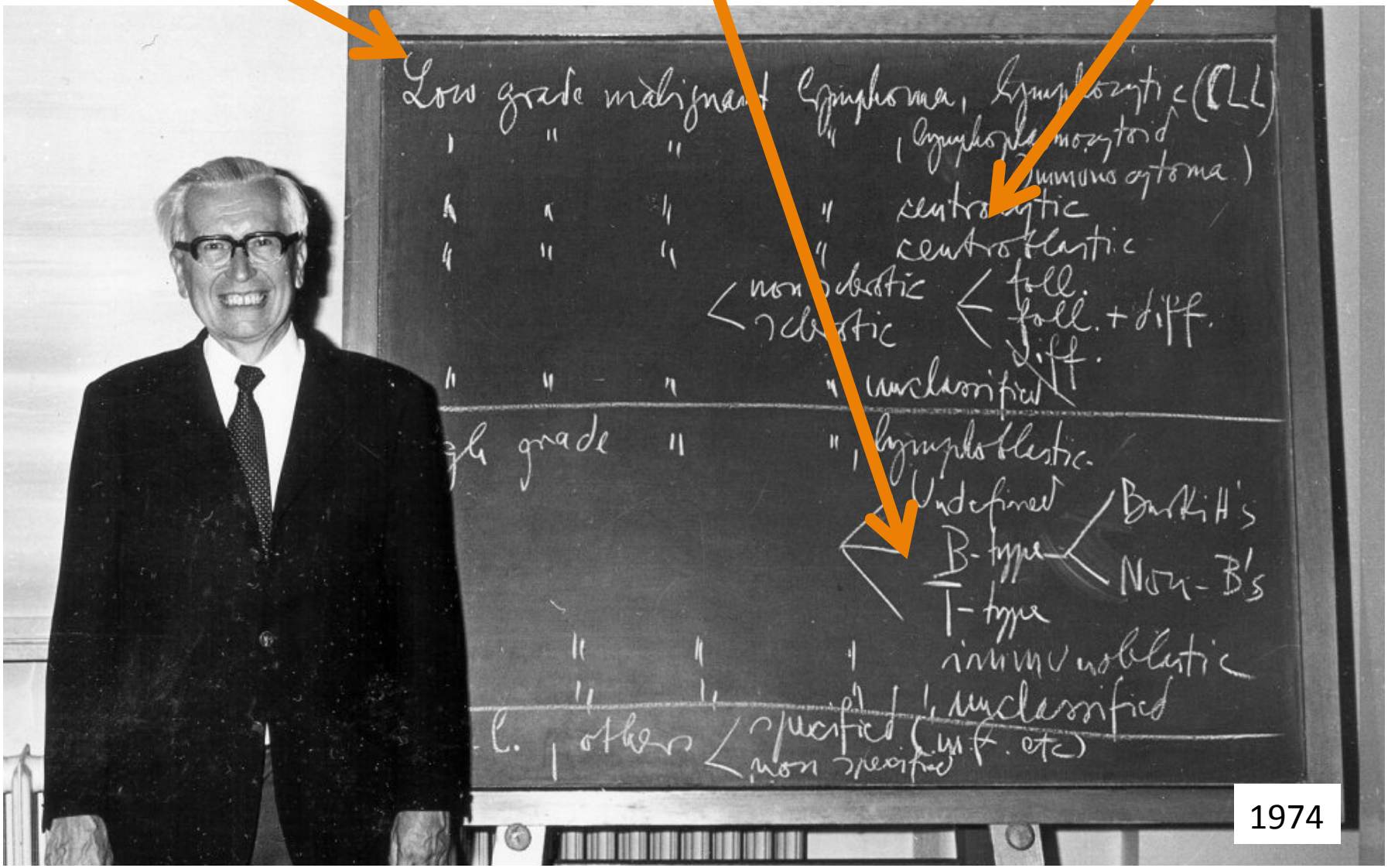
Top 10 Cancer Sites: 2010, Female, United States—All Races

Incidence of NHL is on the rise...

principle #1:
aggressive *vs* indolent

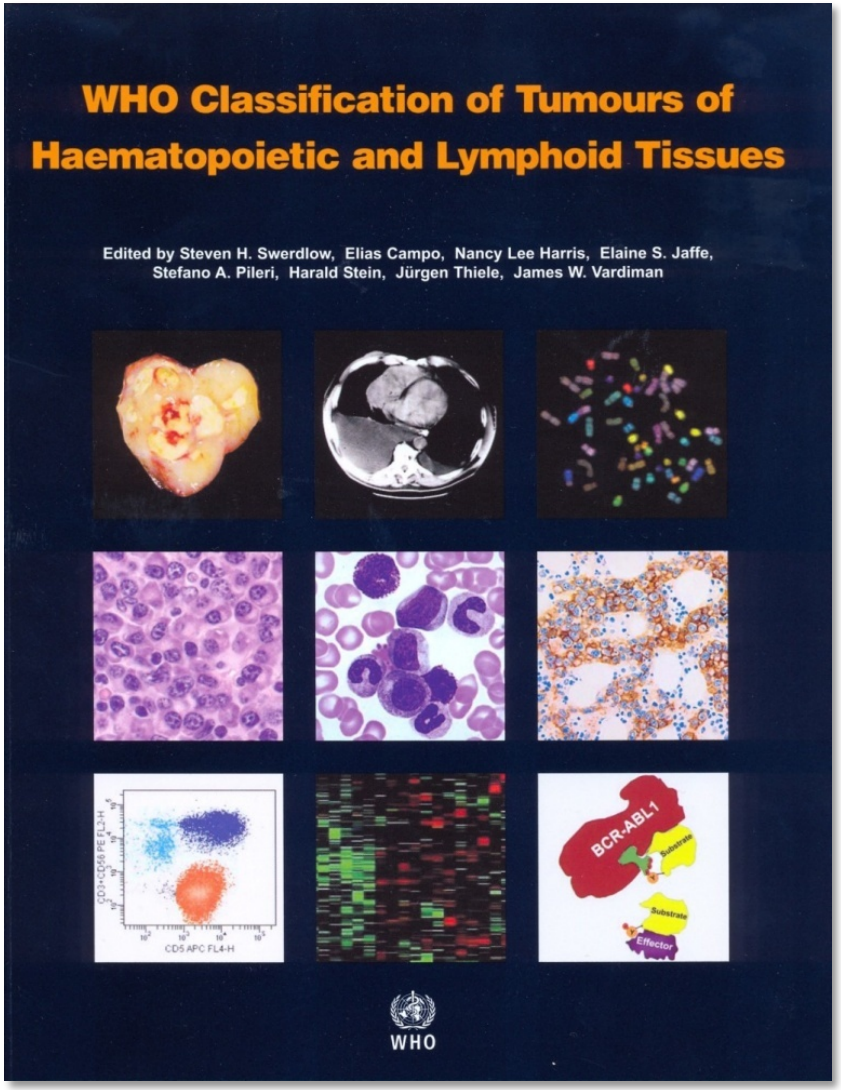
principle #2:
B- *vs* T/NK-cell

principle #3:
„cell-of-origin“



courtesy of W. Klapper; used with kind permission.

WHO-classification 2008



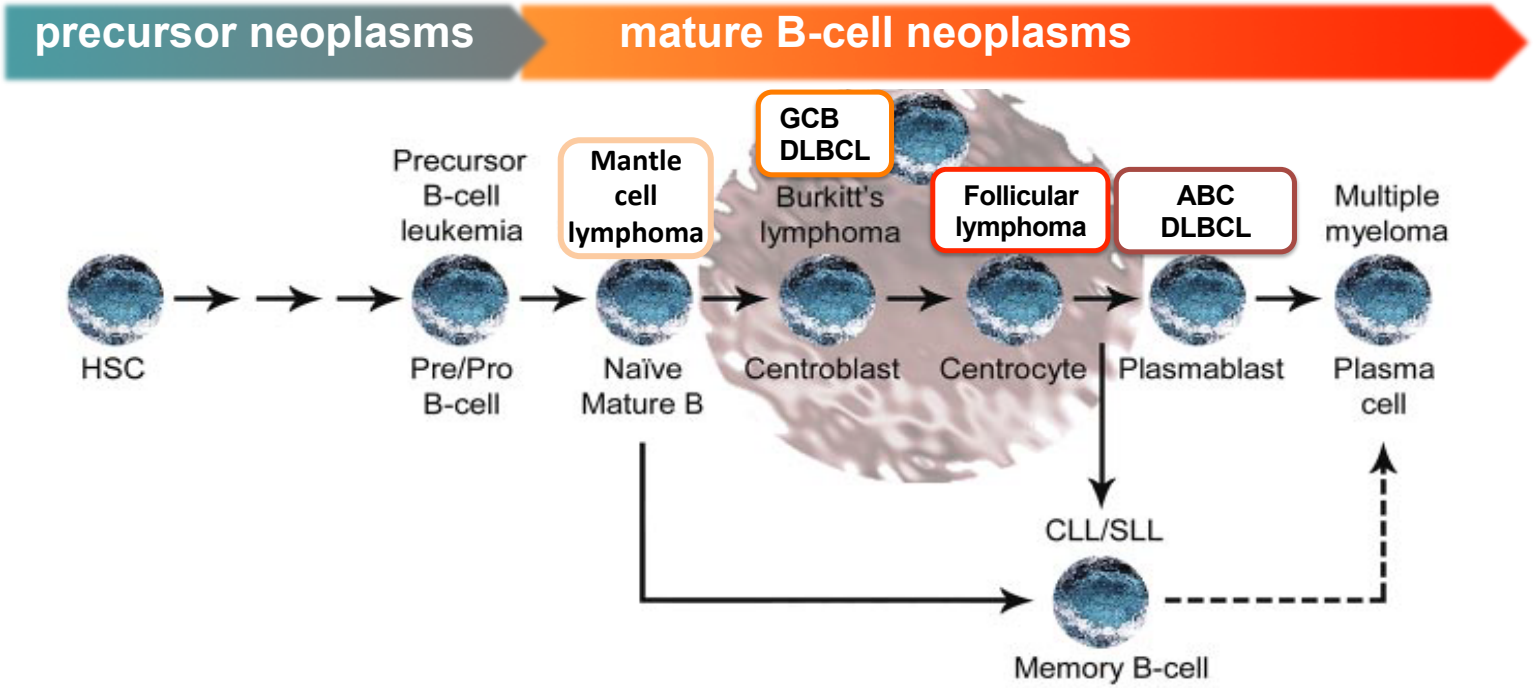
The indolent lymphomas
B-cell neoplasms
Small lymphocytic lymphoma/B-cell chronic lymphocytic leukemia
Lymphoplasmacytic lymphoma (± Waldenstrom's macroglobulinemia)
Plasma cell myeloma/plasmacytoma
Hairy cell leukemia
Follicular lymphoma (grade I and II)
Marginal zone B-cell lymphoma
Mantle cell lymphoma•
T-cell neoplasms
T-cell large granular lymphocyte leukemia
Mycosis fungoides
T-cell prolymphocytic leukemia
Natural killer cell neoplasms
Natural killer cell large granular lymphocyte leukemia
The aggressive lymphomas
B-cell neoplasms
Follicular lymphoma (grade III)
Diffuse large B-cell lymphoma
Mantle cell lymphoma•
T-cell neoplasms
Peripheral T-cell lymphoma
Anaplastic large cell lymphoma, T/null cell
The highly aggressive lymphomas
B-cell neoplasms
Burkitt's lymphoma
Precursor B lymphoblastic leukemia/lymphoma
T-cell neoplasms
Adult T-cell lymphoma/leukemia
Precursor T lymphoblastic leukemia/lymphoma

Lymphoid neoplasms

The WHO classification

- lists > 50 distinct lymphoid neoplasms
- aims to define clinically relevant, non-overlapping entities based on
  - clinical features
  - morphology & immunophenotype
  - genetics

Swerdlow et al, IARC, 2008



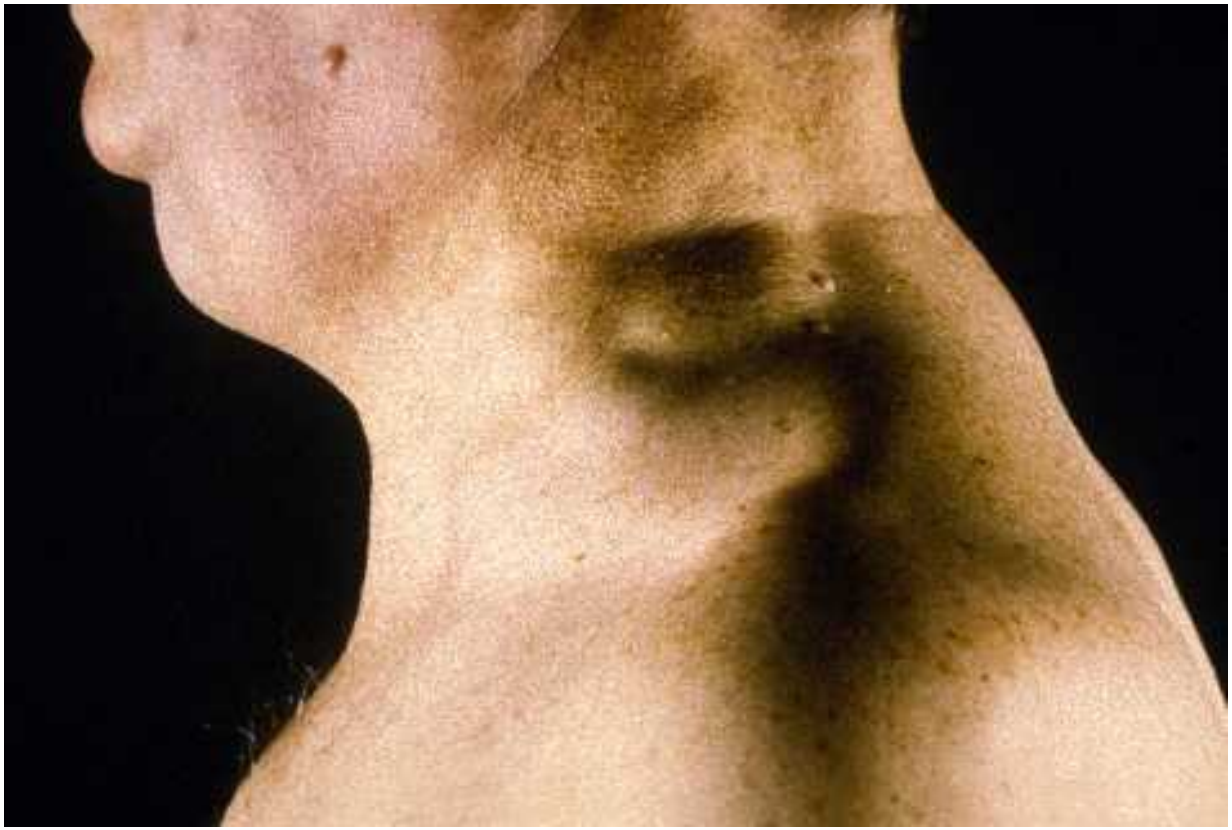
Weigert & Weinstock, Blood 2012

Lymphoid neoplasms: clinical presentation

Clinical course:

determined by the dynamics of infiltration, displacement and effacement

- of the lymphatic system
- of extra-lymphatic organs (bone marrow, liver, lung, brain...)



by definition *> 1cm*

differentials *(some):*

- *metastases*
- *infections*
- *various forms of vasculitis*
- *storage diseases*

Lymphoid neoplasms: clinical presentation

Clinical course:

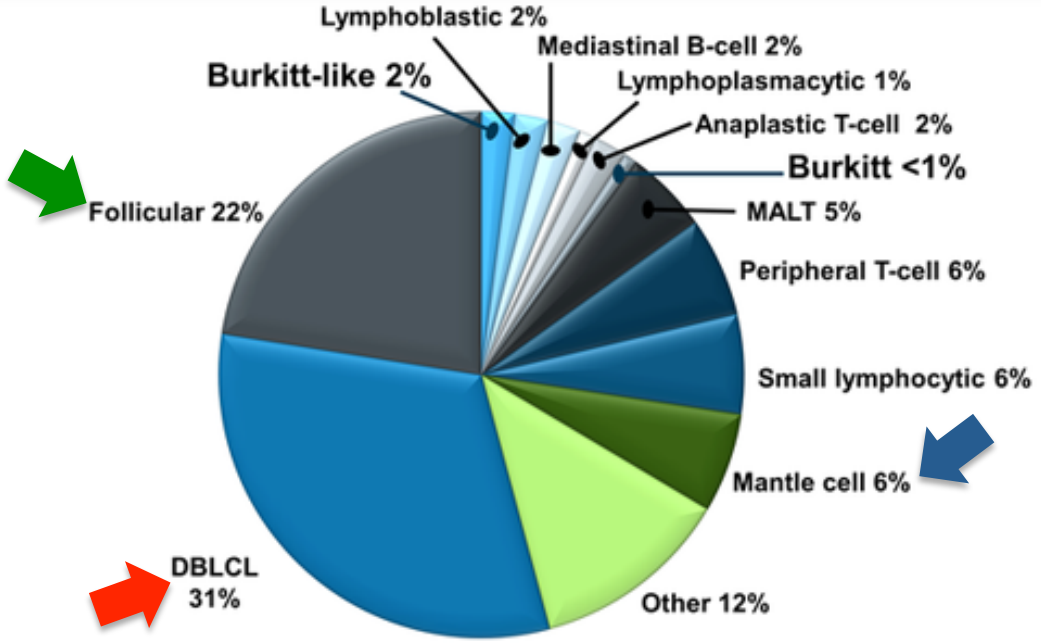
determined by the dynamics of infiltration / displacement and effacement

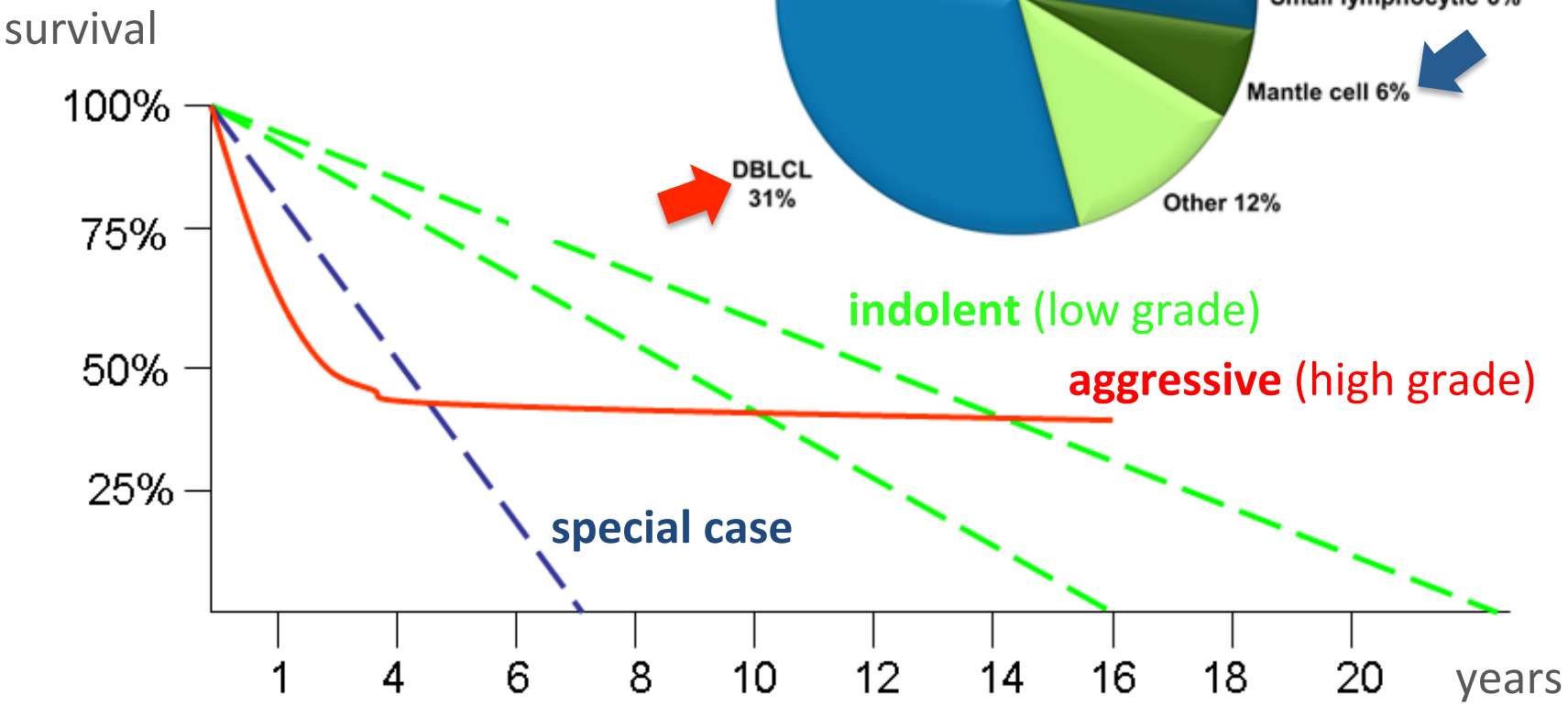
- of the lymphatic system
- of extra-lymphatic organs (bone marrow, liver, lung, brain...)

Symptoms:

- enlargement and impaired function of infiltrated organs
- impaired hematopoiesis
- impaired / dysregulated immunity
- B-symptoms: fever, night sweats, loss of body weight

Lymphoid neoplasms: clinical course





Chromosomal aberrations in malignant lymphoma

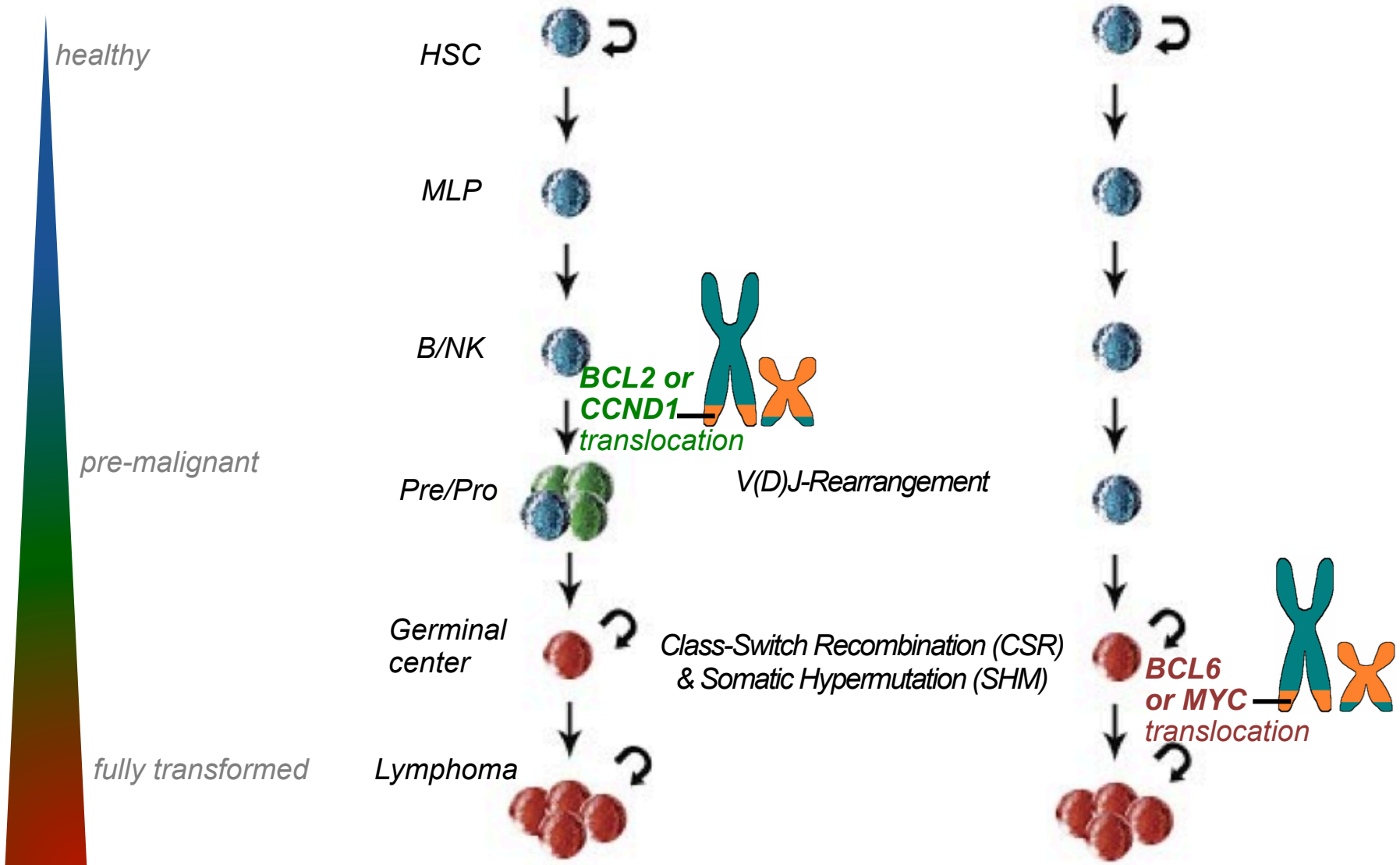
Chromosomal Aberration	Lymphoma Entity	Genes
t(14;18)(q32;q21)	Follicular lymphoma, Diffuse large B-cell lymphoma	*BCL2, IGH*
t(8;14)(q24;q32)	Burkitt's lymphoma	*c-MYC, IGH*
t(8;22)(q24;q11)		*c-MYC, IGL*
t(2;8)(p11;q24)		*c-MYC, IGK*
t(11;14)(q13;q32)	Mantle cell lymphoma B-CLL (rarely)	*CCND1, IGH*
t(11;18)(q21;q21)	Marginal zone lymphoma, Extranodal MALT lymphoma	*API2, MALT1*
t(14;18)(q32;q21)		*MALT1, IGH*
t(1;14)(p22;q21)		*BCL10, IGH*
t(1;2)(p22;p11)		*BCL10, IGK*
t(14;18)(q32;q21)	CLL/SLL	*BCL2, IGH*
t(2;18)(p11;q21)		*BCL2, IGK*
t(18;22)(q21;q11)		*BCL2, IGL*
t(14;19)(q32;q13)		*BCL3, IGH*
t(9;14)(p13;q32)	Lymphoplasmacytic lymphoma	*PAX5, IGH*
t(3;14)(q27;q32)* t(3;22)(q27;q11) t(2;3)(p11;q27)	Diffuse large B-cell lymphoma (de novo)	*BCL6, IGL* *BCL6, IGK*
2p13–15 amp	Diffuse large B-cell lymphoma (extranodal)	*REL amplification*
t(2;5)(p23;q35)**	Anaplastic large cell lymphoma	*ALK, NPM1*

* a variety of other *BCL6* translocation partners have been described.

