Unmet challenges in high risk hematological malignancies: from benchside to clinical practice

Scientific Board:
Marco Ladetto (Alessandria)
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Torino Incontra Centro Congressi

UNIVERSITÀ DEL PIEMONTE ORIENTALE

The BIOLOGY of HIGH RISK CLL

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Disclosures

Roche (Advisory Board)

Janssen (Advisory Board)

Gilead (Advisory Board)

Amgen (Advisory board; research support)

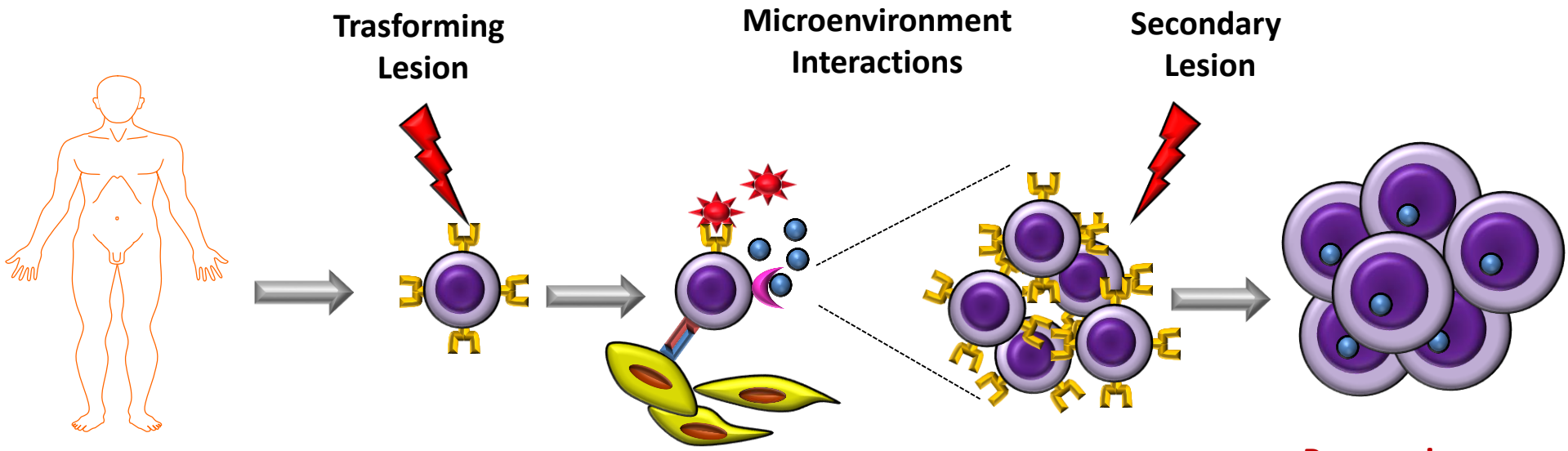
Morphosys (Advisory Board)

Abbvie (Advisory Board)

Outline

- **The genetic landscape of CLL**
- Molecular prognosticators of CLL
- Molecular predictors of CLL
- Richter syndrome biomarkers
- Novel biomarkers

Pathogenesis of CLL



Predisposition

Polygenic
IRF4
IRF8
MYC
Other

Initiation

del13q
+12
MYD88

Promotion/Accumulation

Signaling pathways
BCR
NF-kB
TLR
CD38
VLA-4 integrins
NOTCH
CXCR4

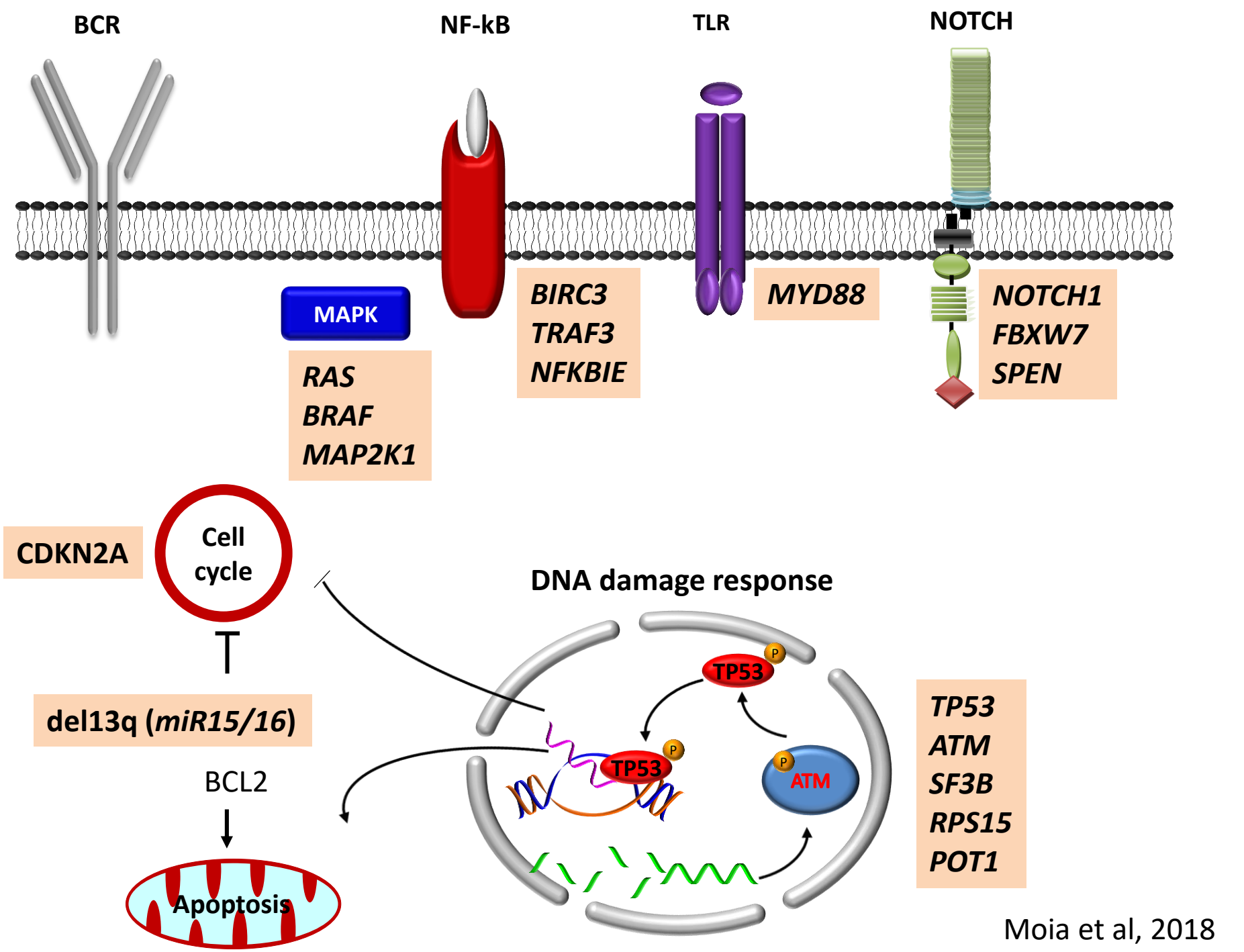
Progression Chemorefractoriness Transformation

TP53
NOTCH1
SF3B1
BIRC3
ATM
MYC
CDKN2A

CLL is genetically heterogeneous and lacks disease defining genetic lesions

- **One of the tumor with the lowest background mutation load (0.6 per Mb)**
- **No unifying gene mutations**
- ***TP53*, *NOTCH1*, *SF3B1*, *ATM* mutated in >5% CLL**

The wordcloud shows the genes that are reported as mutated in CLL by the v77 of the Catalogue of Somatic Mutations in Cancer (COSMIC). The size of the font is proportional to the mutation frequency



Moia et al, 2018

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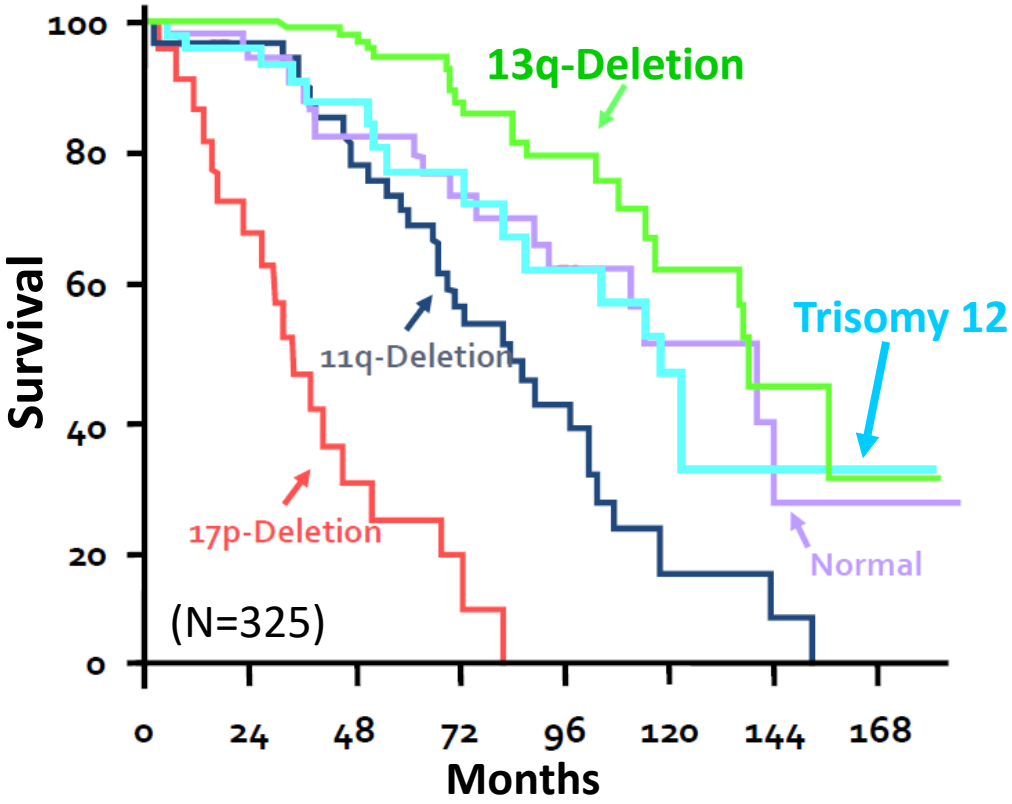
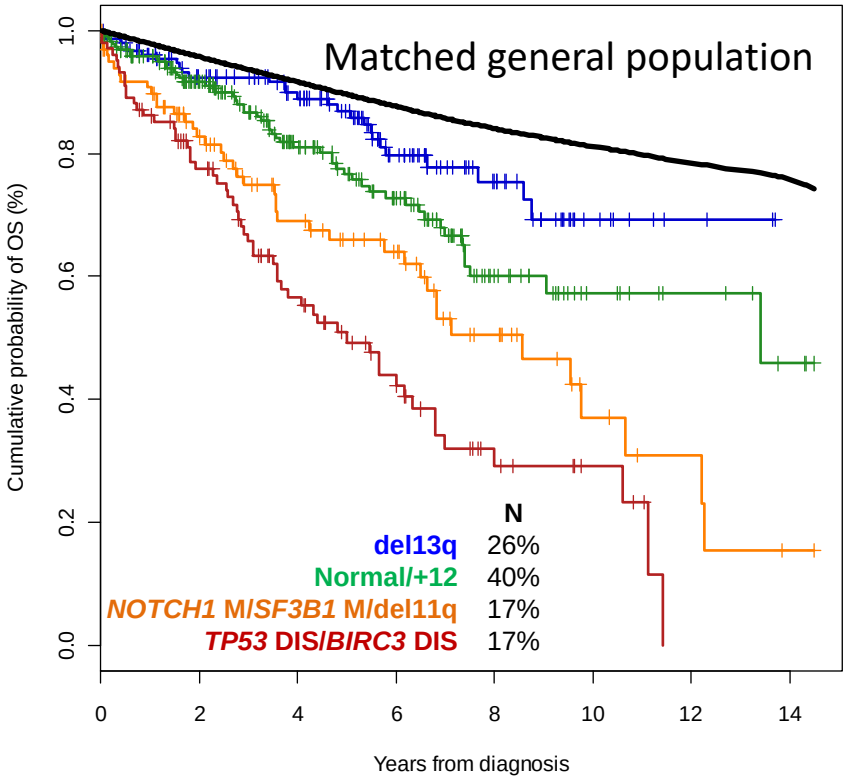
Genetic-based models of CLL prognosis

Cytogenetic model



Mutational- cytogenetic model

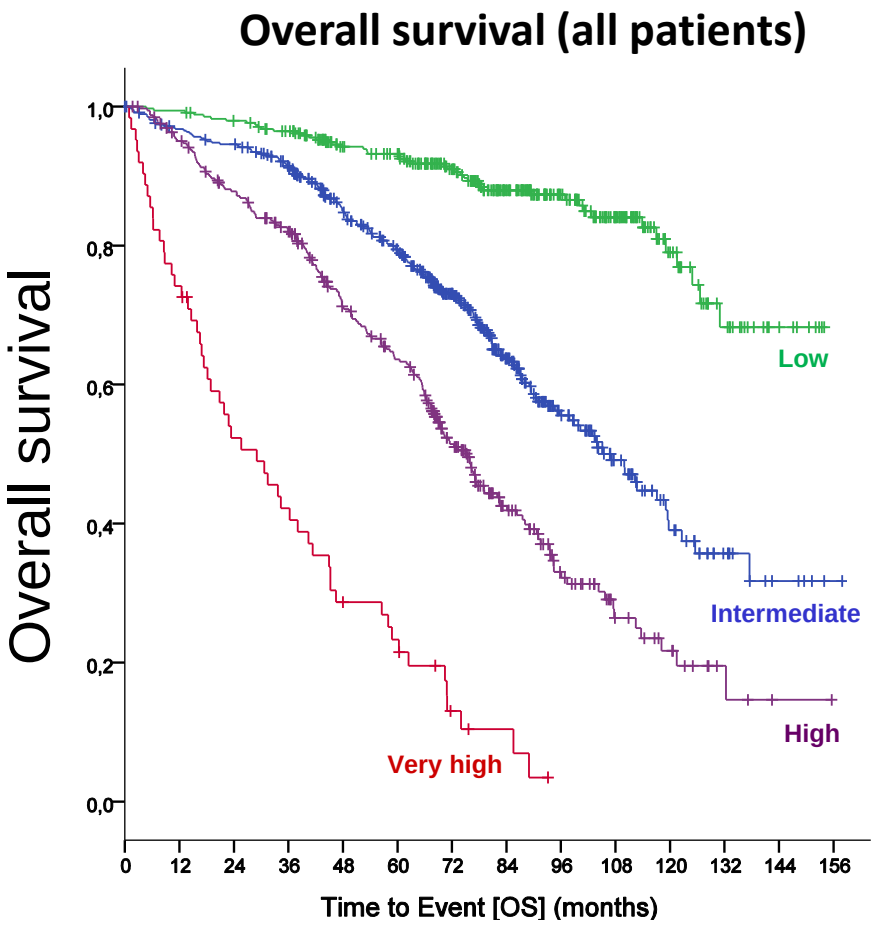


Döhner H, et al. N Engl J Med. 2000
Rossi et al, Blood 2013

CLL-IPI

Variable	Adverse factor	Coeff.	HR	Grading
***TP53* (17p)**	deleted and/or mutated	**1.442**	**4.2**	**4**
***IGHV* status**	Unmutated	**0.941**	**2.6**	**2**
B2M, mg/L	> 3.5	**0.665**	**2.0**	**2**
Clinical stage	Binet B/C **or** Rai I-IV	**0.499**	**1.6**	**1**
Age	> 65 years	**0.555**	**1.7**	**1**
Prognostic Score				**0 – 10**

