Bridging Gaps in Oncology 2018

In collaboration with

Mediterranean multidisciplinary Oncology forum (MMOF) | Hiroshima University

Karmanos Cancer Institute (Wayne State University)

RICHTER's TRANSFORMATION

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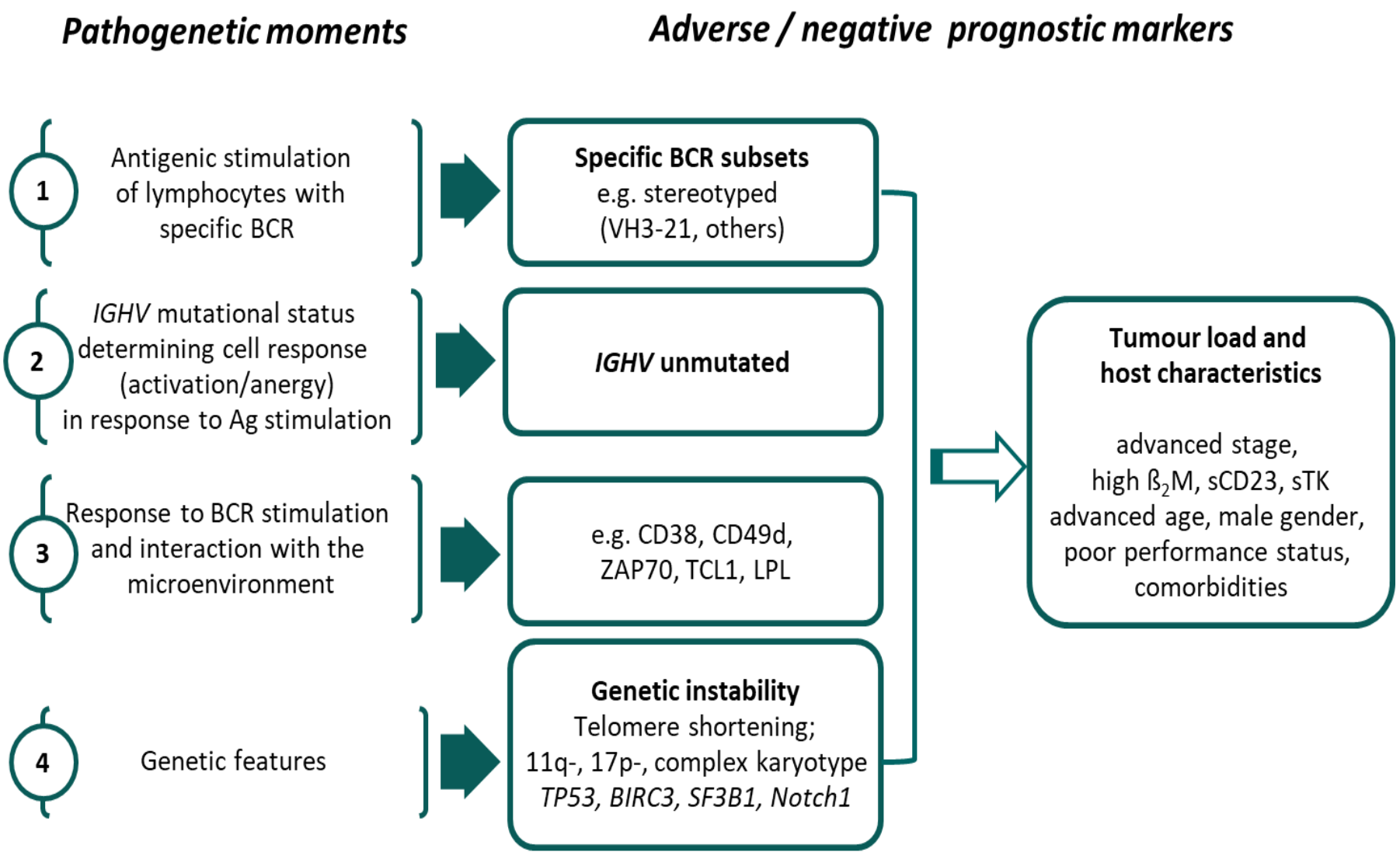
Acknowledgment for advice and preparation of the slide deck
Gianluca Gaidano, M.D., Ph.D.

DISCLOSURE
Antonio Cuneo

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Gilead					X	X	
Janssen					X	X	
Roche					X	X	
Abbvie					X	X	
Sandoz					X		
Mundipharma					X		
Novartis					X		
BMS					X		
Amgen						X	

The pathogenesis of CLL and prognostic biomarkers

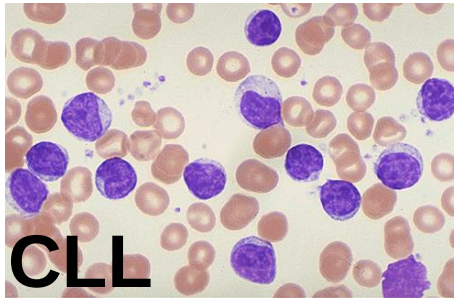


Ag, antigen; β_2M, β2-microglobulin; BCR, B-cell receptor; BIRC3, baculoviral IAP repeat containing 3; IGHV, Ig heavy chain variable region; LPL, lipoproteinlipase; s, serum; SF3B1, splicing factor 3B subunit 1; TCL1, T cell leukaemia/lymphoma 1; TK, thymidine kinase; TP53, tumour protein 53; ZAP70, zeta-associated protein-70.