**>20% of ALCLs have other *2p23* rearrangements.

Weigert et al, TZM Manual 2015

Models of lymphomagenesis



Weigert & Weinstock, Blood 2012

Recurrent gene mutations in lymphoma

Lymphoma Entity	Gene Mutations (relative frequency)
CLL / SLL	*SF3B1* (11%), *TP53* (10%), *NOTCH1* (8%), *BIRC3* (3%), *MYD88* (2%)
Burkitt's lymphoma	*MYC* (40%), *ID3* (34%), *GNA13* (20-25%), *ARID1A* (10-15%), *SMARCA4* (10-15%), TP53 (20%), RHOA (8%)
Diffuse large B-cell lymphoma	*PCLO* (35%), *PIM1* (31%), *MLL2* (29%), *CREBBP* (29%), *TP53* (24%), *TNRSF14* (22%), CARD11 (20%), GNA13 (20%), MEF2B (18%), CD79B (16%), EZH2 (14%), BTG1 (16%), HIST1H1C (14%), MYD88 (12%), TMSL3 (12%) EP300 (10%), CD58 (10 %)
Follicular lymphoma	*MLL2* (50-82%), *CREBBP* (33-75%), *TNFRSF14* (20-35%), *EZH2* (12-27%), GNA13 (5-21%), EP300 (9-15%), TNFAIP3/A20 (11-22%) CARD11 (12%), STAT6 (11%), MEF2B (10%), BCL2 Hypermutation (76%), TP53 (<5%)
Hairy cell leukemia	*BRAF* V600E (up to 100%)
Mantle cell lymphoma	*ATM* (41%), *CCND1* (35%), *WHSC1* (10%), *MLL2* (14%), *TP53* (<10%), *BIRC3* (<10%), MEF2B (<10%)
Waldenström's macroglobulinemia	*MYD88* L265P (91%), *CXCR4* (28%), *ARID1A* (17%)
Angioimmunoblastic T-cell lymphoma	*TET2* (76%), *RHOA* G17V (68%), *DNMT3A* (33%), *IDH2* (20%)

Lohr, PNAS 2012; Pasqualucci, Nature 2011; Pasqualucci, Nature 2011; Odejide & Weigert, Blood 2014; Sakata-Yanagimoto, Nature Genetics 2014; Sakata-Yanagimoto, Nature Genetics 2014; Beà, PNAS 2013; Treon, NEJM 2012; Roccaro, Blood 2014; Baliakas, Leukemia 2014; Love, Nature Genetics 2012; Tiacci, NEJM 2011; Pastore, Lancet Oncol 2015.

Clinical implication of genetics in malignant lymphoma

Established (primarily in diagnostics)

- *VDJ* rearrangement: clonality
- somatic hypermutation: pre- *vs* post- germinal center
- hallmark translocations (mutations): diagnosis & classification

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Evolving (towards biology-adapted treatment strategies)

- molecular prognostication
- seizing the molecular ontogeny
- molecular treatment stratification
- understanding the molecular biology

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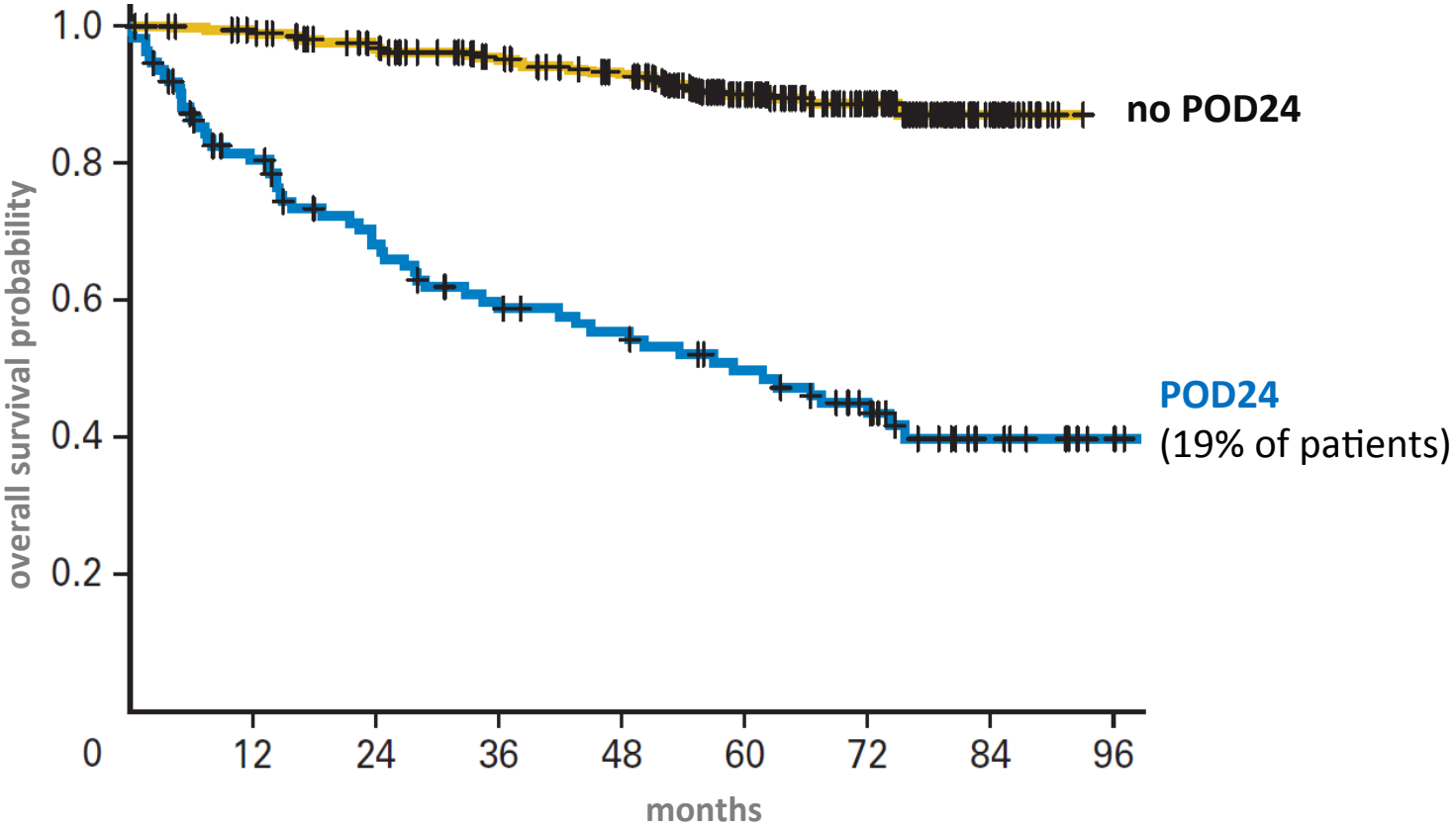
Follicular lymphoma (FL)

- FL is among the most **common** lymphomas worldwide[1]
- Advanced stage disease still considered **incurable**[2]
- **Immunochemotherapy** is current standard for symptomatic patients[2]
- FL is a **clinically and molecularly heterogeneous disease**[3,4]

[1]Anderson, Ann Oncol 1998; [2]Hiddemann, Leukemia 2014; [3]Kridel, JCI 2014; [4]Pastore, Lancet Oncology 2015

Clinical heterogeneity of FL

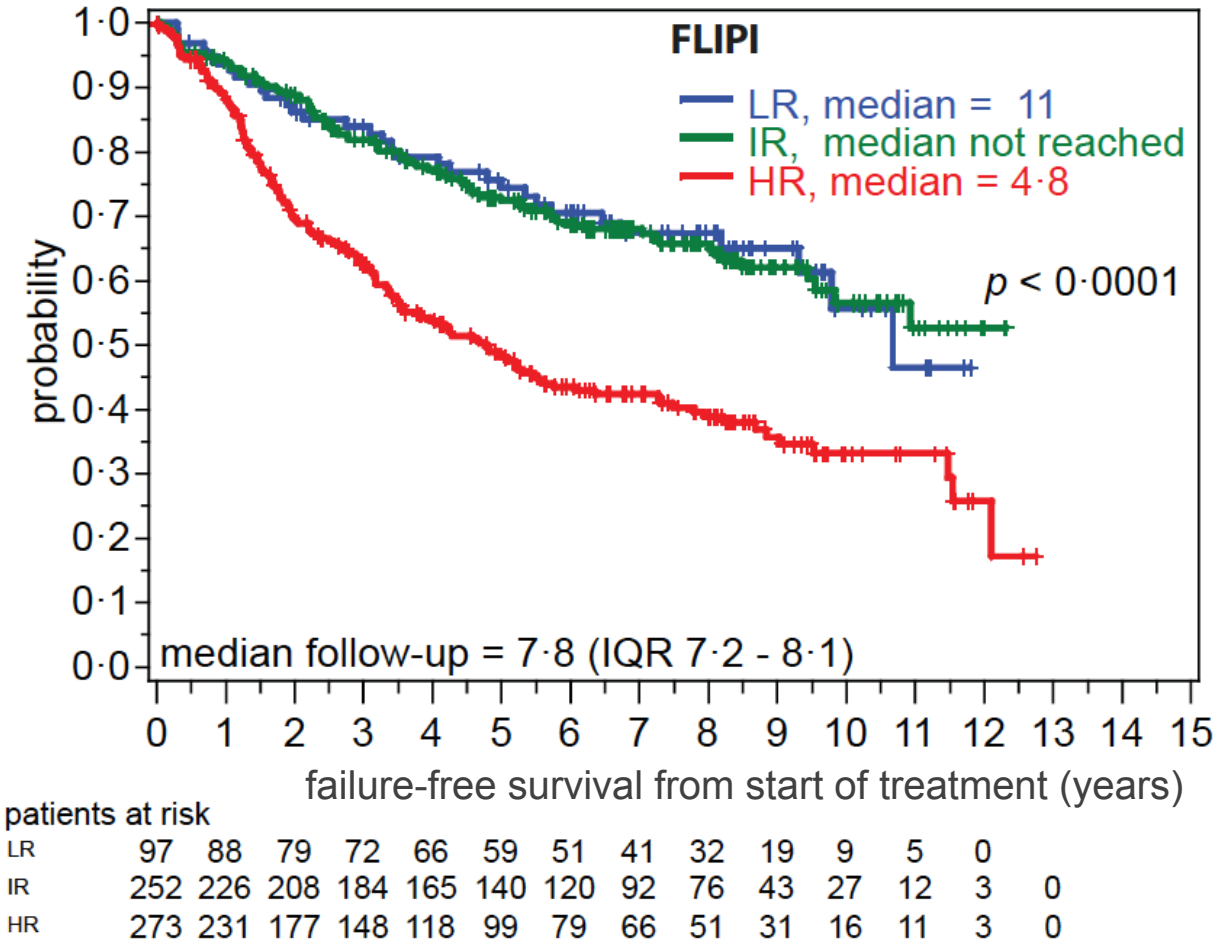


Casulo et al., JCO 2015

The clinical challenge in FL

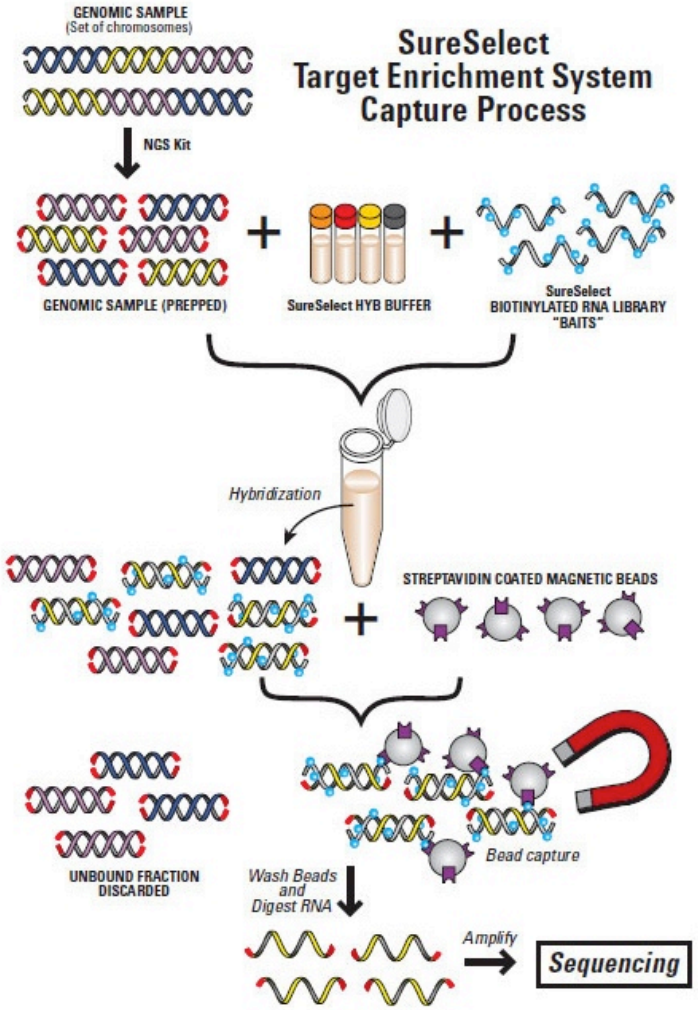
„How to identify patients likely to have poor outcome with standard treatment?”

The FLIPI



Buske et al., Blood 2006; Pastore et al., Lancet Oncology 2015

Target enrichment & sequencing of 74 genes



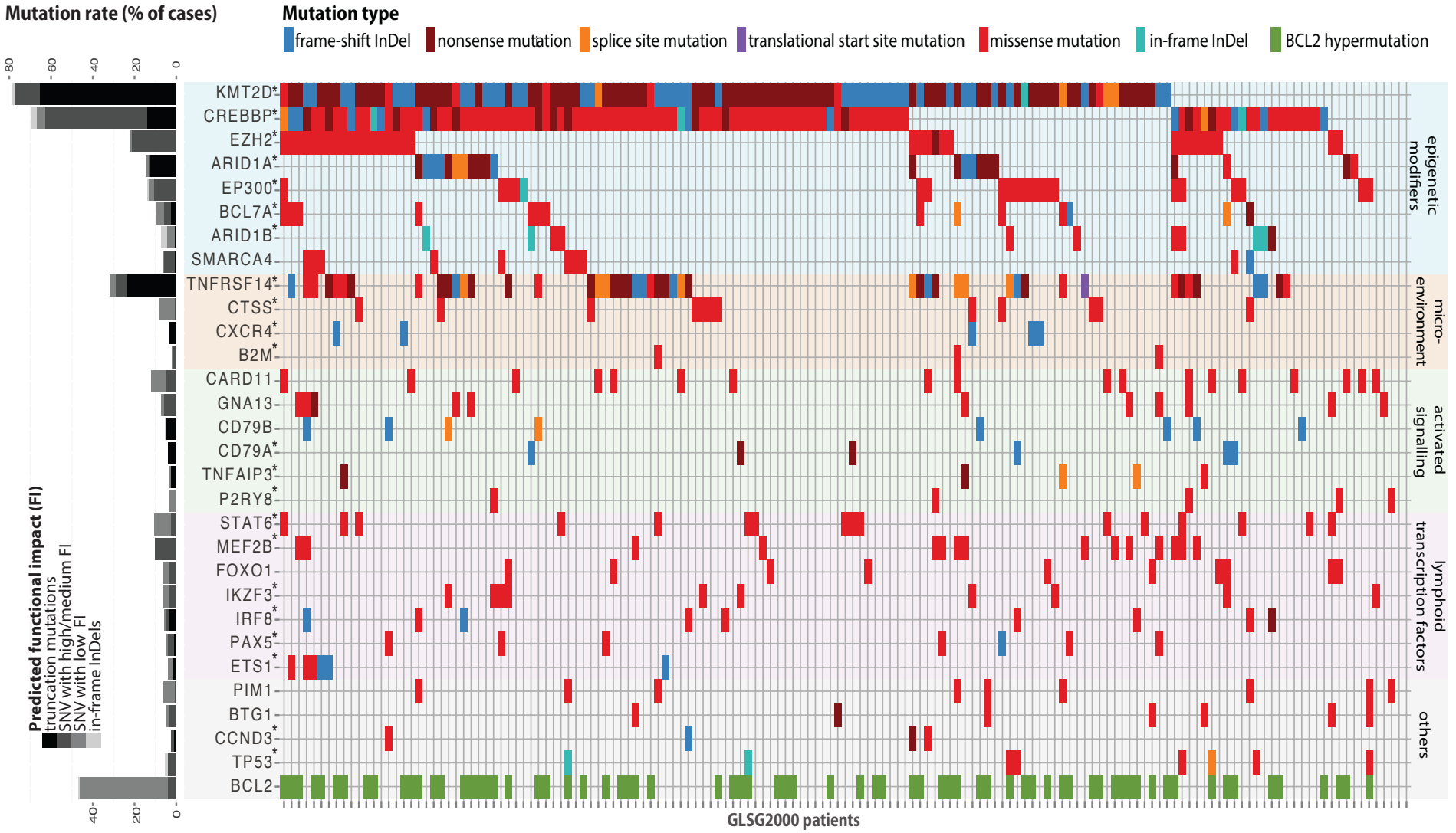
FL study cohorts

		GLSG Training cohort	BCCA Validation cohort	*p-value*
Patients	number of evaluable* patients	151	107	
	male (%)	78 (52)	59 (55)	*0·67*
Clinical Risk Factors	>60 years (%)	57 (38)	59 (55)	*0·0083*
	> 4 nodal sites (%)	106 (70)	78 (73)	*0·74*
	LDH elevated (%)	49 (32)	22 (21)	*0·074*
	Hb < 120 g/L (%)	32 (21)	12 (11)	*0·062*
	ECOG > 1 (%)	8 (5)	16 (15)	*0·016*
	FLIPI high risk (%)	77 (51)	53 (50)	*0·92*
Treatment	first line treatment	R-CHOP**	R-CVP***	
	maintenance treatment	IFNα	Rituximab	
	number of patients (intention-to-treat)	151	93	
Outcome	5-year FFS (%) [number of FFS events]	66 [63]	58 [48]	
	5-year OS (%) [number of deaths]	83 [33]	74 [32]	
	median follow-up for OS (years)	7·7 (IQR 5·5 – 9·3)	6·7 (IQR 5·7 – 9·3)	

*All patients had

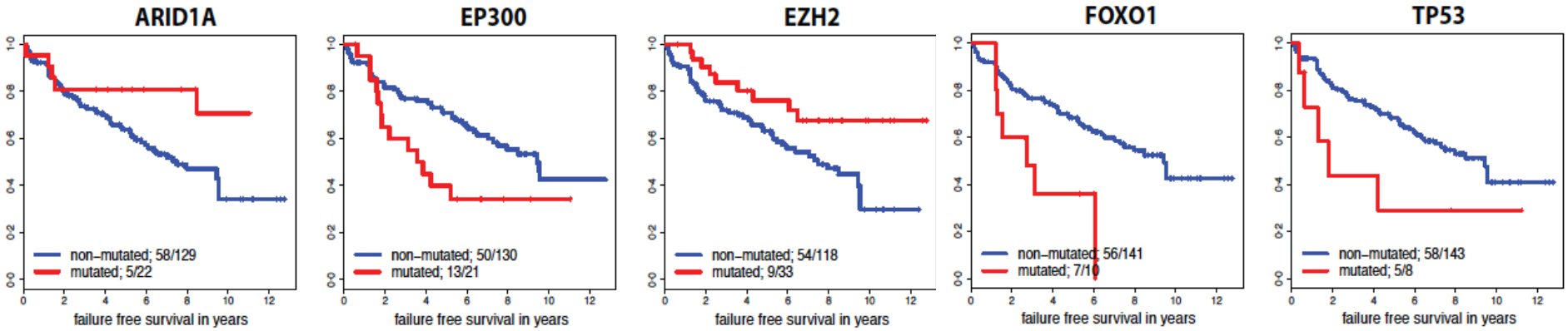
- FL grade 1, 2, or 3A confirmed by an expert hematopathologist
- advanced stage or bulky disease considered ineligible for irradiation
- symptomatic disease requiring systemic treatment
- an available biopsy specimen obtained ≤12 months prior to therapy initiation
- received a combination of rituximab and chemotherapy as 1st line treatment

DNA sequencing of 74 genes: *GLSG* training cohort



Pastore et al., Lancet Oncol 2015

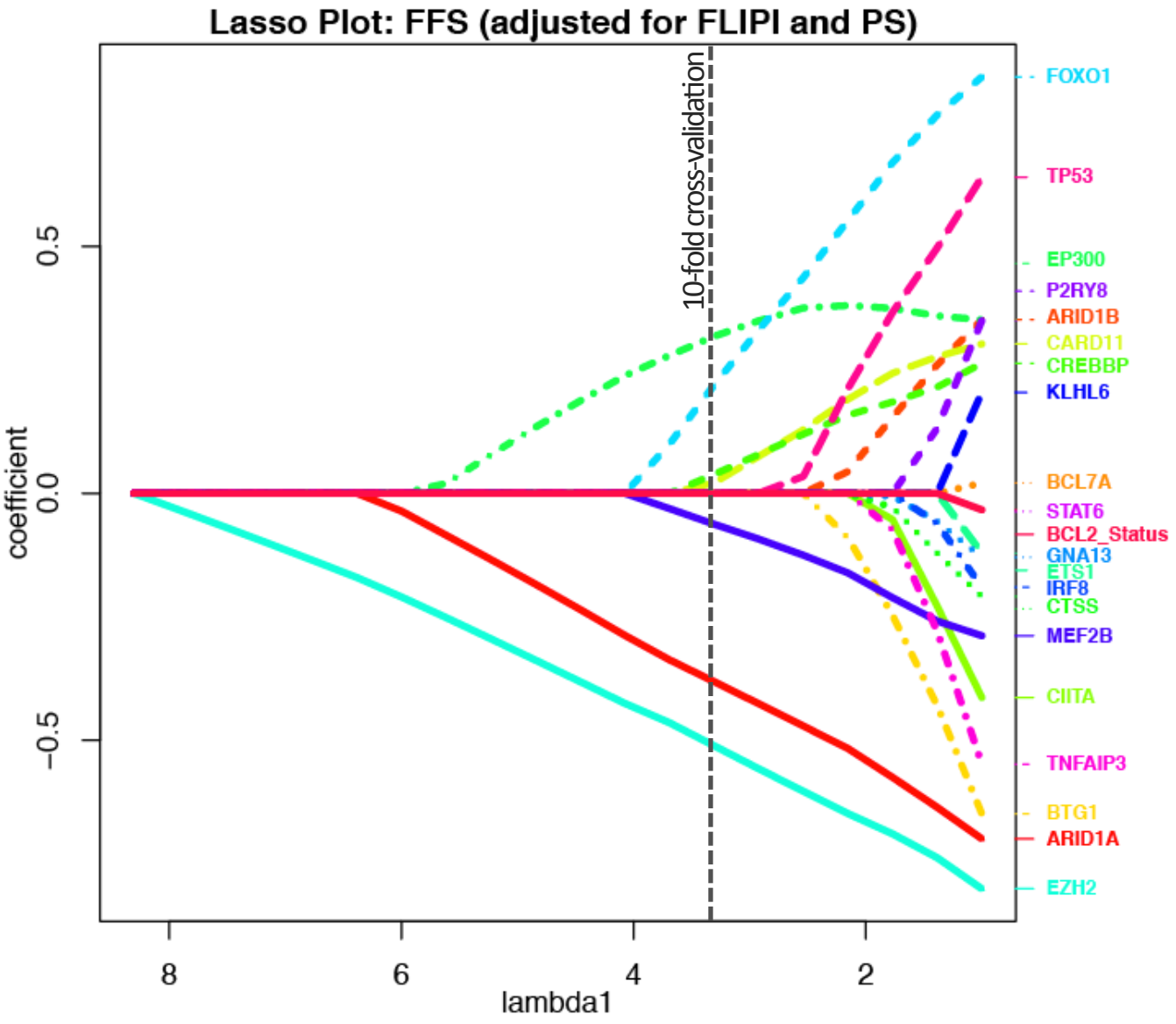
Failure free survival (FFS)



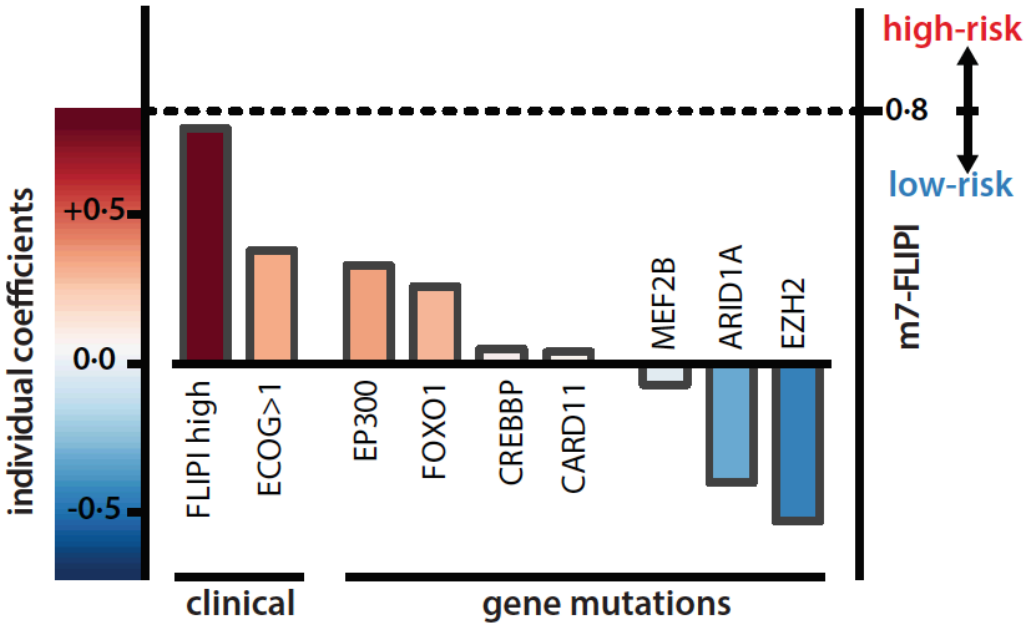
	Univariate			With adjustment for FLIPI and ECOG		
Gene	HR	p-value	p-value Holm	HR	p-value	p-value Holm
FOXO1	2·74	0·013	0·47	2·67	0·018	0·62
EP300	1·99	0·028	0·95	2·00	0·028	0·91
EZH2	0·46	0·030	0·99	0·42	0·018	0·62
ARID1A	0·42	0·064	> 0·99	0·40	0·049	> 0·99
TP53	2·18	0·096	> 0·99	2·85	0·029	0·91

Pastore et al., Lancet Oncol 2015

L1-penalized Cox regression (Lasso)