Risk group	Score	Patients N (%)	5-year OS, %
Low	**0 – 1**	340 (29)	93.2
Intermediate	**2 – 3**	464 (39)	79.4
High	**4 – 6**	326 (27)	63.6
Very High	**7 – 10**	62 (5)	23.3



International CLL-IPI working group. Lancet Oncol 2016

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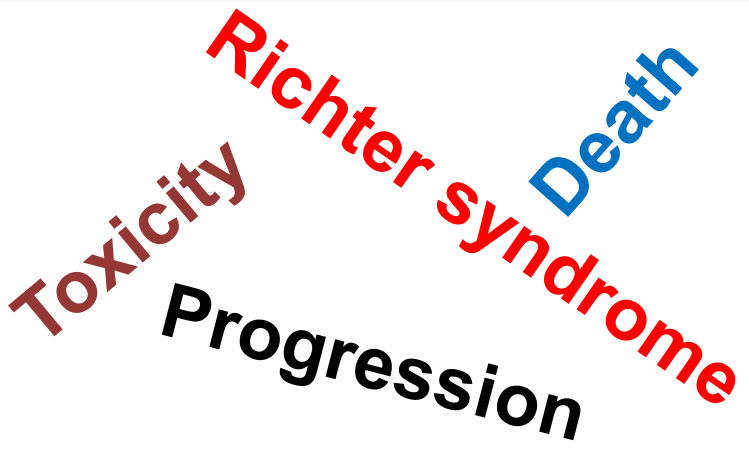
Clinical applications of predictive and prognostic biomarkers in CLL

Predictive biomarkers

Prognostic biomarkers

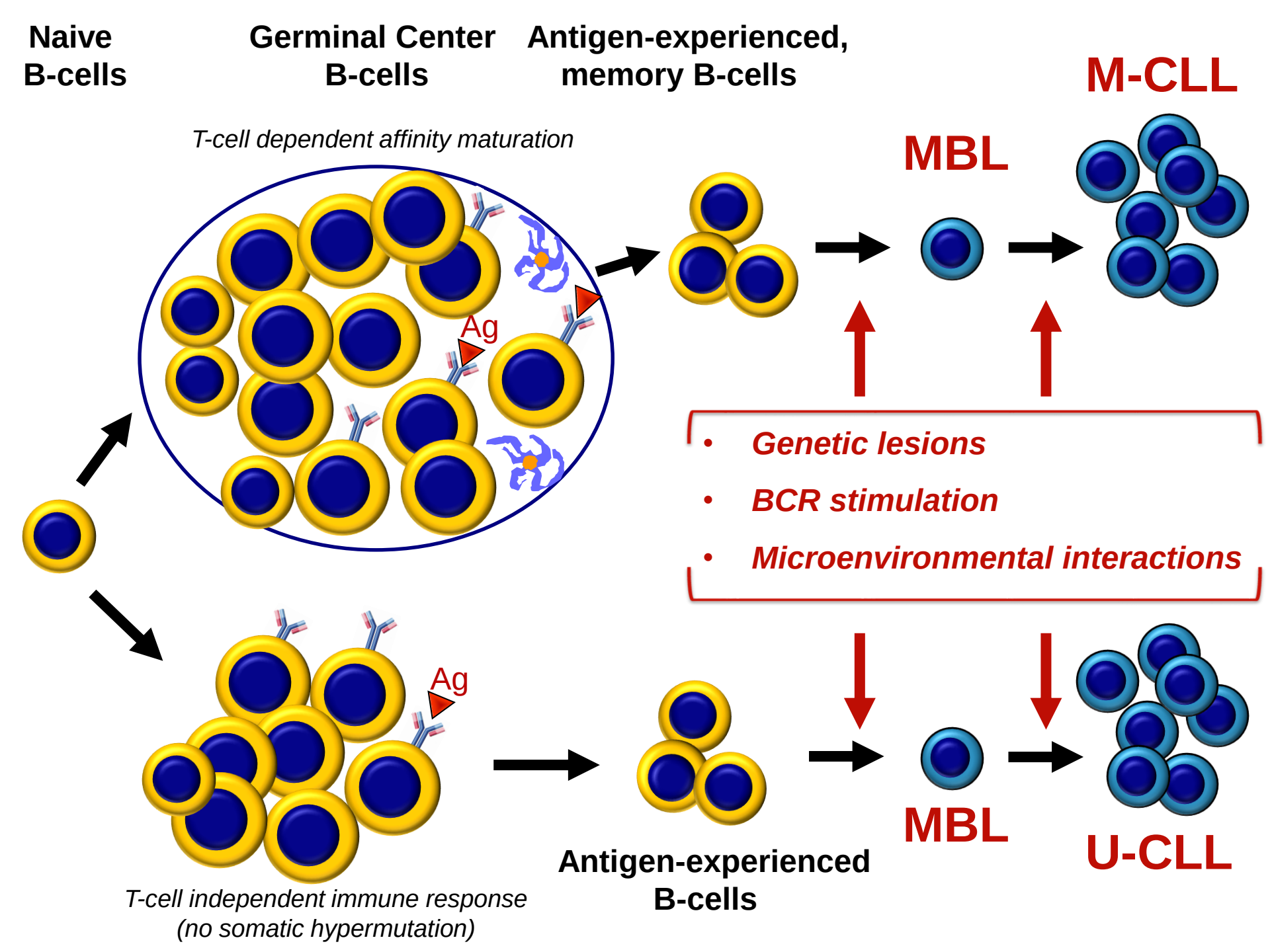


Treatment tailoring

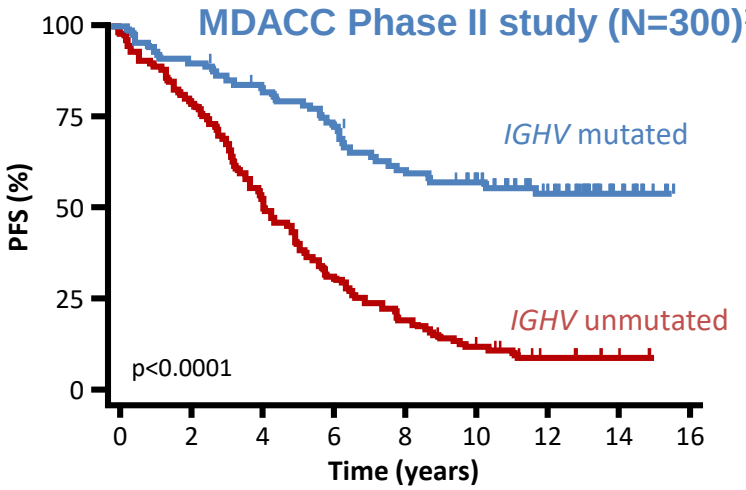
Patient counseling

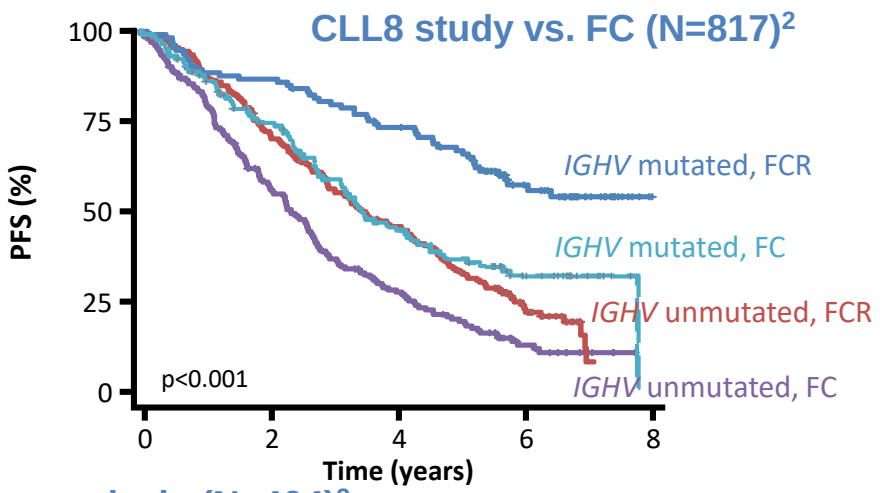
Frequency of follow-up

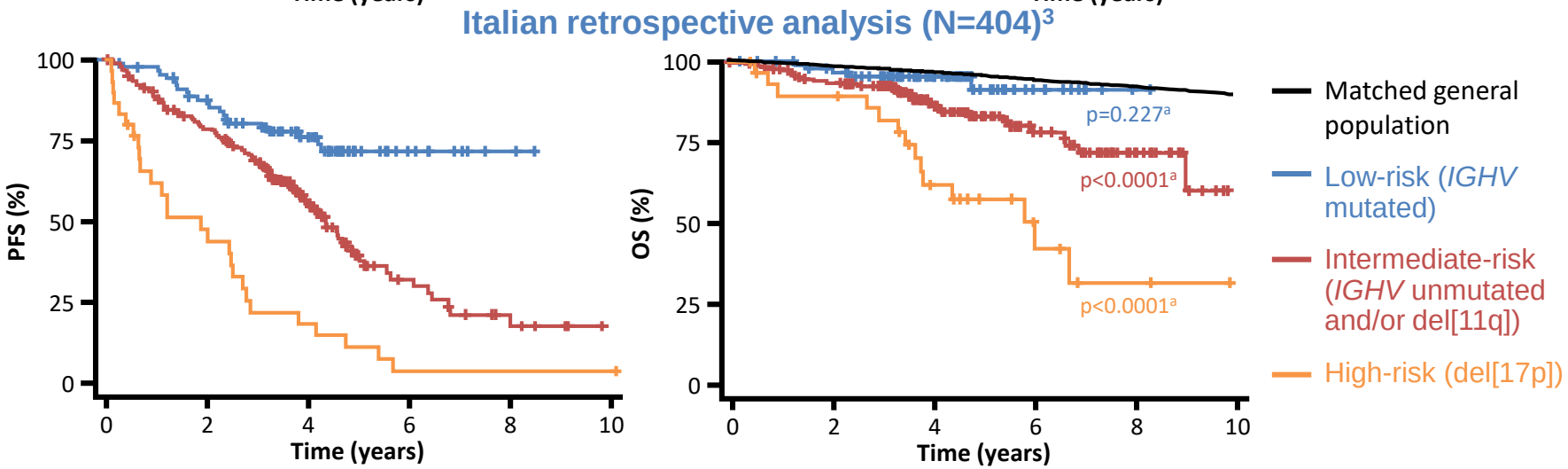
Identify those apropriate for early intervention trials


Naive
B-cells
Germinal Center
B-cells
Antigen-experienced,
memory B-cells
M-CLL
T-cell dependent affinity maturation
MBL
Ag
Genetic lesions
BCR stimulation
Microenvironmental interactions
Ag
MBL
U-CLL
Antigen-experienced
B-cells
T-cell independent immune response
(no somatic hypermutation)

IGHV mutated patients gain the greatest benefit from FCR







[a] p-value vs. matched general population
FCR: fludarabine, cyclophosphamide, rituximab; MDACC: MD Anderson Cancer Center; OS: overall survival; PFS: progression-free survival

1. Thompson PA, *et al. Blood* 2016; 127:303–309. 2. Fischer K, *et al. Blood* 2016; 127:208–215. 3. Rossi D *et al. Blood* 2015; 126 1921–1924.

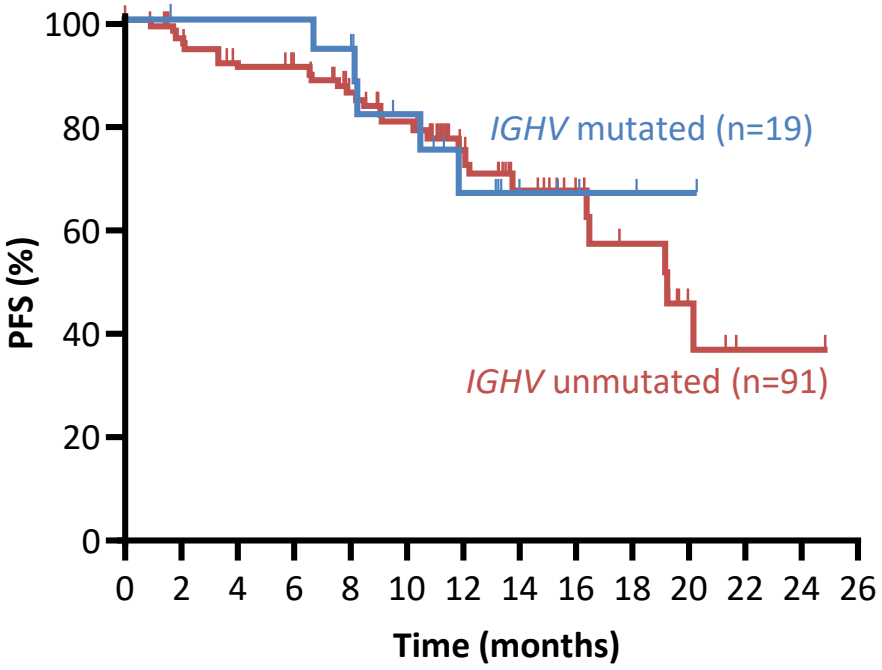
Guideline recommendations for *IGHV* analysis in clinical practice

	Recommendation	When
iwCLL	Not generally indicated	-
BCSH	Not recommended	-
NCCN	Not generally indicated	-
ESMO	Desirable	Before treatment

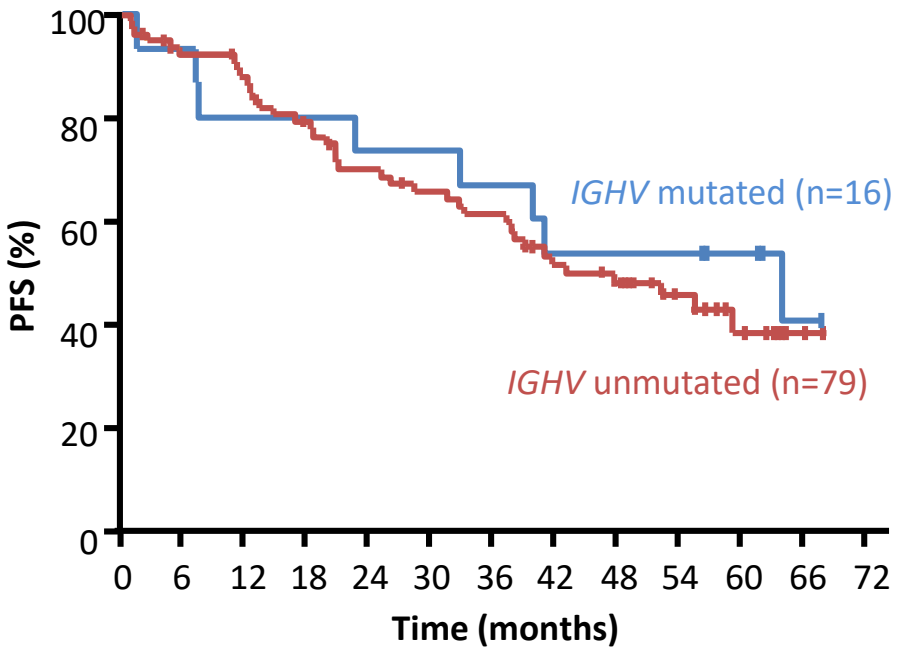
Hallek et al. Blood. 2008;
Oscier et al. Br J Haematol. 2013
Zelenetz et al J Natl Cancer Inst 2015
Eichhorts et al, Ann Oncol 2015.