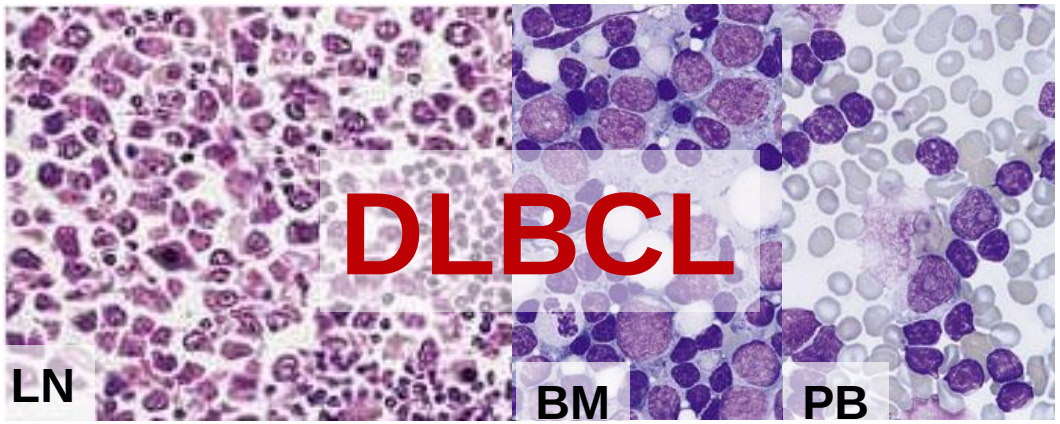
Outline

- **Definition of Richter syndrome**
- Frequency of Richter syndrome
- Genetics of Richter syndrome
- Reasons for treatment failure in Richter syndrome
- Investigational treatment approaches for Richter syndrome