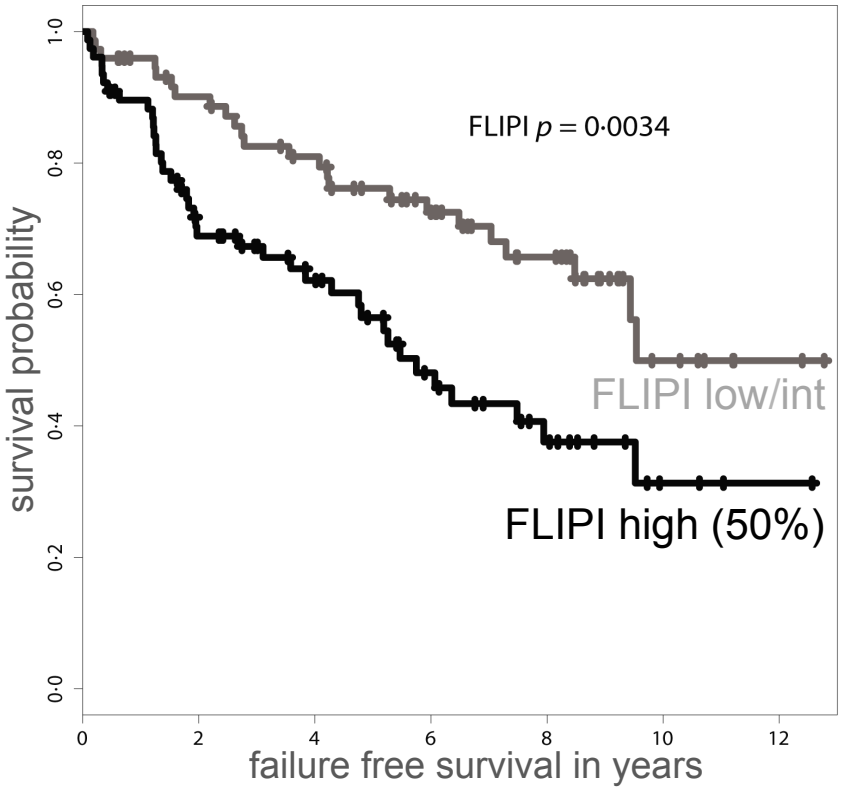


Clinicogenetic risk model: “m7-FLIPI“

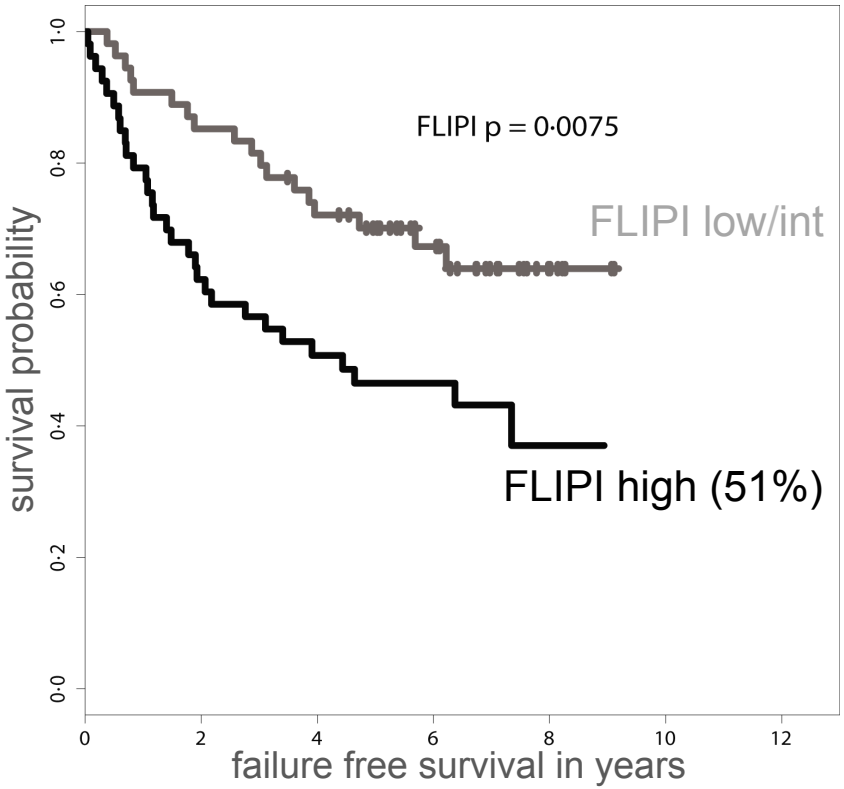


Failure-Free Survival (FFS)

GLSG training cohort



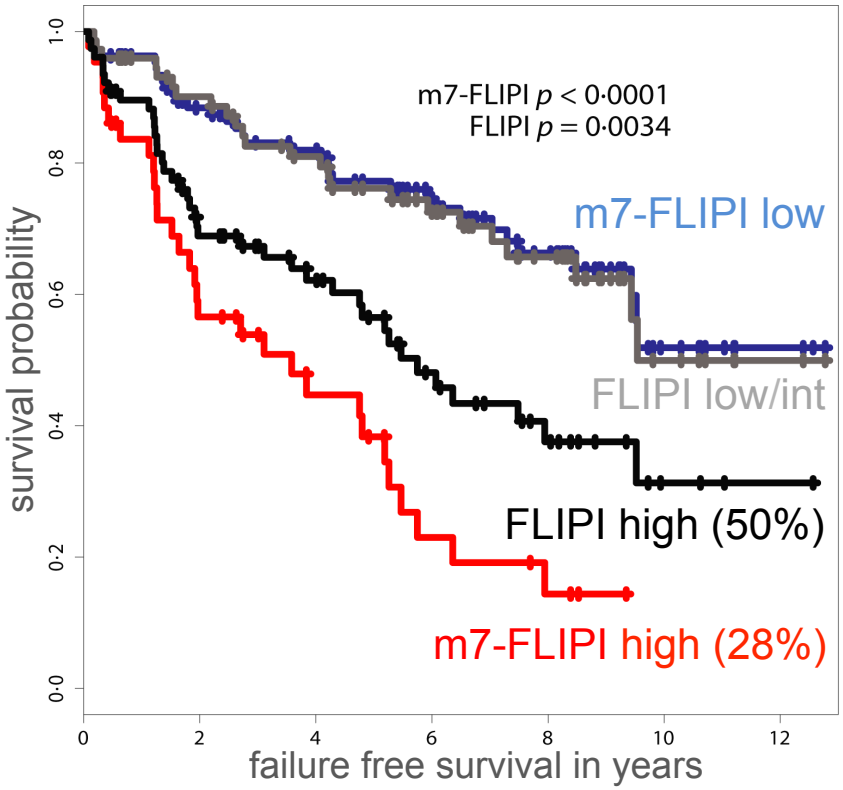
BCCA validation cohort

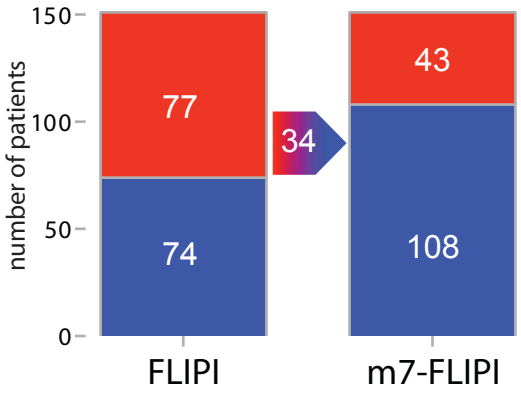


Pastore et al., Lancet Oncol 2015

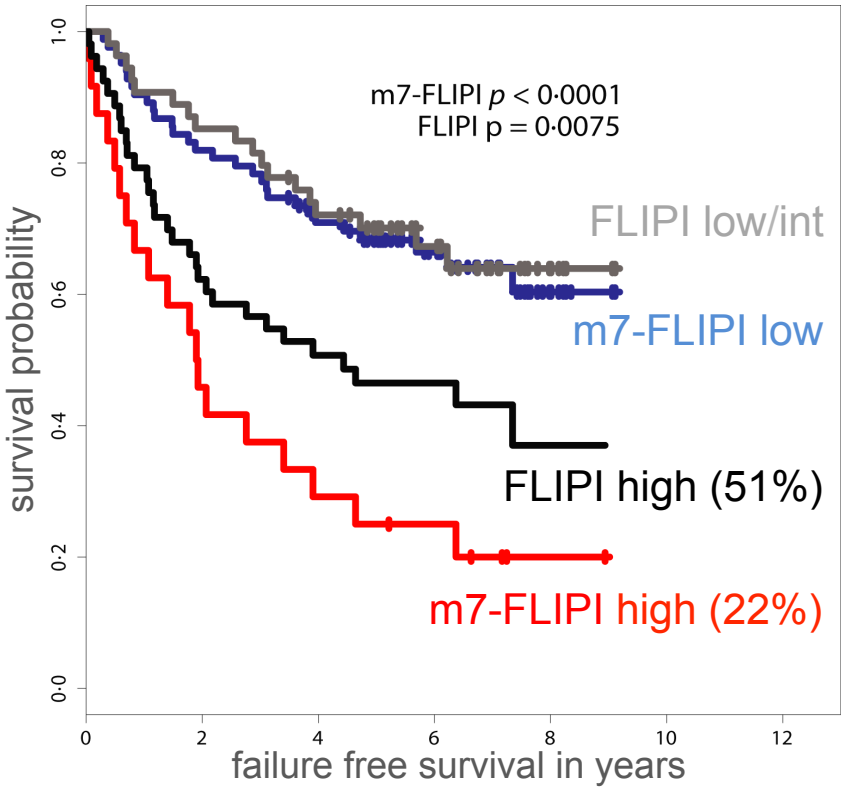
Failure-Free Survival (FFS)

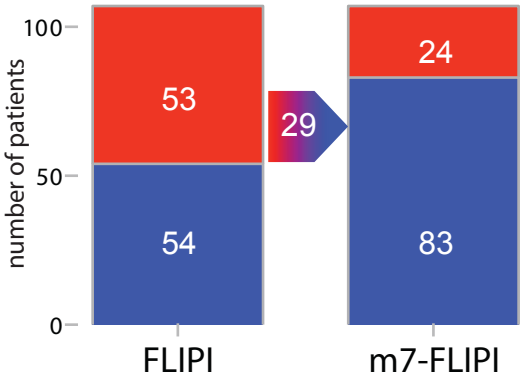
GLSG training cohort



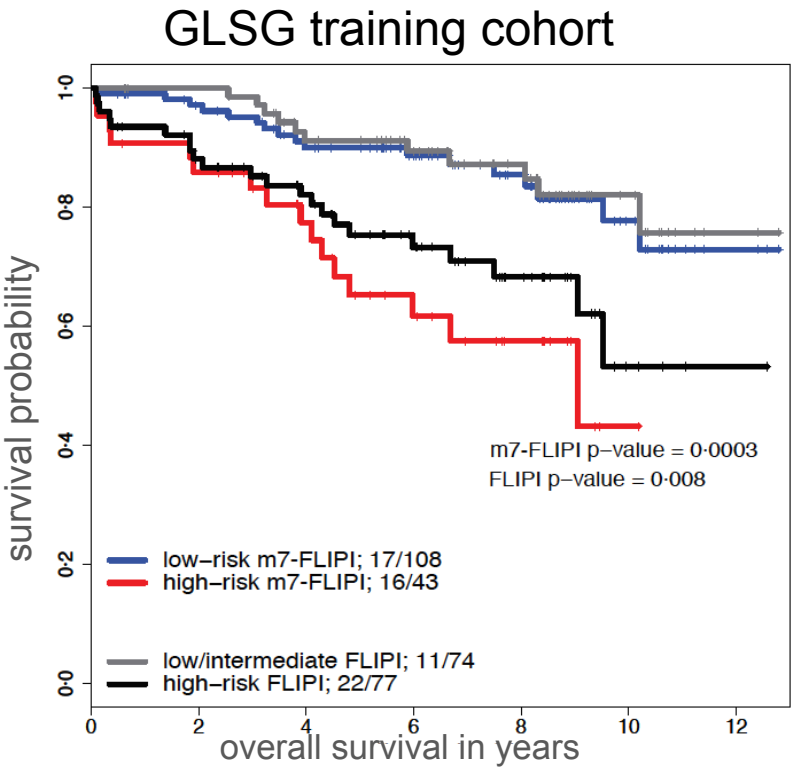


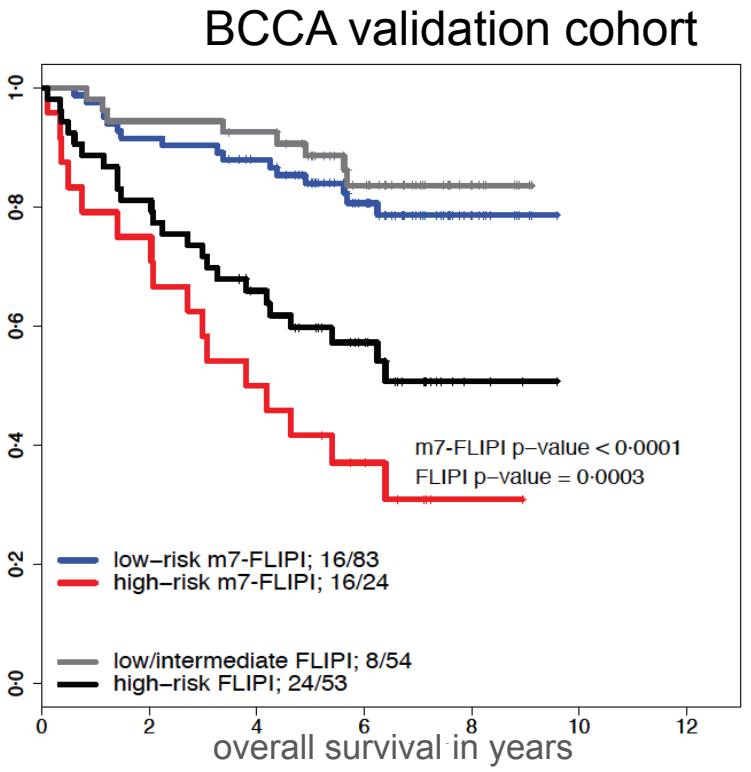
BCCA validation cohort

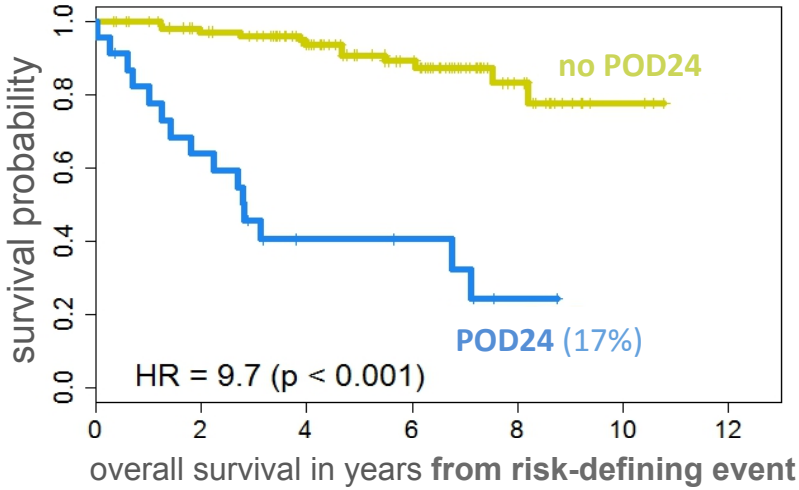


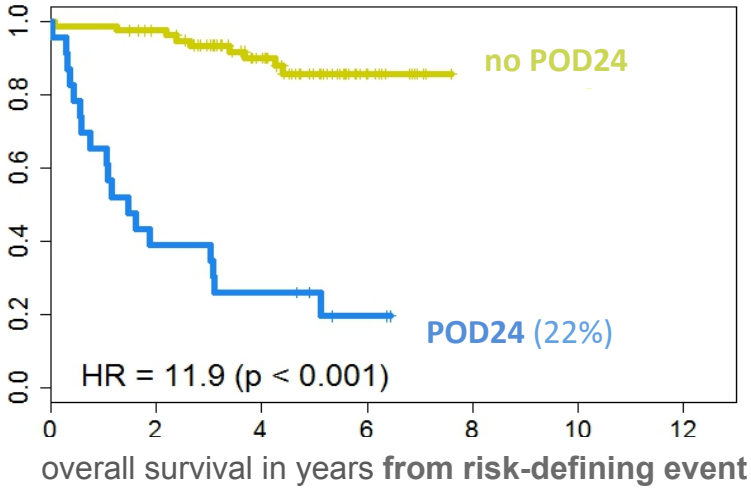


Overall survival: *pre-* versus *post-treatment* risk classifiers

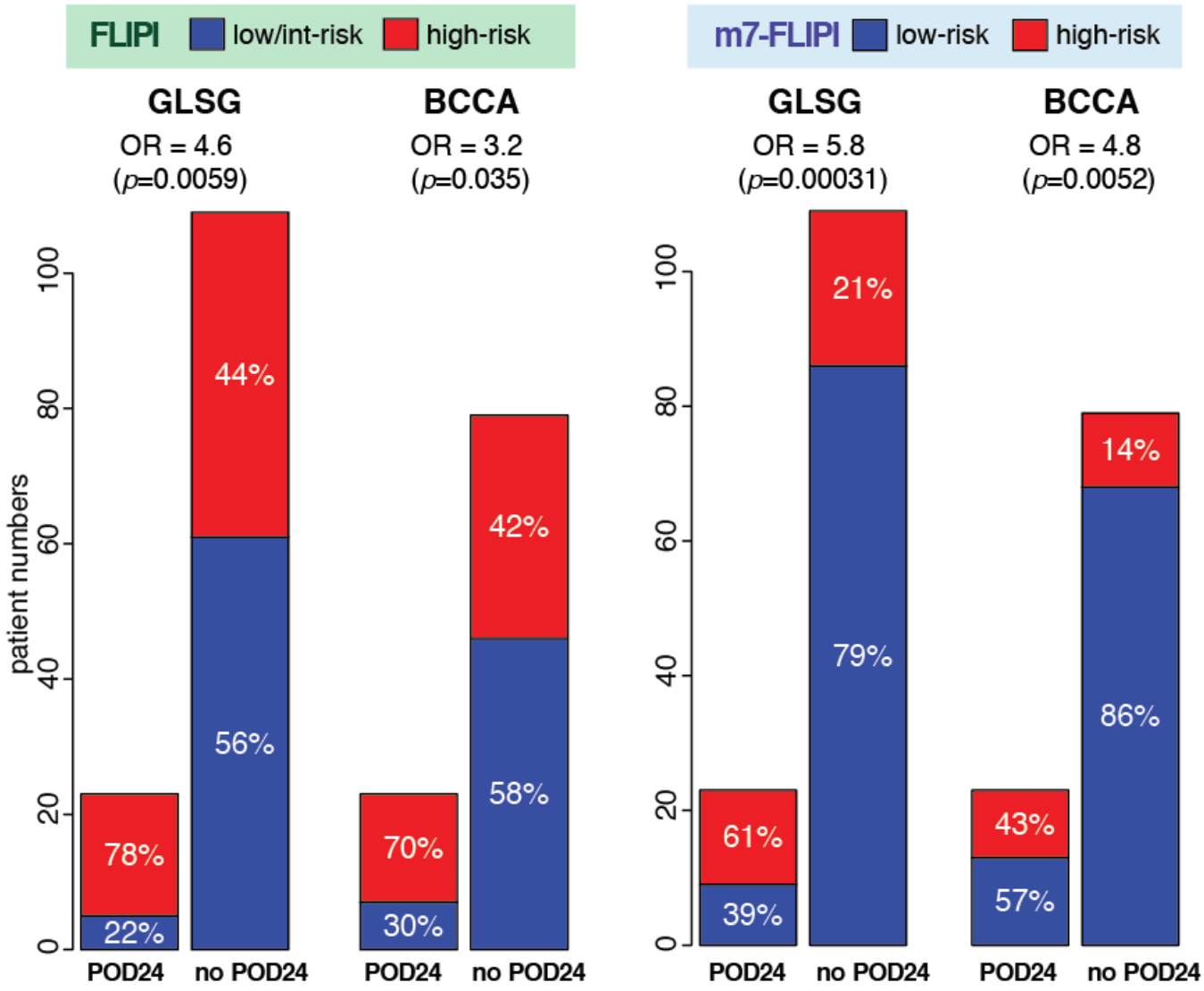




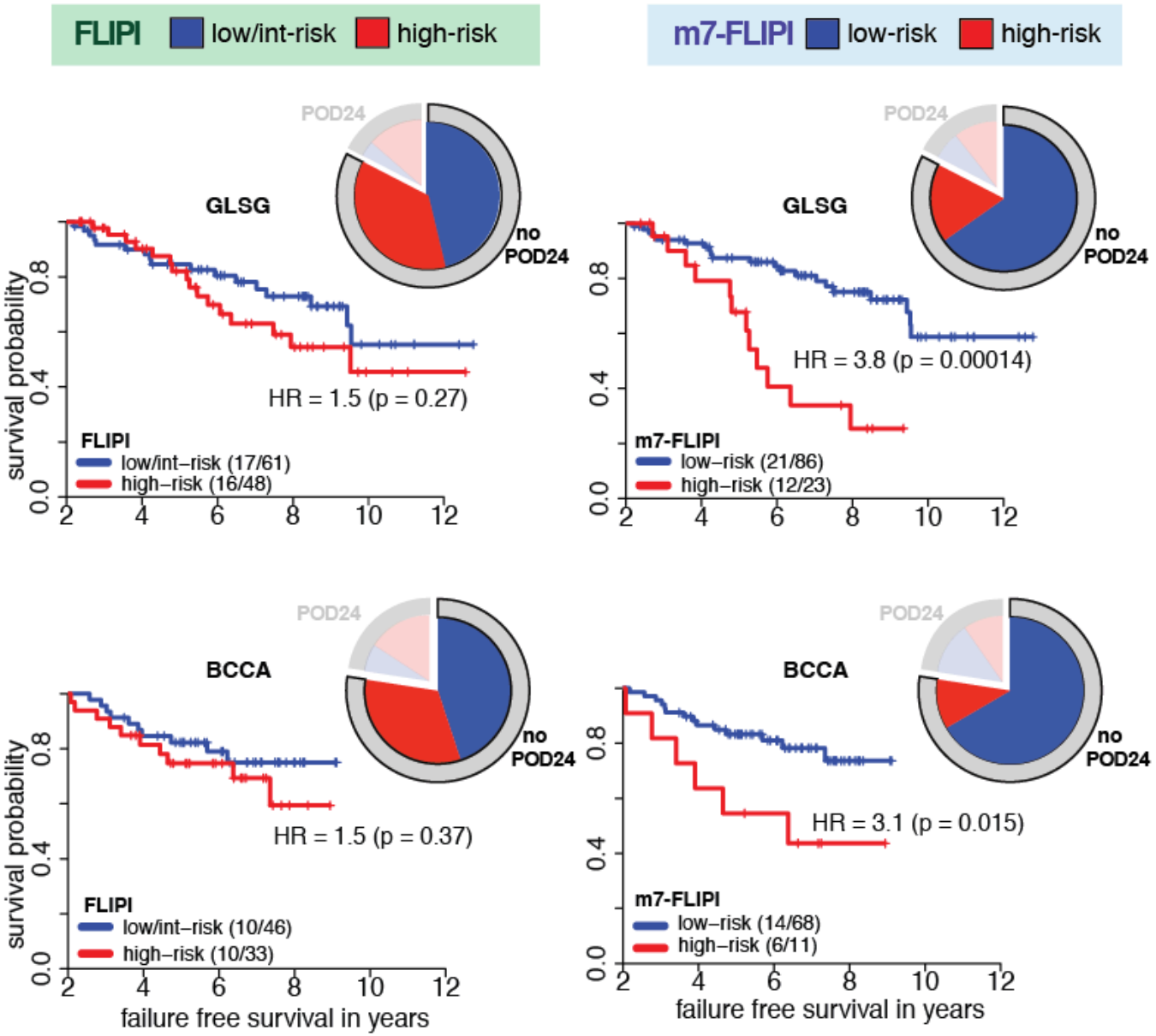




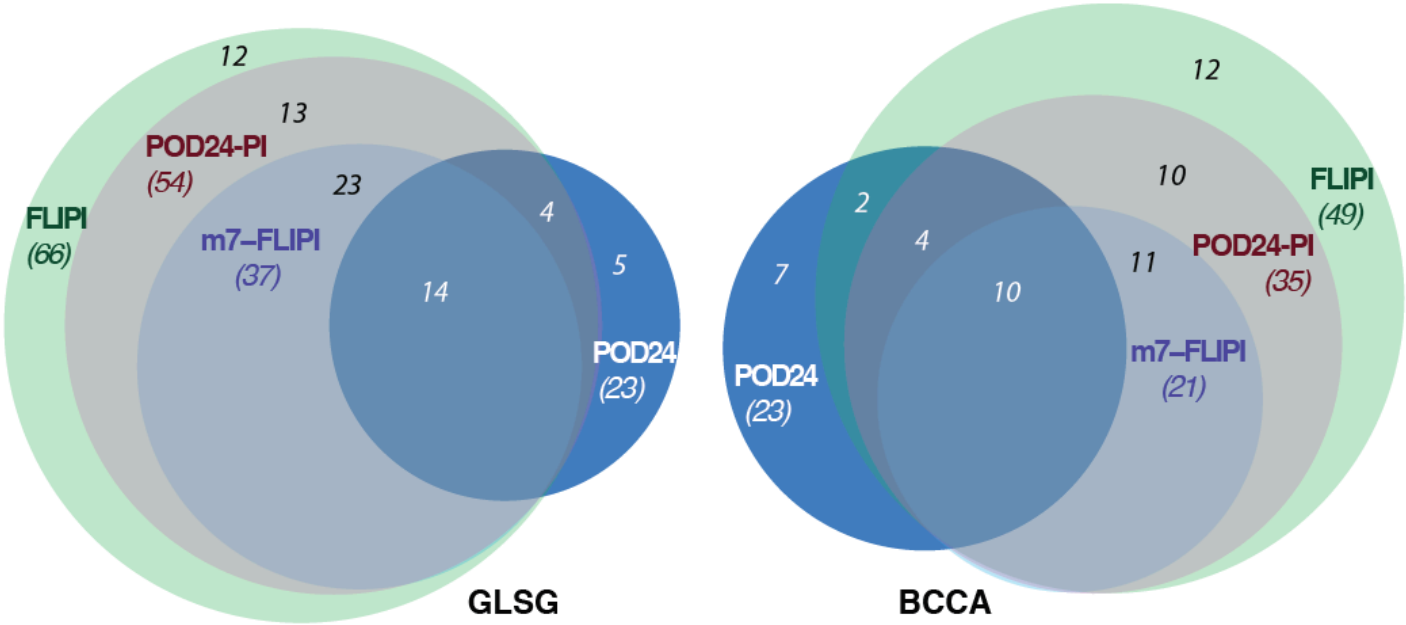
Pre-treatment risk models for POD24: FLIPI and m7-FLIPI



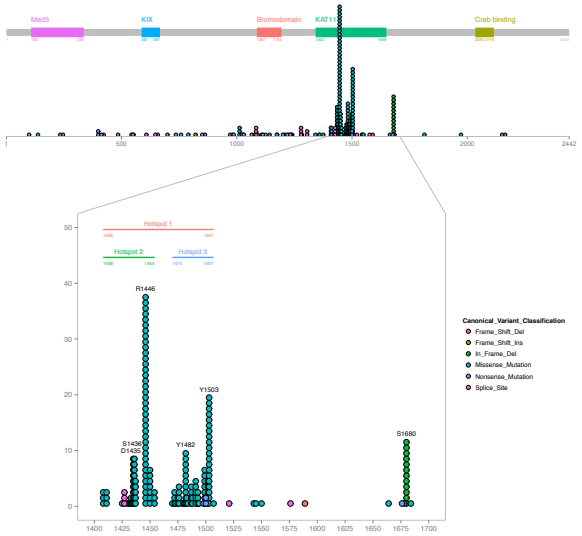
Pre-treatment risk models in non-POD24 patients



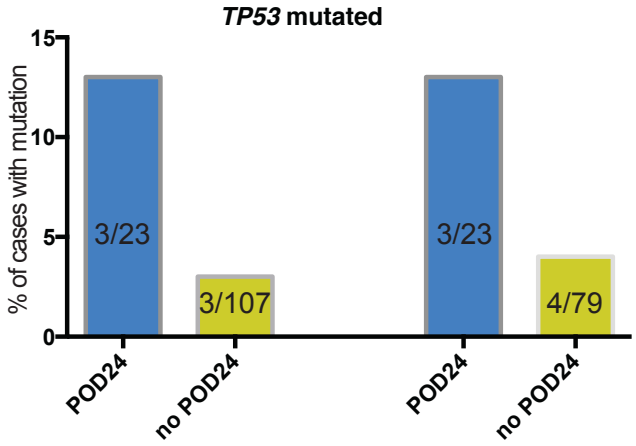
Need to refine / improve *pre-treatment* risk models



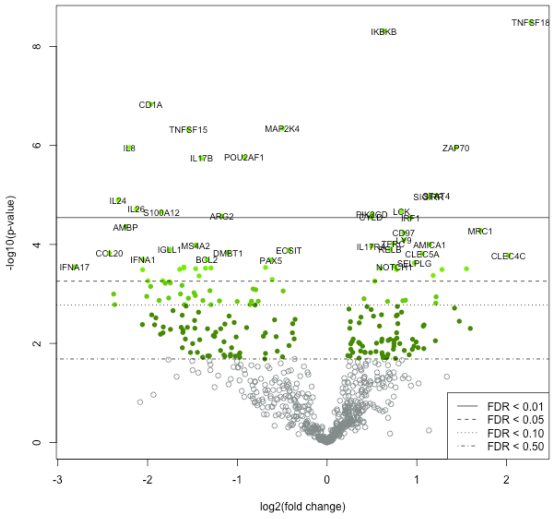
E.g., binary vs. multi-dimensional data?