BCRi are efficacious regardless of *IGHV* status

Analysis of idelalisib-treated patients with R/R CLL from Phase III Study 116/117

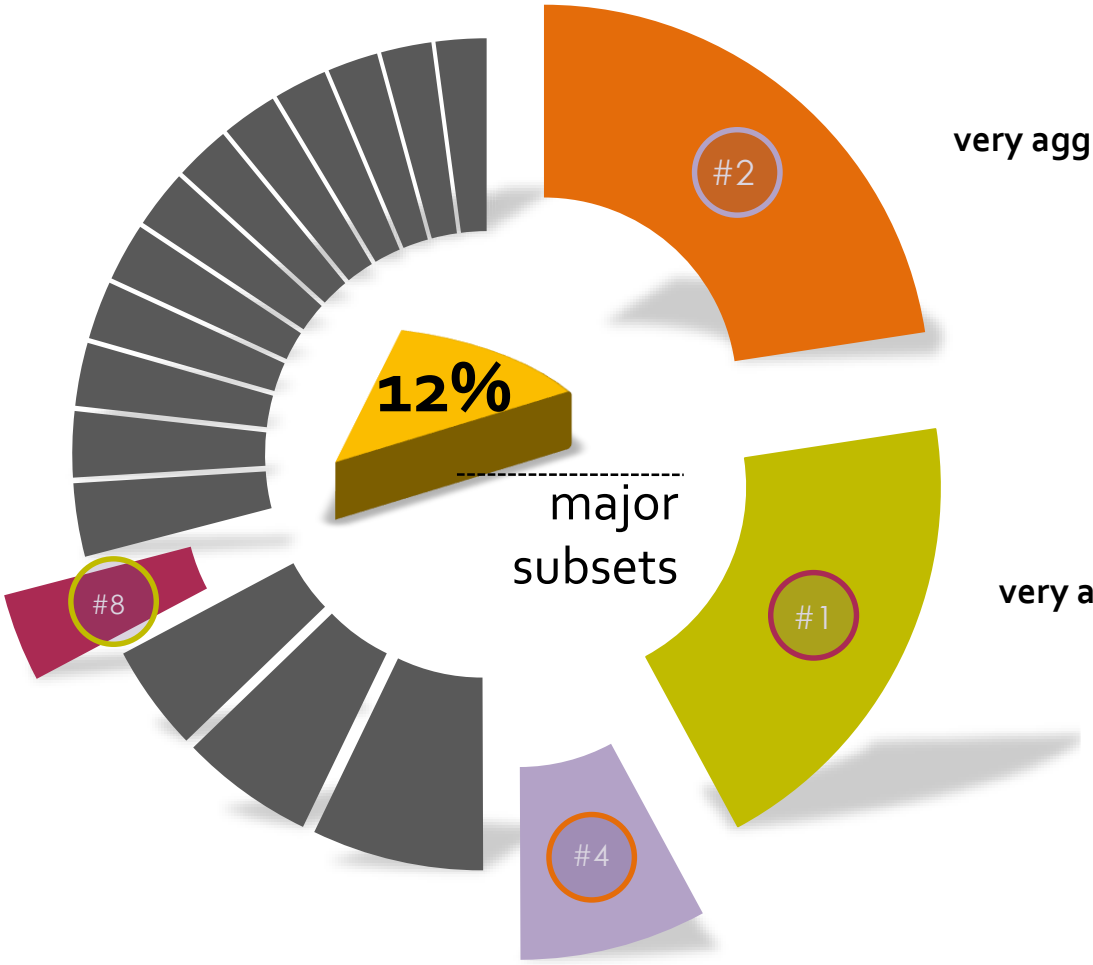


Analysis of ibrutinib-treated patients with R/R CLL/SLL from Phase Ib/II Study PCYC-1102/1103



Sharman JP, *et al.* ASH 2014, #330; O'Brien S, *et al*. ASH 2016, #233

Major stereotyped subsets represent distinct CLL variants



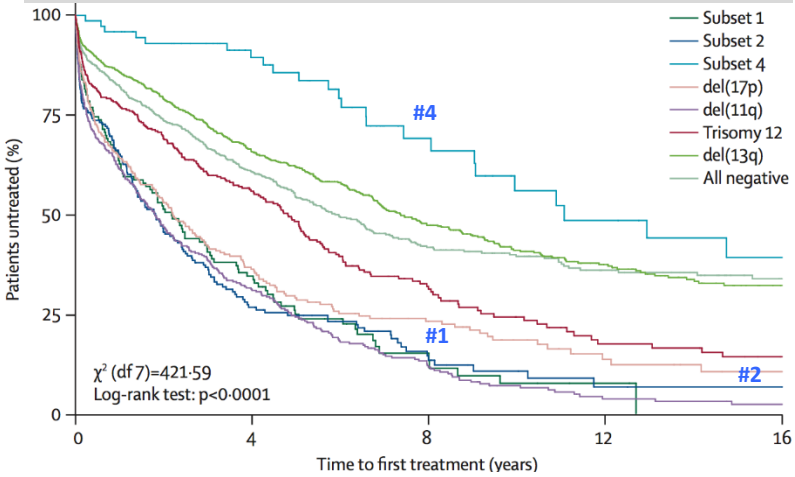
Tobin et al. Blood 2003; Ghiotto et al. J Clin Invest 2004; Stamatopoulos et al. Blood 2007; Chu et al. Blood 2008; Catera et al. Mol Med 2008; Rossi et al. Clin Cancer Res 2009; Sutton et al. Blood 2009; Chu et al. Blood 2010; Marincevic et al. Haematologica 2010; Maura et al. PLosOne 2011; Ntoufa et al. Mol Med 2012; Agathangelidis et al. Blood 2012; Strefford et al. Leukemia 2013; Rossi et al. Blood 2013; Papakonstantinou et al Mol Med 2013; Vardi et al. Clin Cancer Res 2013; Sutton et al. Mol Med 2014; Mansouri et al. J Exp Med 2015

Courtesy of K Stamatopoulos

BcR stereotypy refines prognostication in CLL

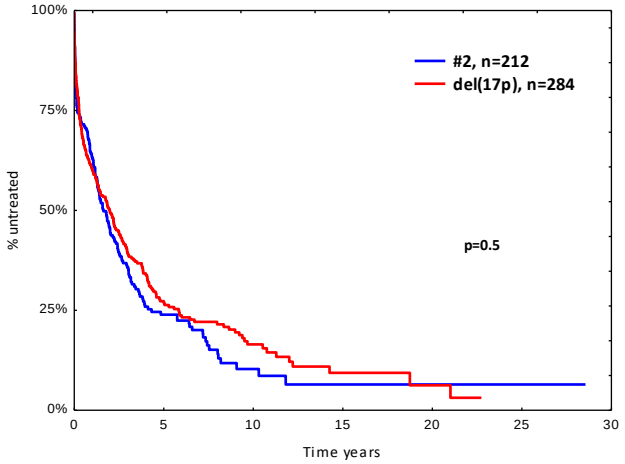
Distinct clinical outcomes for subsets #1, #2 and #4, independently of genomic aberrations or SHM status

Baliakas et al. Lancet Haematol. 2014



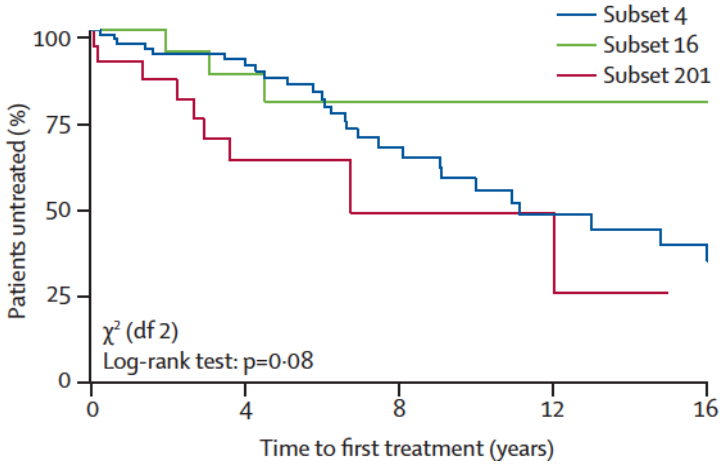
Subset #2 is as bad as CLL with TP53 aberrations though essentially devoid of such lesions

Baliakas et al. Blood 2015



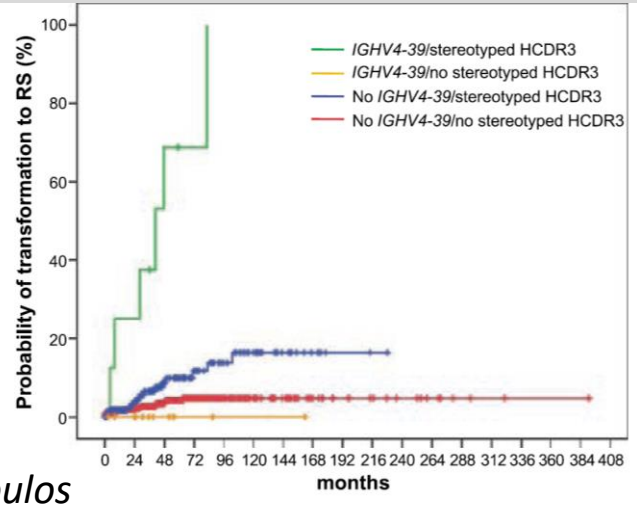
All express IGHV4-34, all concern IG mutated CLL, yet the outcome is different

Xochelli et al. Clin Cancer Res 2017



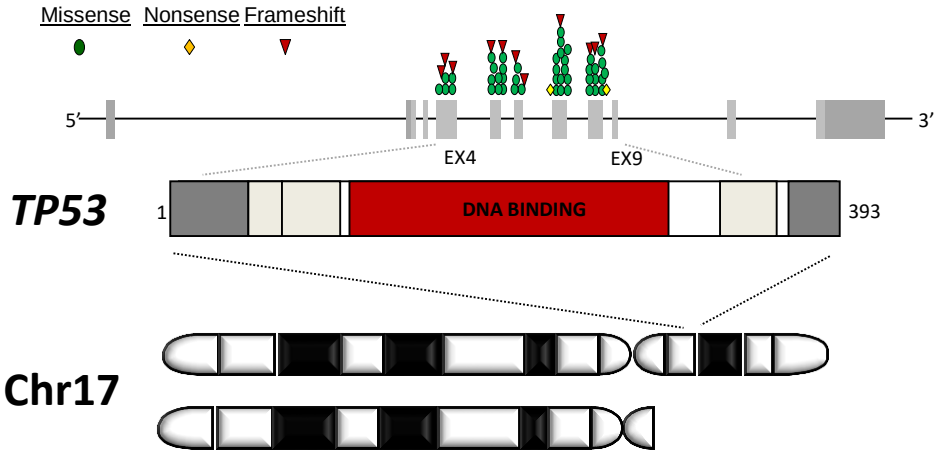
Subset #8: the highest risk for Richter's transformation amongst all CLL