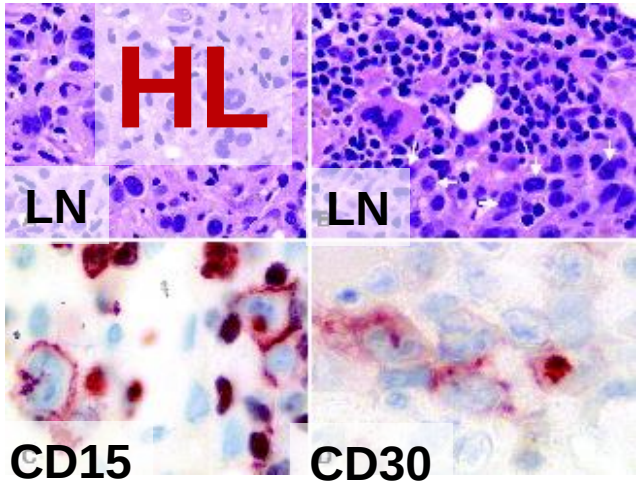
Definition of Richter syndrome



95-99%



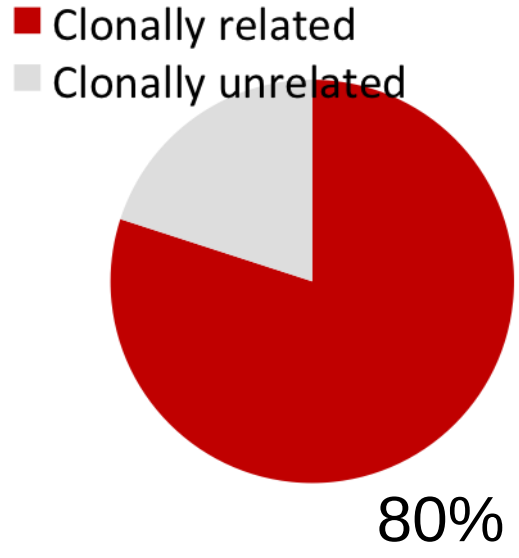
1-5%

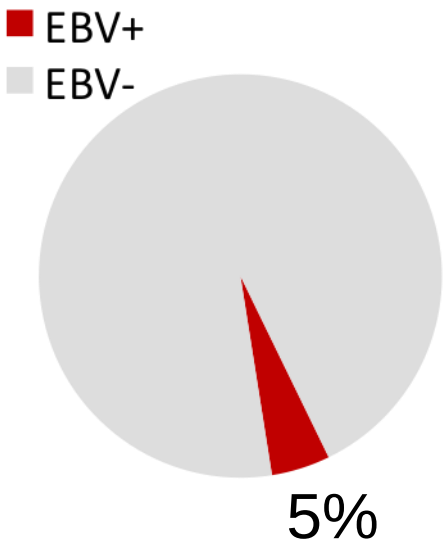


Müller-Hermelink HK, et al, WHO Classification 2008

DLBCL vs HL variants of Richter syndrome

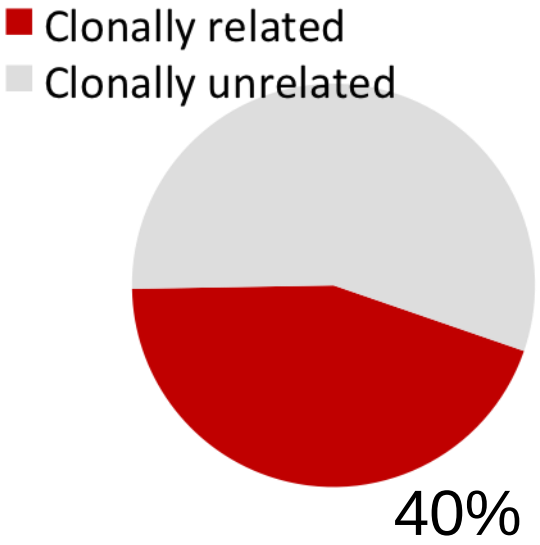
DLBCL variant

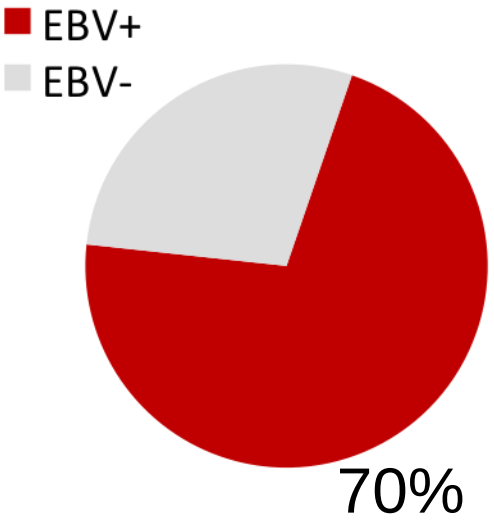




Median OS: <1 y

HL variant





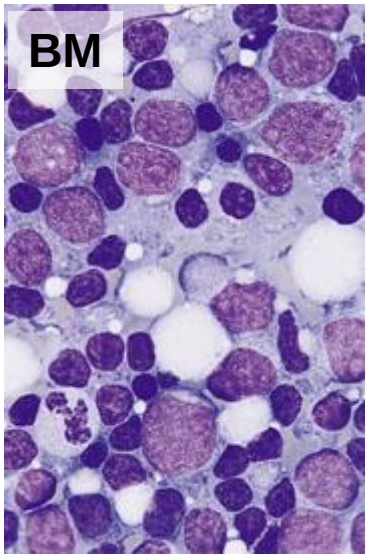
Median OS: 4 y

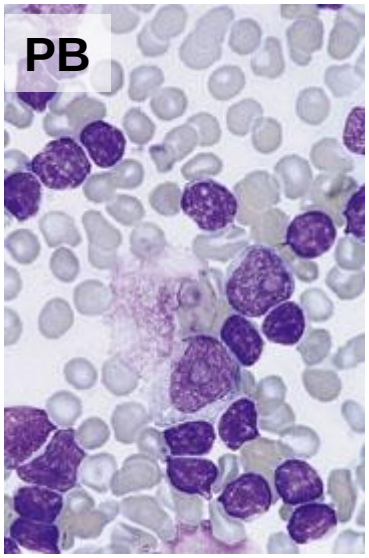
Abruzzo et al, Am J Surg Pathol 2002; 26: 630-6 O'Brien et al, Cancer 2003; 98: 2657-663 Thornton et al, Leuk Res 2005; 29: 389-95 Ammatuna et al, Leuk Lymphoma 2009; 50:; 857-8 Kanzler et al, Blood 2000; 95:1023-31 Tsimberidou et al, Cancer 2006; 107: 1294-302 Rossi D, et al, Clin Cancer Res 2009; 115: 4415-22, Xiao et al, Hum Pathol 2016;55:108-16

