



IOR
Un istituto
affiliato all'USI

Richter syndrome biology

(increased rate of Richter syndrome under NA?)

Davide Rossi, M.D., Ph.D.

Hematology

IOSI - Oncology Institute of Southern Switzerland

IOR - Institute of Oncology Research

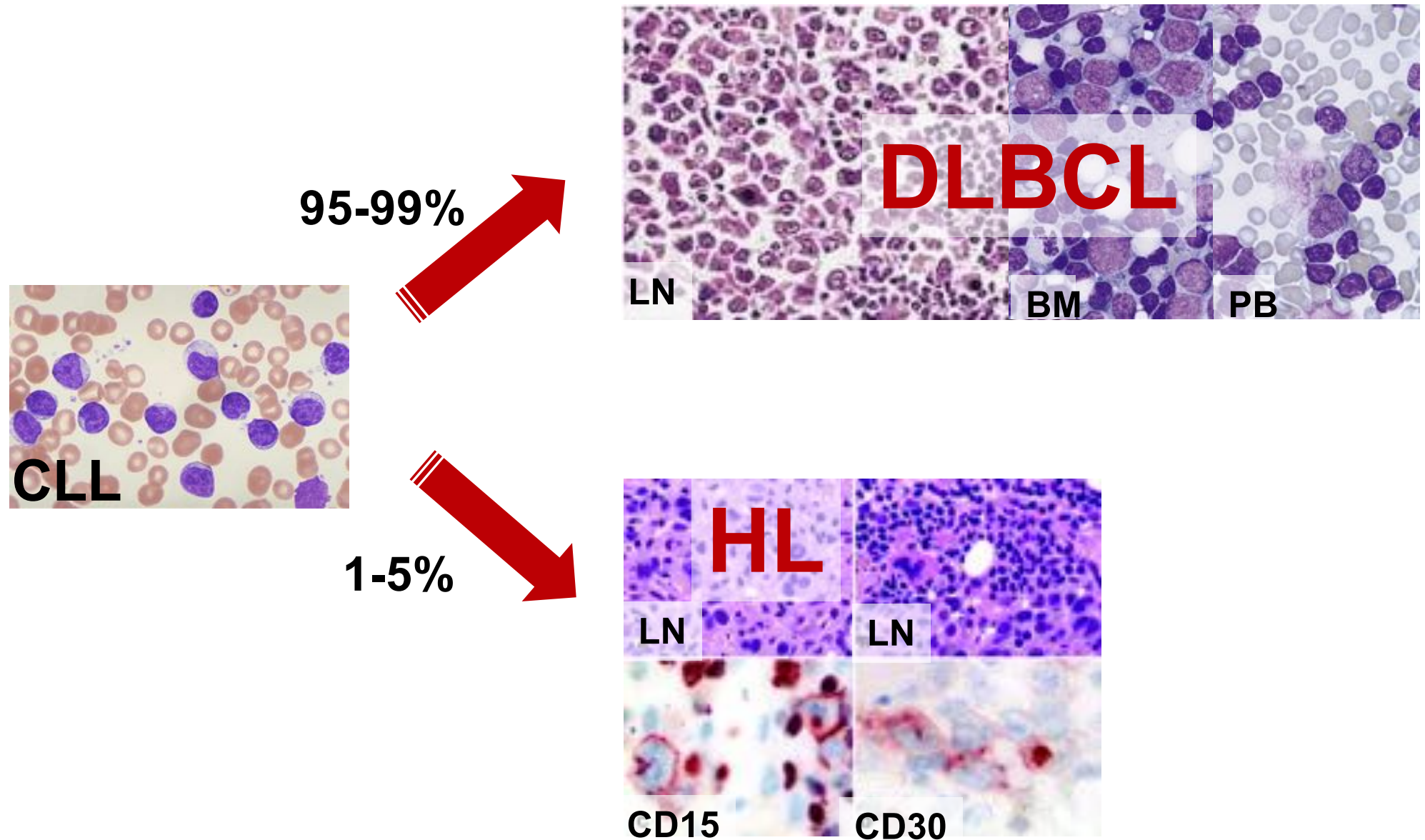
USI – Università' della Svizzera Italiana

Bellinzona - Switzerland

Research Support:	Gilead, Abbvie, Janssen, Cellestia, Xeneticbio
Employee	No
Consultant	No
Major Stockholder	No
Speakers Bureau	No
Honoraria	Gilead, Abbvie, Janssen, Roche, AstraZeneca, Loxo
Scientific Advisory Board	Gilead, Abbvie, Janssen, AstraZeneca, MSD, Loxo