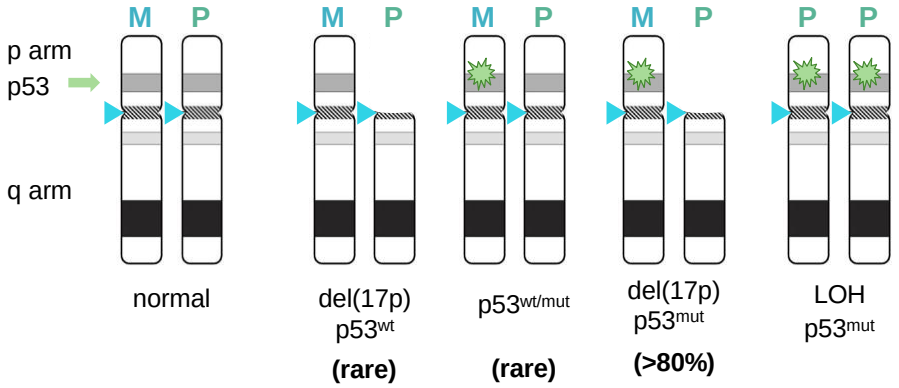
Rossi et al. Clin Cancer Res. 2009

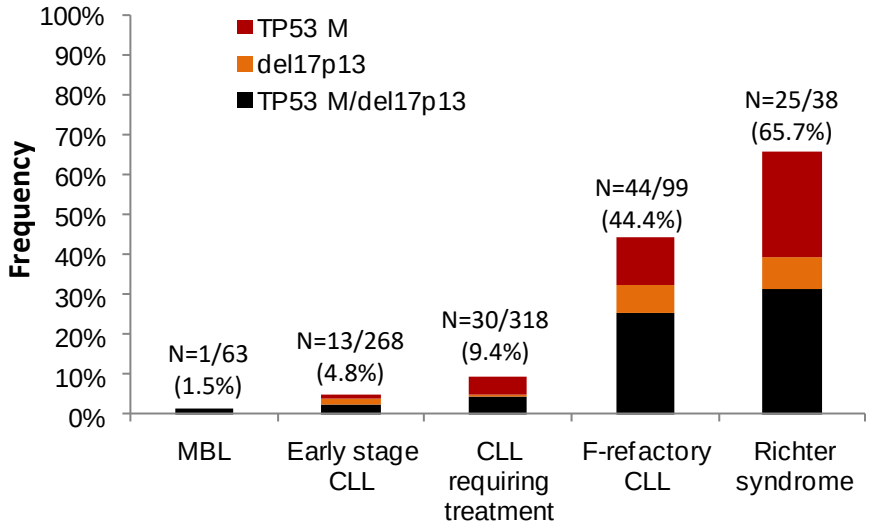


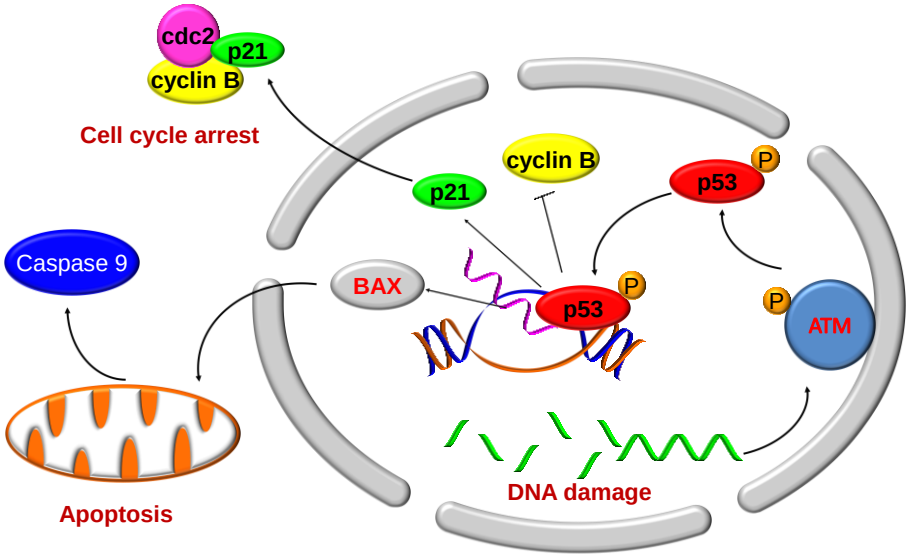
Courtesy of K Stamatopoulos

TP53 abnormalities in CLL



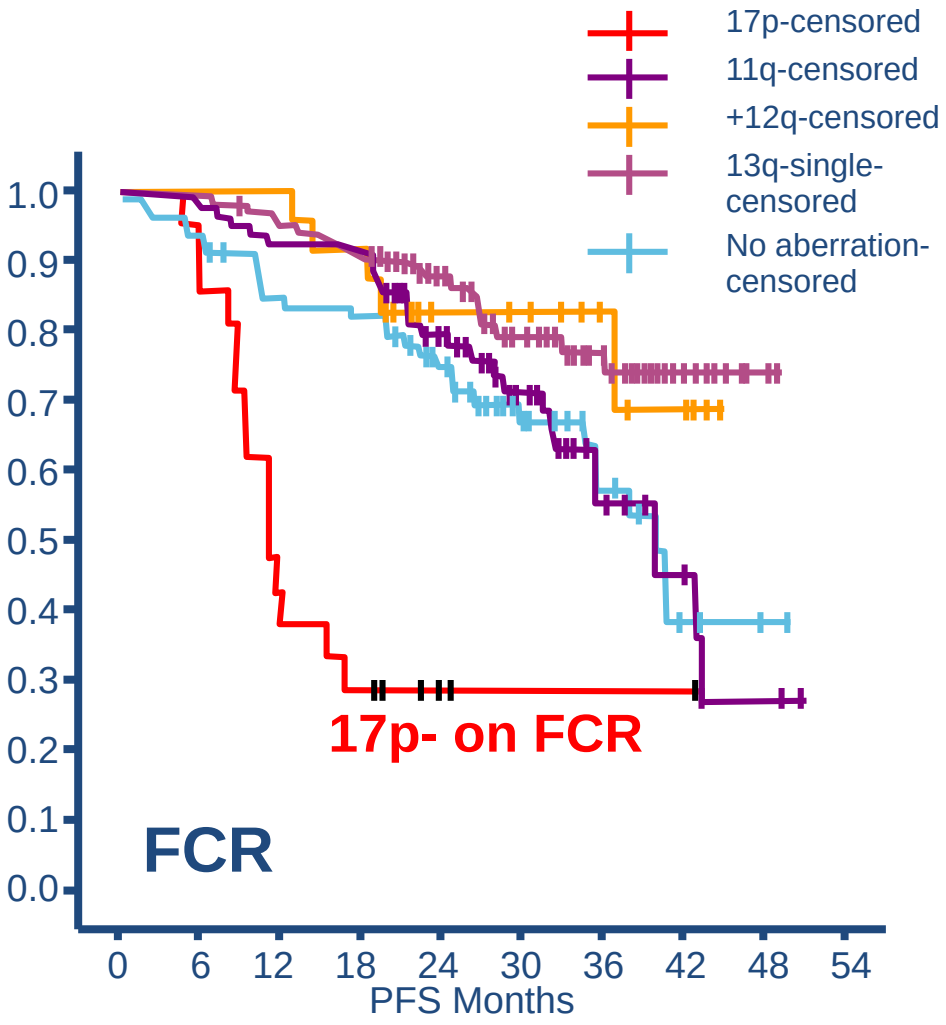




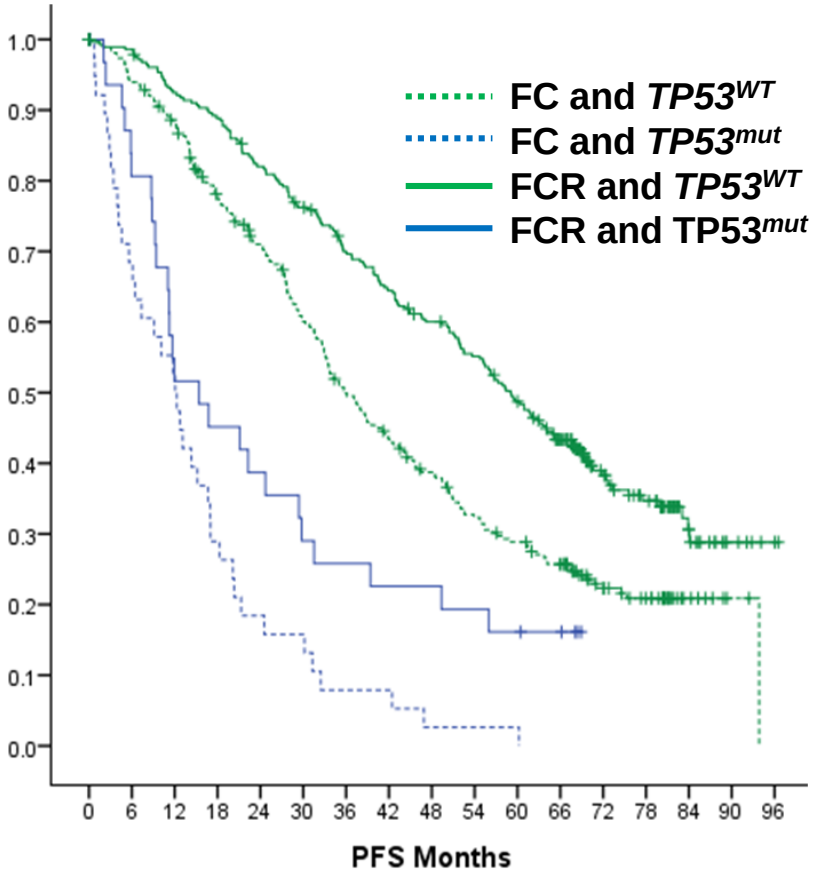


Dohner et al, New Engl J Med 2000 ; Rasi et al, Haematologica 2012; Zainuddin et al, Leuk Res 2011; Zenz et al J Clin Oncol 2010;Rossi et al Blood 2011; Rossi et al Blood 2014

TP53 abnormalities in CLL



Hallek et al, Lancet 2010

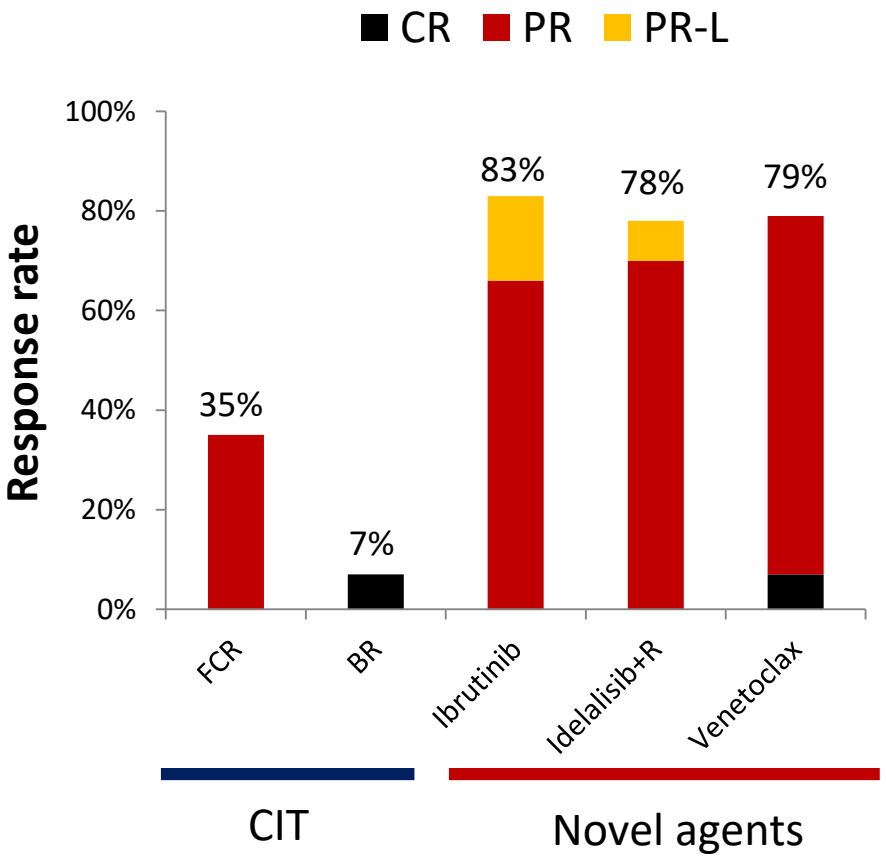


Stilgenbaueret al, Blood 2014

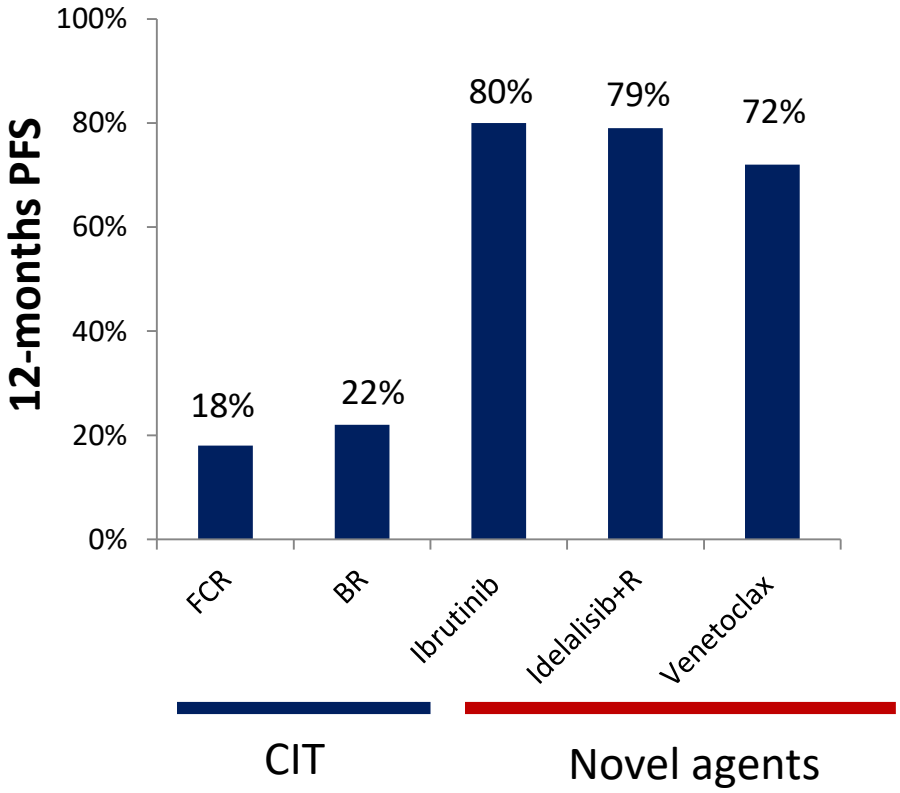
Chemoimmunotherapy (CIT) vs novel agents in *TP53* disrupted CLL

Relapsed/Refractory CLL

Response rate



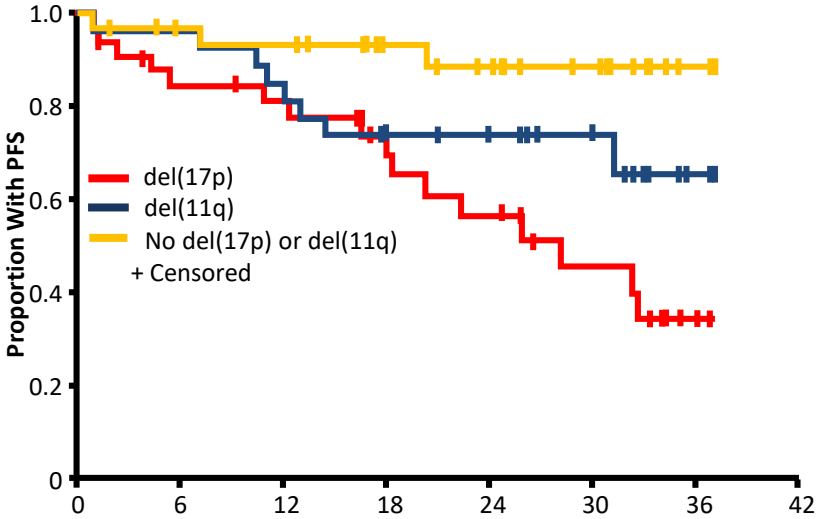
PFS



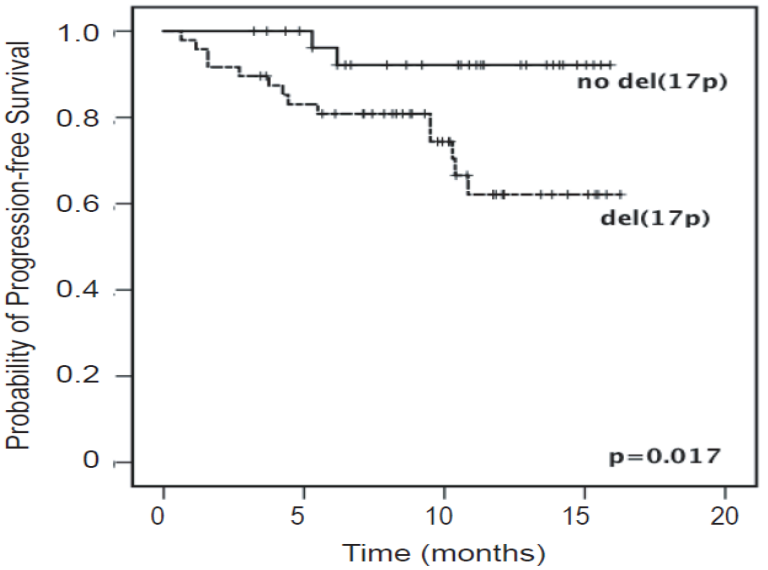
Badoux Blood 2011; Fisher J Clin Oncol 2011; O'Brien, ASH 2014; Sharman ASH 2014; Byrd ASH 2015; Stilgenbauer, ASH 2015

TP53 disruption is a prognostic biomarker in CLL treated with novel agents

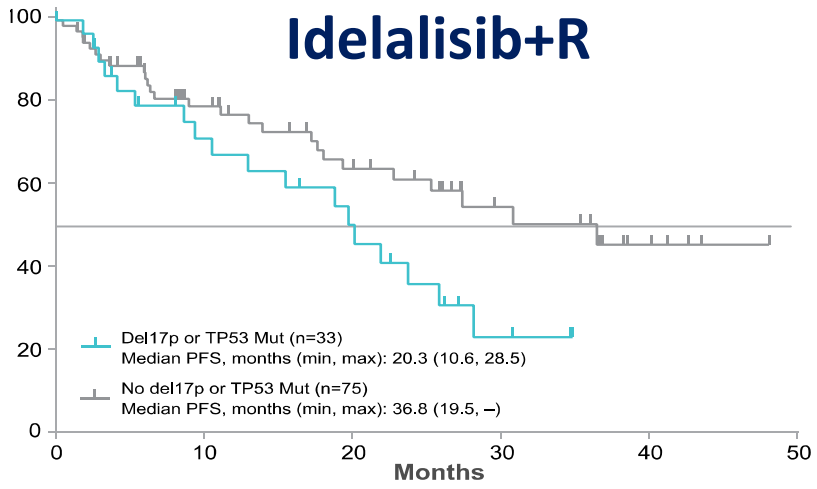
Ibrutinib in trials



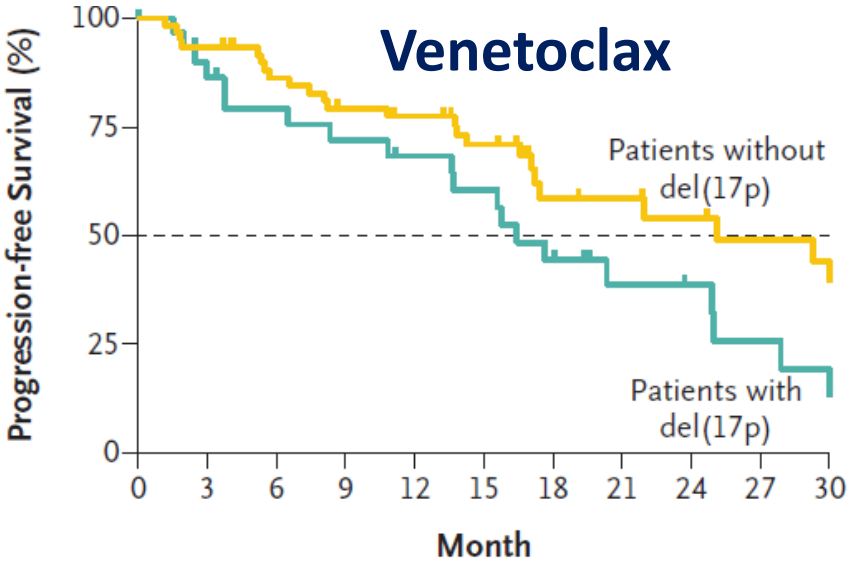
Ibrutinib in real-world practice



Idelalisib+R



Venetoclax



Byrd JC, Blood 2015; Thompson PA, Cancer 2015; Winqvist M, Haematologica 2016; Barrientos, ASCO,2015, 7011; Roberts, et al New Engl J Med 2016

Guideline recommendations for *TP53* analysis in clinical practice

	When	What
iwCLL	Before treatment	17p deletion
ERIC	Before treatment	*TP53* mutation
BCSH	Before treatment	17p deletion and *TP53* mutation
NCCN	Before treatment	17p deletion and *TP53* mutation
ESMO	Before treatment	17p deletion and *TP53* mutation

Hallek et al. Blood. 2008;
Oscier et al. Br J Haematol. 2013
Pospisilova et al. Leukemia. 2012
Zelenetz et al J Natl Cancer Inst 2015
Eichhorts et al, Ann Oncol 2015.