Clinical clues of Richter transformation

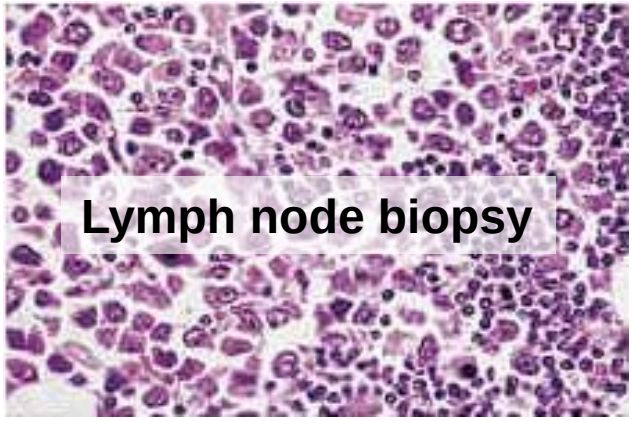
Clinical suspicion of RS

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

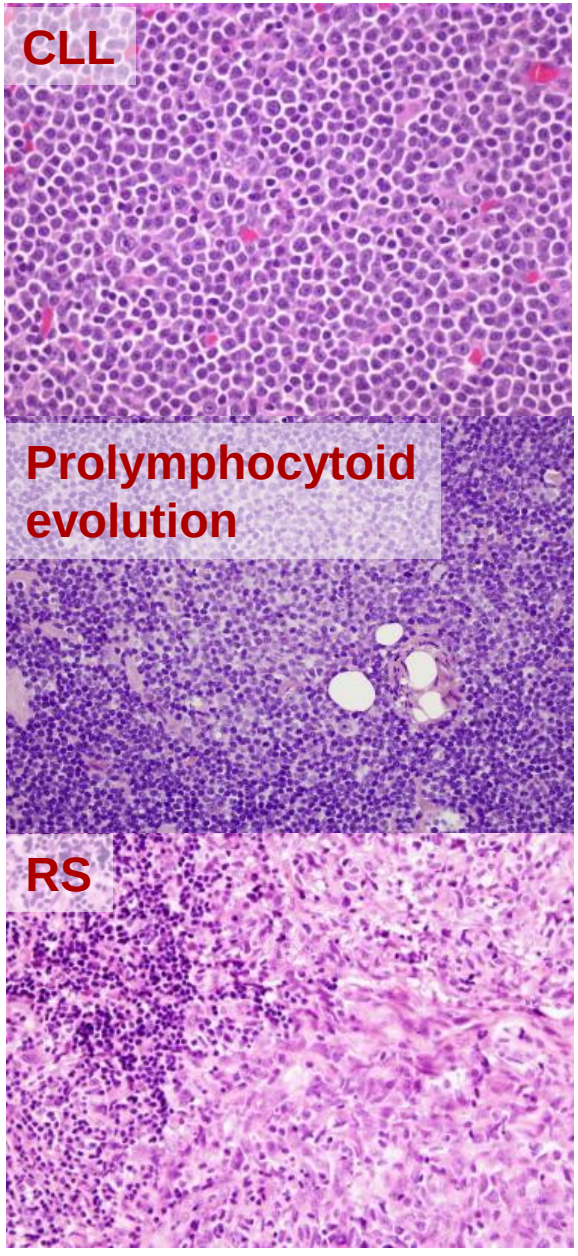


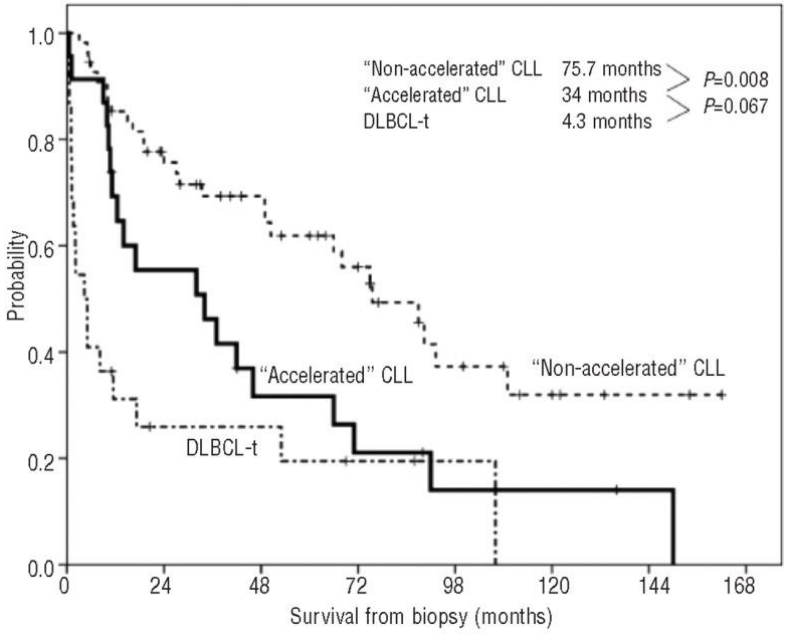


BIOPSY IS MANDATORY (PET-guided)



Differential diagnosis: prolymphocytoid evolution





Ginè et al, Haematologica 2010

After pathology revision, ~20% of 'RS' are downgraded to CLL in prolymphocytoid evolution

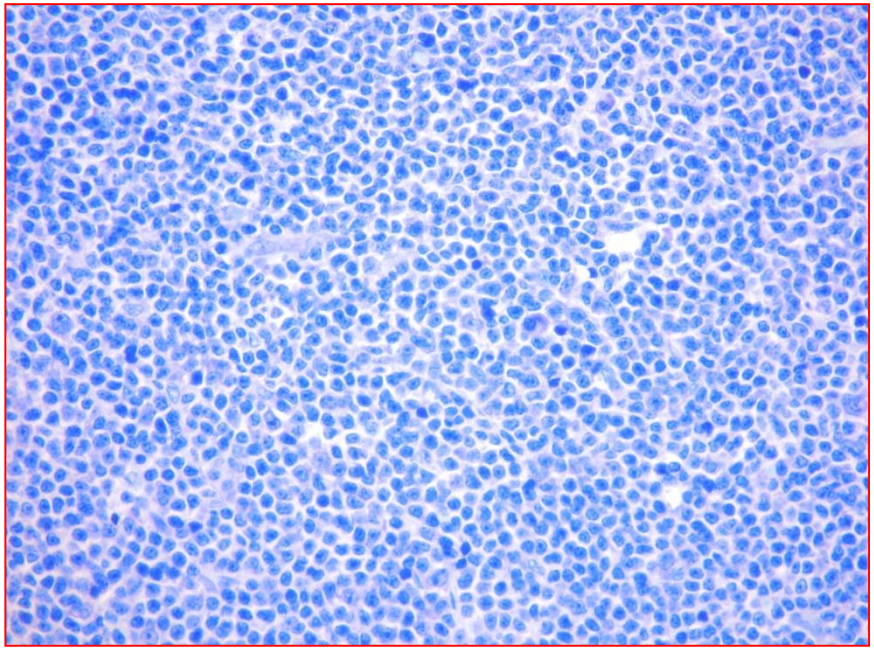
Soilleux et al, Histopathology 2016

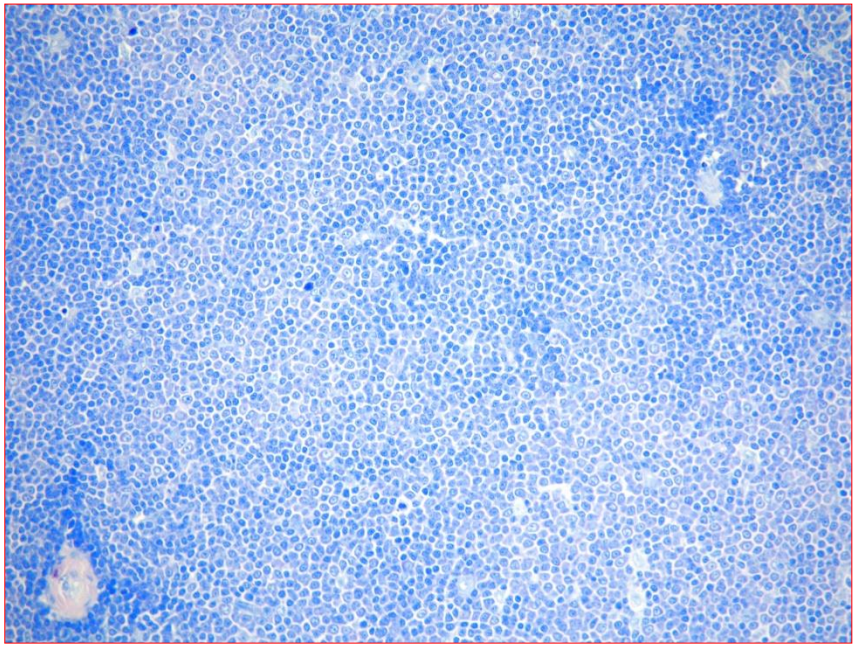
PROLIFERATION CENTERS IN CLL CORRELATION WITH CYTOGENETIC AND CLINICOBIOLOGICAL FEATURES IN 183 CONSECUTIVE PATIENTS ANALYZED ON TISSUE MICROARRAYS