E.g., additional / novel gene mutations?



E.g., other biomarkers / -omics data?



Evolving principle #1

Integration of molecular markers for improved prognostication

Ongoing:

- additional validation (*e.g.*, additional patient cohorts) & standardization
- iterative improvement (*e.g.*, integration of additional biomarkers)
- functional characterization of candidate mutations

Perspective:

- developing a tool for patient stratification and risk-/ biology-adapted treatment

Clinical implication of genetics in malignant lymphoma

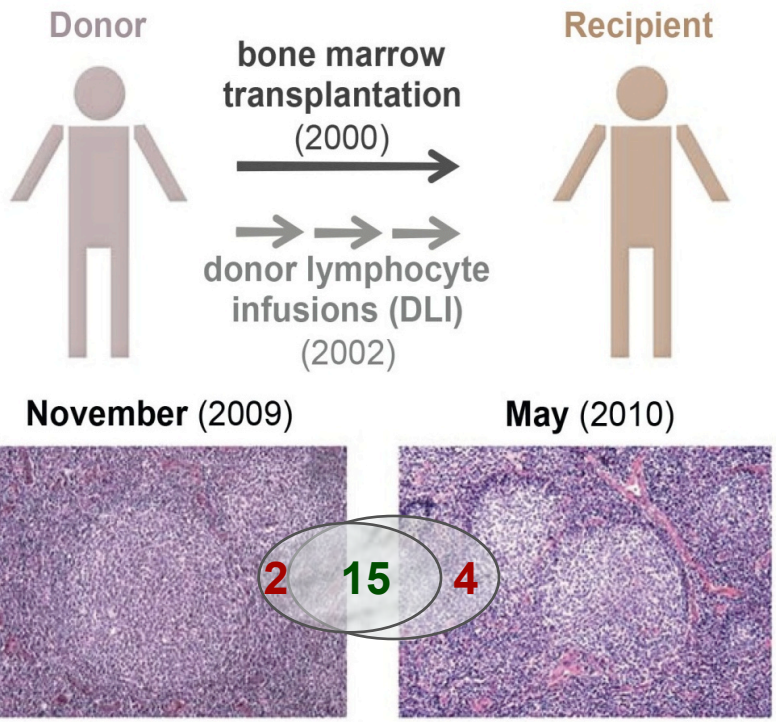
Established (primarily in diagnostics)

- *VDJ* rearrangement: clonality
- somatic hypermutation: pre- *vs* post- germinal center
- hallmark translocations (mutations): diagnosis & classification

Evolving (towards biology-adapted treatment strategies)

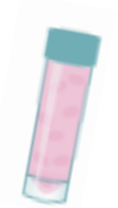
- molecular prognostication
- **seizing the molecular ontogeny**
- molecular treatment stratification
- understanding the molecular biology

Molecular ontogeny in donor-derived follicular lymphomas (FL)



✔ Derived from identical ancestor

✔ Exome Seq: shared *vs* unique somatic, non-silent mutations

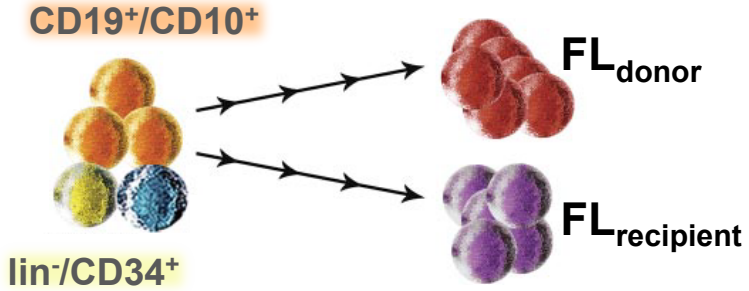


✔ contained FL ancestor cells

✔ contained **shared** mutations

***I.e., c*omplex genetic alterations were acquired > 7 years earlier**

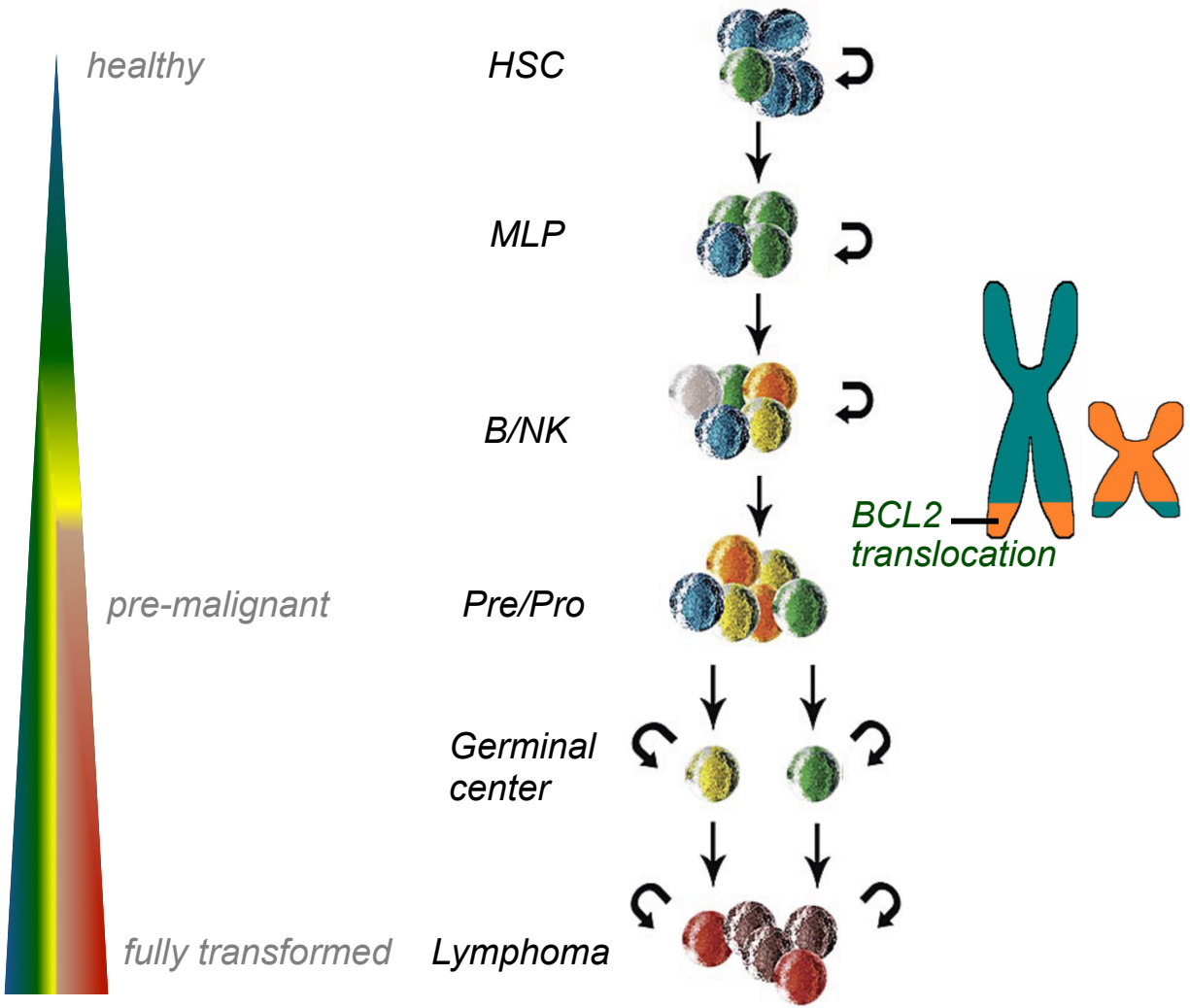
✔ contained shared mutations



✔ **contained a subset of shared mutations**

Weigert et al, Cancer Discovery 2012; Weigert & Weinstock, Blood 2012

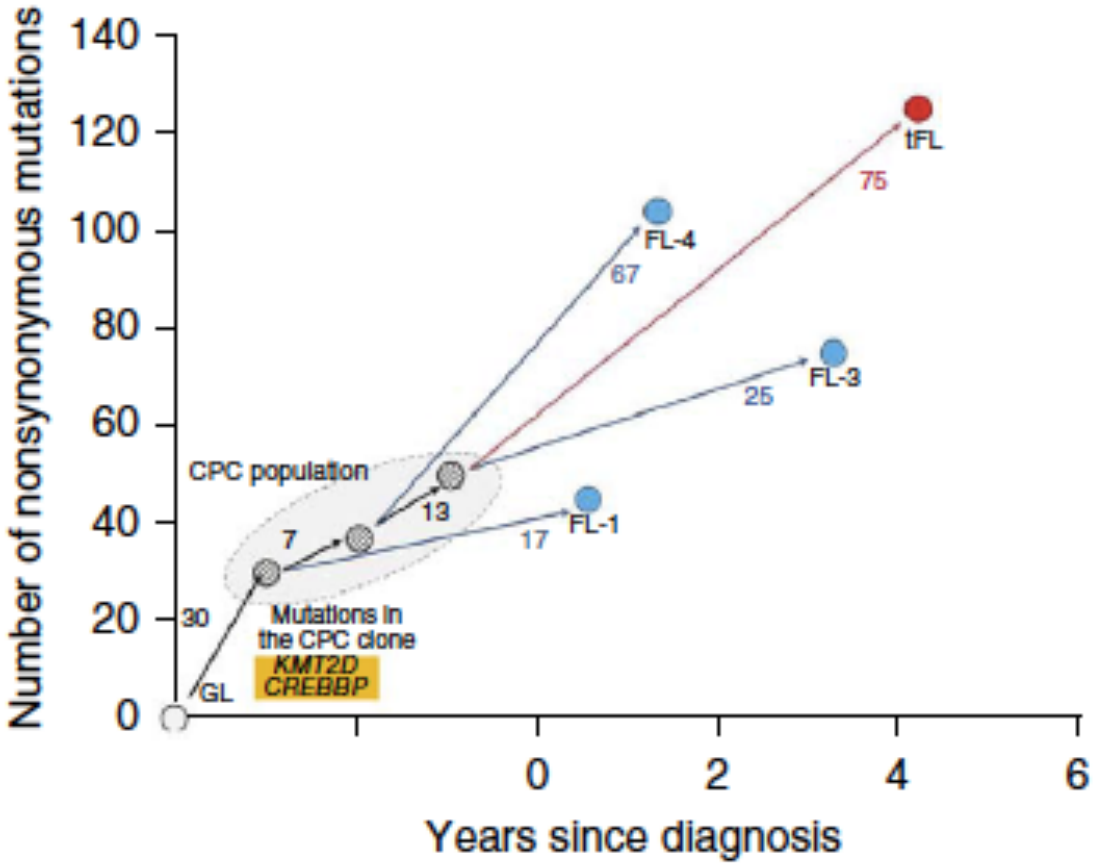
Proposed model of oncogenic evolution in FL



Weigert & Weinstock, Blood 2012

Supported by: Couronne, NEJM 2012; Quivaron, Cancer Cell 2011; Kikushige, Cancer Cell 2011; Damm, Cancer Discovery 2014

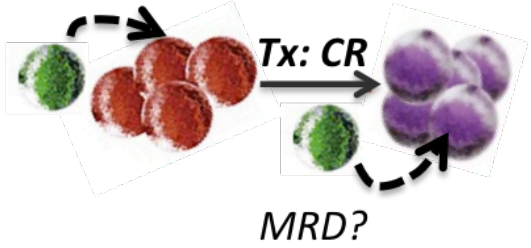
Common precursor cells (CPC) give rise to relapses and histologic transformation in FL: divergent evolution pattern



Okosun et al, Nat Genet 2013; Pasqualucci et al, Cell Reports 2014

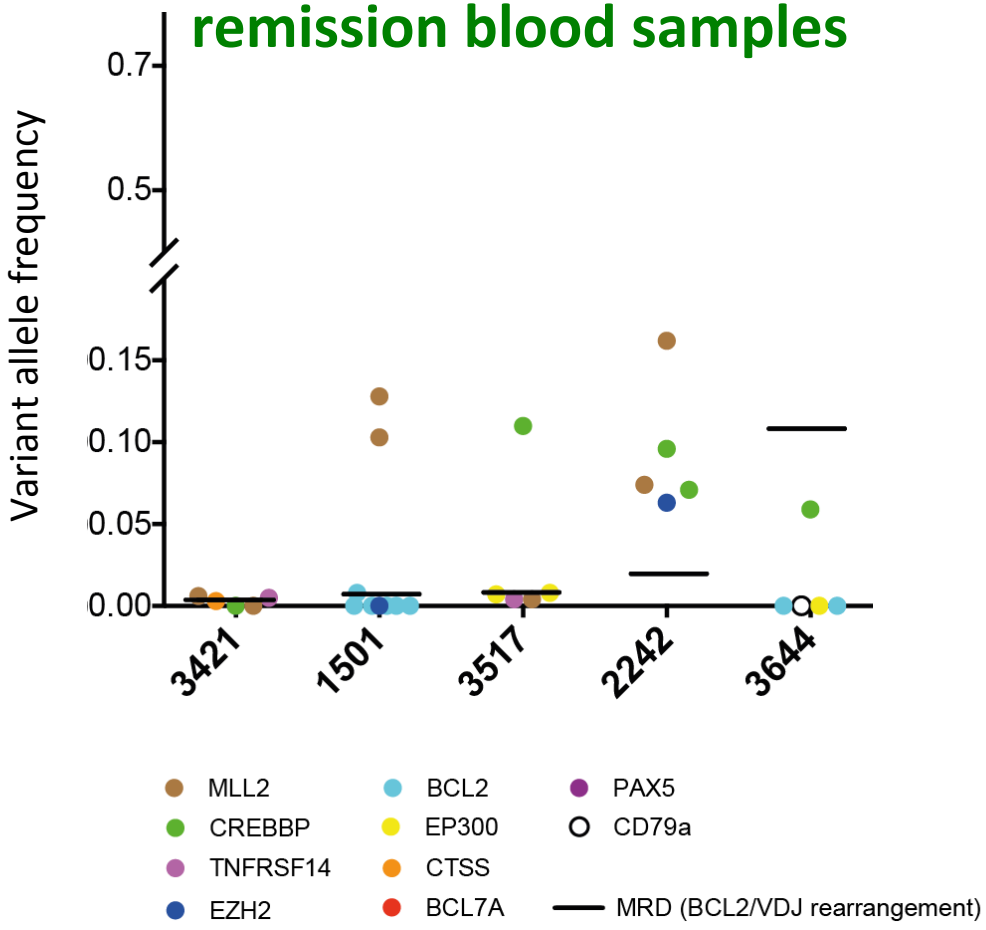
Are CPCs detectable?

	initial diagnosis	*relapse*
MLL2	**K2548fs / T4787fs**	**K2548fs / T4787fs** Q809fs
CREBBP	**D1435V**	**D1435V**
SMARCA4	G883D	
EZH2	Y646S	
TP53	L336* / T284P	
PTEN	V85_splice	
GNA13	G95R / G60A	
ARID1A		C1968*
TNFAIP3/A20		C607*



unpublished data

Detection of lymphoma-specific mutations in remission blood samples



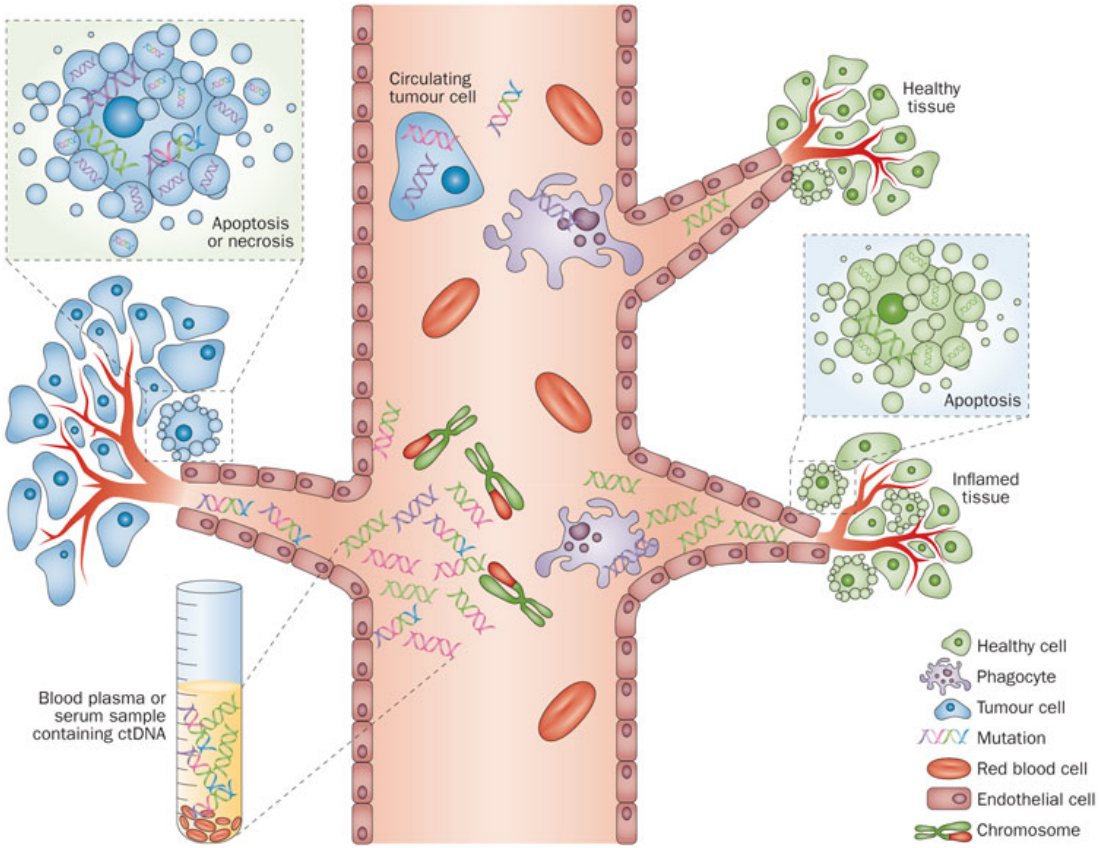
unpublished data

Evolving principle #2

Early acquired / persisting mutations are promising candidates

- for detection of minimal residual disease (MRD)
- for therapeutic targeting to eradicate / cure the disease

Perspective:
Detection of lymphoma-specific mutations in cell-free DNA (cfDNA)



Crowley, Nat Rev Clin Oncol. 2013

e.g., Ash Alizadeh et al., ASH 2015

Clinical implication of genetics in malignant lymphomas

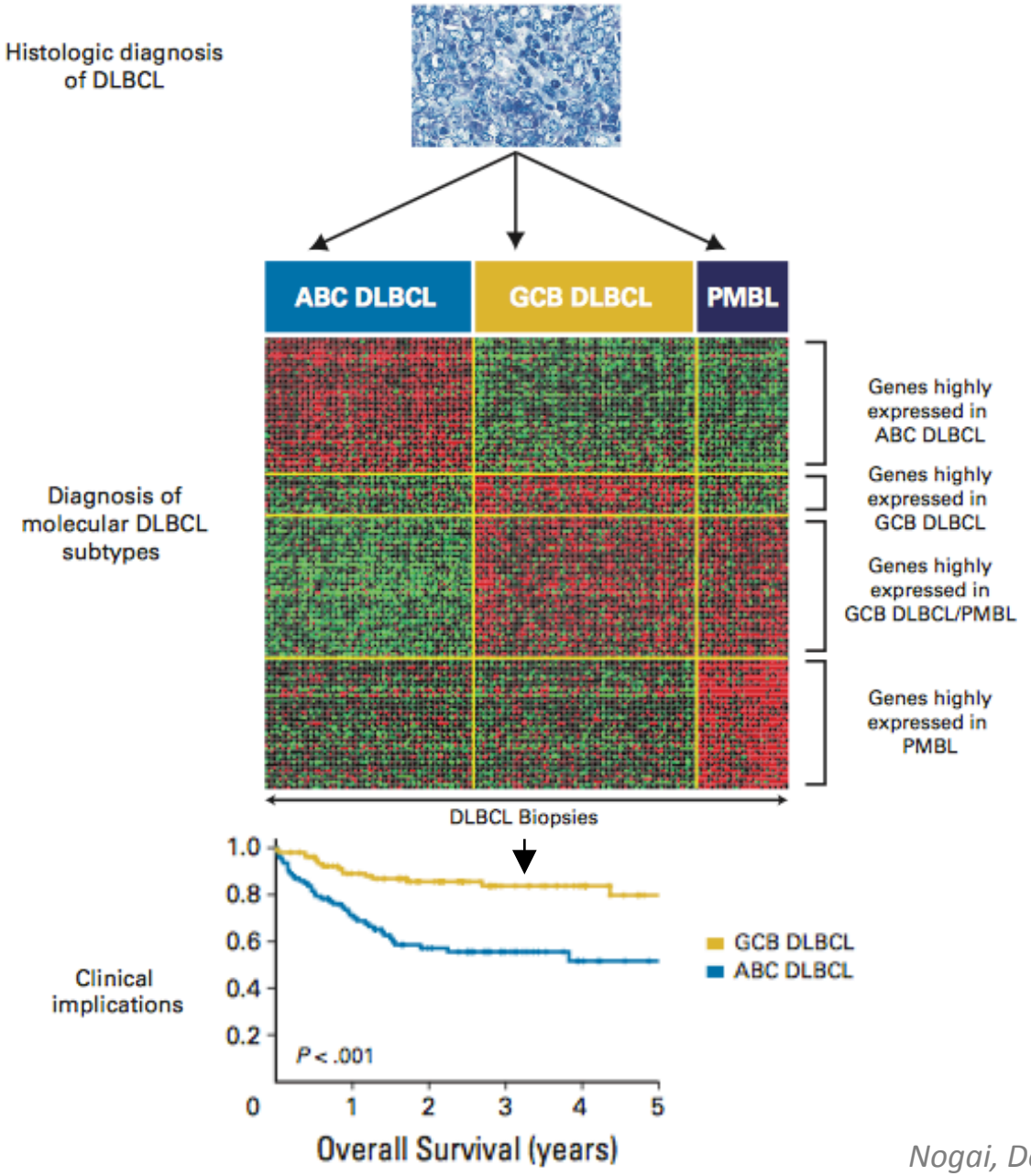
Established (primarily in diagnostics)

- *VDJ* rearrangement: clonality
- somatic hypermutation: pre- *vs* post- germinal center
- hallmark translocations (mutations): diagnosis & classification

Evolving (towards biology-adapted treatment strategies)

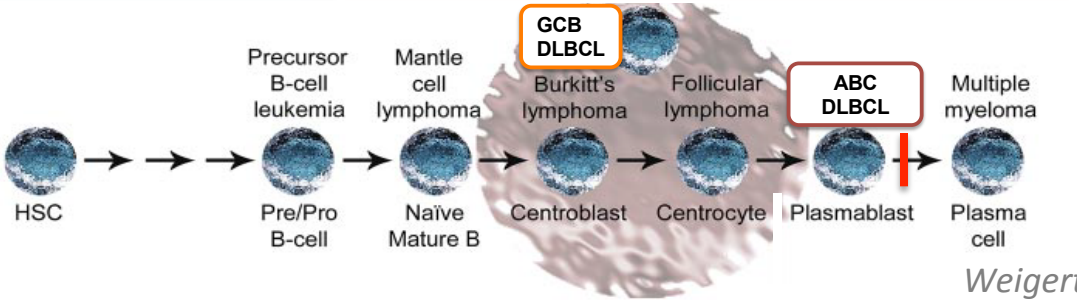
- molecular prognostication
- seizing the molecular ontogeny
- **molecular treatment stratification**
- understanding the molecular biology