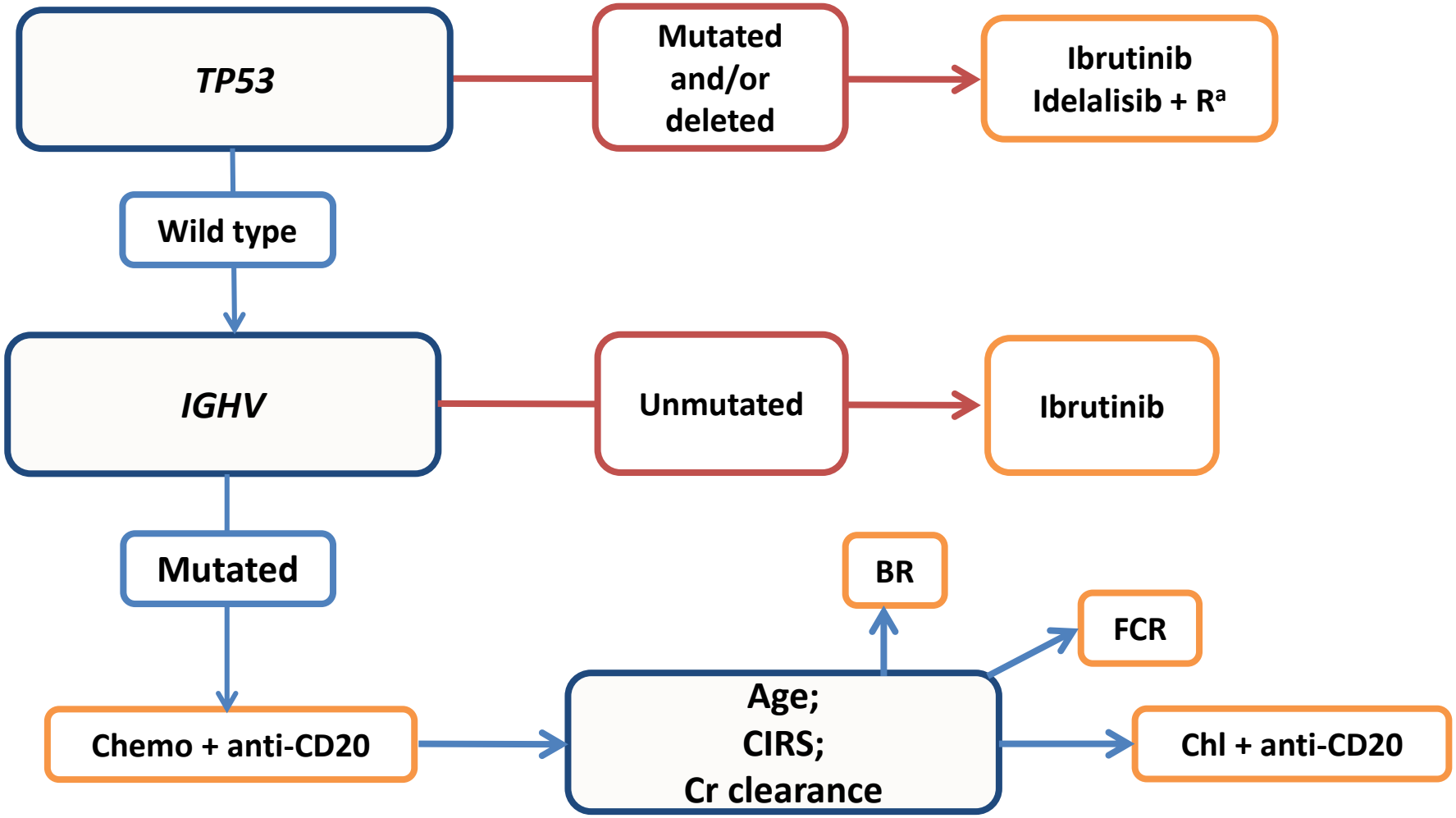
Harmonization of *TP53* mutation analysis

european research initiative on CLL

TP53 Guidelines
TP53 Network
TP53 Certification
TP53 Manual

http://www.ericll.org/pages/networks/tp53network/ericmanualfortp53mutationalanalysis/!

Biomarkers may inform first line treatment



[a] In patients who are not eligible for any other therapies
Chl: chlorambucil; CIRS: Cumulative Illness Rating Scale; Cr: creatinine

Personal view

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- The genetic landscape of CLL
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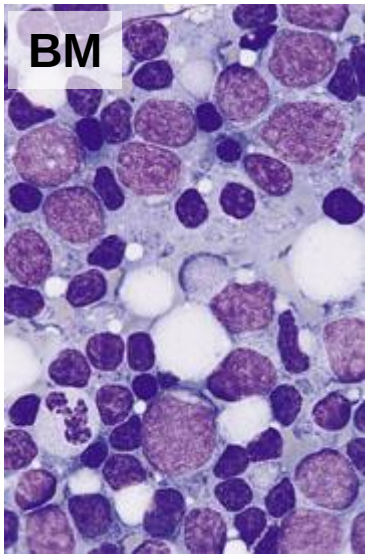
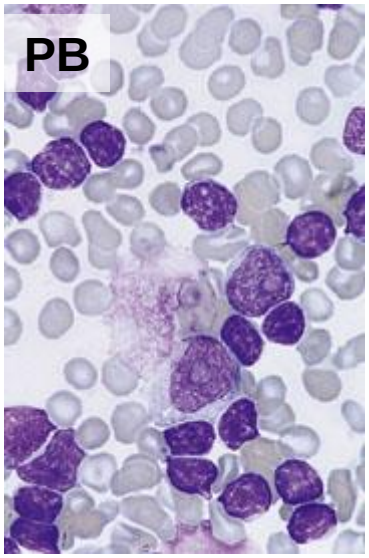
- Novel biomarkers

Clinical clues of Richter transformation

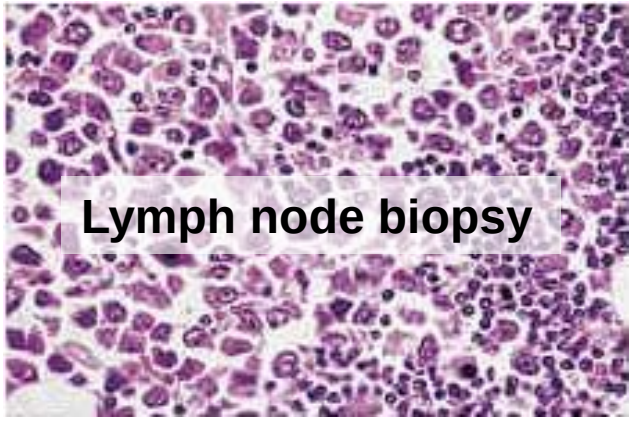
Clinical suspicion of RS

- Bulky disease
- Extranodal involvement
- B symptoms
- High LDH

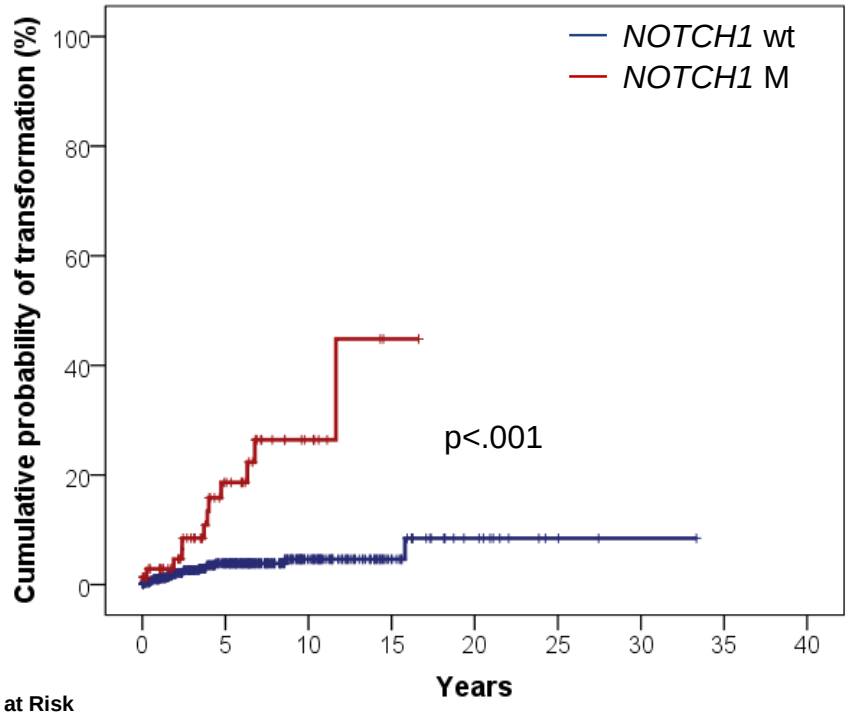




BIOPSY IS MANDATORY (PET-guided)

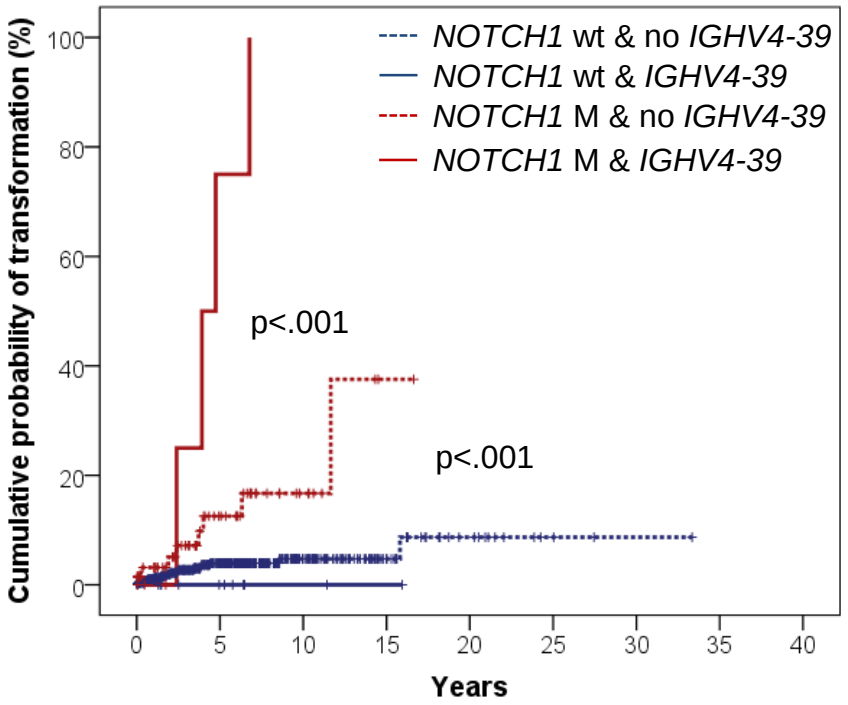


Risk of Richter transformation according to *NOTCH1* mutation status and IGHV usage at CLL diagnosis



No. at Risk									
NOTCH1 wt	531	279	92	31	11	3	1	0	0
NOTCH1 M	74	28	8	1	0	0	0	0	0

	Events	Total	5-year risk	95% CI
NOTCH1 wt	18	531	3.9%	2.0-5.8
NOTCH1 M	12	74	18.6%	7.3-29.9



No. at Risk									
NOTCH1 wt & no *IGHV4-39*	519	273	90	30	11	3	1	0	0
NOTCH1 wt & *IGHV4-39*	12	12	12	12	0	0	0	0	0
NOTCH1 M & no *IGHV4-39*	67	27	8	1	0	0	0	0	0
NOTCH1 M & *IGHV4-39*	7	1	0	0	0	0	0	0	0

	Events	Total	5-year risk	95% CI
NOTCH1 wt & no *IGHV4-39*	18	519	4.0%	2.1-5.9
NOTCH1 wt & *IGHV4-39*	0	12	0	
NOTCH1 M & no *IGHV4-39*	8	67	12.5%	2.9-22.1
NOTCH1 M & *IGHV4-39*	4	7	75.0%	32.5-100

TP53 disruption, *MYC* activation and *CDKN2A* loss contribute to CLL transformation to Richter syndrome