Sezione di Ematologia
Azienda Ospedaliero-Universitaria di Ferrara

Ciccone M et AL, Leukemia. 2012 Mar;26(3):499-508

RESULTS (Histology): 183 cases undergoing lymph node biopsy for disease progression and LN size > 3 cm)



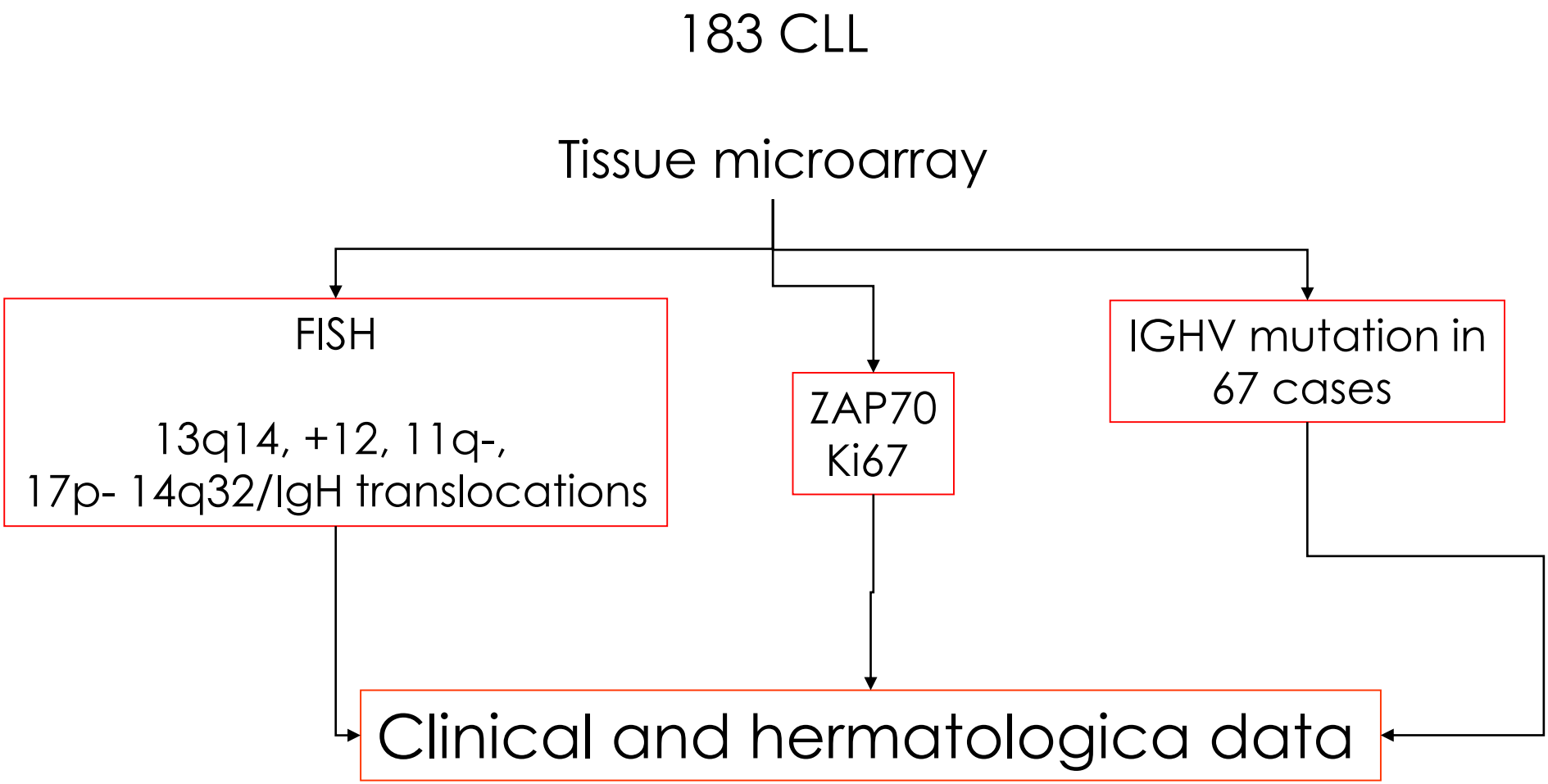


"typical" **CLL (small, ill-defined PCs)**

"PCs-rich" **CLL confluent PCs**

108 (59.1%) patients

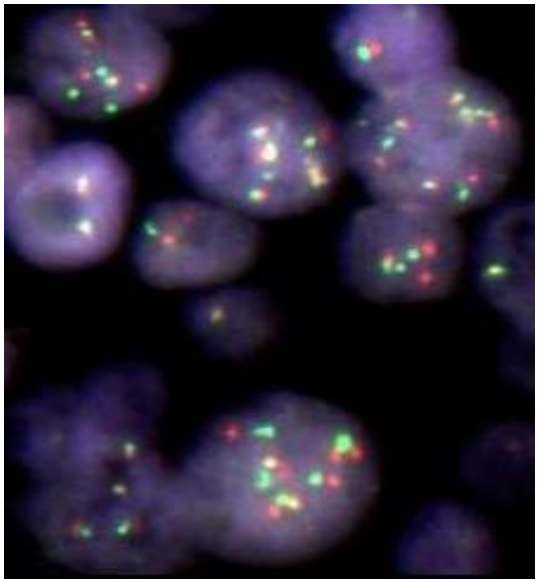
75 (40.9%) patients

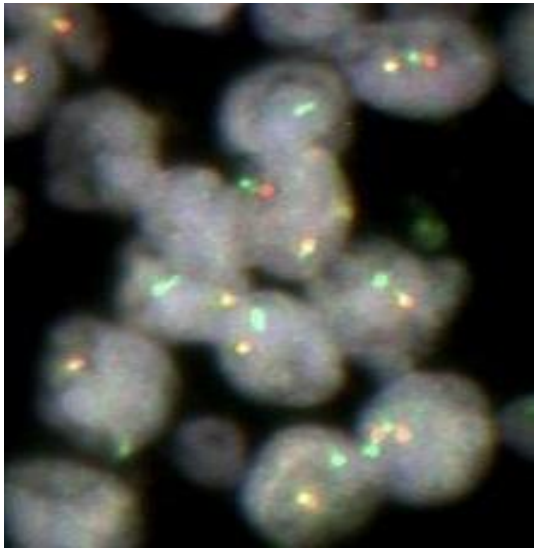

183 CLL
Tissue microarray
FISH
13q14, +12, 11q-,
17p- 14q32/IgH translocations
ZAP70
Ki67
IGHV mutation in
67 cases
Clinical and hermatologica data

RESULTS (FISH) (ii)

Frequency of chromosome aberrations

ABNORMALITY	FREQUENCY (101 cases (hyerarchical))	183 cases
17p-	17/101	15.6%
11q-	20/101	24.7%
14q32	16/101	30.8%
+12	11/101	24.7%
13q-	15/101	36.7%

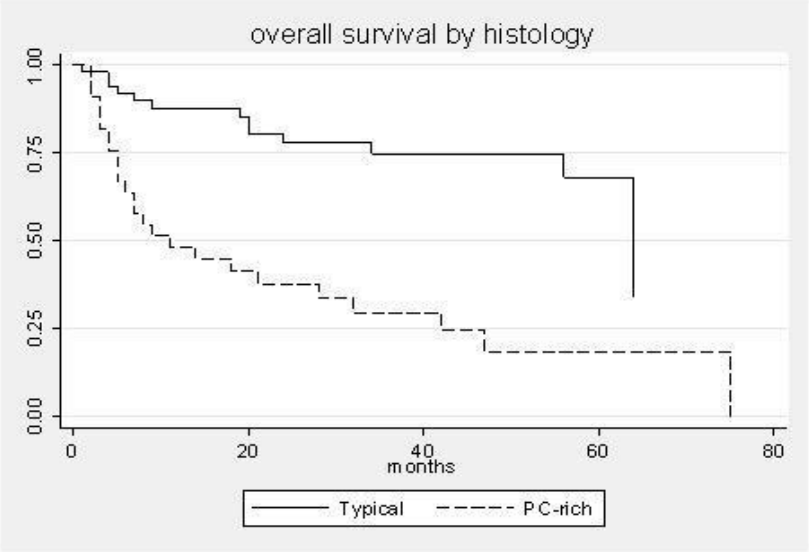




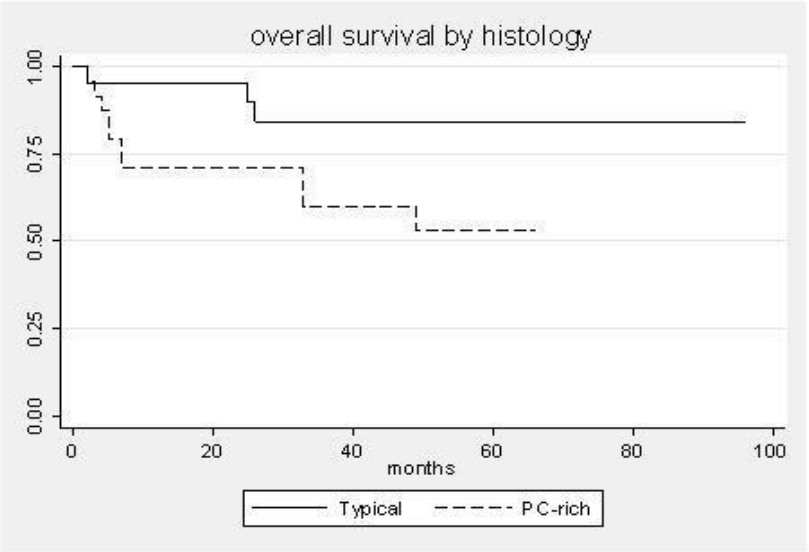
	Typical (N°. of cases)	*PCs- rich (N°. of cases)*	*p value*
Age (median)	63.9 (sd 10.4)	65.0 (sd 12.3)	Ns
Sex (F/M)	24/40	17/20	ns
Stage at biopsy (0-II / III-IV)	27/25	15/18	ns
17p- (No/Yes)	62/2	22/15	<0.001
11q- (No/Yes)	49/15	26/11	Ns
14q32 translocation (No/Yes)	50/14	18/19	0.002
+12 (No/Yes)	53/8	25/12	0.021
13q- (No/Yes)	35/29	27/10	ns
High-risk FISH (No/yes) (11q- and/or 17p-)	48/16	16/21	0.001

Figure 4

A



B



Survival by histology in patients with a full set of clinicobiologic data

Survival by histology in the remaining patients

****Cox proportional-hazards analysis:***
PCs-rich pattern retained predictive value of poor outcome (HR 2.74, 95% CI 1.16–6.51, P=0.0022)

Ciccone M et AL, Leukemia. 2012 Mar;26(3):499-508

Differential diagnosis: criteria for Richter

Criteria for differentiating DLBCL-type RS from histologically aggressive CLL have been proposed and include the occurrence of:

i) large B-cells with nuclear size equal or larger than macrophage nuclei or more than twice a normal lymphocyte;

ii) diffuse growth pattern of large cells (not just presence of small foci)