1. Classification

Definition of Richter syndrome

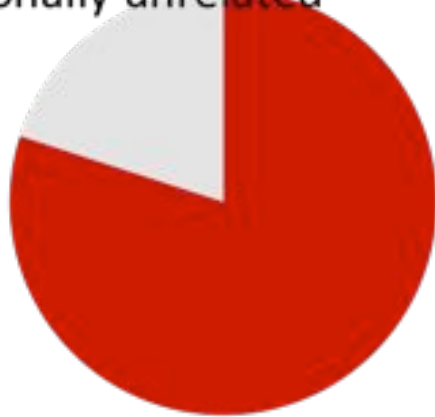


DLBCL vs HL variants of Richter syndrome



DLBCL variant

■ Clonally related
■ Clonally unrelated



80%

■ EBV+
■ EBV-

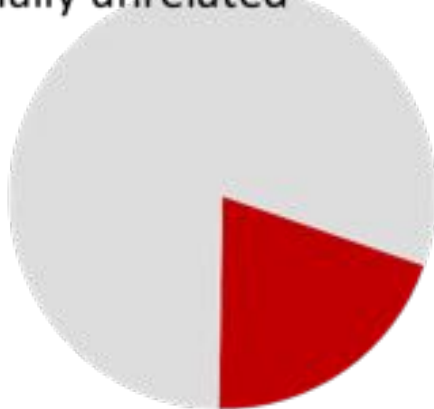


5%

Median OS: <1 y

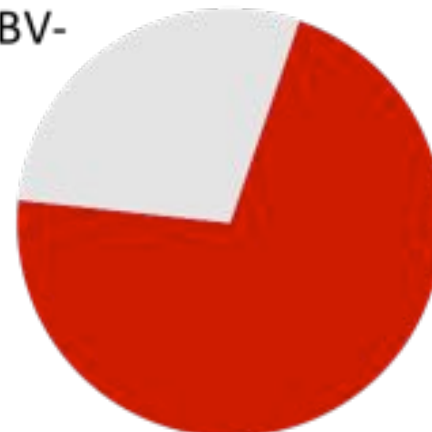
HL variant

■ Clonally related
■ Clonally unrelated



40%

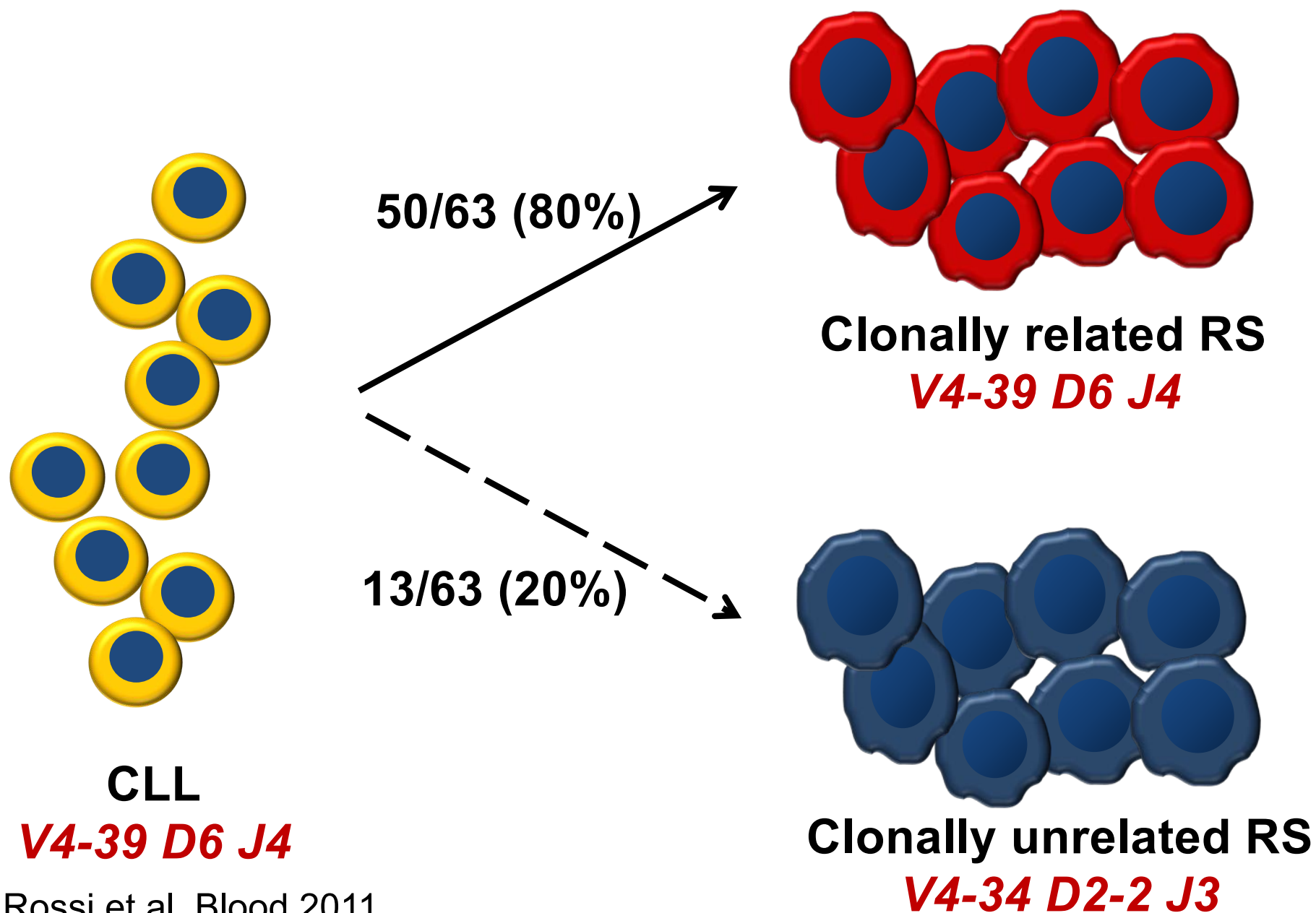
■ EBV+
■ EBV-



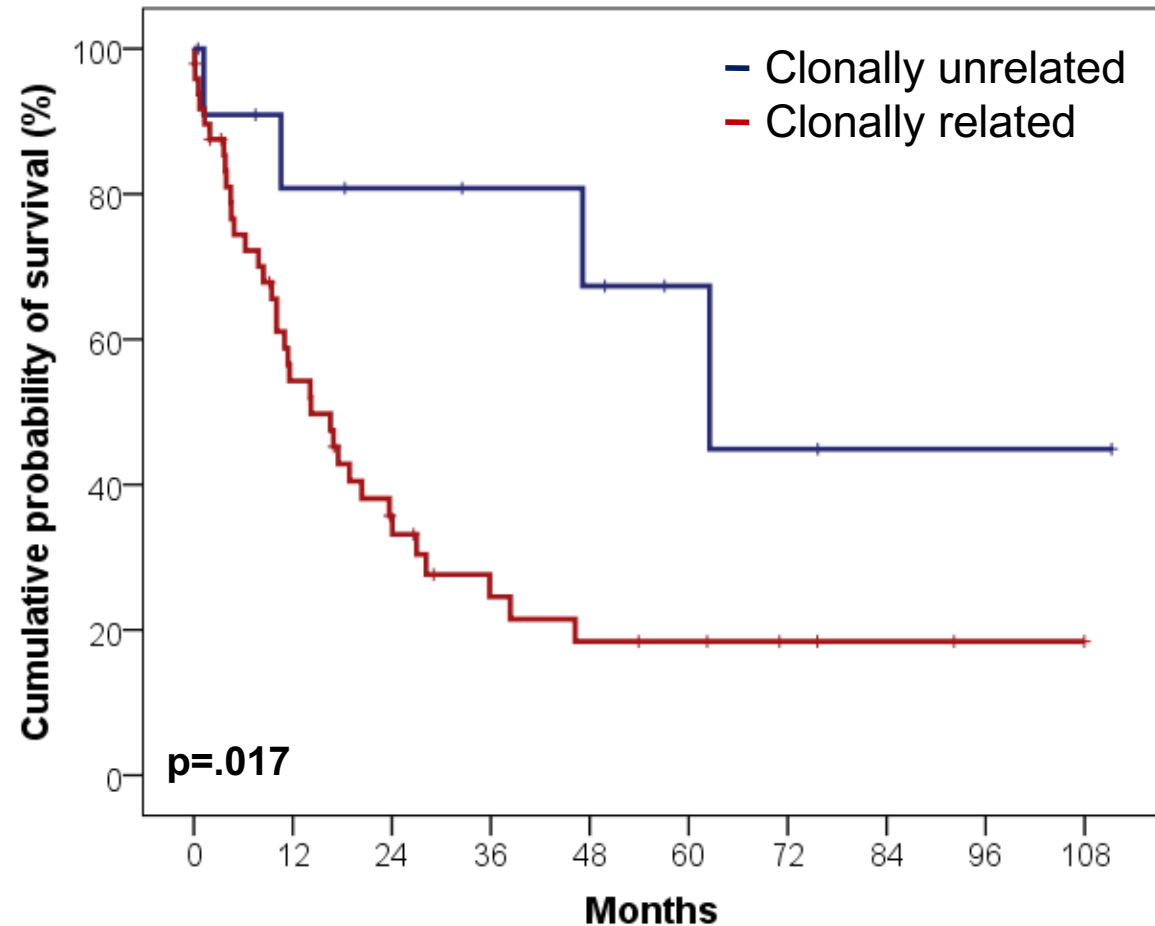
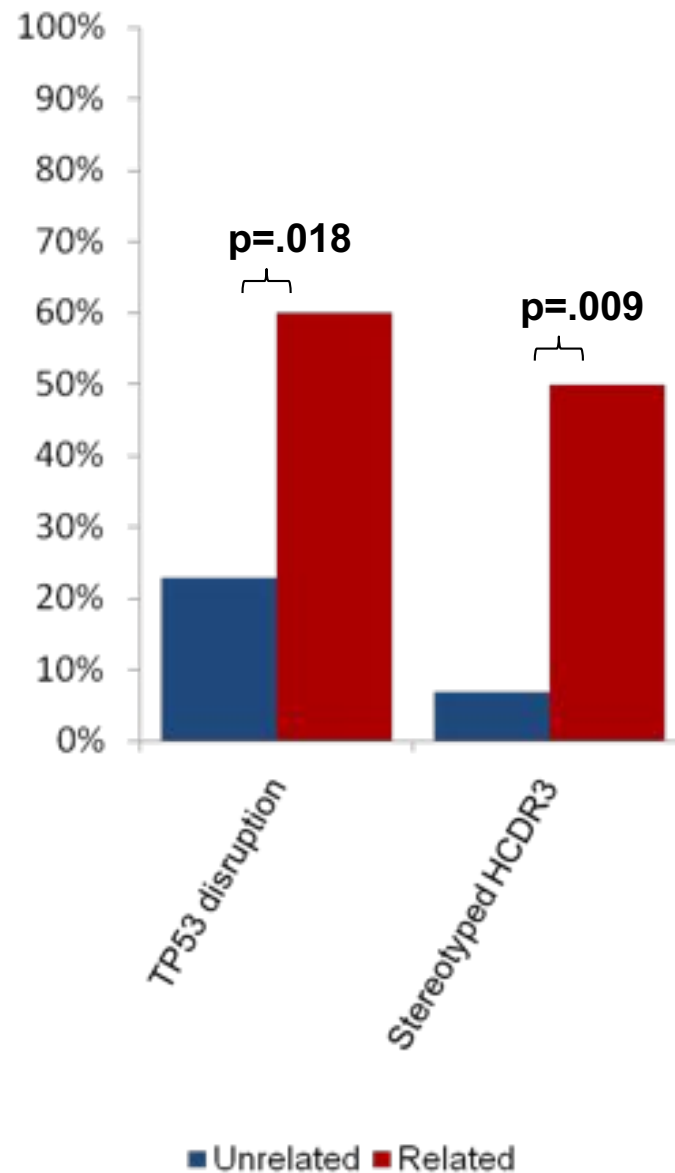
70%