MYC **translocation amplification**

NOTCH1 **mutations**

MYC **activation**

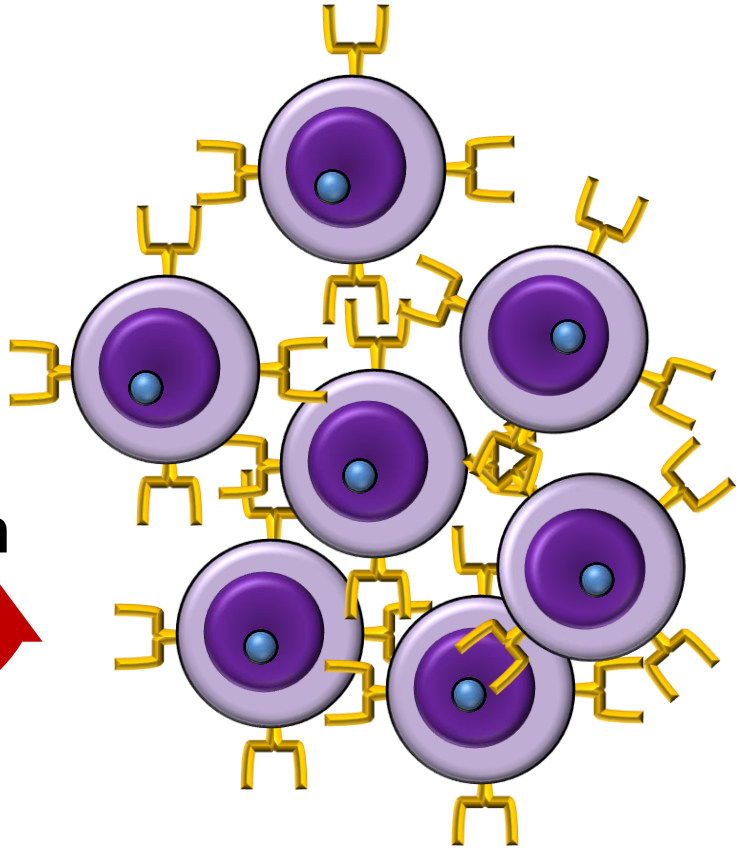
TP53 **disruption**

MGA **mutations**

transformation

CLL

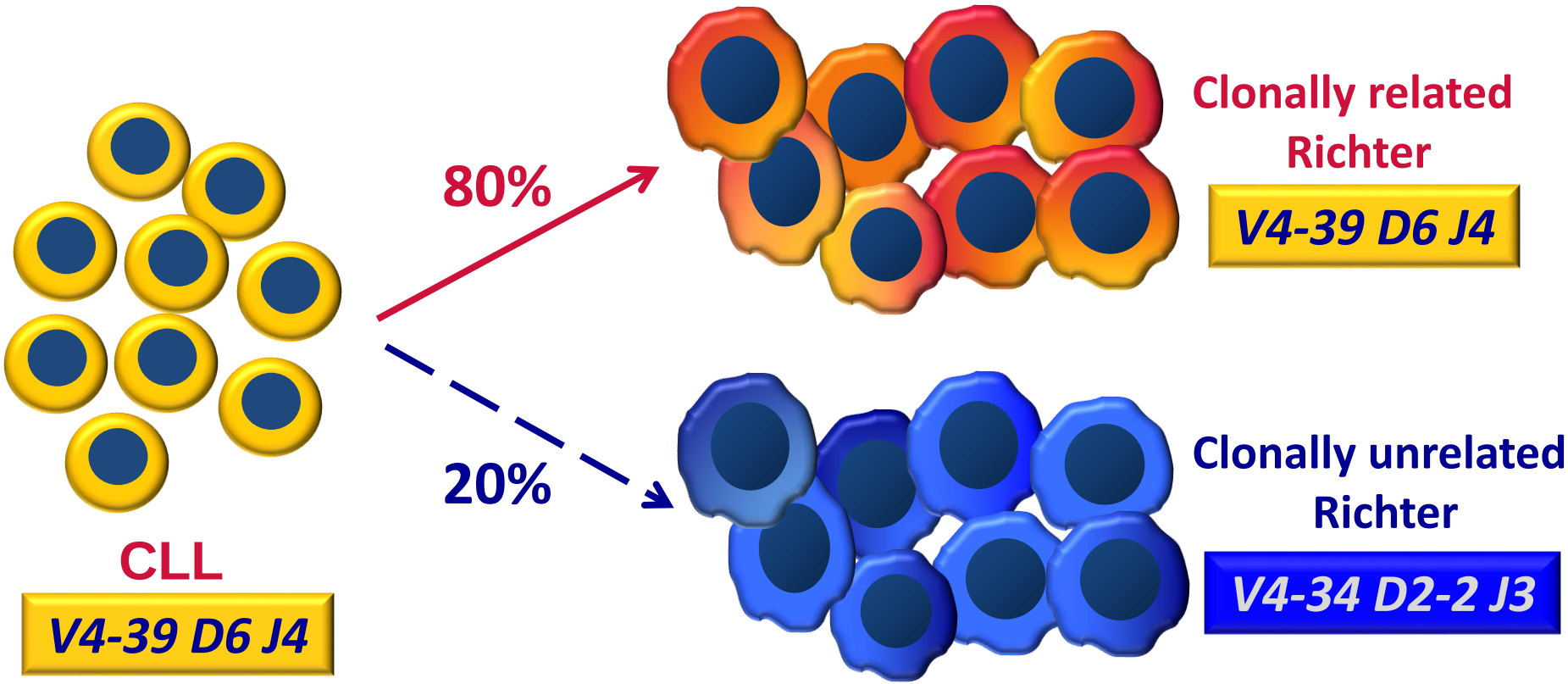
CDKN2A **loss**



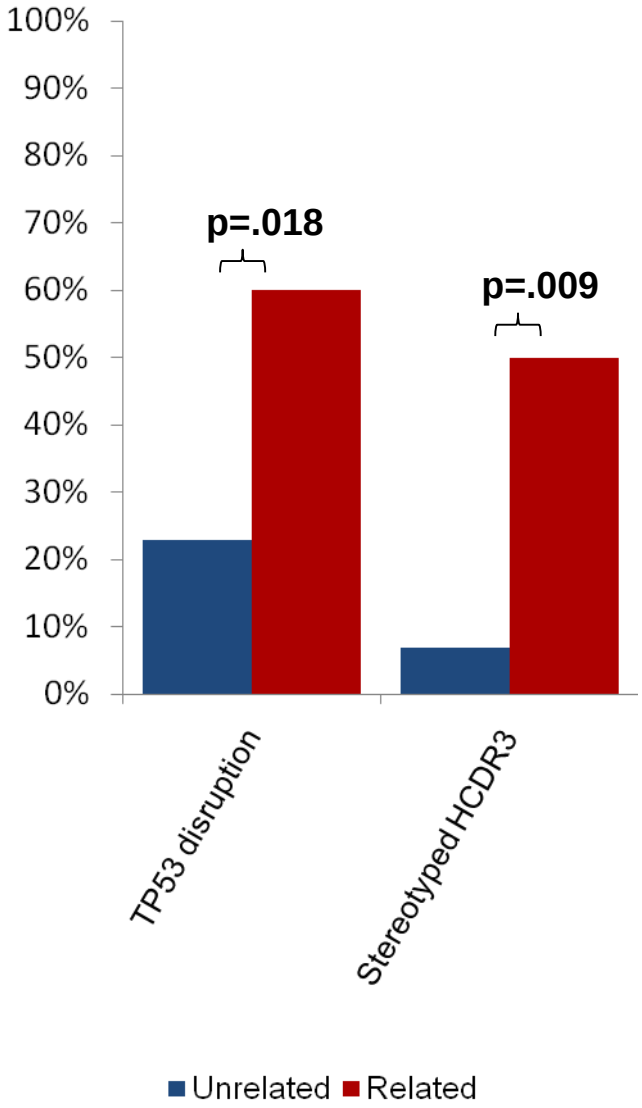
DLBCL (Richter)

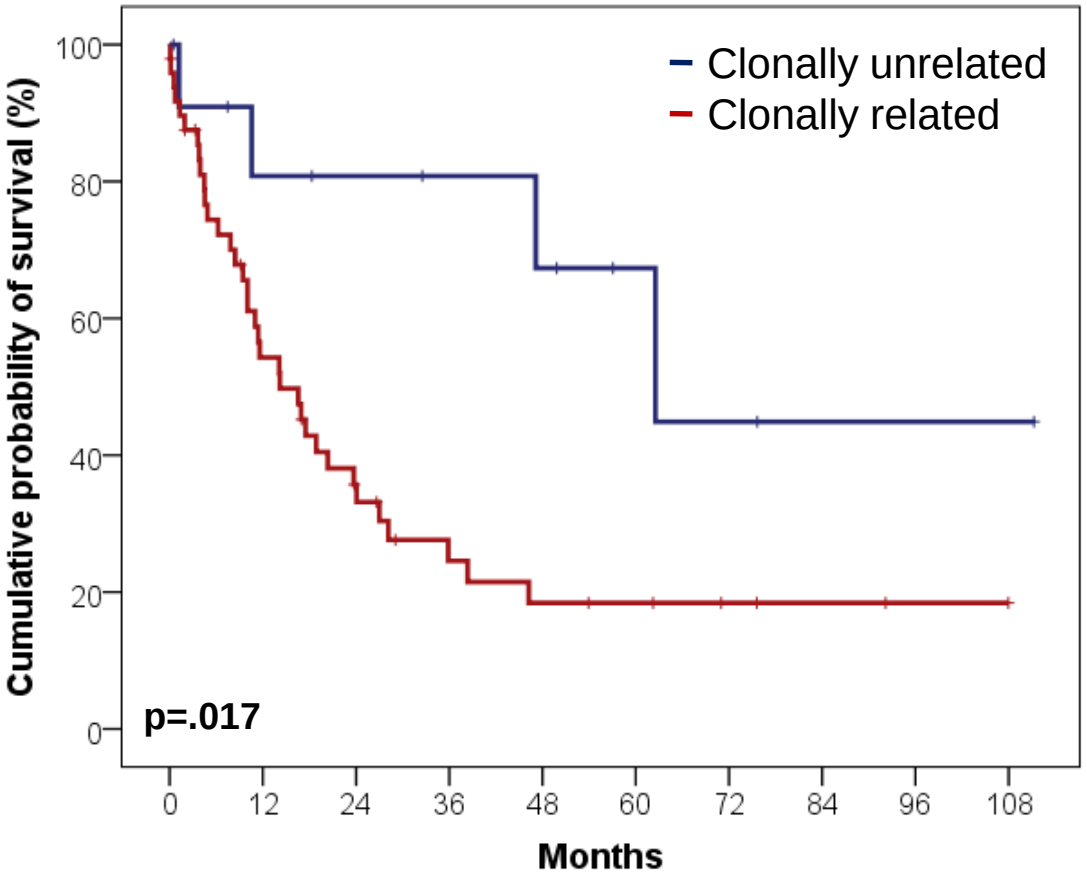
Fabbri, et al. J Exp Med 2011
Rossi, et al. Blood 2011
Rossi, et al. Blood 2012
Rossi, et al. Leuk Lymphoma 2012
Chigrinova et al, Blood, in press

Clonal relationship of Richter syndrome



The genetic profile of clonally unrelated RS differs from that of clonally related RS





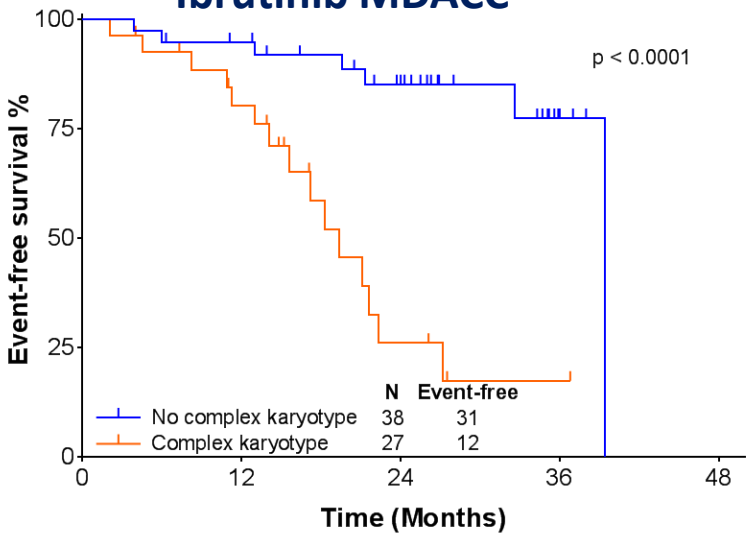
Rossi et al, Blood 2011; Rossi and Gaidano, 2018

Outline

- The genetic landscape of CLL
- Molecular prognosticators of CLL
- Molecular predictors of CLL
- Richter syndrome biomarkers
- **Novel biomarkers**

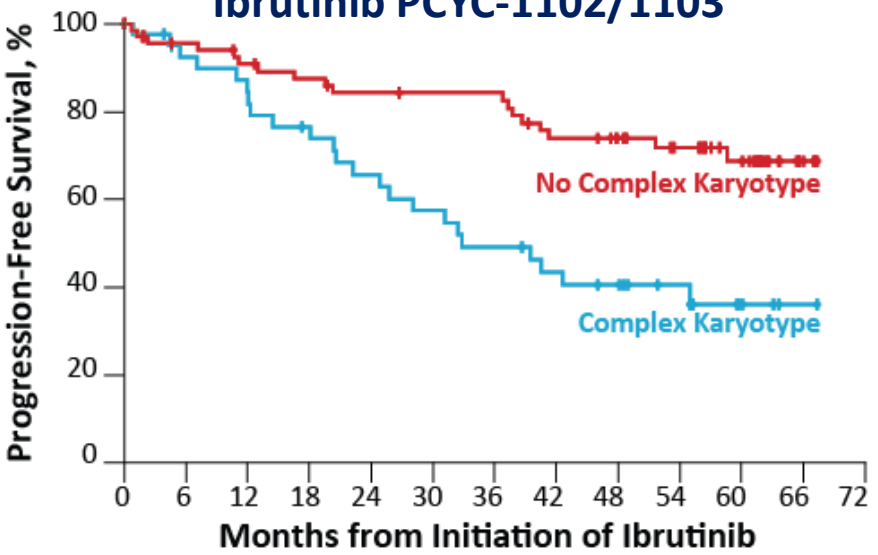
Complex Karyotype in the novel agent era

Ibrutinib MDACC



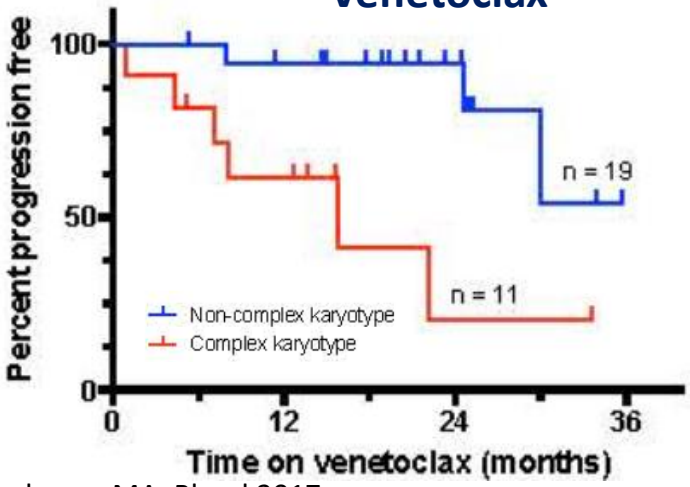
Thompson PA, ASH 2014, Oral Presentation #22