By applying these criteria, up to 20% of cases diagnosed as DLBCL-type RS would be more appropriately classified as histologically aggressive CLL

Soilleux EJ, Histopathology 2016

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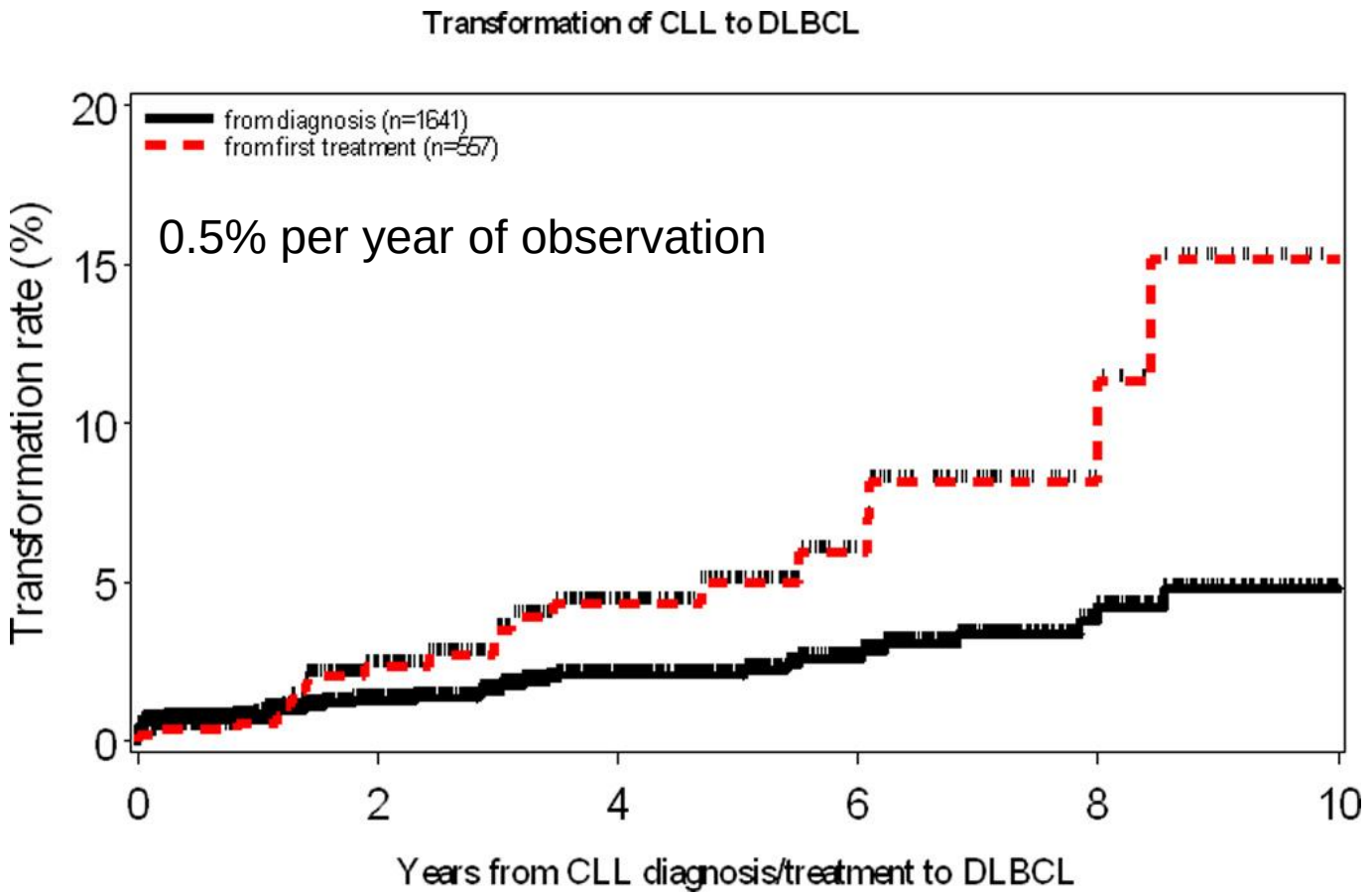
Cumulative incidence of Richter syndrome “then”