Median OS: 4 y

Clonally related vs unrelated DLCL variant of Richter syndrome

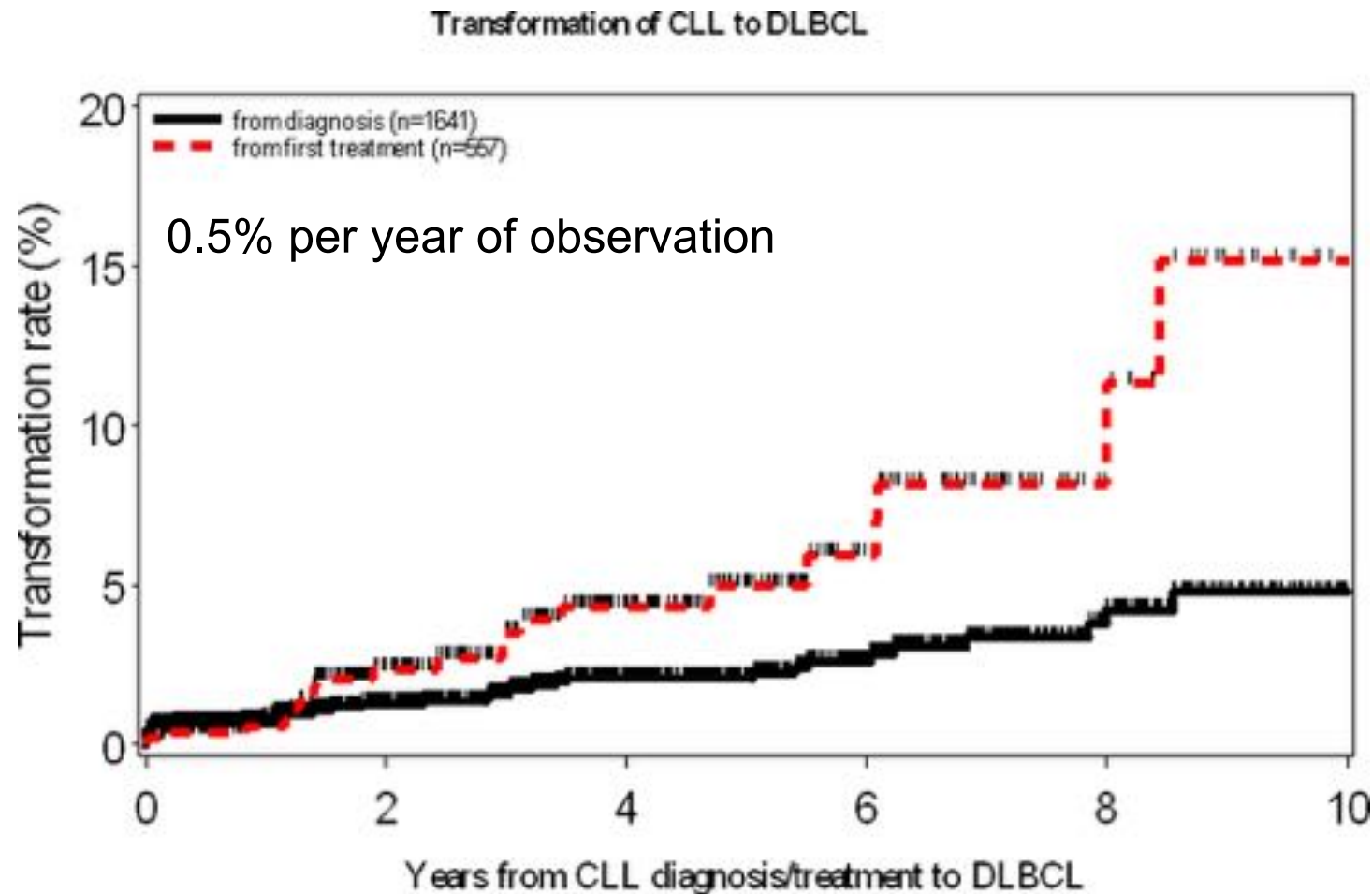


Clonally unrelated Richter syndrome are de novo DLBCL with better outcome

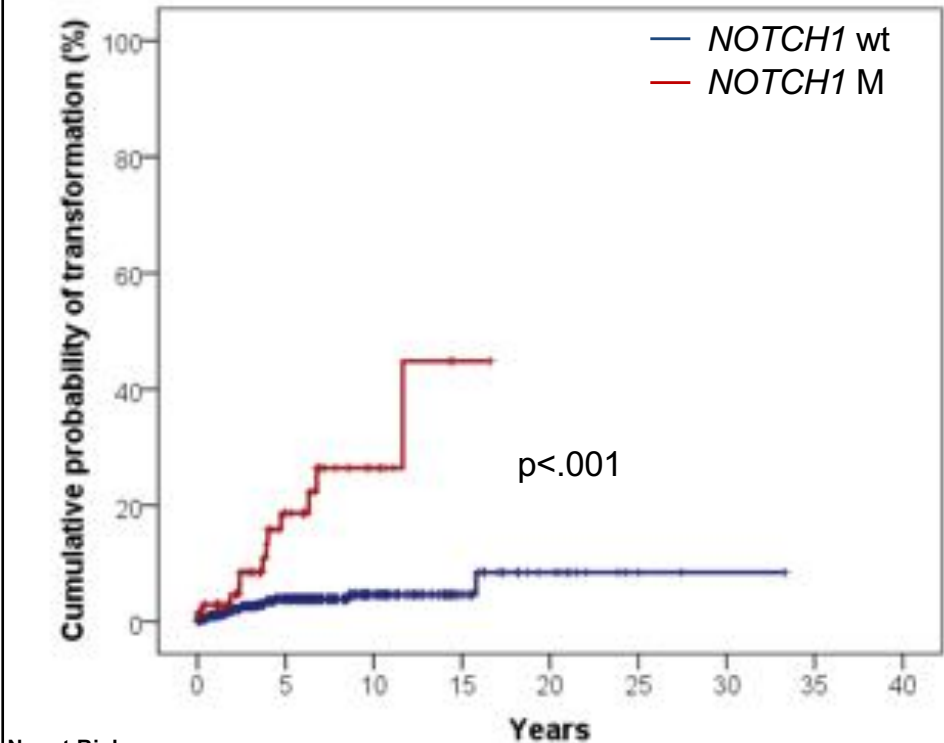


2. Incidence/risk factors

Cumulative incidence of RS

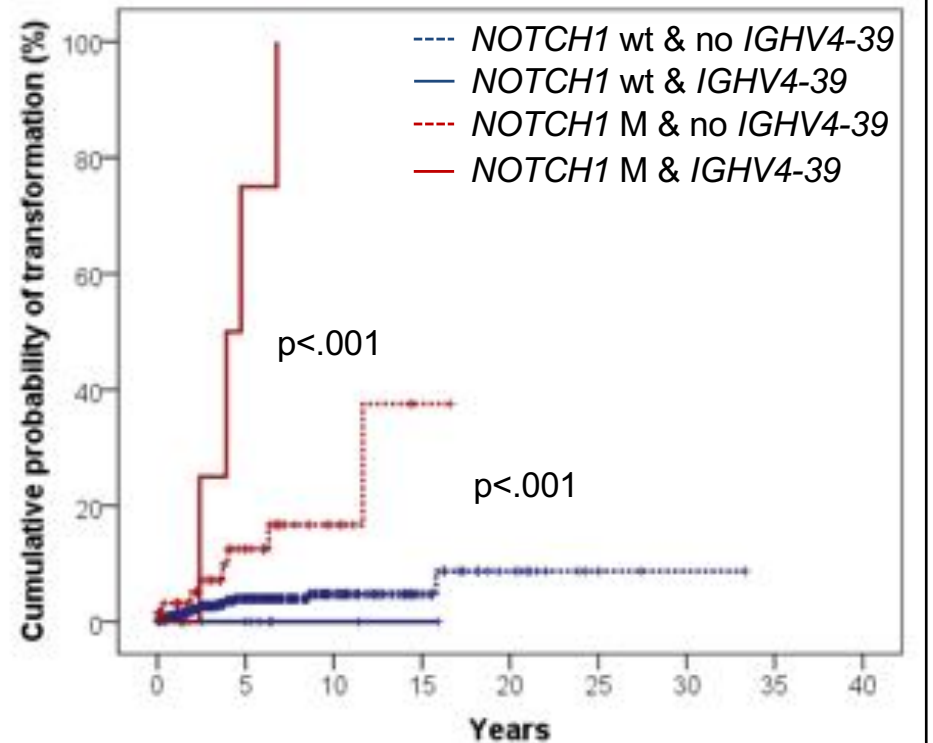


Risk of Richter transformation according to *NOTCH1* mutation status and subset 8 usage CLL diagnosis



No. at Risk	0	5	10	15	20	25	30	35	40
<i>NOTCH1</i> wt	531	279	92	31	11	3	1	0	0
<i>NOTCH1</i> M	74	28	8	1	0	0	0	0	0

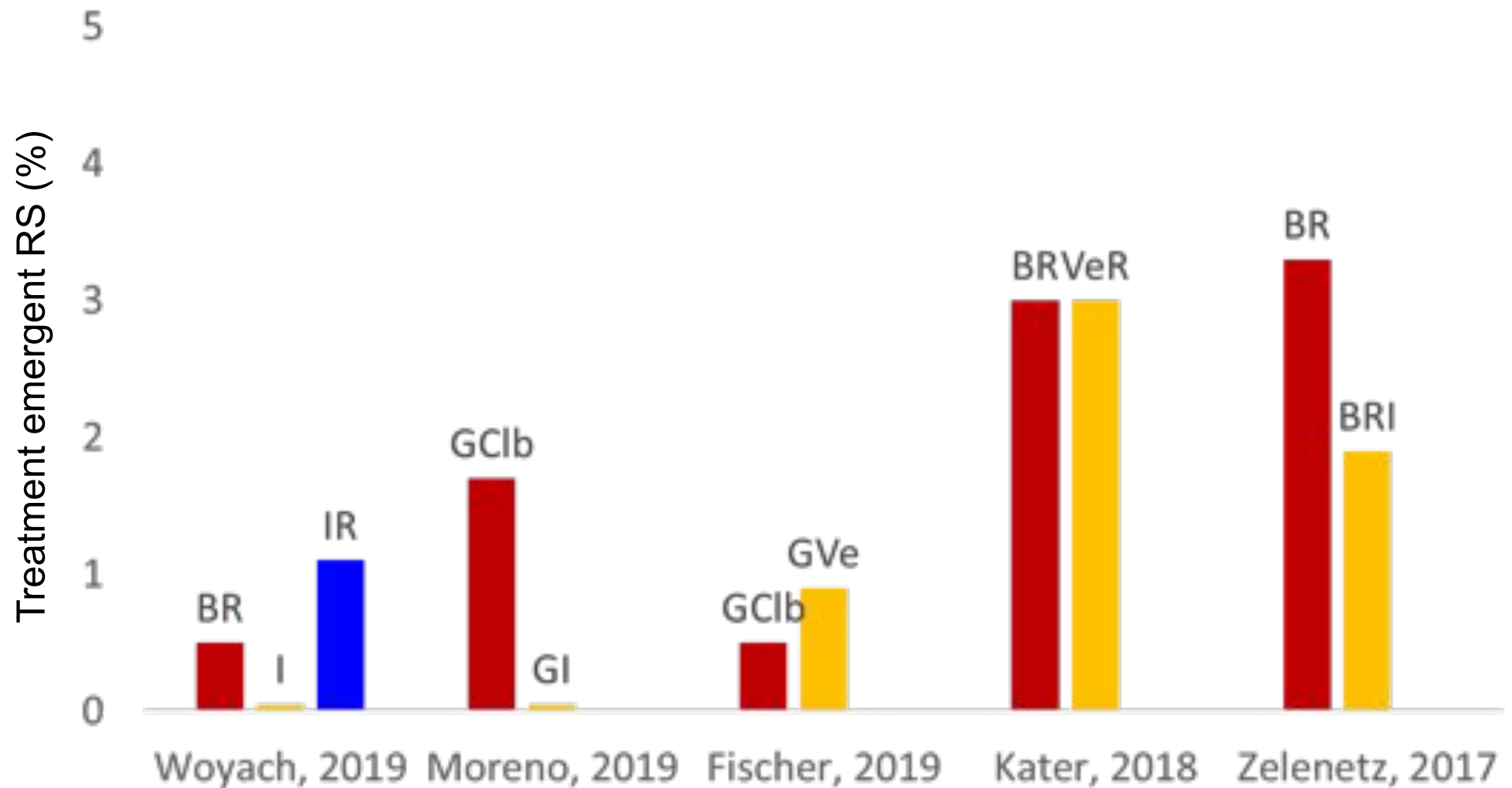
	Events	Total	5-year risk	95% CI
<i>NOTCH1</i> wt	18	531	3.9%	2.0-5.8
<i>NOTCH1</i> M	12	74	18.6%	7.3-29.9



No. at Risk	0	5	10	15	20	25	30	35	40
<i>NOTCH1</i> wt & no <i>IGHV4-39</i>	519	273	90	30	11	3	1	0	0
<i>NOTCH1</i> wt & <i>IGHV4-39</i>	12	12	12	12	0	0	0	0	0
<i>NOTCH1</i> M & no <i>IGHV4-39</i>	67	27	8	1	0	0	0	0	0
<i>NOTCH1</i> M & <i>IGHV4-39</i>	7	1	0	0	0	0	0	0	0