Ibrutinib PCYC-1102/1103



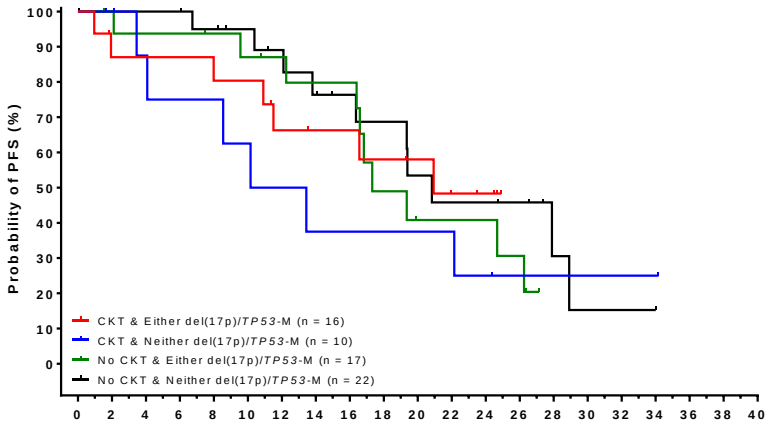
O'Brien S, et al. ASH 2016; 233

Venetoclax



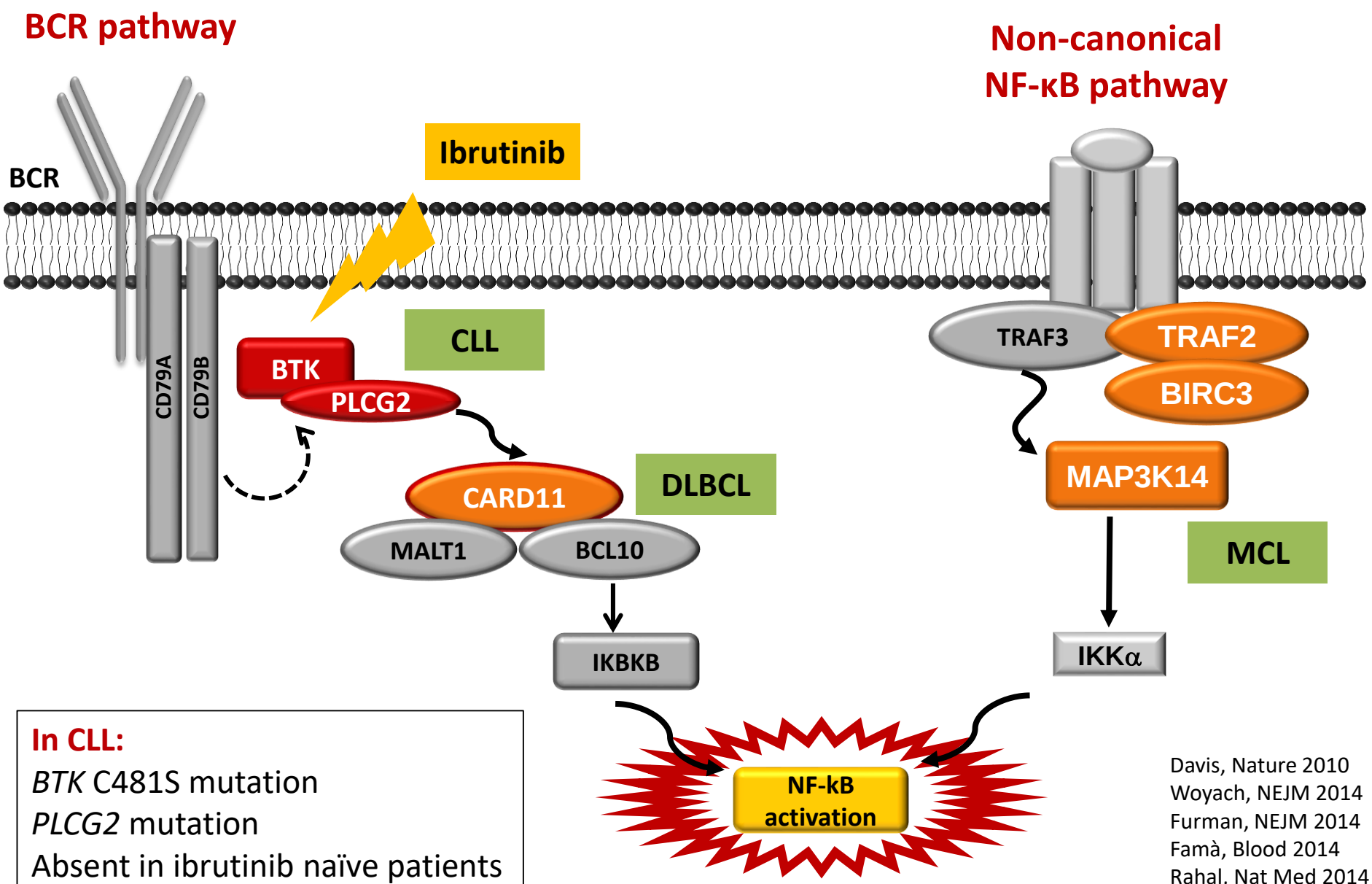
Anderson MA, Blood 2017

Idelalisib-R GS 0116/0117



Kreuzer, et al. Abstract #192, ASH, 2016.

Molecular mechanisms of resistance to ibrutinib



In CLL:

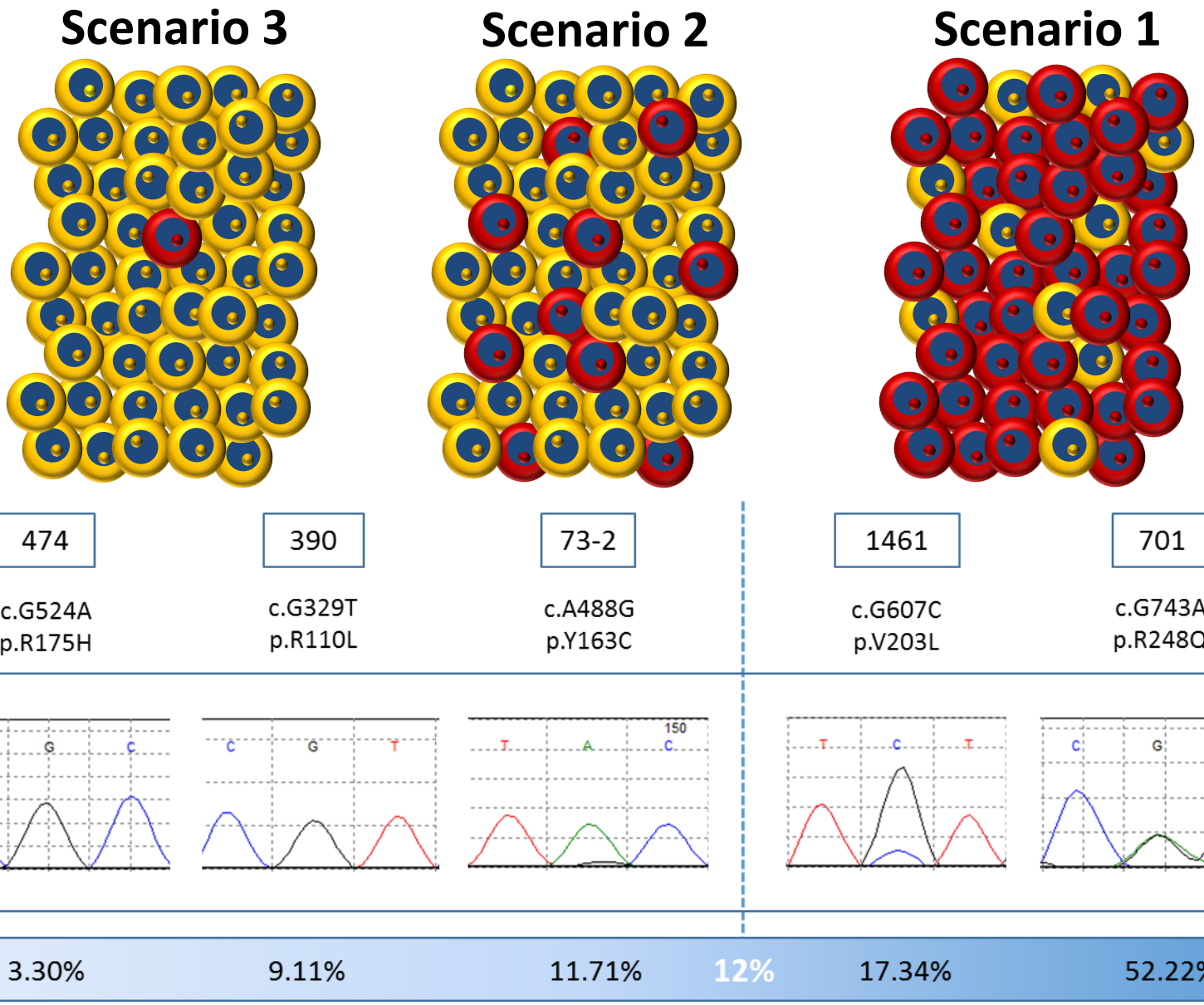
BTK C481S mutation

PLCG2 mutation

Absent in ibrutinib naïve patients

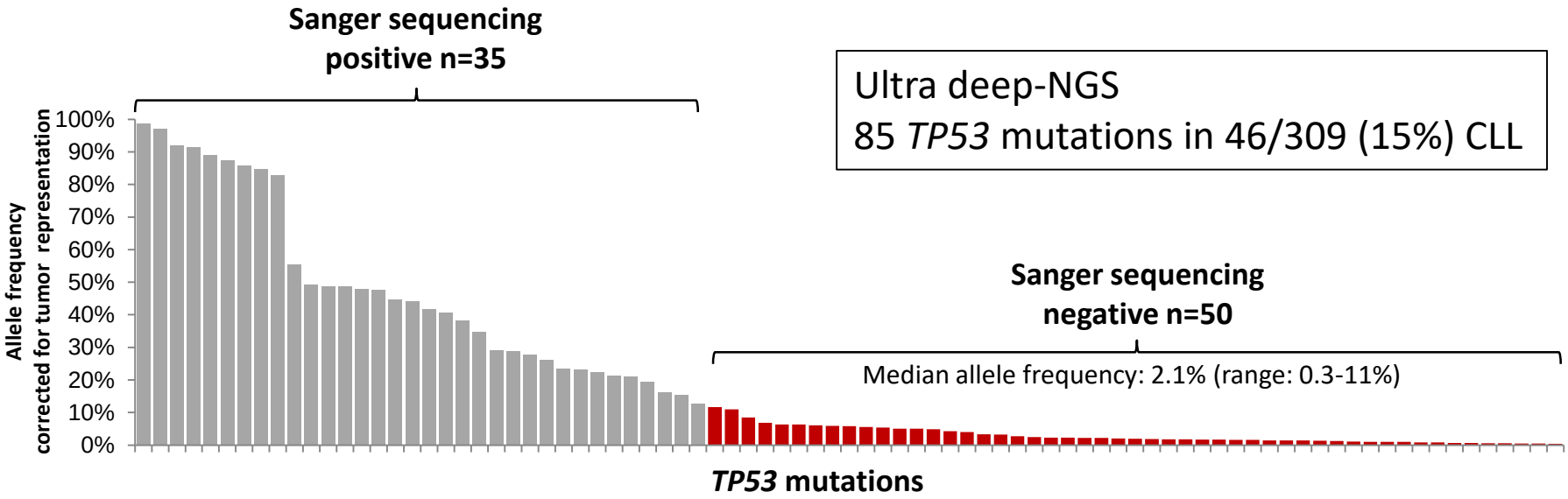
Davis, Nature 2010
Woyach, NEJM 2014
Furman, NEJM 2014
Famà, Blood 2014
Rahal, Nat Med 2014