Diffuse large B-cell lymphoma (DLBCL): not a single disease

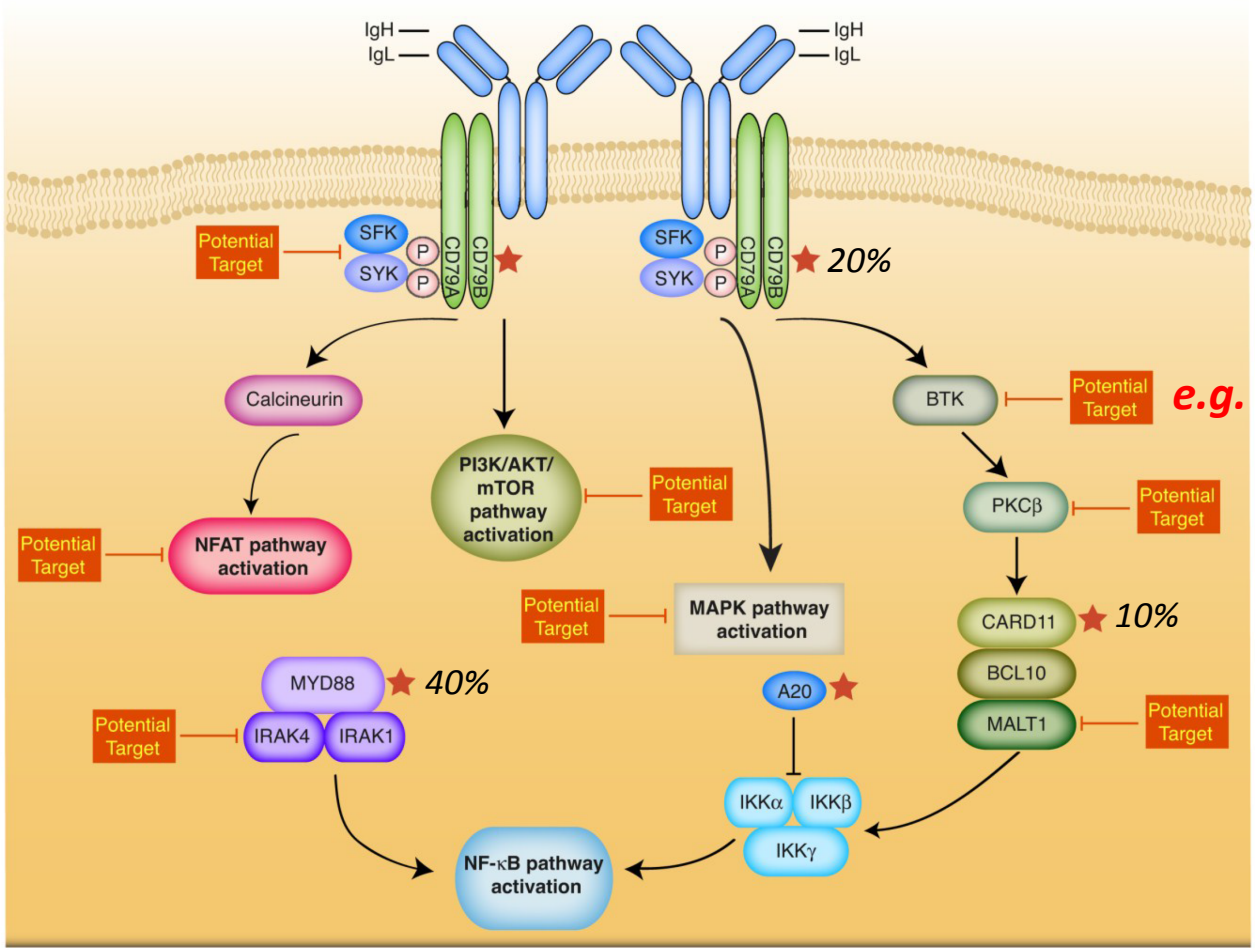


Nogai, Dörken, and Lenz, JCO 2011

Activated B-cell like (ABC) DLBCL: distinct biology



Weigert & Weinstock, Blood 2012



e.g. ibrutinib

Lenz, Cancers 2015

Ibrutinib for relapsed / refractory de-novo DLBCL

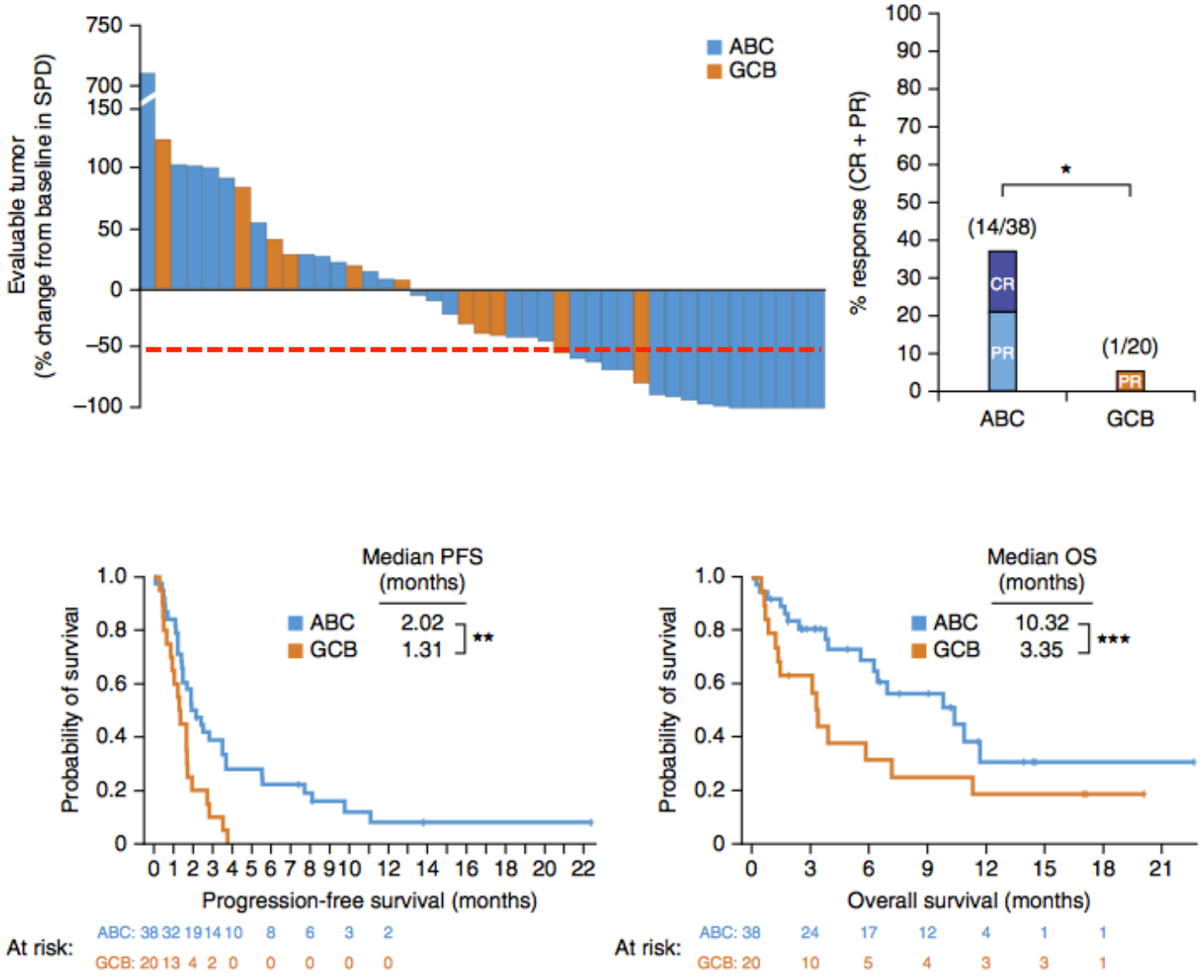
Table 1 Baseline characteristics by DLBCL subtype

Characteristics	ABC (*N* = 38)	GCB (*N* = 20)	Unclassified (*N* = 17)	Unknown (*N* = 5)
Median age, years (range)	60 (34–89)	65 (28–92)	63 (44–85)	65 (58–78)
Sex (male)	66%	70%	82%	60%
ECOG performance score ≥ 2	5%	20%	24%	40%
RIPI (poor)	63%	59%	50%	60%
Median time from diagnosis, months (range)	19 (4–118)	17 (11–104)	21 (7–332)	19 (9–57)
Median number of prior regimens (range)	3 (1–7)	3.5 (1–7)	3 (1–4)	3 (1–3)
Prior ASCT	13%	30%	24%	40%
Chemotherapy-refractory disease	66%	65%	59%	50%

Overall response rate (ORR):	25% (20/80)
Partial responses (PR):	n = 12
Complete responses (CR):	n = 8
Median post-treatment follow-up:	11.5 months
Median progression-free survival (PFS):	1.6 months
Median overall survival (OS):	6.4 months

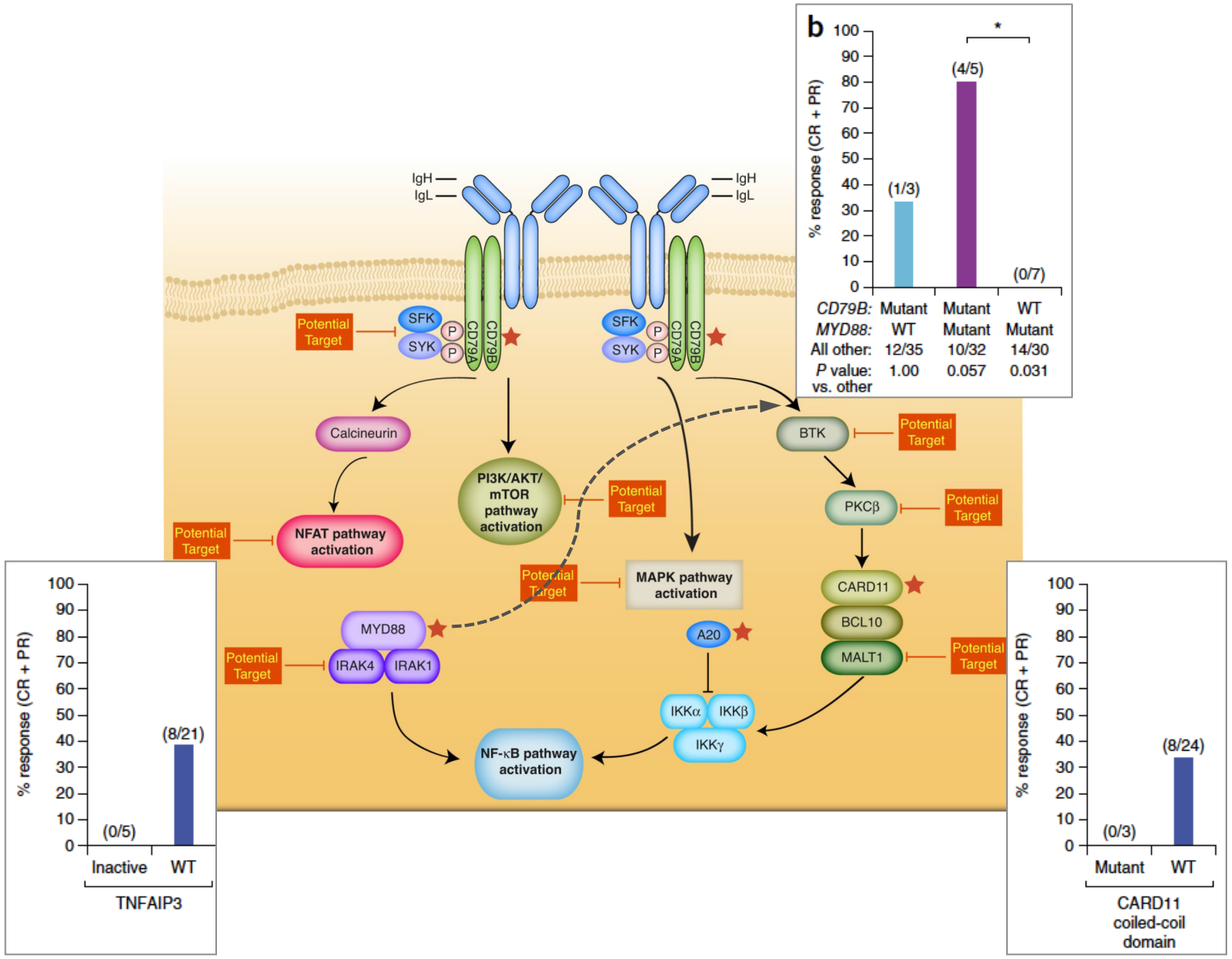
Wilson et al, Nature Medicine 2015

Treatment outcome by DLBCL subtype

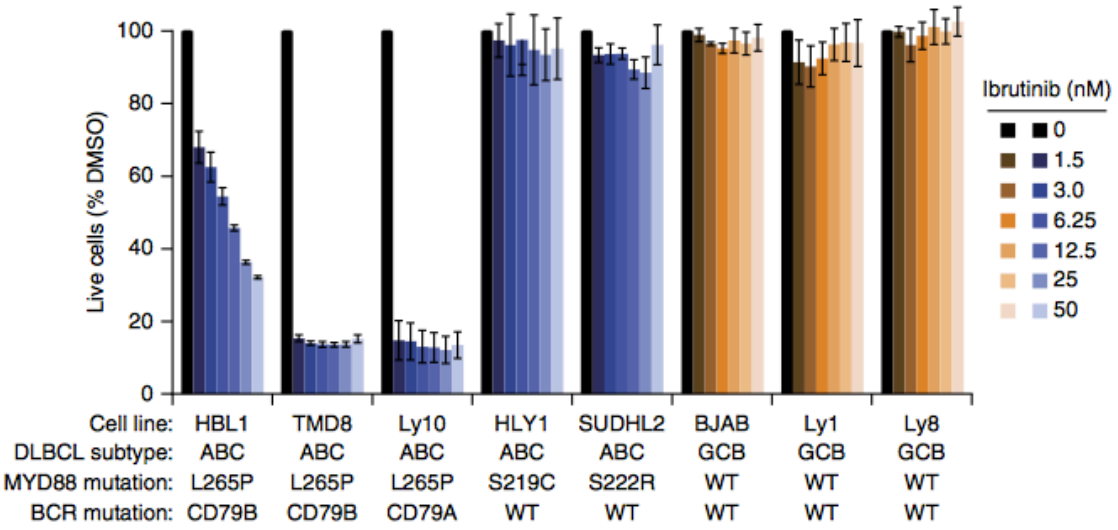


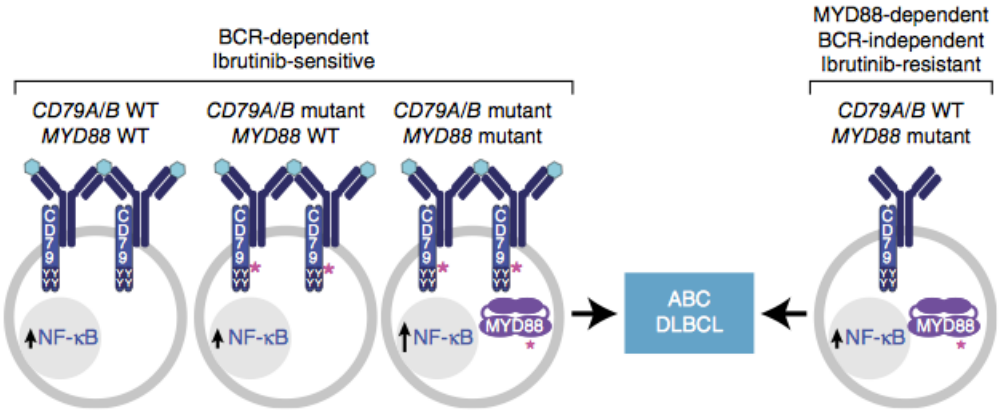
Wilson et al, Nature Medicine 2015

Gene mutations determine ibrutinib sensitivity



DLBCL subtype and gene mutations determine ibrutinib sensitivity





Evolving principle #3

Integrative molecular analyses provide a foundation for the development of biology-adapted treatment strategies

Clinical implication of genetics in malignant lymphoma

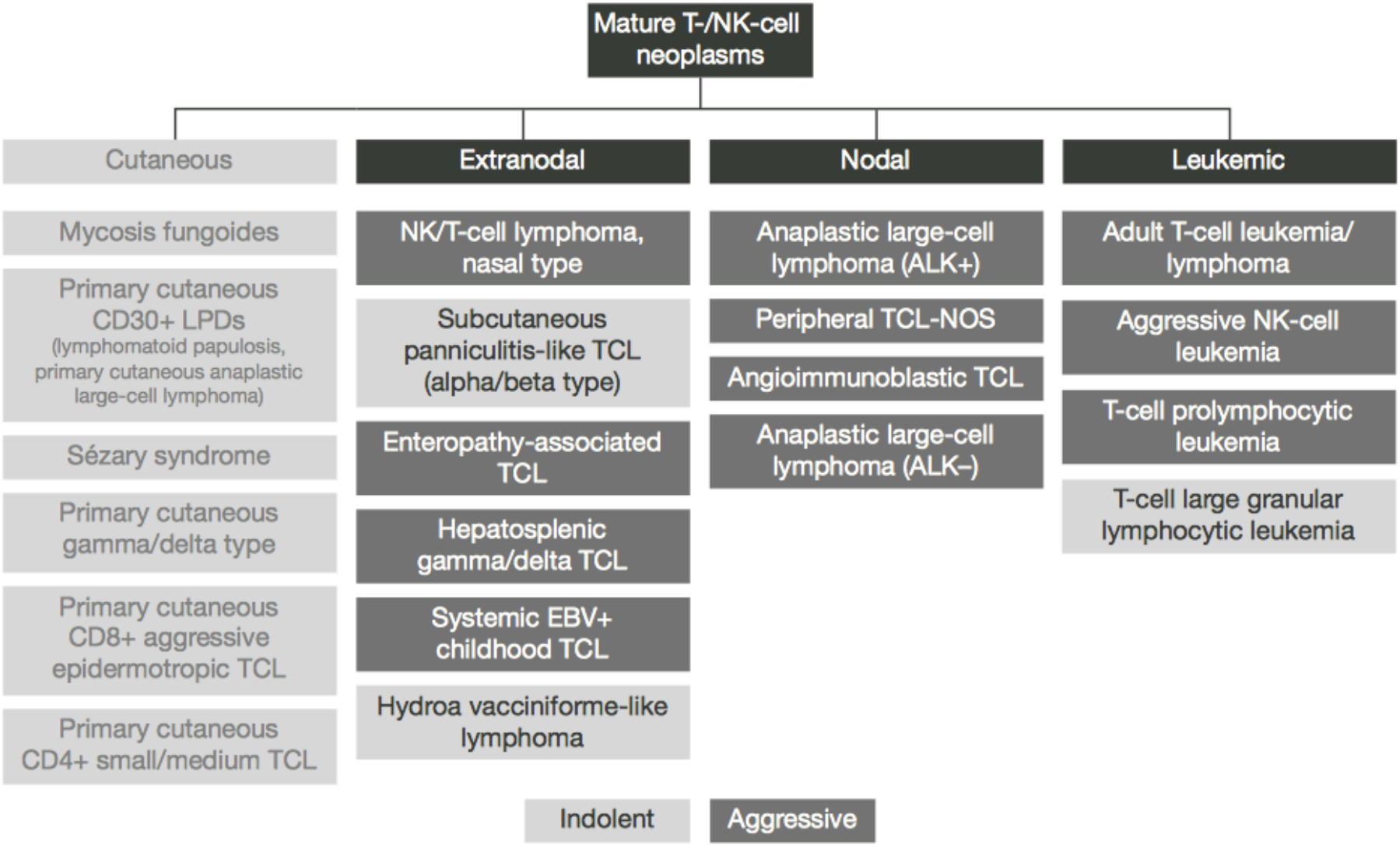
Established (primarily in diagnostics)

- *VDJ* rearrangement: clonality
- somatic hypermutation: pre- *vs* post- germinal center
- hallmark translocations (mutations): diagnosis & classification

Evolving (towards biology-adapted treatment strategies)

- molecular prognostication
- seizing the molecular ontogeny
- molecular treatment stratification
- **understanding the molecular biology**

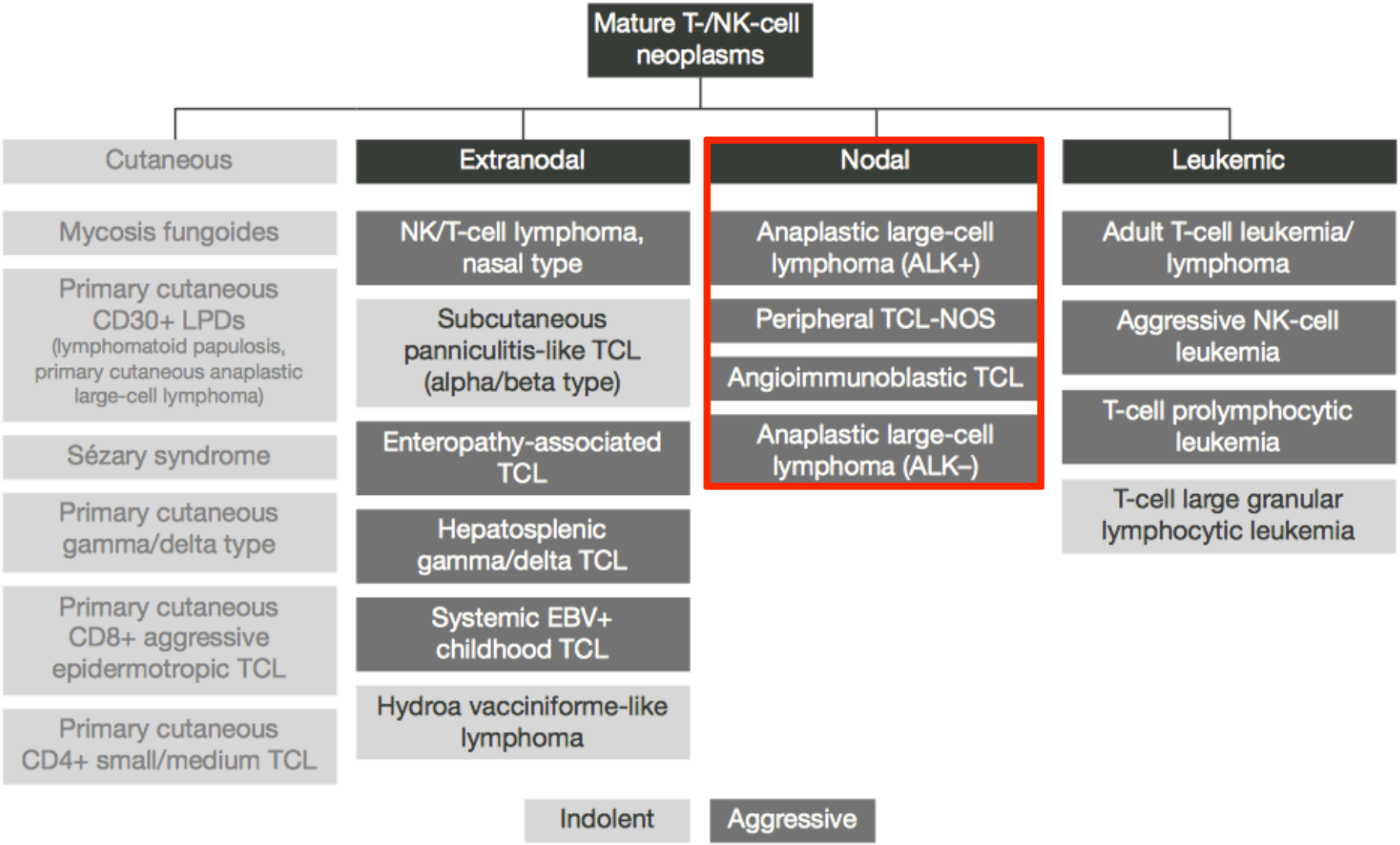
Taxonomy of TCL



from Zinzani et al., 2016

Swerdlow et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, 2008

Taxonomy of TCL



from Zinzani et al., 2016

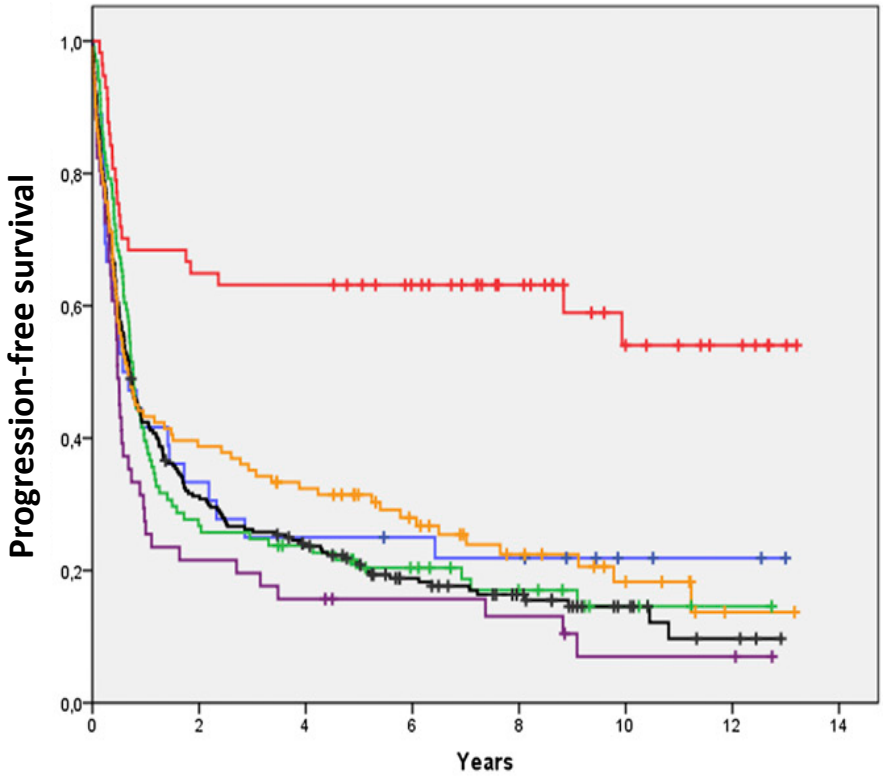
Swerdlow et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, 2008

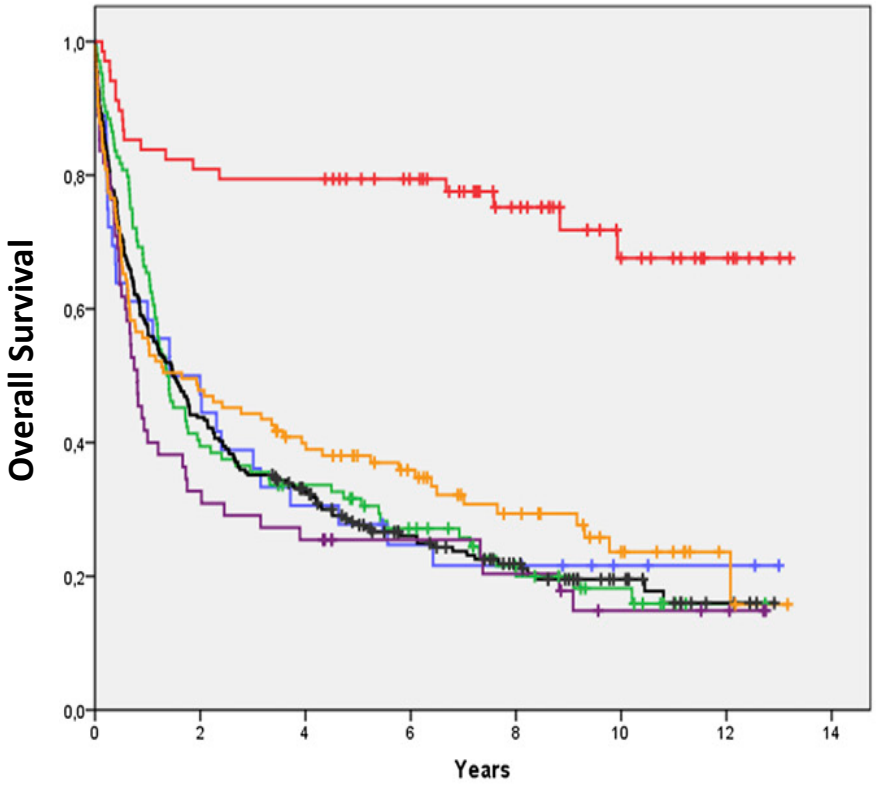
Epidemiology of TCL

	North America (%)	Europe (%)	Asia (%)
PTCL-NOS	34.4	34.3	22.4
AITL	16.0	28.7	17.9
ALCL, ALK+	16.0	6.4	3.2
ALCL, ALK–	7.8	9.4	2.6
NKTCL	5.1	4.3	22.4
ATLL	2.0	1.0	25.0
Enteropathy-type TCL	5.8	9.1	1.9
Hepatosplenic TCL	3.0	2.3	0.2
Primary cutaneous ALCL	5.4	0.8	0.7
SCPTCL	1.3	0.5	1.3
Unclassifiable TCL	2.3	3.3	2.4