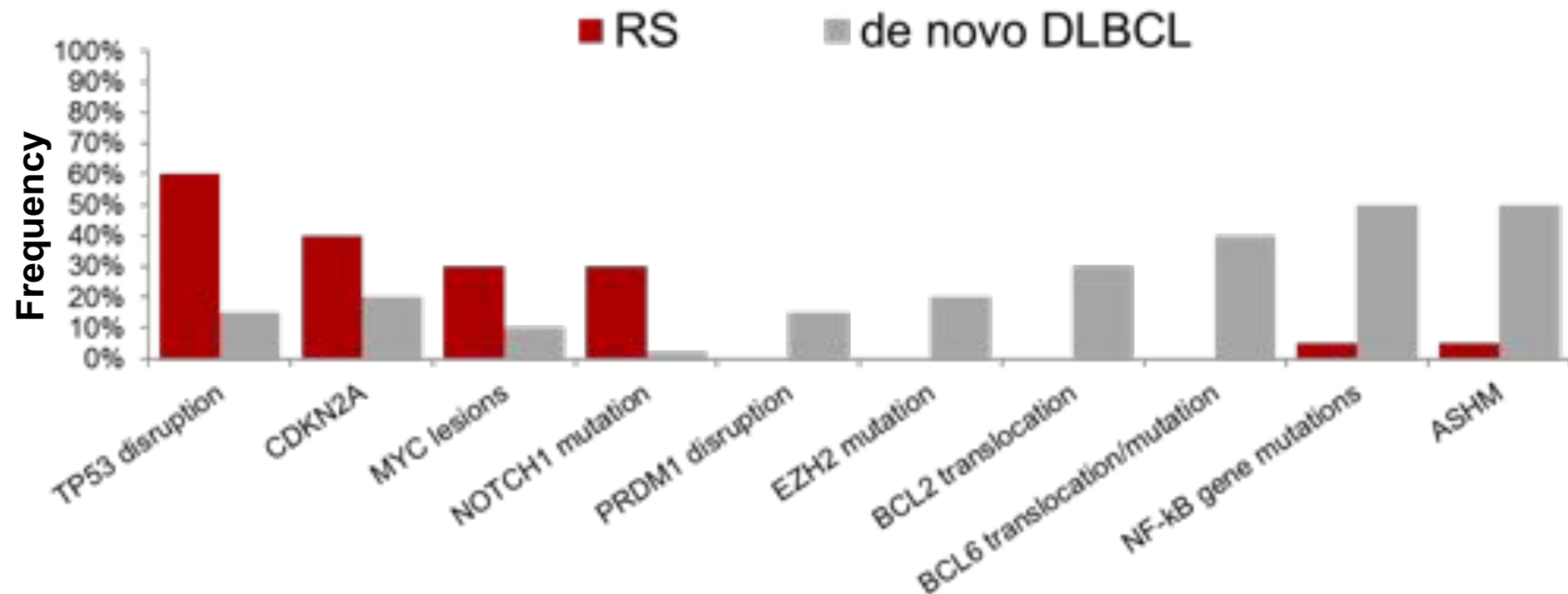
	Events	Total	5-year risk	95% CI
<i>NOTCH1</i> wt & no <i>IGHV4-39</i>	18	519	4.0%	2.1-5.9
<i>NOTCH1</i> wt & <i>IGHV4-39</i>	0	12	0	
<i>NOTCH1</i> M & no <i>IGHV4-39</i>	8	67	12.5%	2.9-22.1
<i>NOTCH1</i> M & <i>IGHV4-39</i>	4	7	75.0%	32.5-100

Incidence of RS



3. Genetics in the CIT era

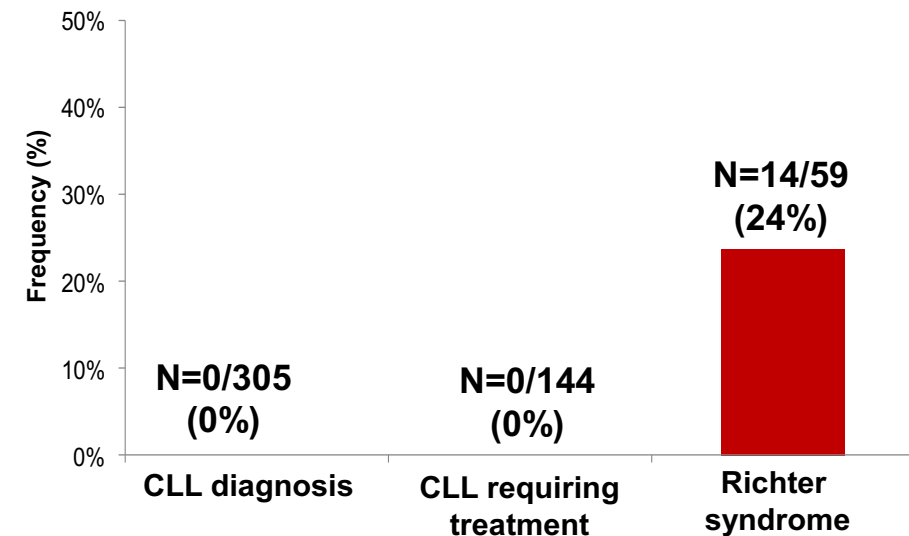
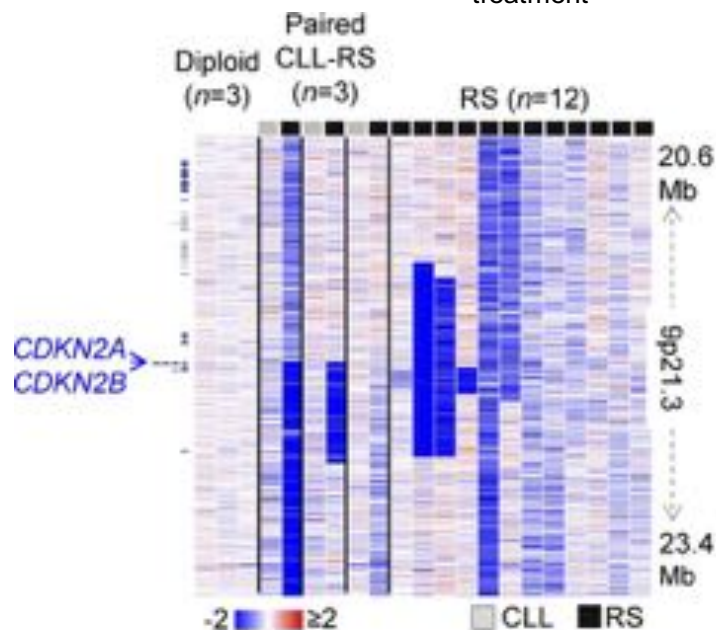
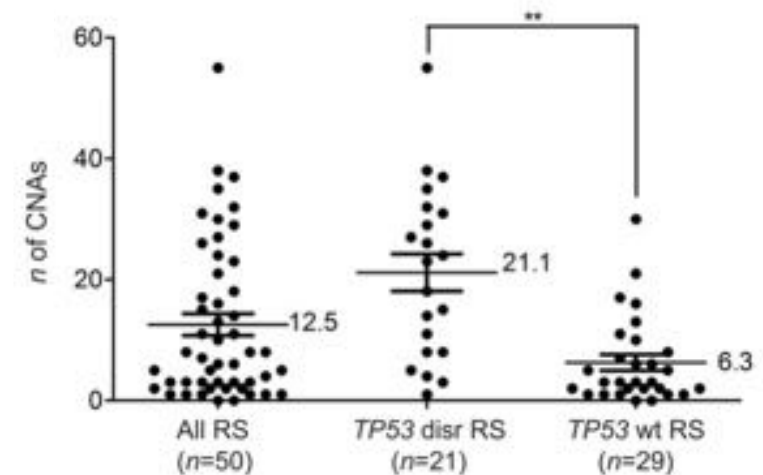
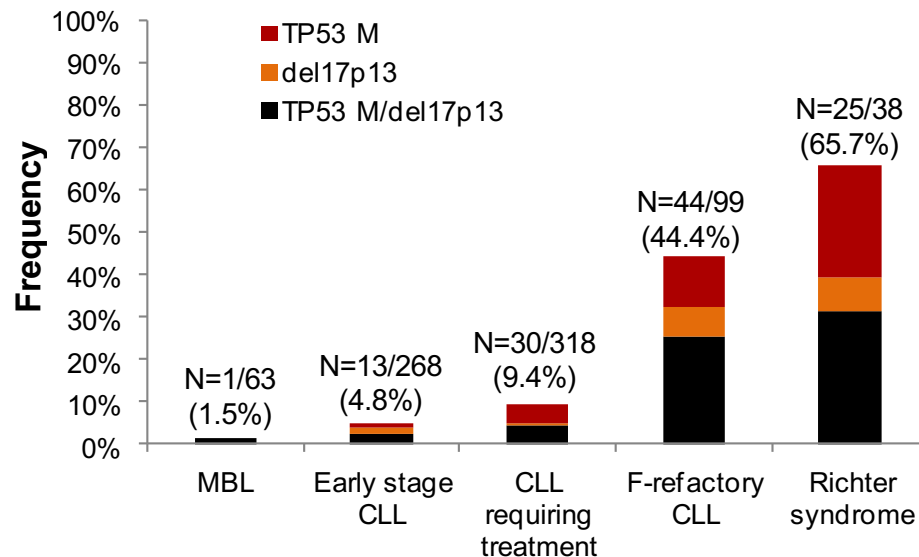
The genetic profile of Richter syndrome (RS) differs from that of *de novo* DLBCL



Lesions of *TP53*, *NOTCH1*, *MYC* and *CDKN2A* recapitulates 90% RS



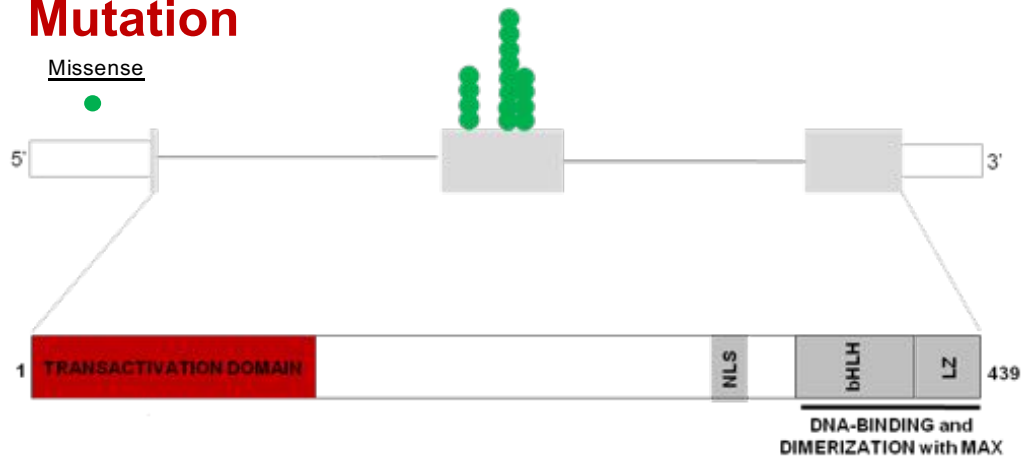
Apoptosis and cell cycle pathway mutations in Richter syndrome