Clonal architecture of *TP53* mutated CLL

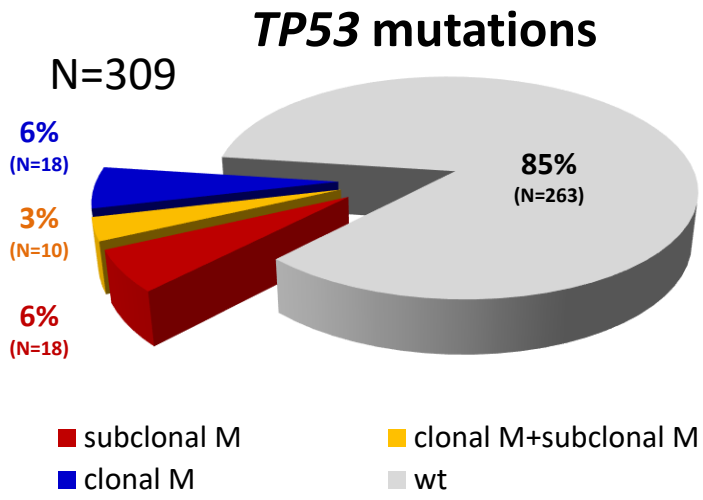


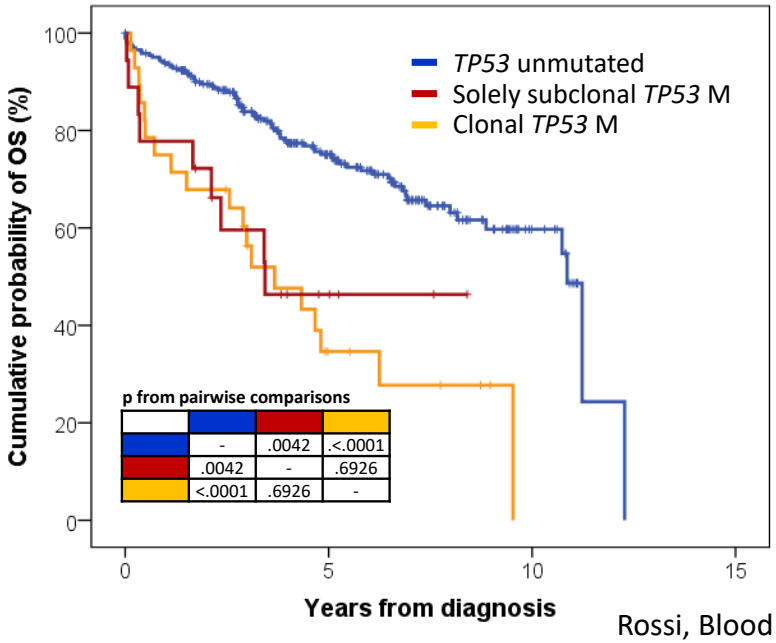
Nadeu F et al Blood 2016

Small *TP53* mutated subclones in untreated CLL



Ultra deep-NGS
85 *TP53* mutations in 46/309 (15%) CLL

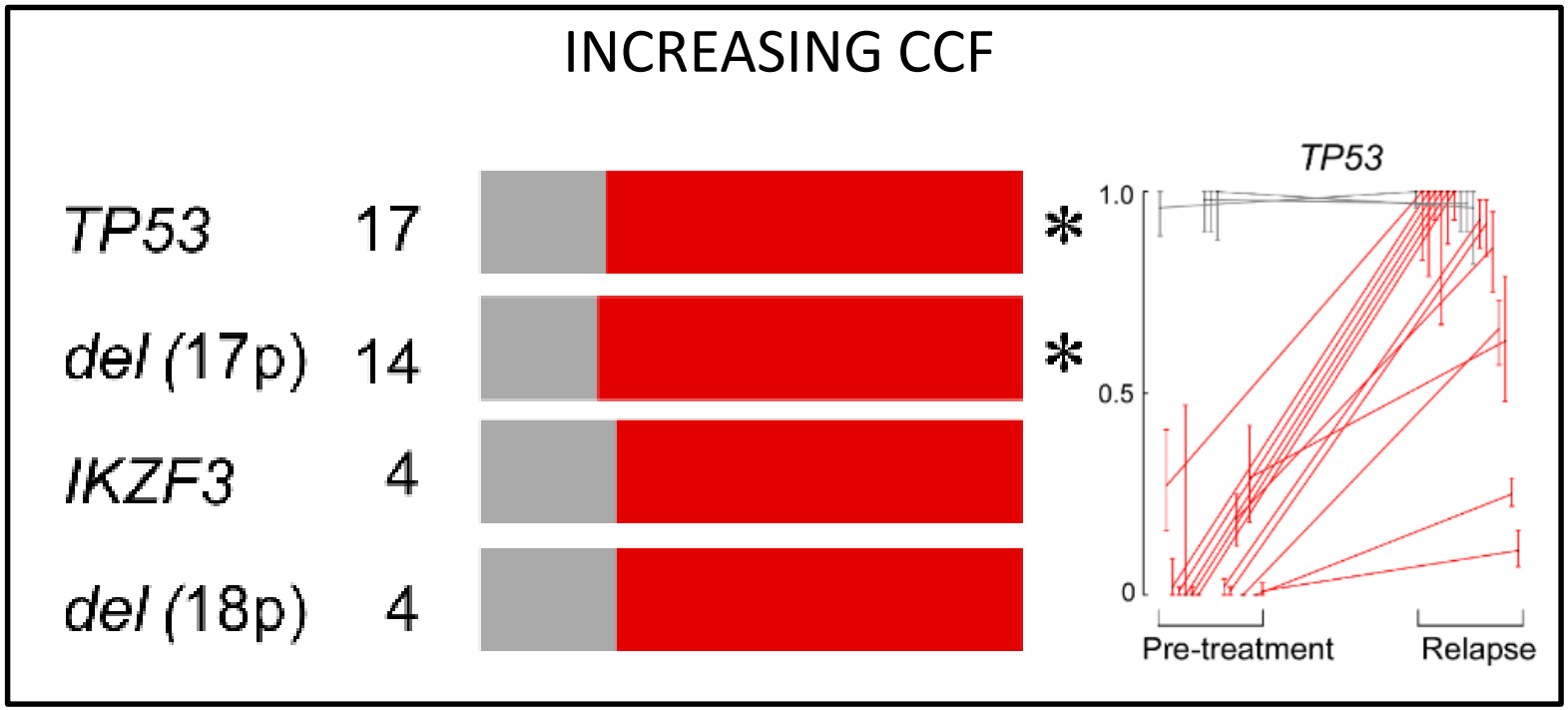




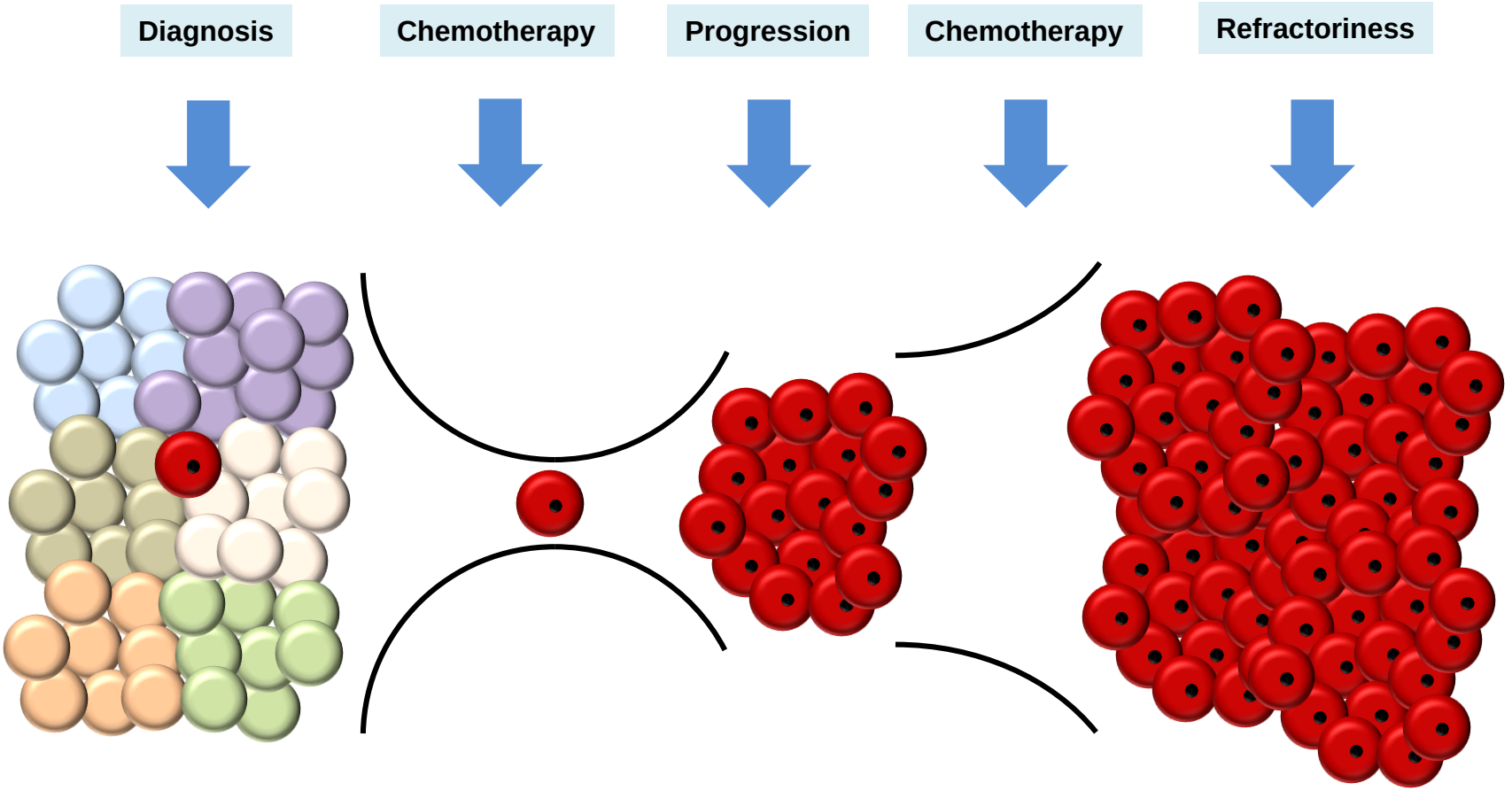
* *TP53* mutations and 17p13 deletion

Rossi, Blood 2014

TP53 subclone evolution in CLL treated within the CLL8 trial



Landau, Nature 2015



NGS | Sanger

Rossi, Blood 2014; Malcikova, Leukemia 2015; Landau, Nature 2015; Nadeu, Blood 2016

Summing up

- CLL is characterized by a marked degree of molecular heterogeneity, since few mutations recur patients at a frequency >5%
- *TP53* disruption identifies a genetic category of high risk CLL, predicts chemoimmunotherapy failure and mandates treatment with innovative drugs, including ibrutinib, idelalisib or venetoclax
- Mutated *IGHV* gene represent a predictive biomarker for identifying patients that may benefit the most from chemoimmunotherapy with FCR
- Novel molecular prognosticators and predictors are under scrutiny, but their application in the clinical practice is premature

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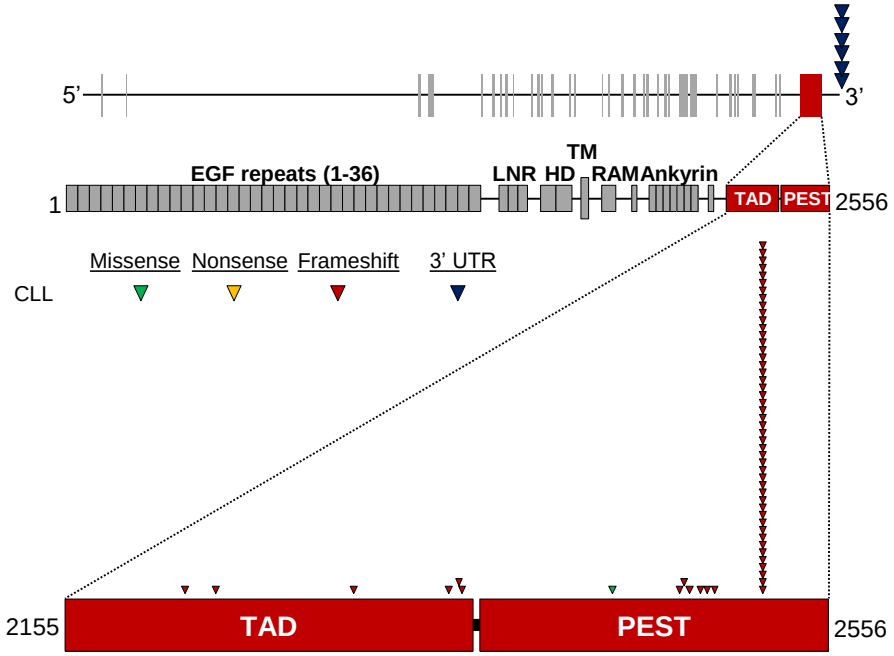
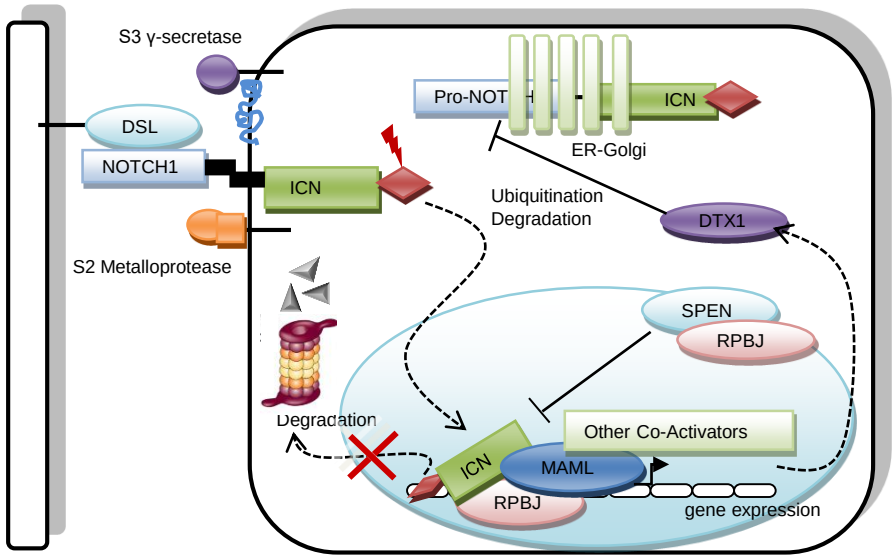
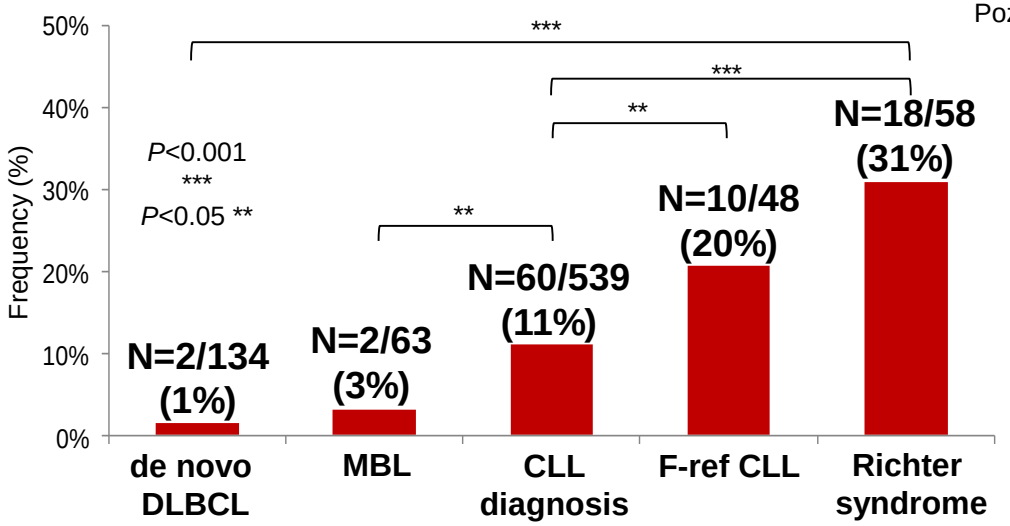
NOTCH1 mutations in CLL





Arruga F et al. Leukemia 2013
Arruga F et al. Leukemia 2016
Fabbri G et al. PNAS 2017
Pozzo F et al. Leukemia 2017

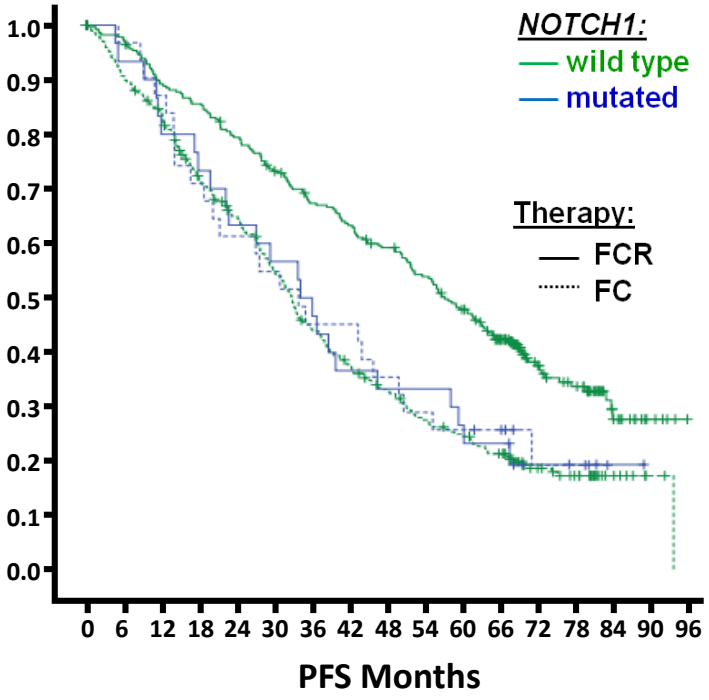


MYC (proliferation)
DUSP22 (migration)
CD20 (anti CD20)

Fabbri, et al. J Exp Med 2011
Puente, et al. Nature 2011
Wang, et al. New Engl J Med 2011
Rossi, et al. Blood 2012
Rasi, et al. Haematologica 2012

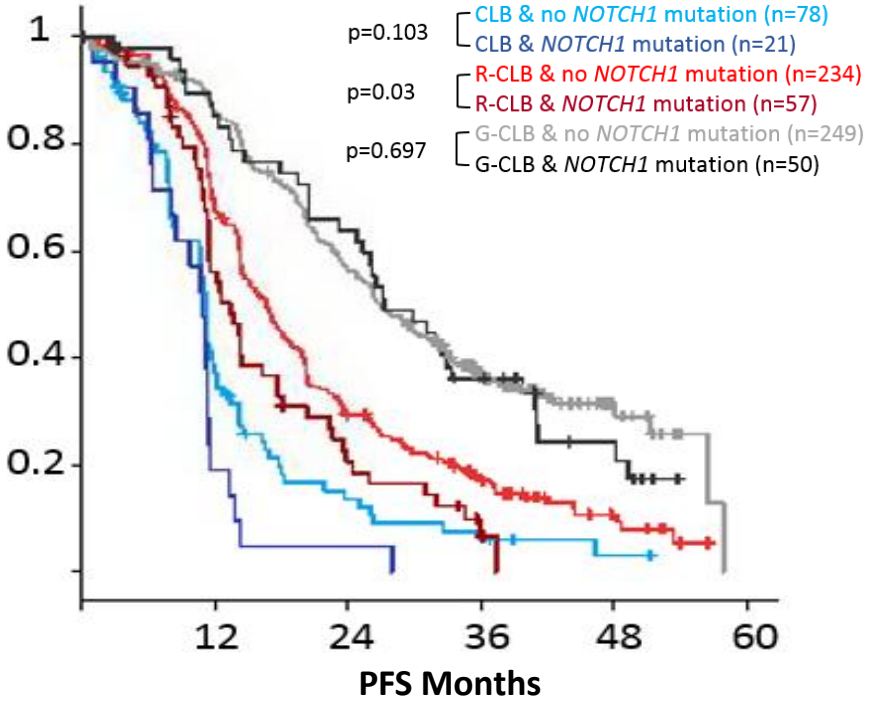
NOTCH1 mutations as predictive marker for no benefit from addition of rituximab to chemotherapy

GCLLSG CLL8



Stilgenbauer S et al. Blood 2013

GCLLSG CLL11



Estenfelder S et al. Blood 2016 128:3227