International T-Cell Lymphoma Project, J Clin Oncol, 2008

Swedish Lymphoma Registry

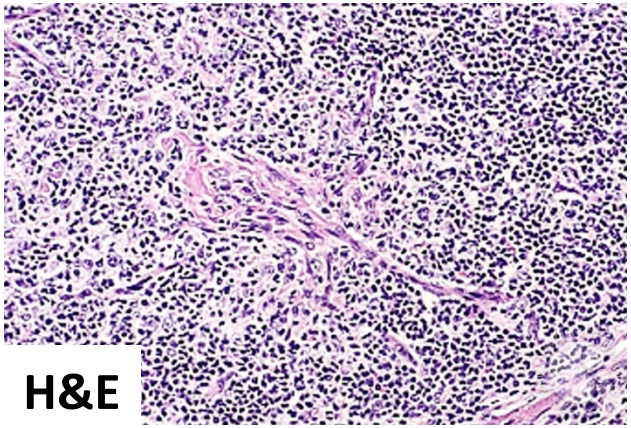




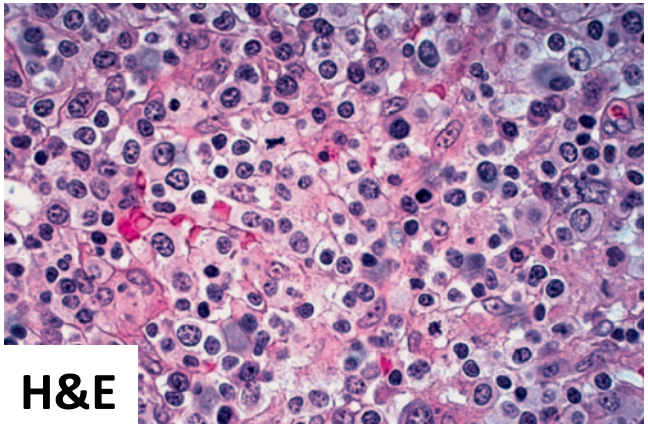
ALK+ ALCL
ALK- ALCL
ALKu ALCL
PTCL-NOS
AITL
TCL U

Ellin F, et al. Blood. 2014

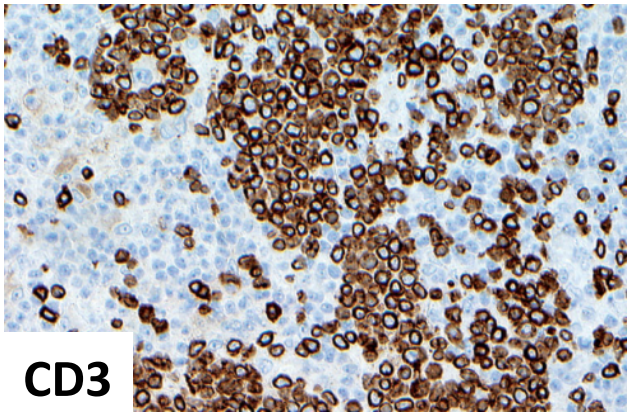
Pathobiologic features of AITL



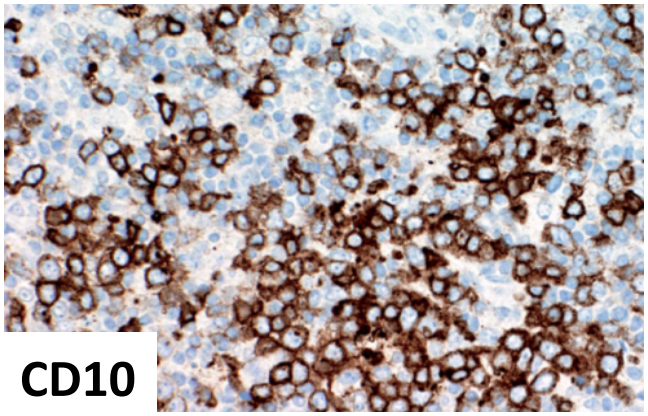
H&E



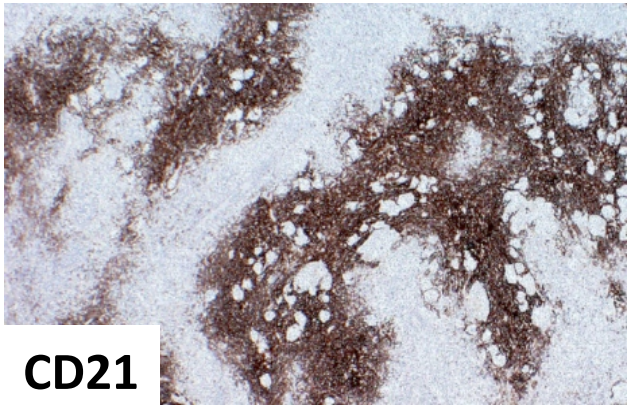
H&E



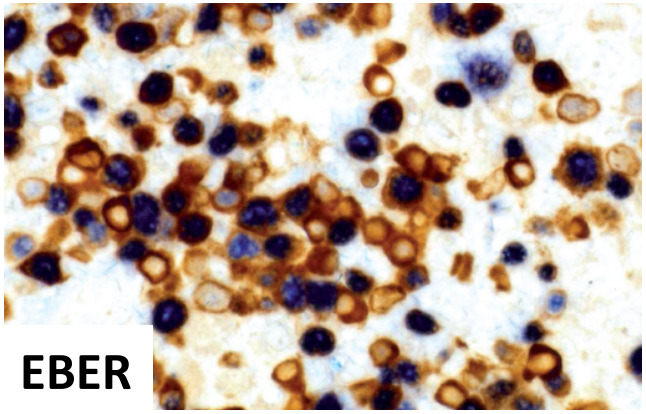
CD3



CD10



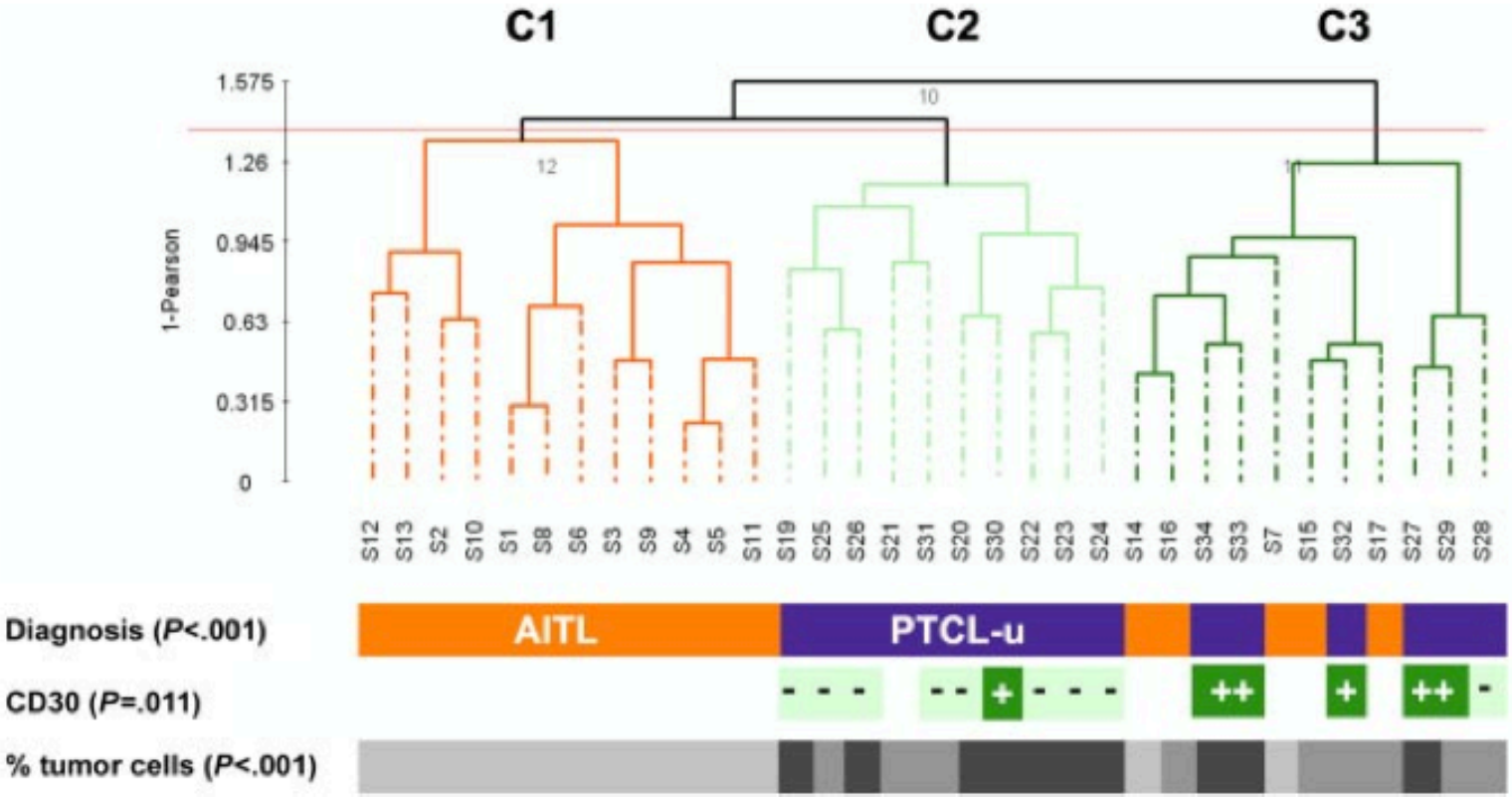
CD21



EBER

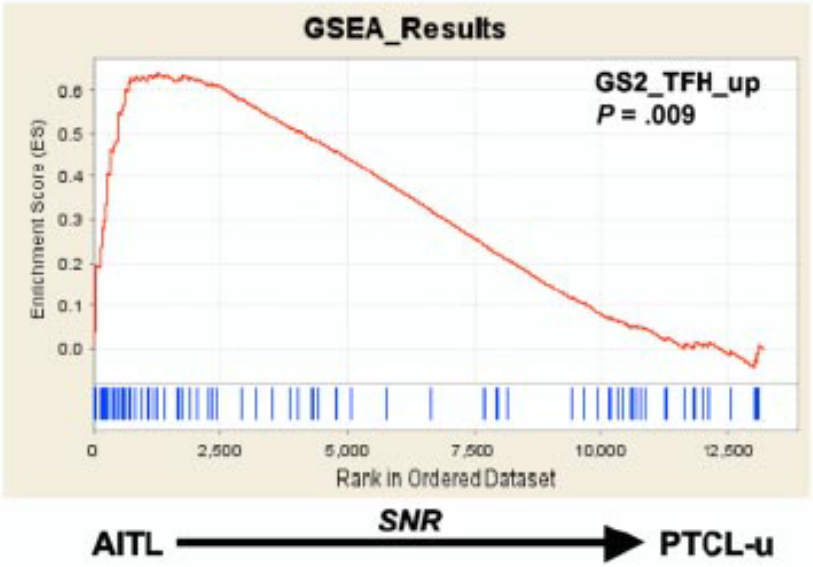
adapted from ASH Image Bank

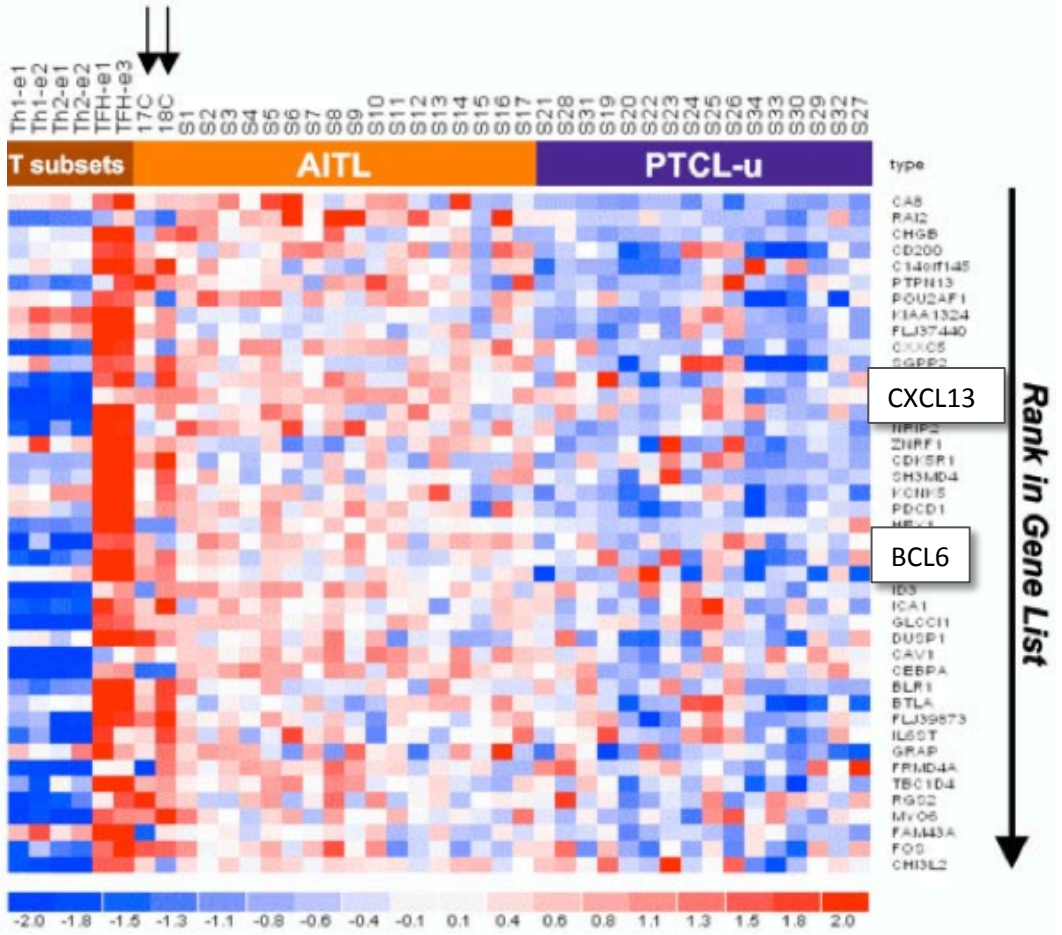
Distinct transcriptional signatures of AITL and PTCL-NOS



de Leval et al., Blood 2007

AITL are derived from T_{FH} cells





de Leval et al., Blood 2007

Study design

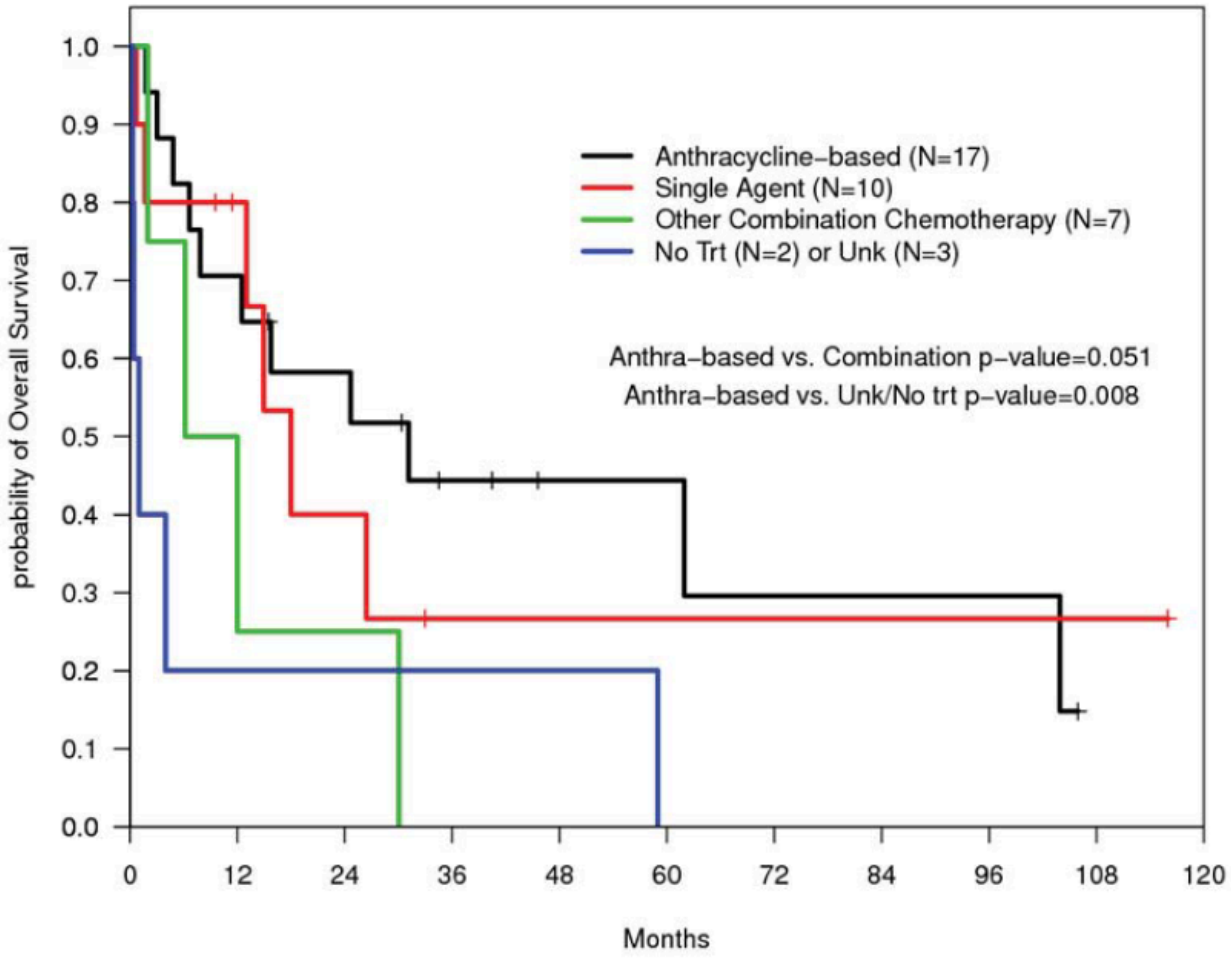
Study cohort: 85 AITL cases from United States and Europe

median age (years) [range]	**69** [30-89]
median OS (months) [95% CI]	**18** [12-31]
Histology pattern II/III (%)	**94**
CXCL13$^+$ (%)	**100**
PD-1$^+$ (%)	**100**
CD4$^+$ (%)	**98.1**
EBER (%)	**66.7**

Oreofo & Weigert et al., Blood 2014

Study design

Study cohort: 85 AITL cases from United States and Europe

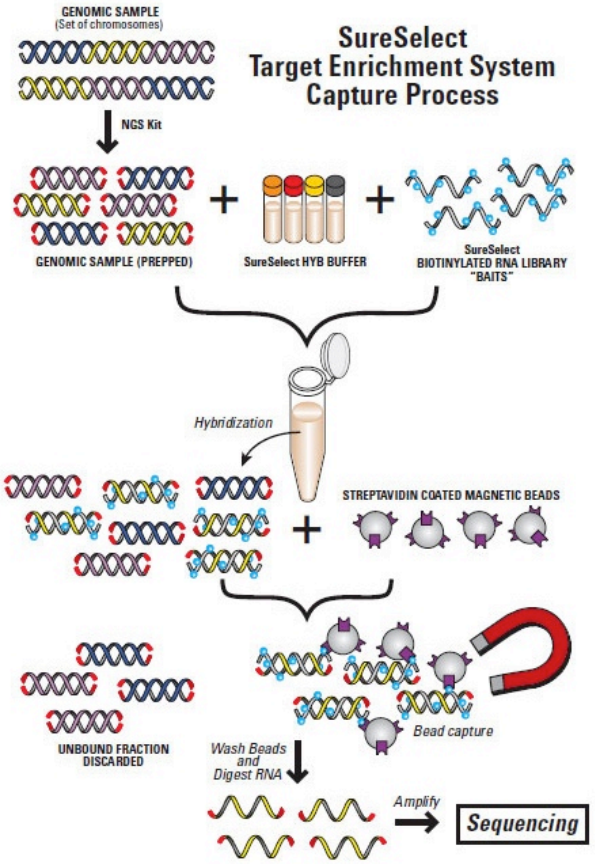


Oreofo & Weigert et al., Blood 2014

Study design

Study cohort: 85 AITL cases from United States and Europe

Target enrichment by hybrid capture and deep sequencing of tumor DNA



- **219 selected genes**
- **Advantage**
  - robust (↑sensitivity, ↓false positive rate)
  - quantitative
  - small amounts of DNA
- **Disadvantage**
  - biased

Study design

Study cohort: 85 AITL cases from United States and Europe

↓

Target enrichment by hybrid capture and deep sequencing of tumor DNA

↓

Validation of mutations by Sanger sequencing or Mass Array Genotyping

↓ ↓

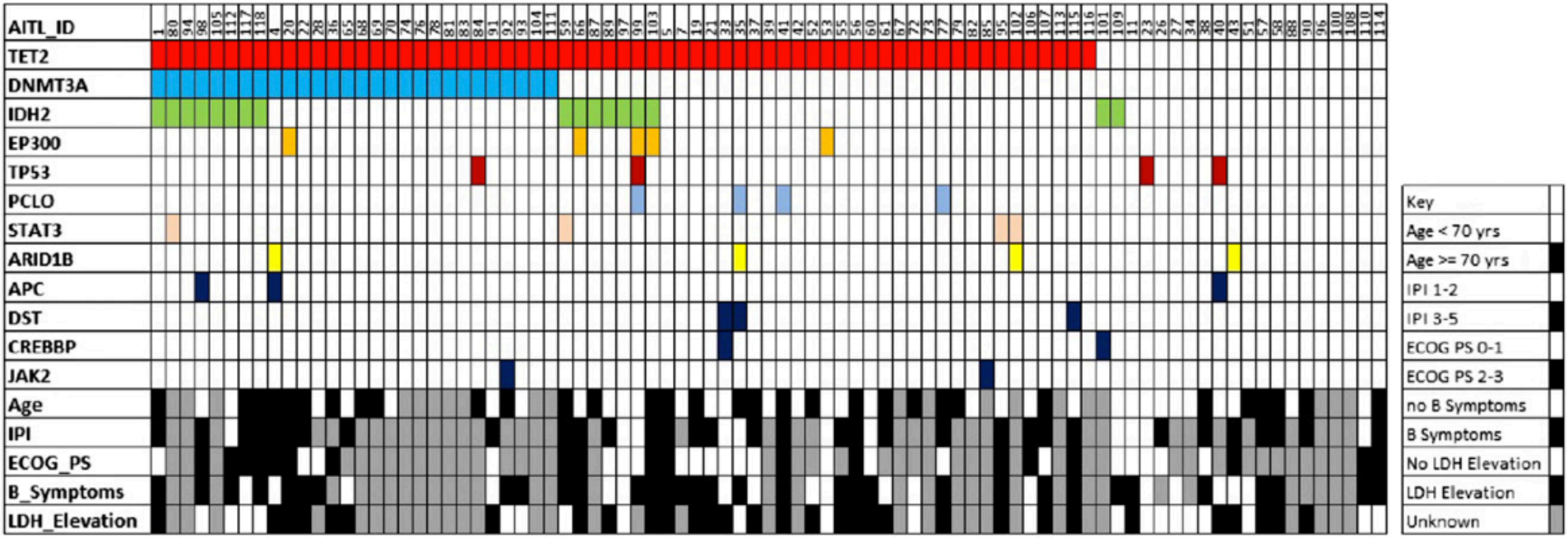
Define the targeted mutational landscape