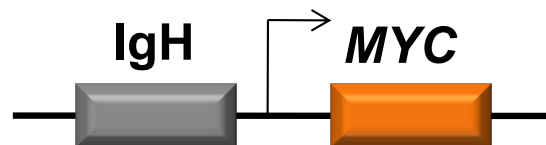
MYC abnormalities in Richter syndrome



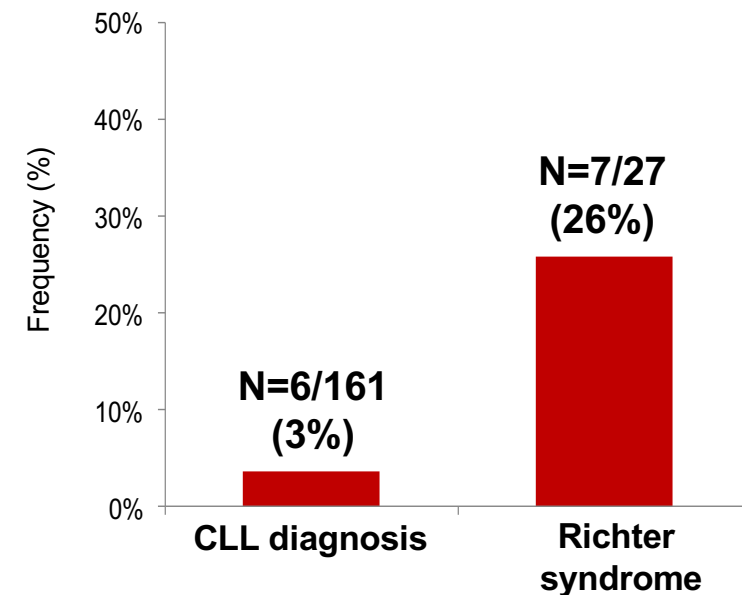
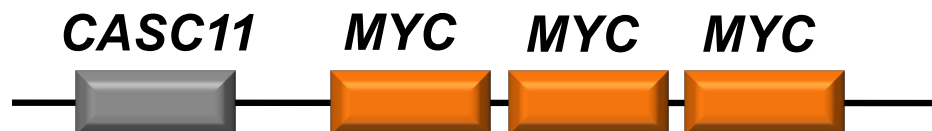
Mutation



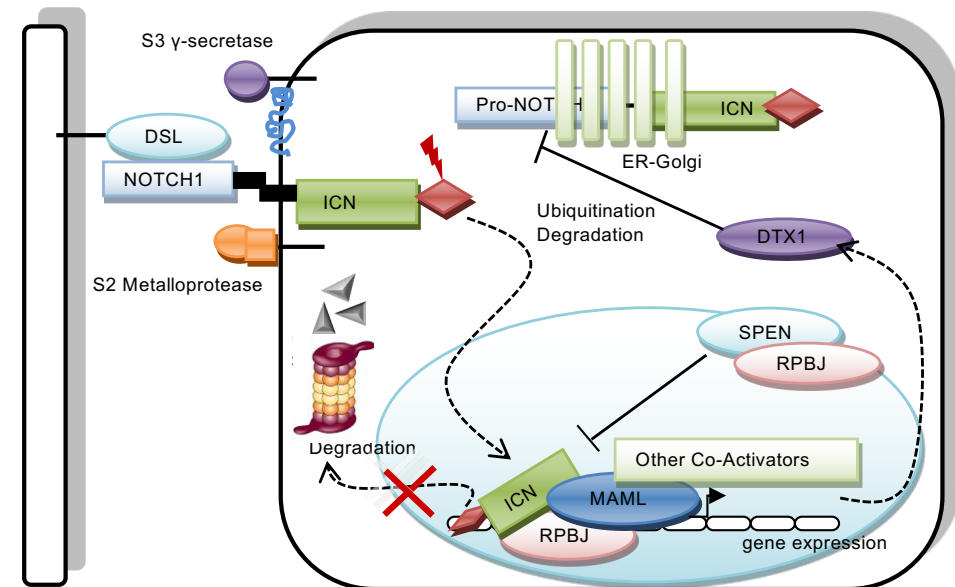
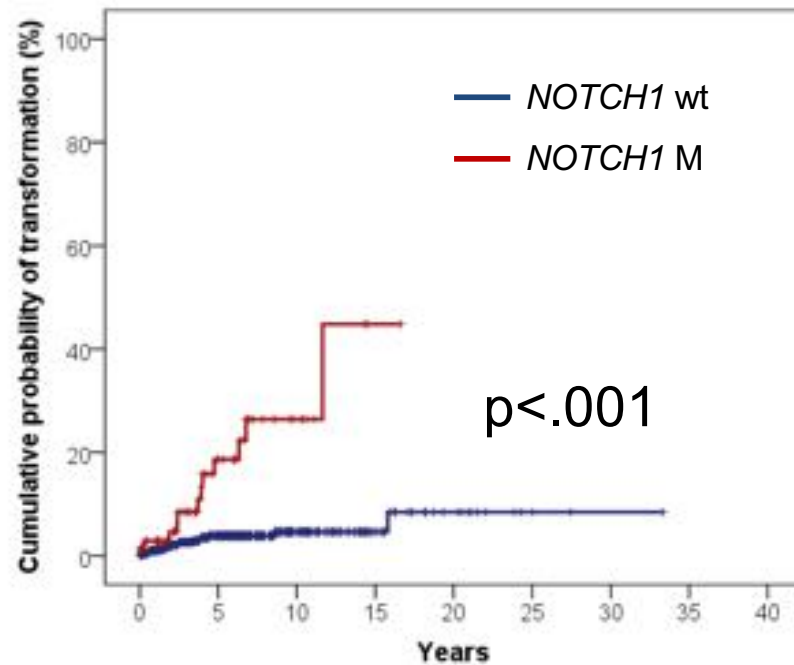
Translocation



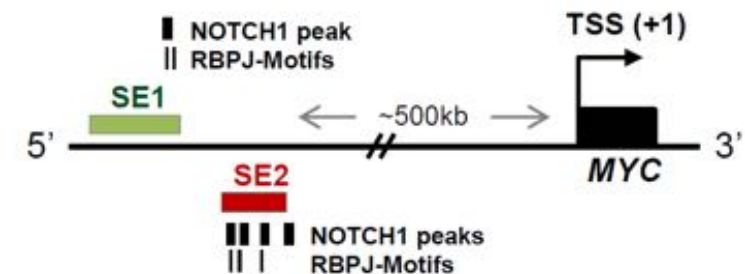
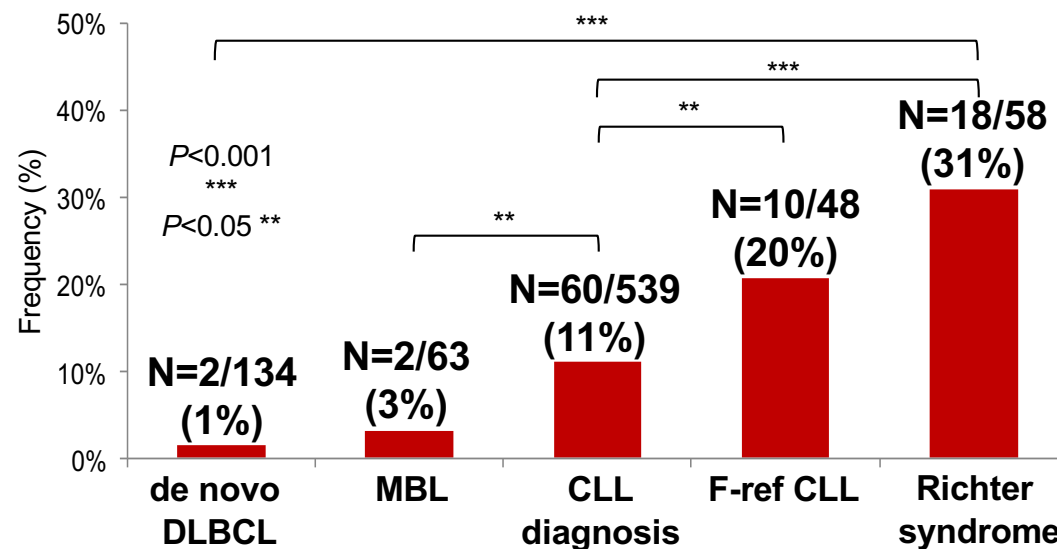
Amplification



NOTCH1 mutations in Richter syndrome

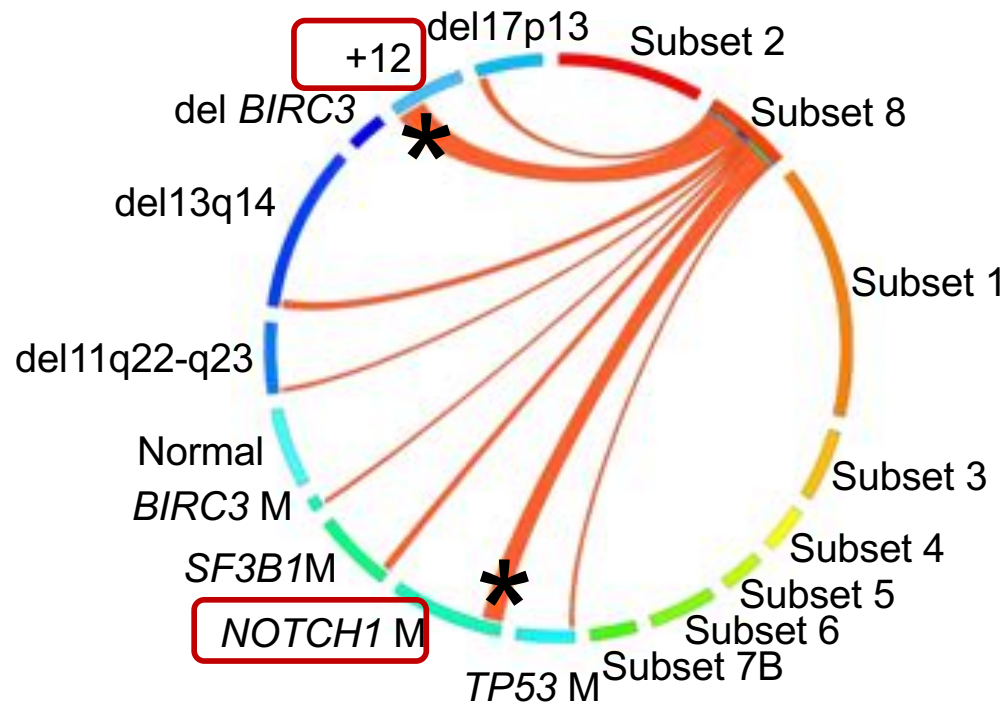


Arruga, et al. Leukemia 2013



Fabbri G, et al. J Exp Med 2011; 208:1389-401
 Puente X, et al. Nature 2011; 475: 101-5
 Rossi D, et al. Blood 2012; 119: 521-9
 Rasi S, et al. Haematologica 2012; 97: 153-4
 Fabbri G et al. J Exp Med 2013; 210: 2273-88
 Fabbri G et al. PNAS 2017

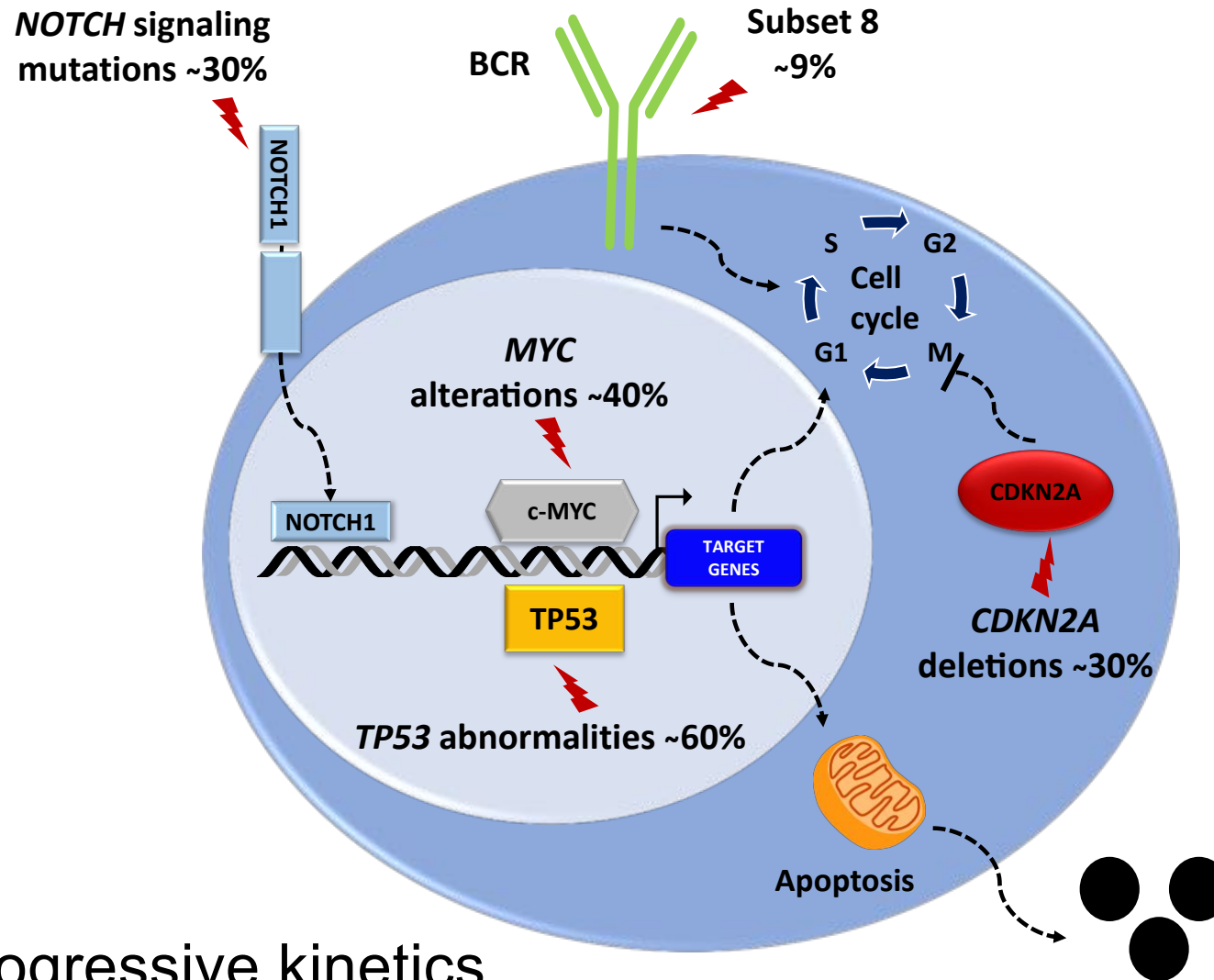
Subset 8 configuration of BCR associates with Richter syndrome



BCR from subset 8 CLL display extreme antigen polyreactivity

Rossi D, et al, Clin Cancer Res 2009; 15: 4415-22
Chu, et al, Blood 2011; 117:2227-36
Rossi D, et al, Blood 2013; 121: 4902-5
Gounari M, et al, Blood 2015; 125: 3580-7

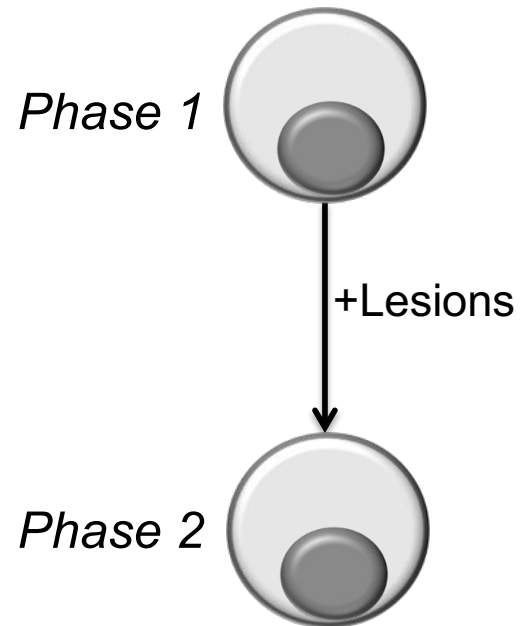
Proliferation and apoptosis are the master cellular programs deregulated in Richter syndrome



Rapidly progressive kinetics
Chemorefractoriness

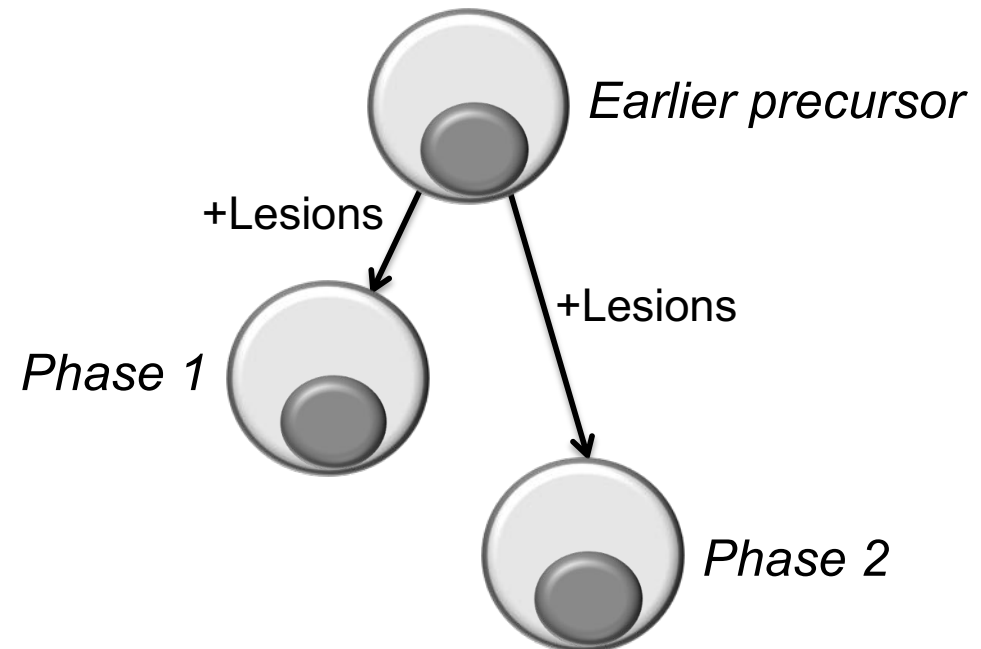
Clonal evolution models

The “linear model”



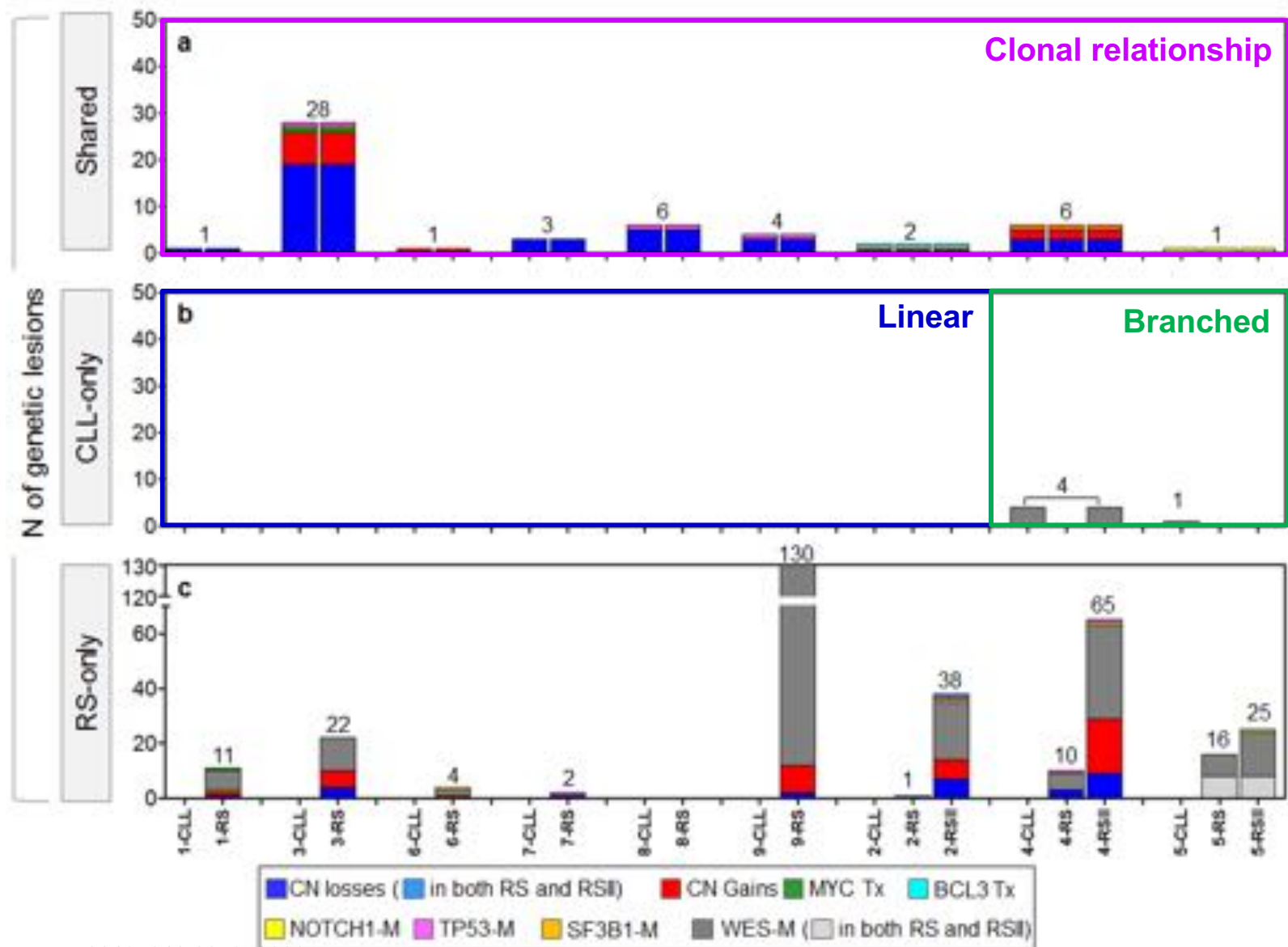
- All Phase 1 lesions present in Phase 2
- Unique lesions in Phase 2