Correlation of somatic mutations with clinical data and outcome

Plenary Paper

Brief Report

A targeted mutational landscape of angioimmunoblastic T-cell lymphoma

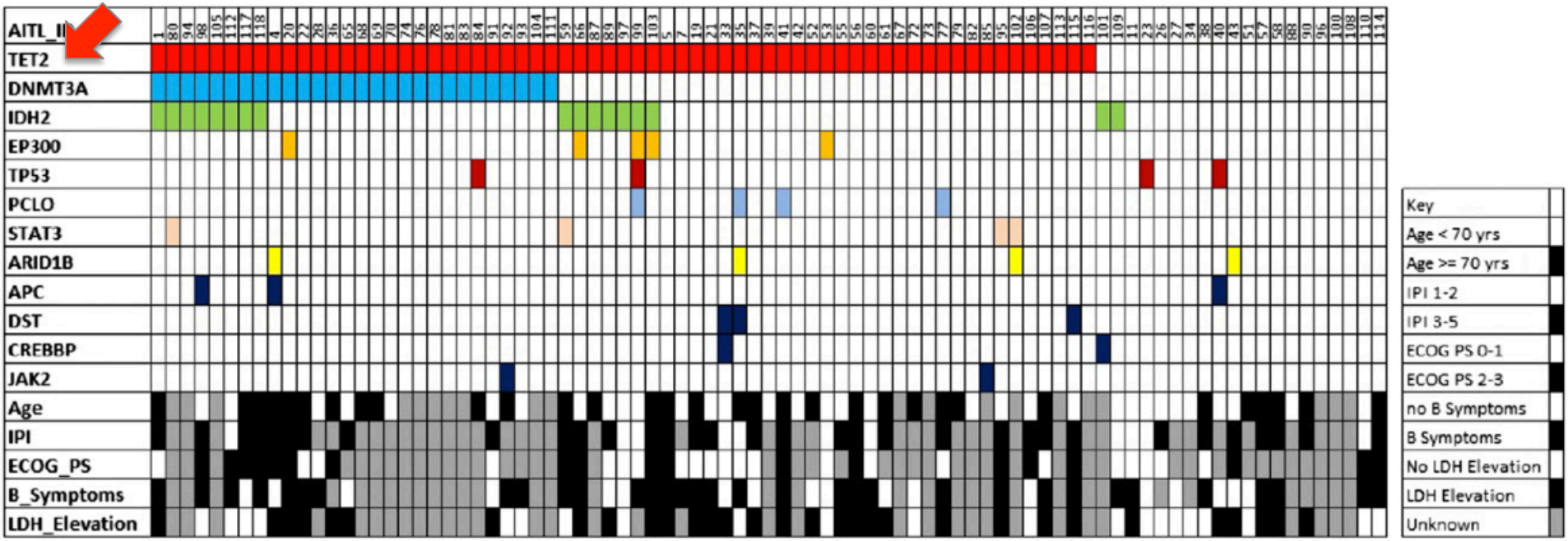


Oreofo & Weigert et al., Blood 2014

Plenary Paper

Brief Report

A targeted mutational landscape of angioimmunoblastic T-cell lymphoma



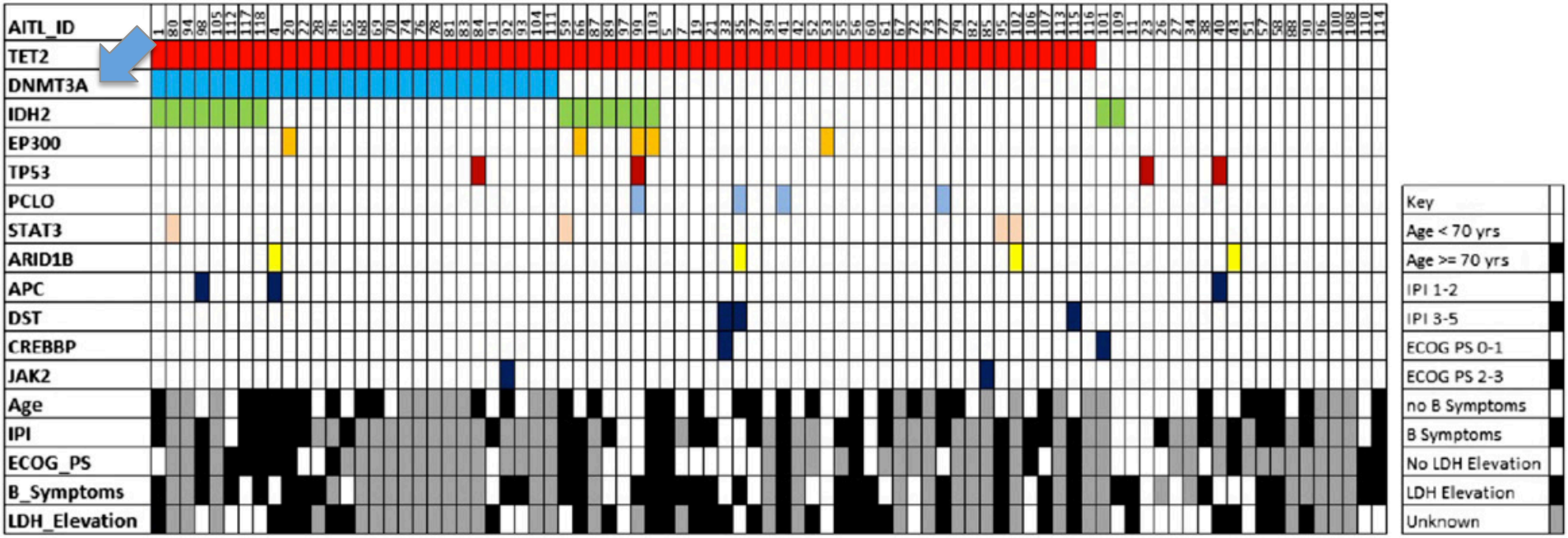
- **76%** of AITL patients harbored ***TET2* mutations**,
  66% thereof habored **≥ 2** *TET2* mutations
- **83%** of *TET2* mutations were **disruptive**
- *TET2* mutations **associated with increased LDH** (p=0.038) and age (p=0.06)

Oreofo & Weigert et al., Blood 2014

Plenary Paper

Brief Report

A targeted mutational landscape of angioimmunoblastic T-cell lymphoma



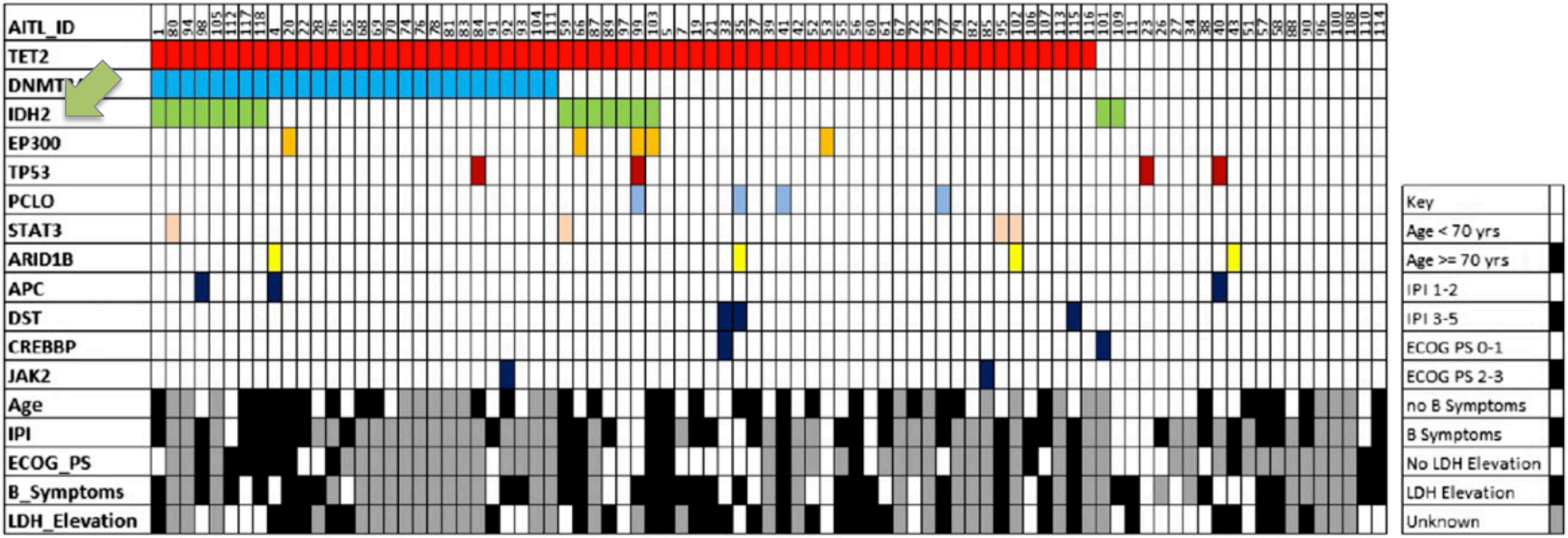
- **28%** of AITL patients harbored ***DNMT3A* mutations**, **100%** thereof **also habored *TET2* mutations** ($p<0.0001$)
- *DNMT3A* mutations **associated with older age** ($p=0.037$)

Oreofo & Weigert et al., Blood 2014

Plenary Paper

Brief Report

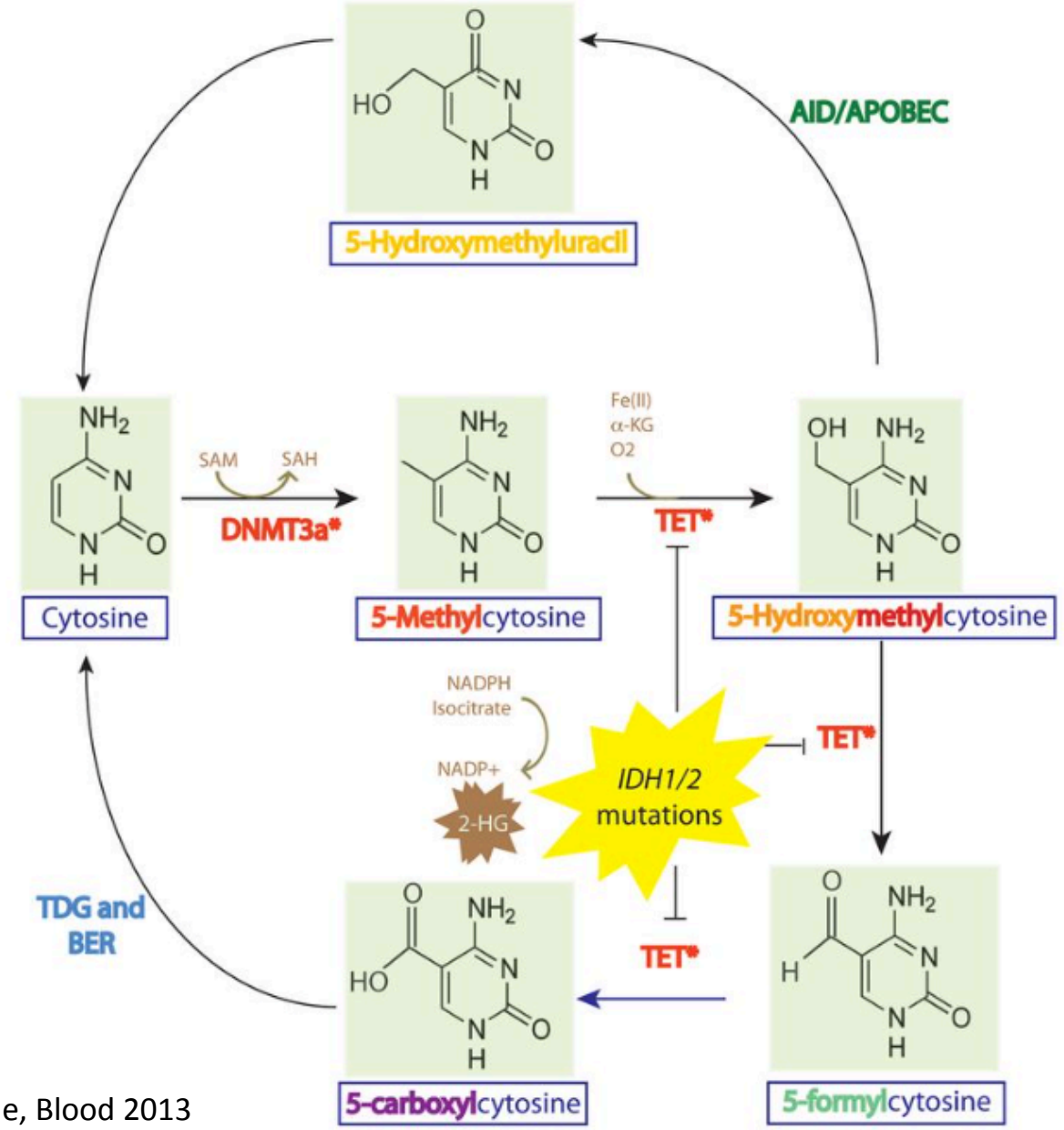
A targeted mutational landscape of angioimmunoblastic T-cell lymphoma



- **17%** of AITL patients harbored ***IDH2*** **mutations** at R172,
  88% thereof **co-occurred with *TET2* mutations** (*p*=0.35)

Oreofo & Weigert et al., Blood 2014

Somatic mutations in epigenetic modifiers: aberrant DNA methylation



Abdel-Wahab & Levine, Blood 2013

Plenary Paper

Brief Report

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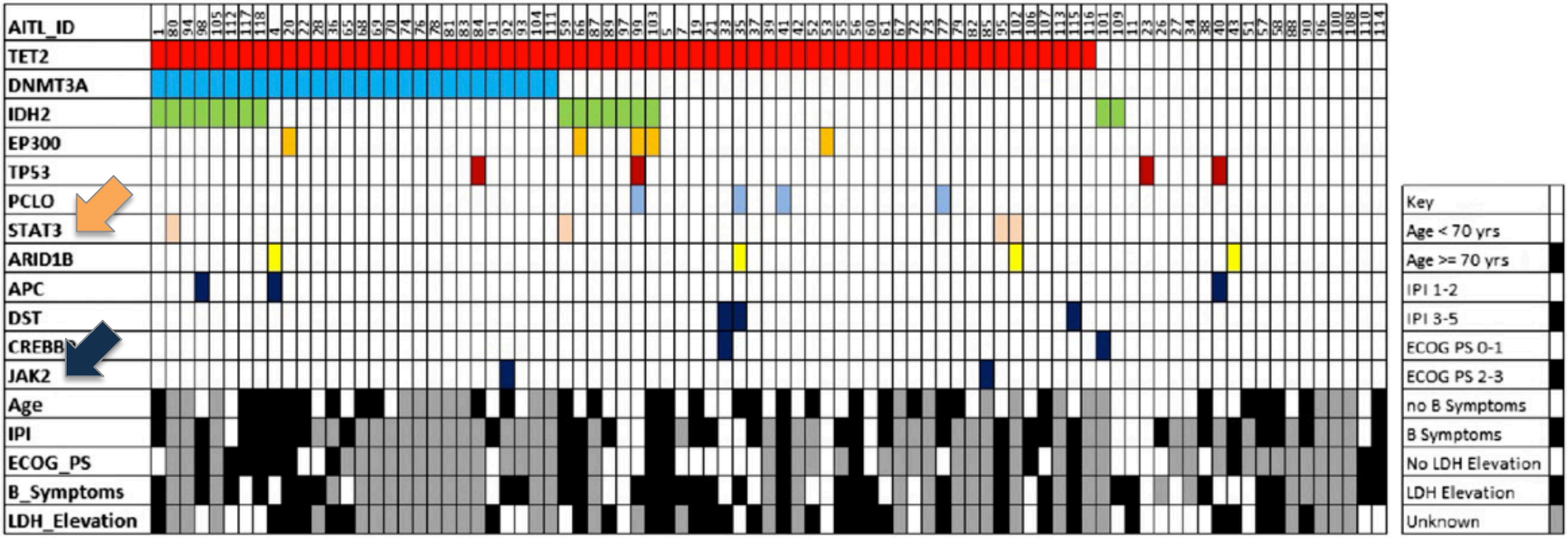
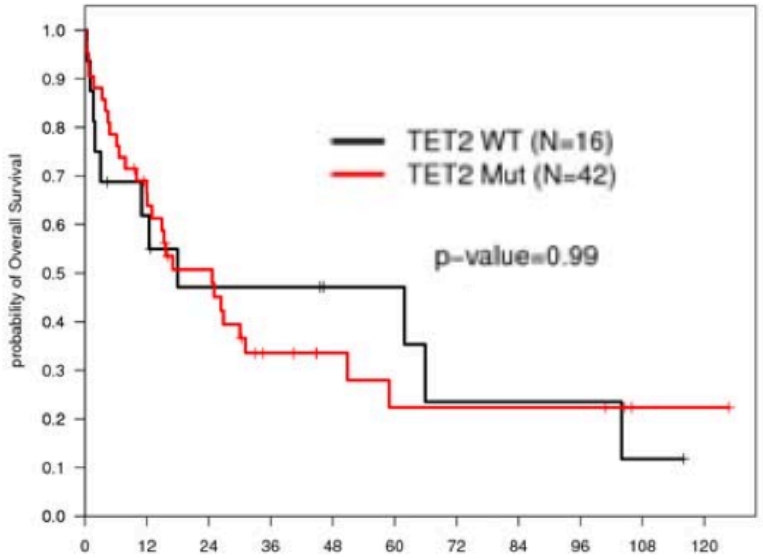
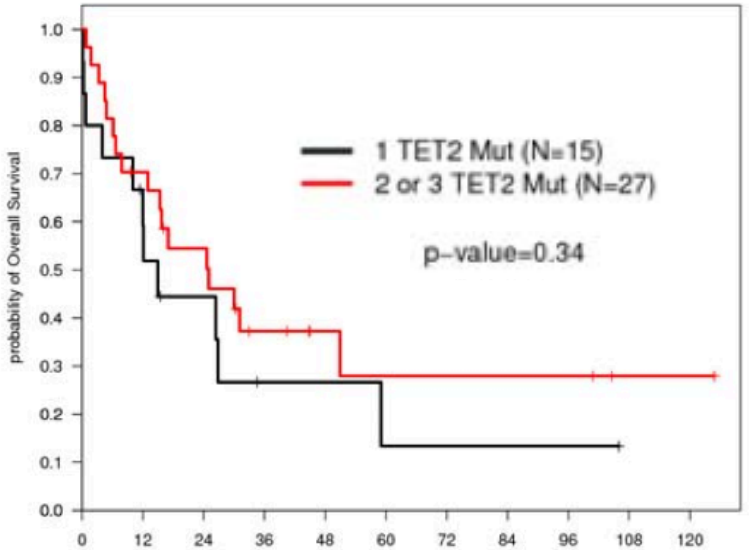


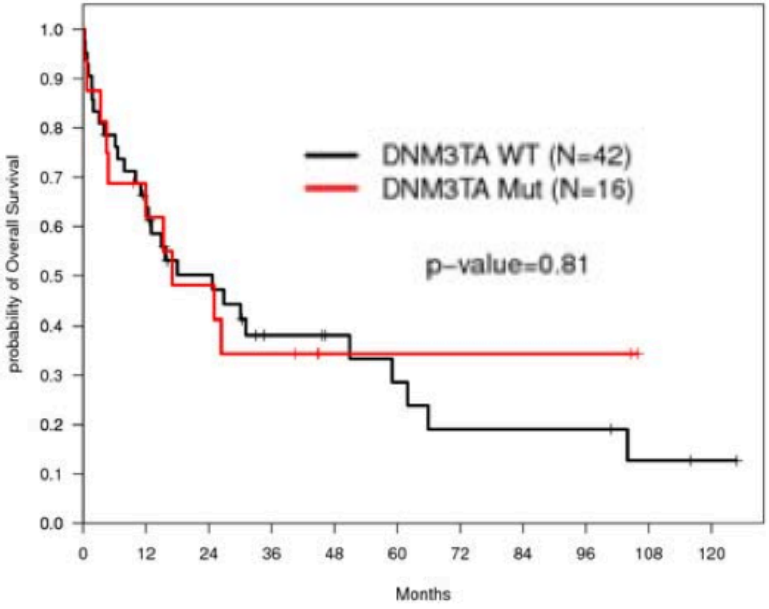
- **Some** additional gain-of-function mutations, *e.g.* in *STAT3* and *JAK2*

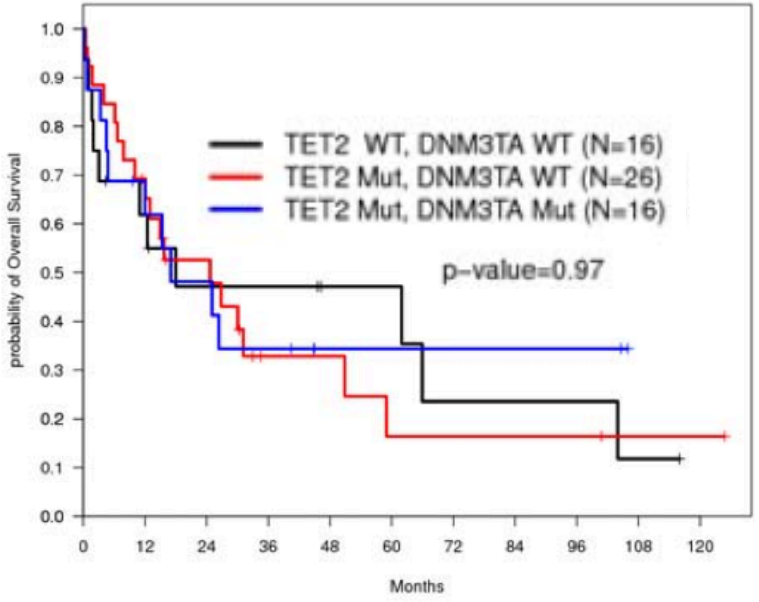
Oreofo & Weigert et al., Blood 2014

Mutations in *TET2* and/or *DNMT3A* do not affect OS



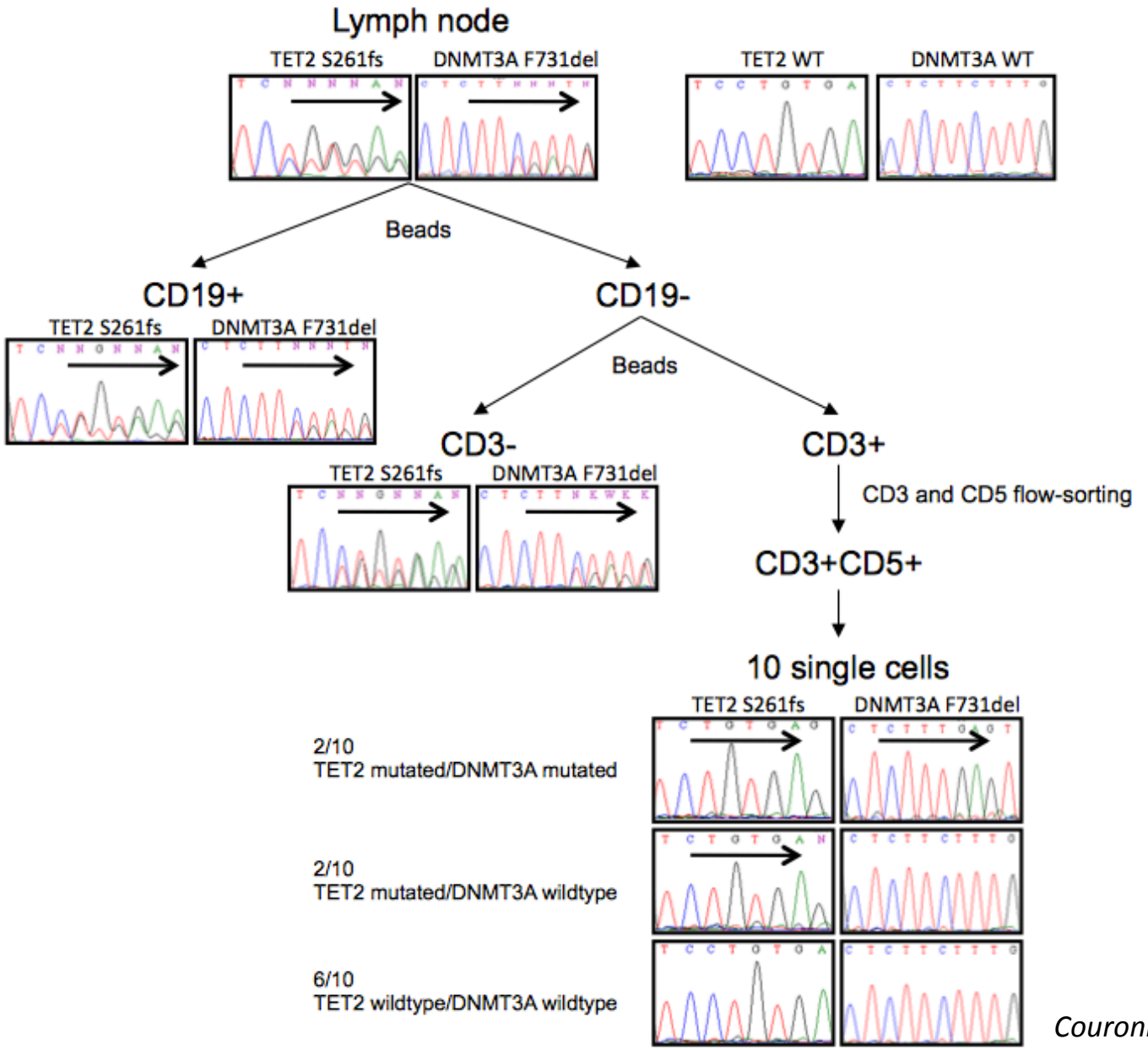






Oreofo & Weigert et al., Blood 2014

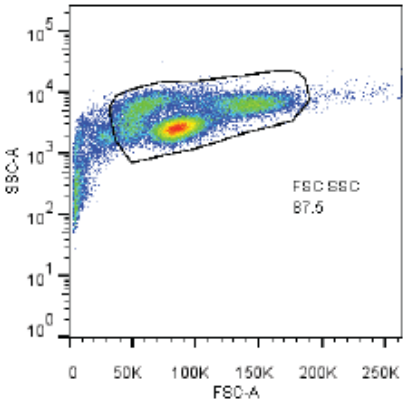
Molecular ontogeny *TET2* and *DNMT3A* mutations