The “branching model”

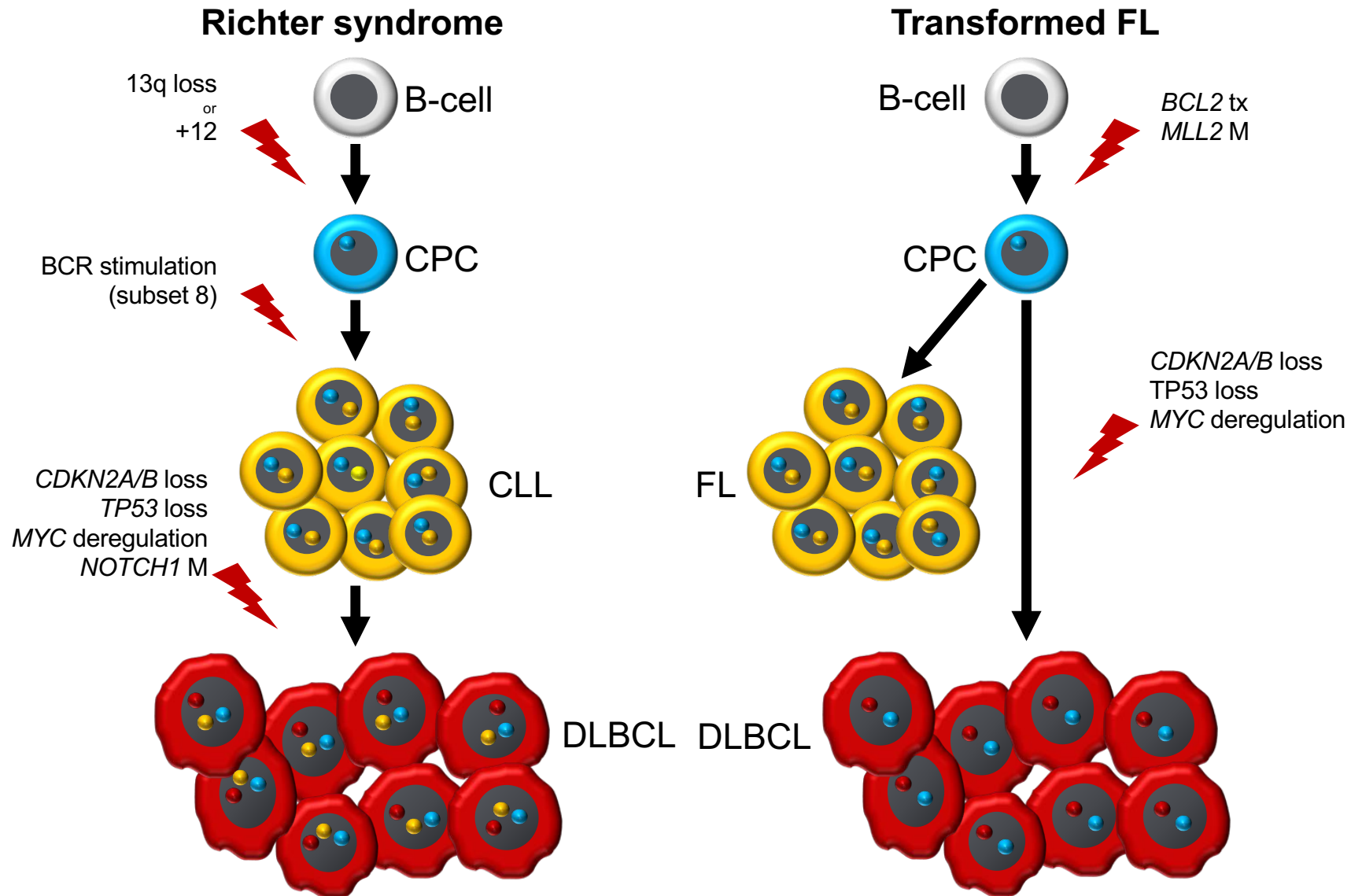


- Set of shared lesions in Phases 1&2
- Unique lesions in Phase 1
- Unique lesions in Phase 2

Most RS arise through a linear pattern of clonal evolution



Clonal evolution models applied to transformed lymphomas

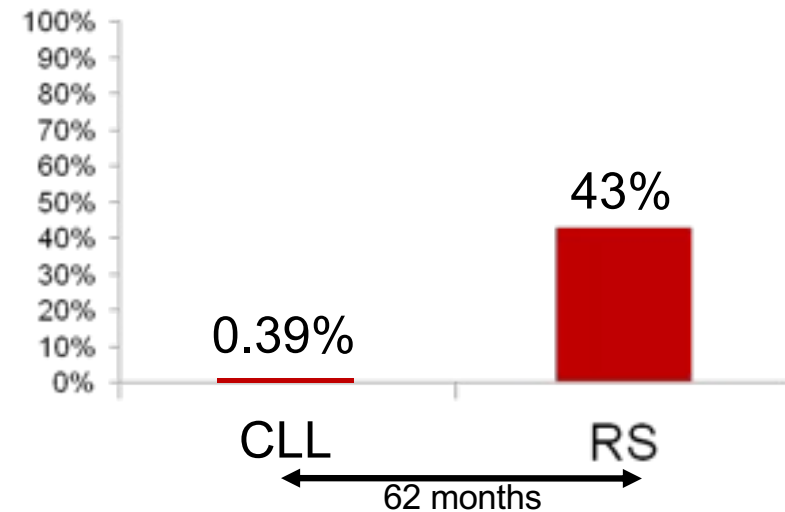
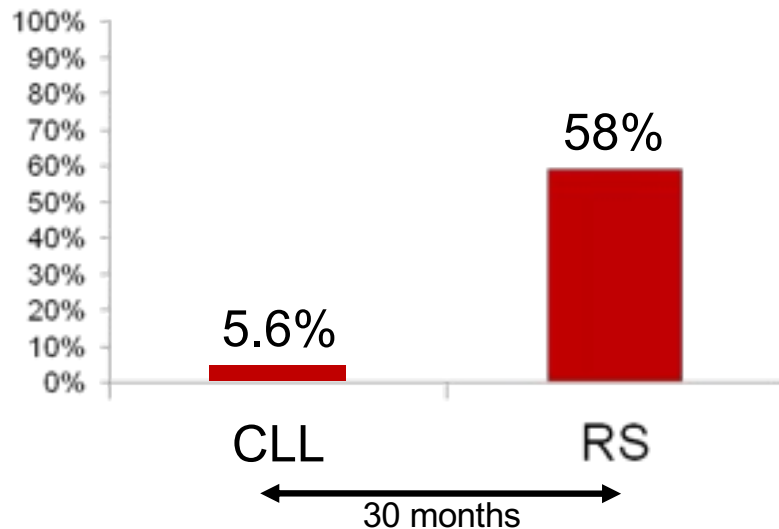


The genetic lesions of Richter syndrome can be detectable at subclonal levels in the initial CLL clone

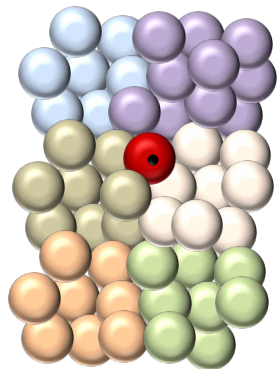


NOTCH 1 EX34: c.7544_7545delCT p.P2515fs*4 (heterozygous)

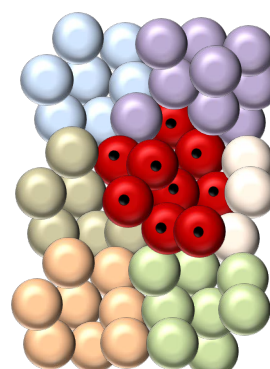
TP53 EX7: c.716A>C p.N239T (heterozygous)



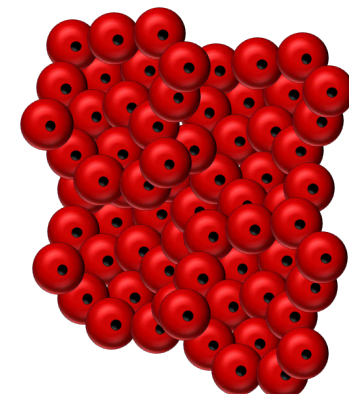
 **RS precursor**



CLL diagnosis



CLL progression



RS transformation

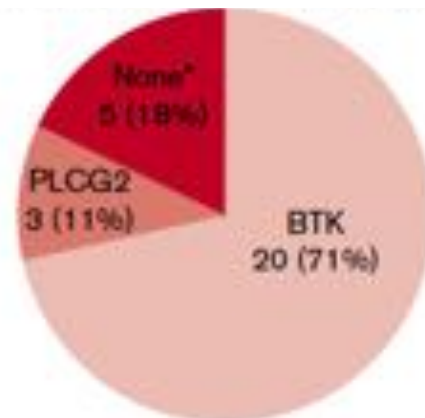
4. Genetics in the NA era

BTK and PLCG2 mutations in Richter syndrome under ibrutinib

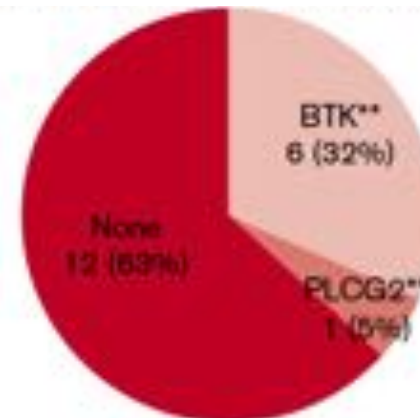


	Total pt	CLLPD	RT
Maddocks ⁶	20	11	9
Burger ¹⁸	5	5	0
Ahn ⁴³	12	9	3
Current study	9	3	6
Total	46	28	18

CLL Simple progression on IBR



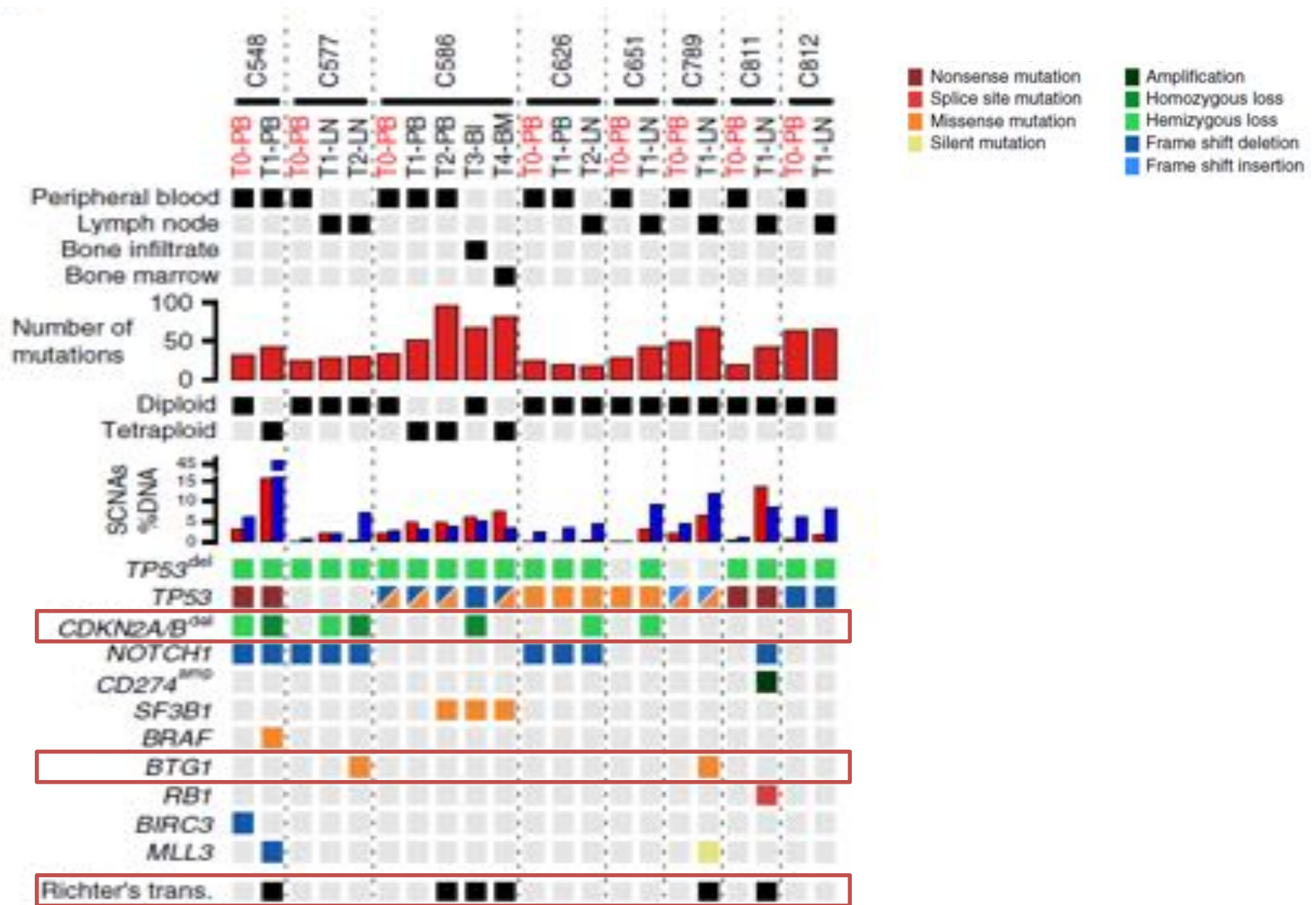
CLL Richter transformation on IBR



BTK: Bruton's tyrosine kinase; CLLPD: chronic lymphocytic leukaemia progressive disease; PLCG2: phospholipase C gamma 2

Kadri S, et al. *Blood Adv* 2017; 1:715–727.

Identified genetic aberrations and patterns of clonal evolution during venetoclax treatment



5. Biological routes

- pAKT expression in RS
- DLBCL development in E μ TCL1:CD19-Cre^{AKT-C}
- PD-L1 expression in RS but not in de novo DLBCL or CLL lymph nodes

Al-Maarri M, *et al.* EHA 2016;S118

Nickel N, *et al.* ASH 2016:2031

Wang *et al.*, ASCO 2018; 7524

Behdad *et al.*, Br J Haematol 2018

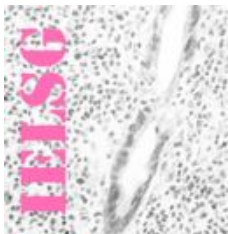
He *et al.*, Am J Surg Pathol 2018

6. Implications for treatment

Richter syndrome vulnerabilities empirically probed in vivo in patients



	Patients	Regimen	ORR	CR
Hillmen, 2016	29	Acalabrutinib	38%	14%
Younes, 2018	29	Nivolumab + Ibrutinib	60%	5%
Tsang, 2016	4	Ibrutinib	75%	25%
Ding, 2016	9	Pembrolizumab	44%	11%
Jain, 2016	3	Nivolumab + Ibrutinib	50%	-
Davids, 2017	7	Venetoclax	43%	0%



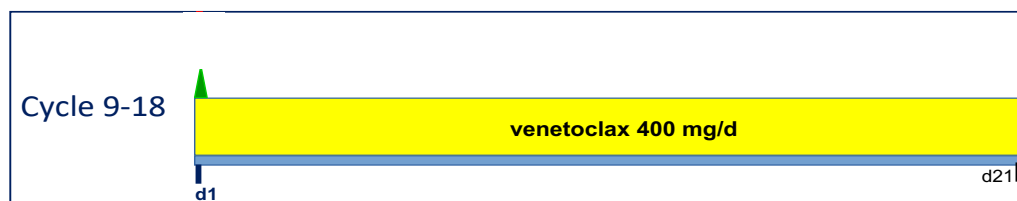
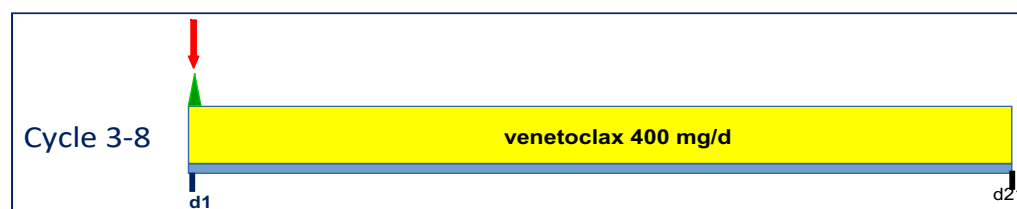
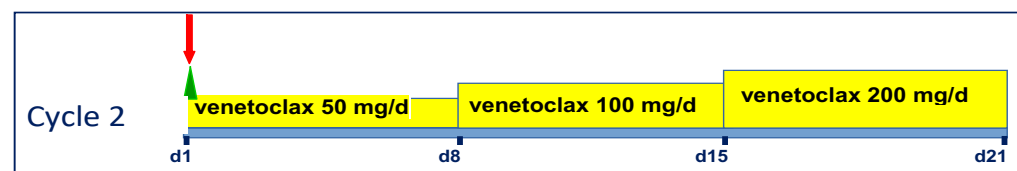
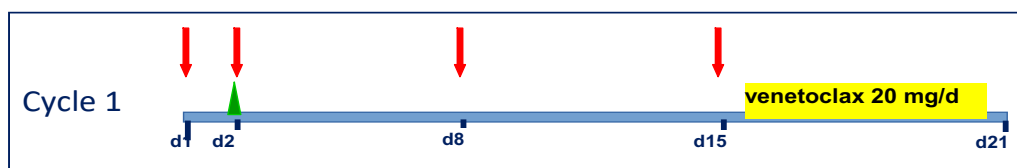
Study MOLTO

A Multi-Center, Open Label, Uncontrolled, Phase II Clinical Trial Evaluating the Safety and Efficacy of Venetoclax in Combination with Atorolimumab and Obinutuzumab in Richter Transformation of CLL

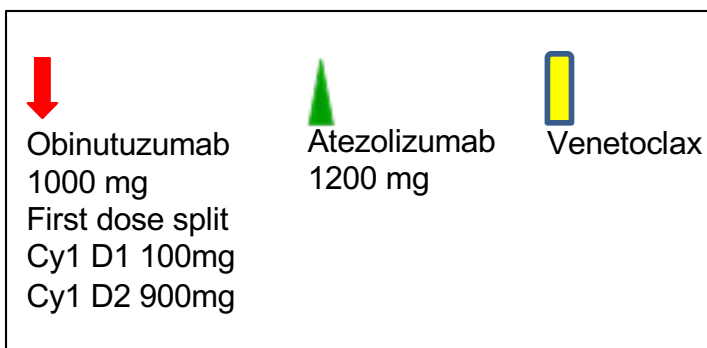
Sponsor: Grande Ospedale Metropolitano Niguarda - Milano, Italy



Schedule



From Cycle 19 to Cycle 35 venetoclax 400 mg/d





IOR
Un istituto
affiliato all'USI

Experimental Hematology

Ferdinando Bonfiglio

Alessio Bruscatin

Adalgisa Condoluci

Francesca Guidetti

Martin Faderl

Gabriela Forestieri

Valeria Spina

Lodovico Terzi di Bergamo

Lymphoma & Genomics

Francesco Bertoni

Franco Cavalli



Clinical Lymphoid tumors

Investigation Program

Bernhard Gerber

Alden Moccia

Anastasios Stathis

Georg Stüssi

Michele Ghielmini

Luca Ceriani

Emanuele Zucca



Luisella Bonomini
Ayda Lüönd

Emanuele Zucca
Franco Cavalli



SWISS NATIONAL SCIENCE FOUNDATION

krebsforschung schweiz
recherche suisse contre le cancer
ricerca svizzera contro il cancro
swiss cancer research



fidinam

FONDATION NELIA ET AMADEO BARLETTA



European Research Council
Scientific Council