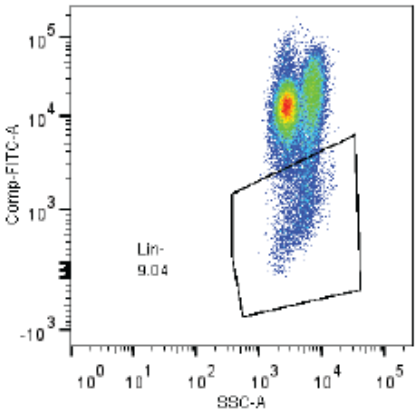
Couronné et al., NEJM 2012

Sorting strategy of PBSCT product

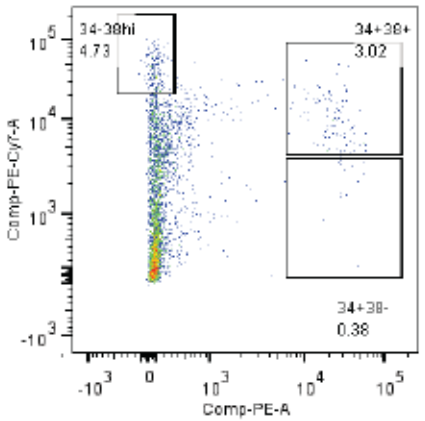
AITL #21 PBSC product



Lineage (Lin) = CD3, 14, 19, 20, 56

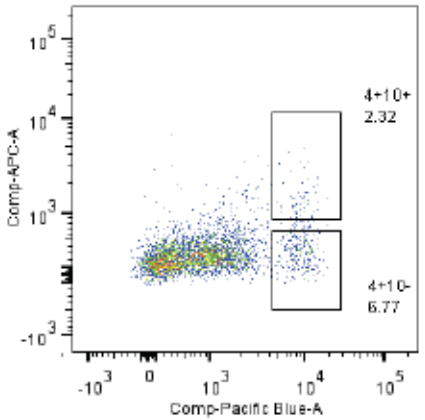


CD38



CD34

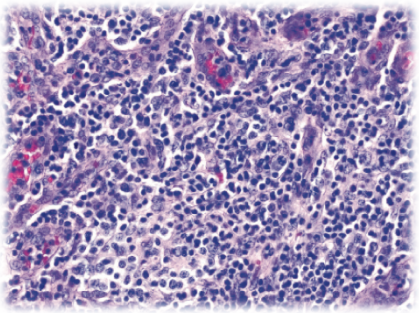
CD10

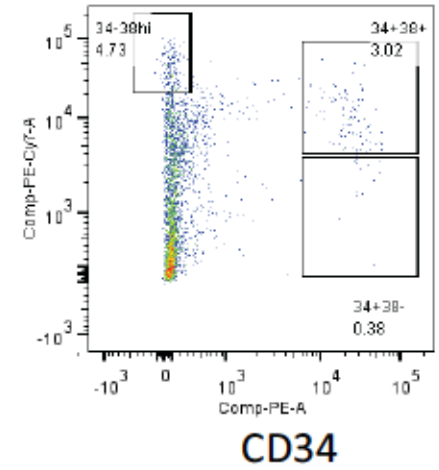


CD4

Oreofo & Weigert et al., Blood 2014

TET2 InDel in a hematopoietic progenitor cell compartment





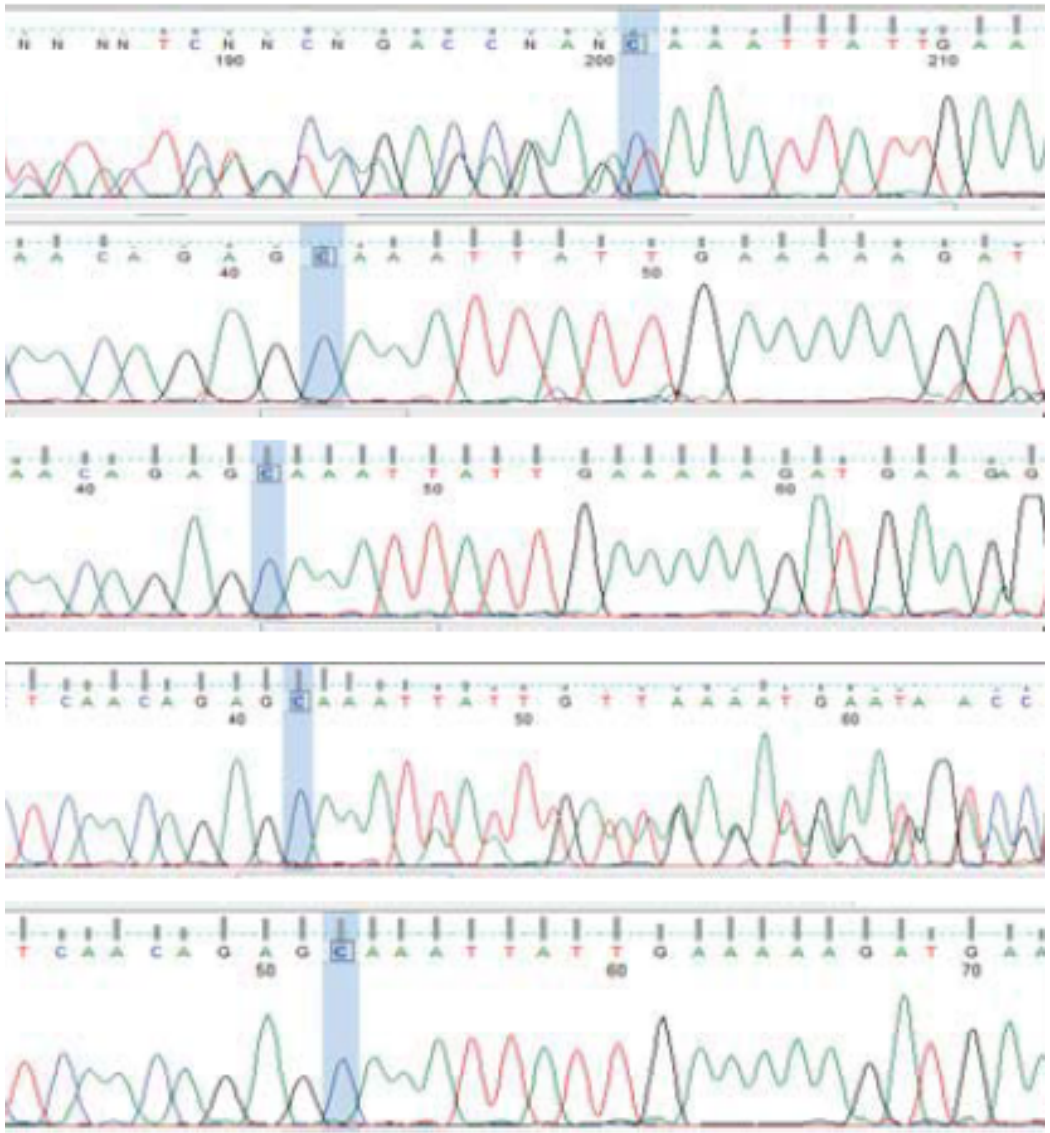
Tumor

Methylcellulose colonies

Unsorted PBSC product

lineage- CD34- CD38+

lineage- CD34+ CD38-

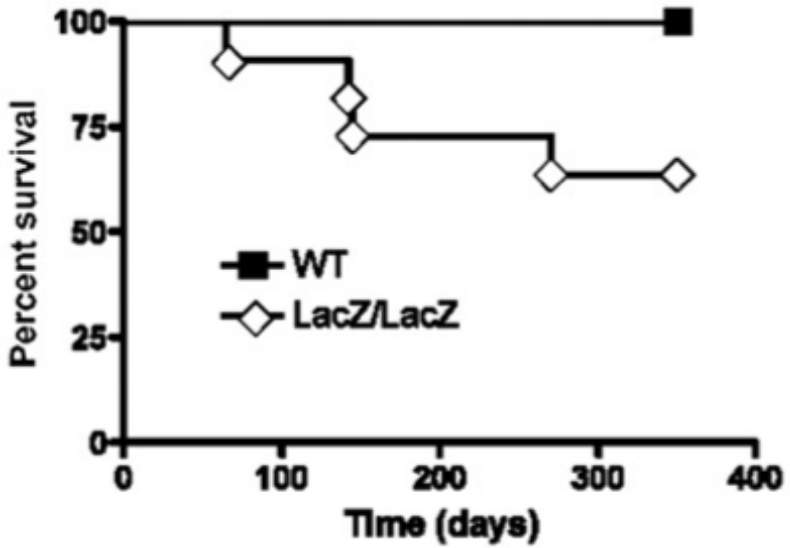


Oreofo & Weigert et al., Blood 2014

TET2 Inactivation Results in Pleiotropic Hematopoietic Abnormalities in Mouse and Is a Recurrent Event during Human Lymphomagenesis

Inactivation of *Tet2* in mouse HSPCs

- ↓ 5hmC marks
- ↑ self-renewal capacity and competitive advantage
- contributes to the development of hematologic abnormalities



$Tet2^{+/+}$

$Tet2^{LacZ/LacZ}$

Quivaron et al., Cancer Cell 2011

Somatic *RHOA* mutations in AITL and PTCL-NOS

- in ~ 70% of AITL
- most *RHOA* mutations encode for dominant-negative p.Gly17Val

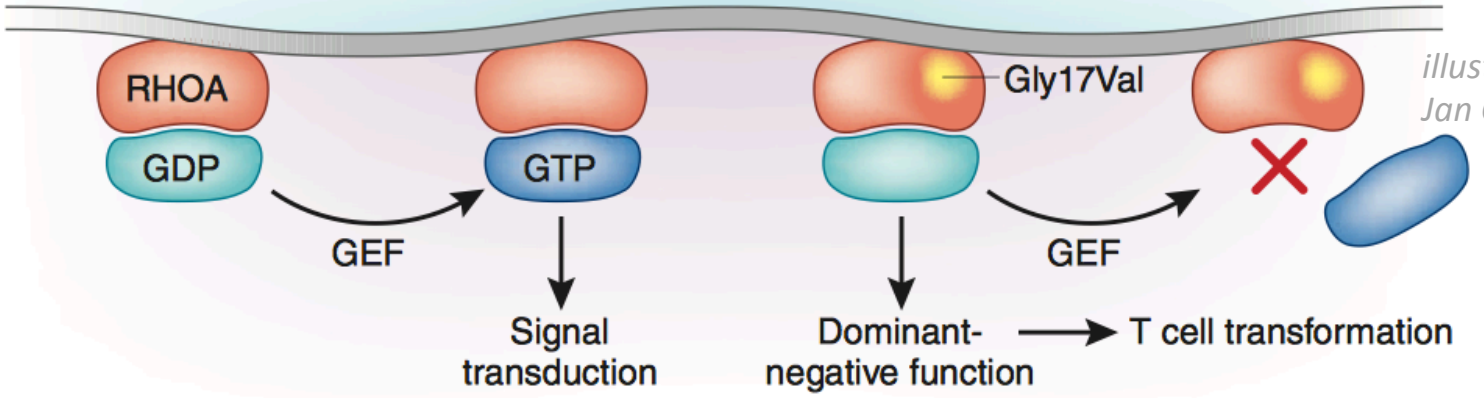


illustration by Jan Cools

Sakata-Yanagimoto et al. & Palomero et al., & Yoo et al., Nature Genetics 2014

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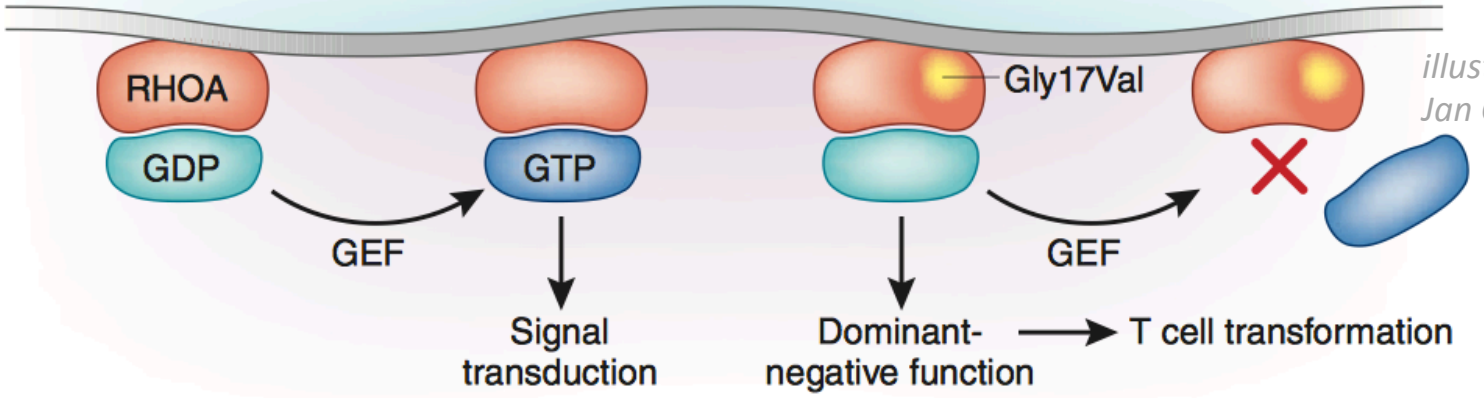
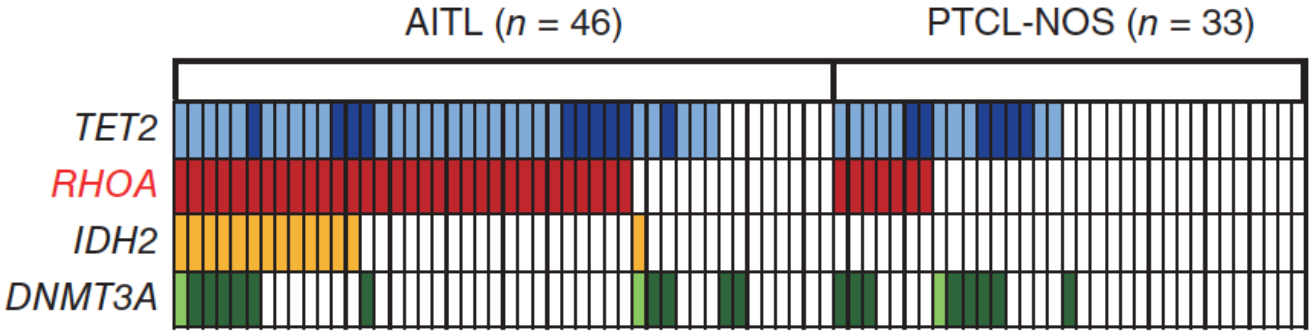


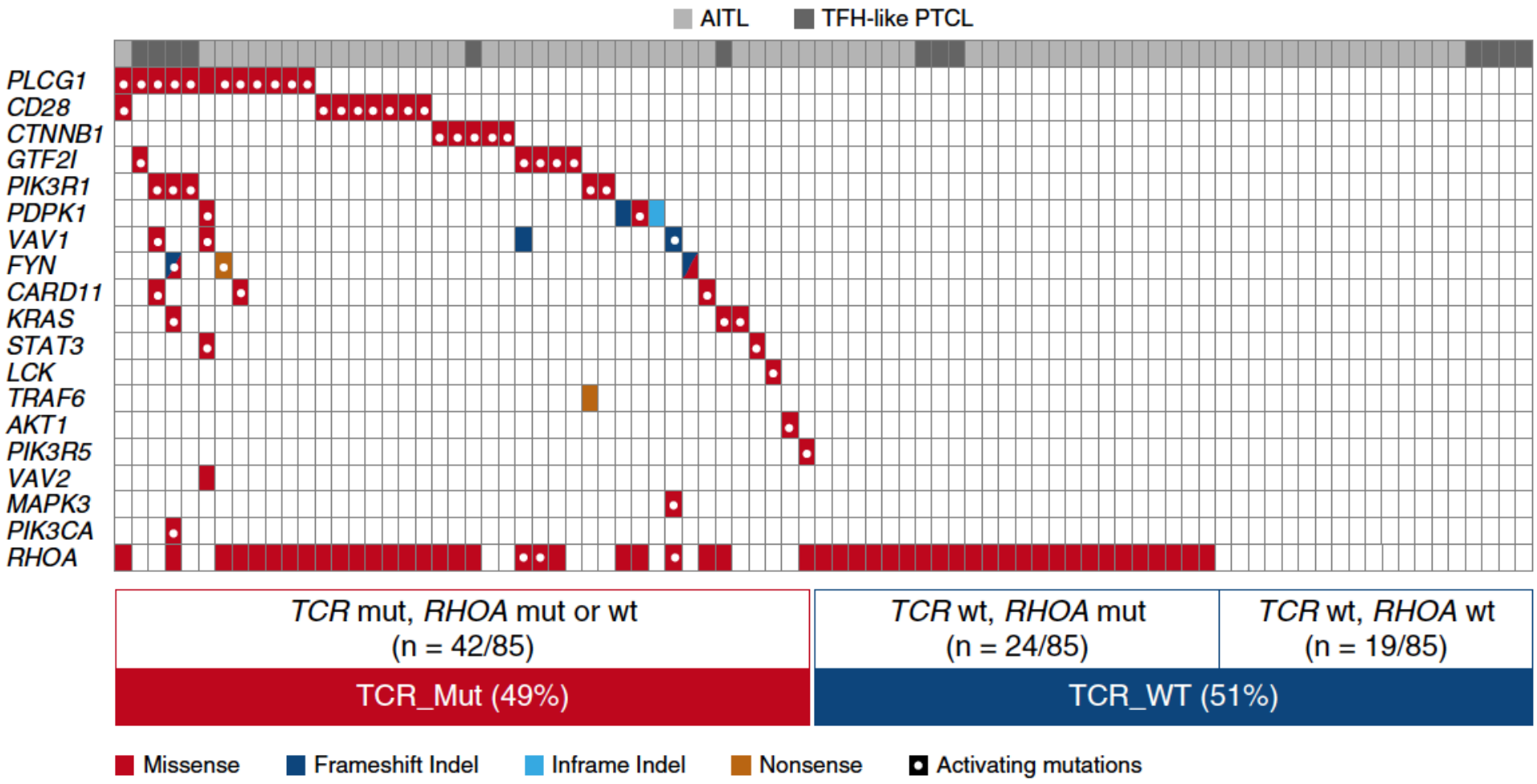
illustration by Jan Cools

- All *RHOA* mutated cases also harbored *TET2* mutations
  - *RHOA* mutations only in tumor cells
  - *TET2* mutations also in non-malignant hematopoietic cells



Sakata-Yanagimoto et al. & Palomero et al., & Yoo et al., Nature Genetics 2014

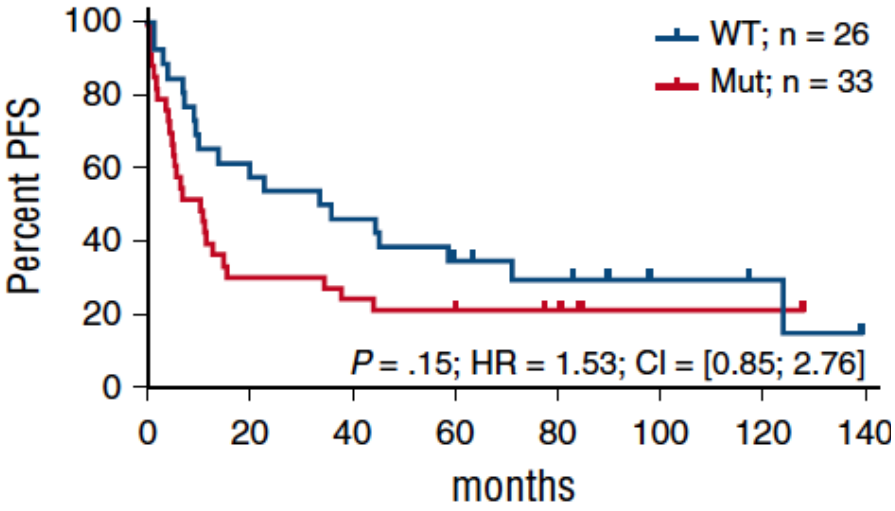
Mutations in TCR signaling-related genes in TFH-derived lymphomas

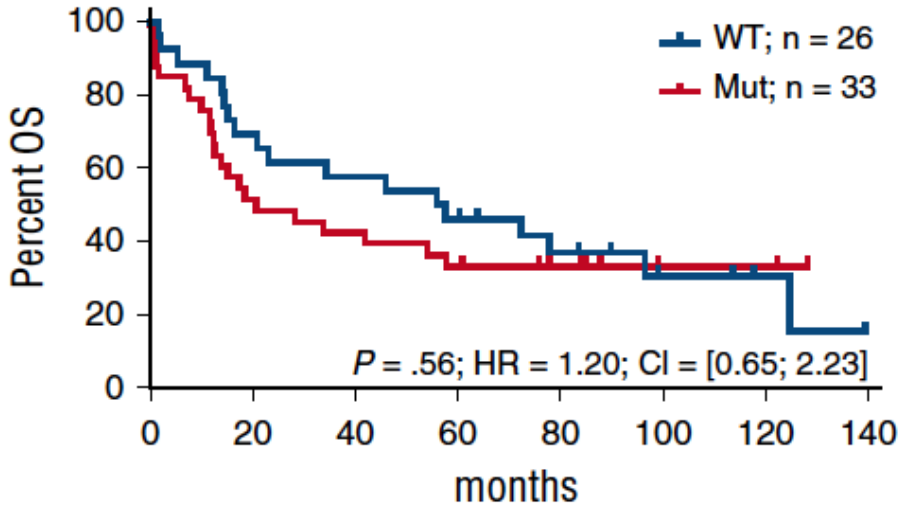


Lee et al., Haematologica 2015; Rohr et al., Leukemia 2016; Vallois et al., Blood 2016

Clinical implication of mutations in TCR signaling-related genes?

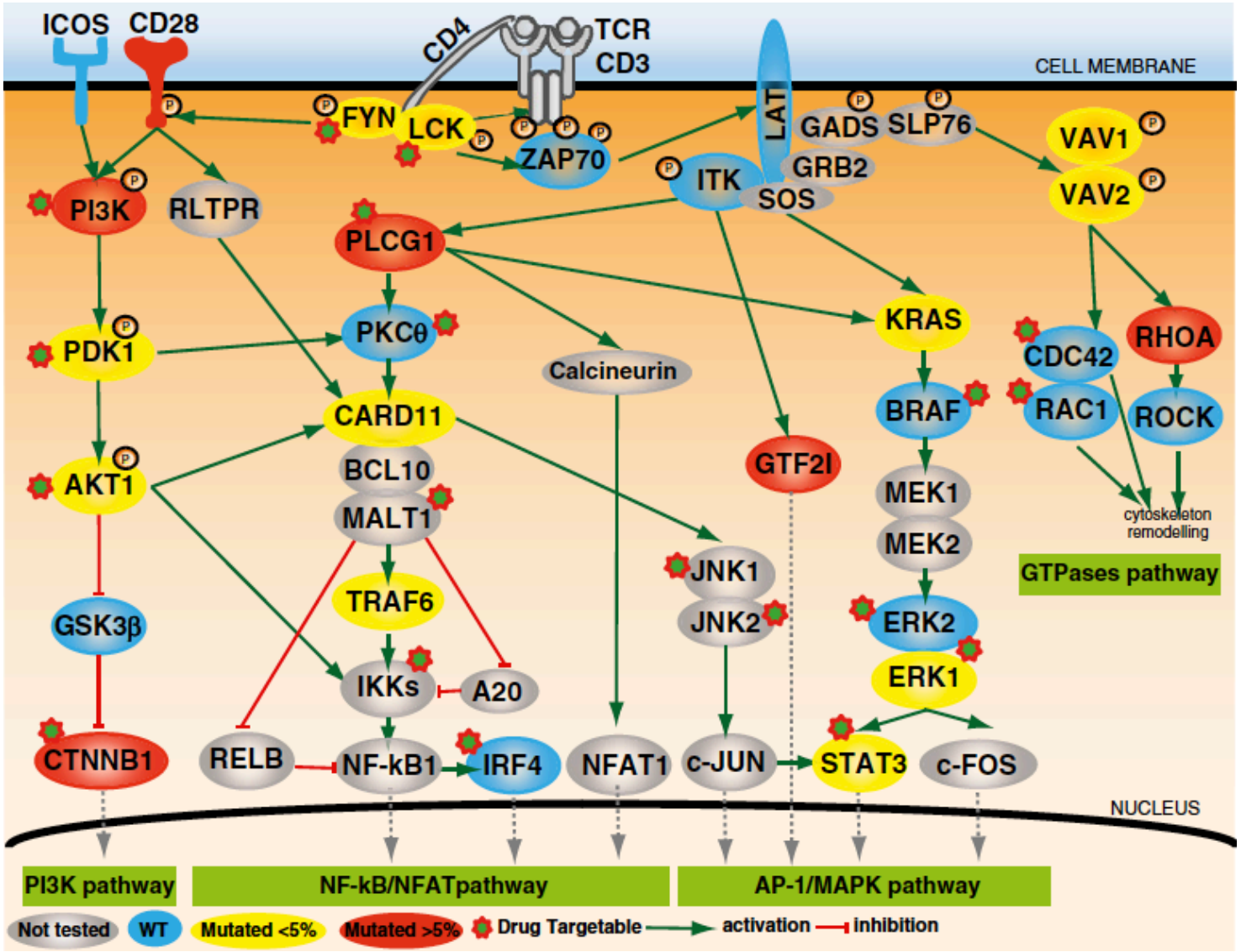
- **Mutations associated with**
  - ↑ TCR signaling and proliferative activity (by GSEA)
  - ↑ early treatment failure (< 6 months) after anthracyclin-based treatment





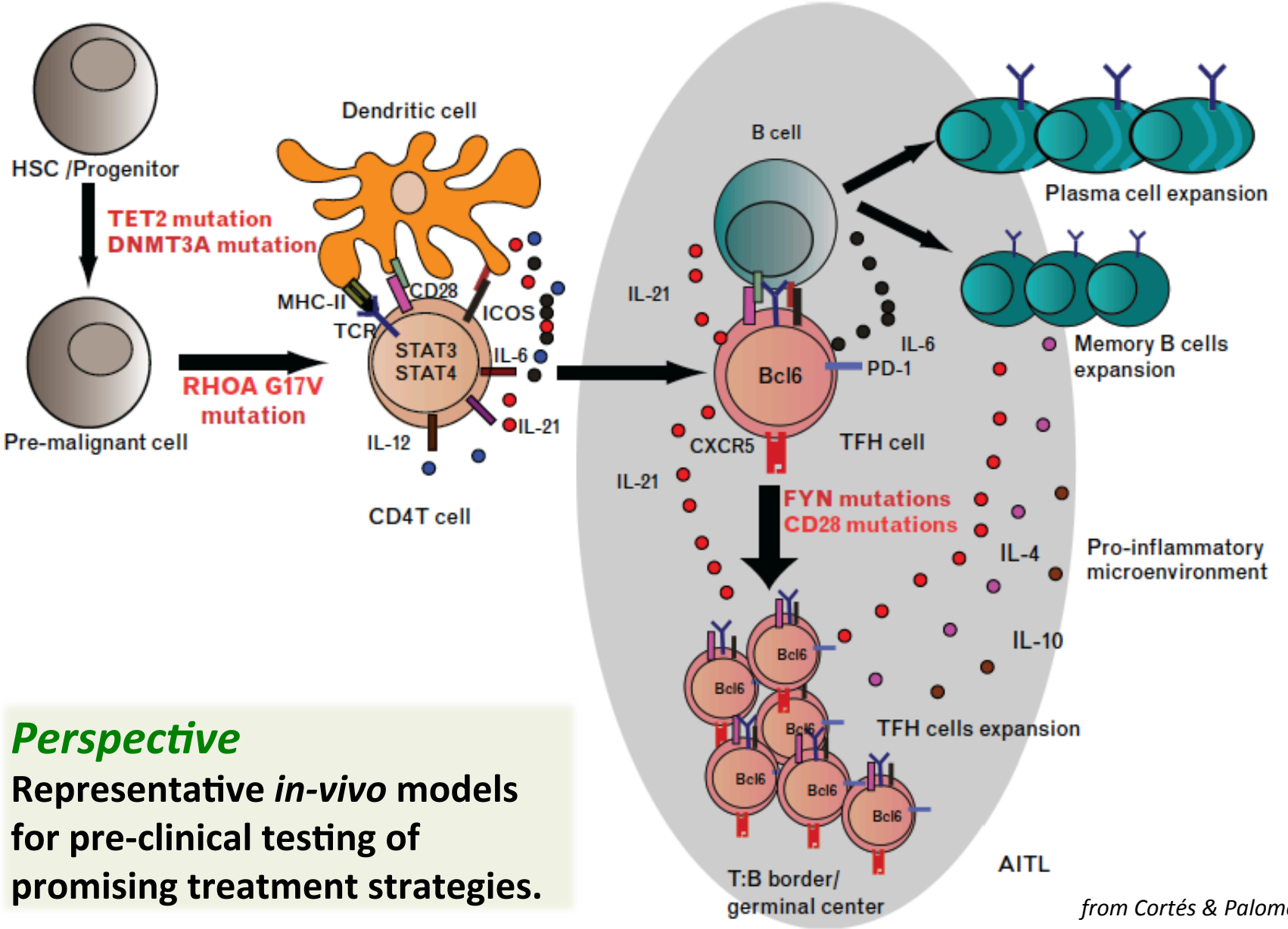
Vallois et al., Blood 2016

Overview: TCR signaling-related gene mutations



Vallois et al., Blood 2016

Summary: Current model of lymphomagenesis of AITL



Perspective

Representative *in-vivo* models for pre-clinical testing of promising treatment strategies.

from Cortés & Palomero, 2016

https://db.bio-m.org/upload/job/13488/datei/2016-K-0367.pdf

http://www.klinikum.uni-muenchen.de/Stellenanzeigen/download/medizin/Doktorand_-Med_-III_-06_12_16.pdf