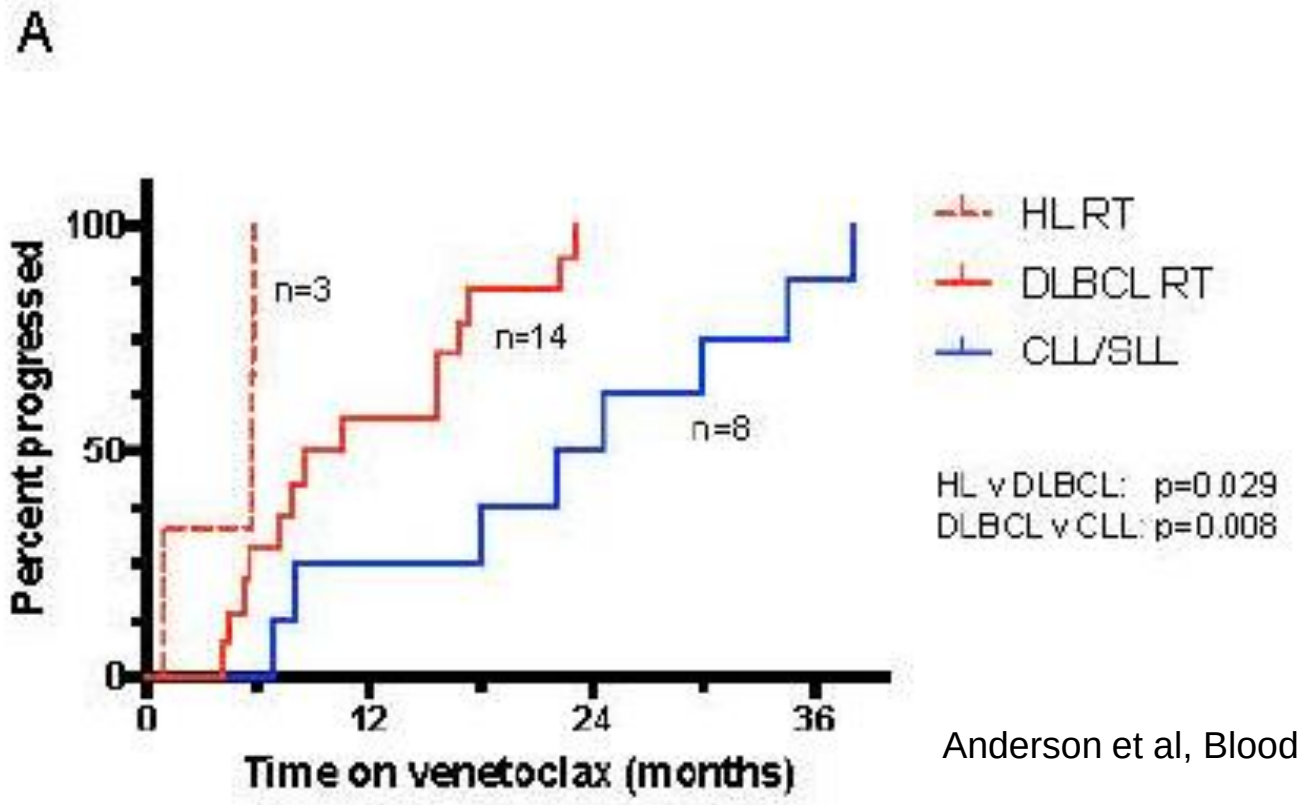
Parikh et al Br J Haematol 2013

Incidence of Richter syndrome "now"

Reference	Total pts	Study population	Treatment	Pts that developed RS	RS prevalence
Burger, 2015	186	Treatment naive	Ibrutinib	0	0%
Byrd, 2014	391	Relapsed	Ibrutinib	4	1%
O'Brien, 2014	29	Treatment naive	Ibrutinib	1	3%
Jain, 2015	127	Relapsed/Refractory	Ibrutinib	7	5%
Farooqui, 2015	51	17p deleted	Ibrutinib	3	6%
Mato, 2016	178	BCRi treated	Ibrutinib, idelalisib	13	7%
Byrd, 2013	85	Relapsed/Refractory	Ibrutinib	7	8%
Seymour, 2017	49	Relapsed/refractory	Venetoclax-rituximab	5	12%
Roberts, 2015	116	Relapsed/Refractory	Venetoclax	18	16%
Seymour, 2017	49	Relapsed/refractory	Venetoclax-rituximab	5	12%
Strati, 2014	63	17p deleted	Heterogeneous	15	23%

Heterogeneity conceivably due to: case mix, 1° line vs R/R, observation time

Richter syndrome in R/R CLL treated with novel agents is an early event



Anderson et al, Blood 2017

In all datasets of R/R CLL treated with novel agents (BCRi, Venetoclax), emergence of Richter syndrome is an early event, suggesting expansion of a clone that had been previously selected by chemotherapy

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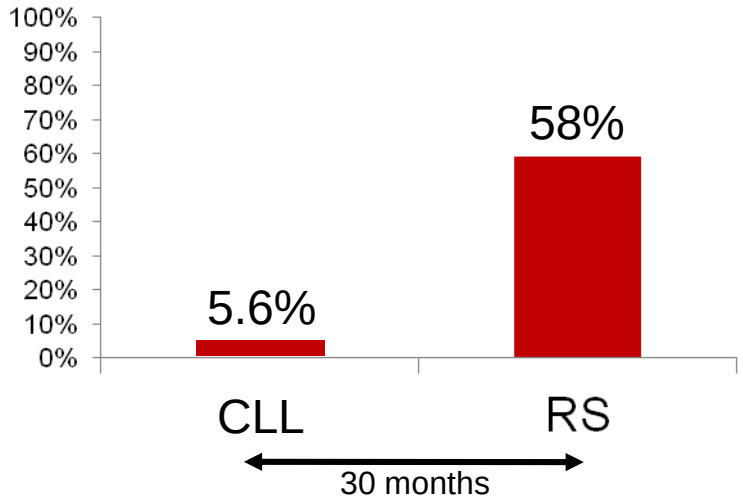
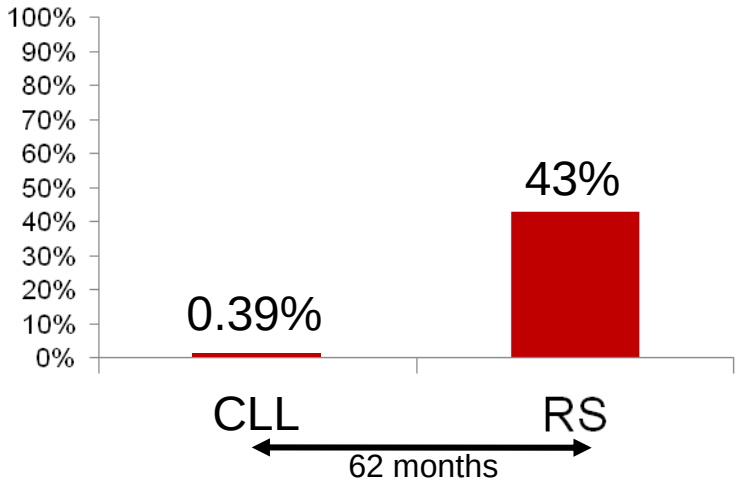
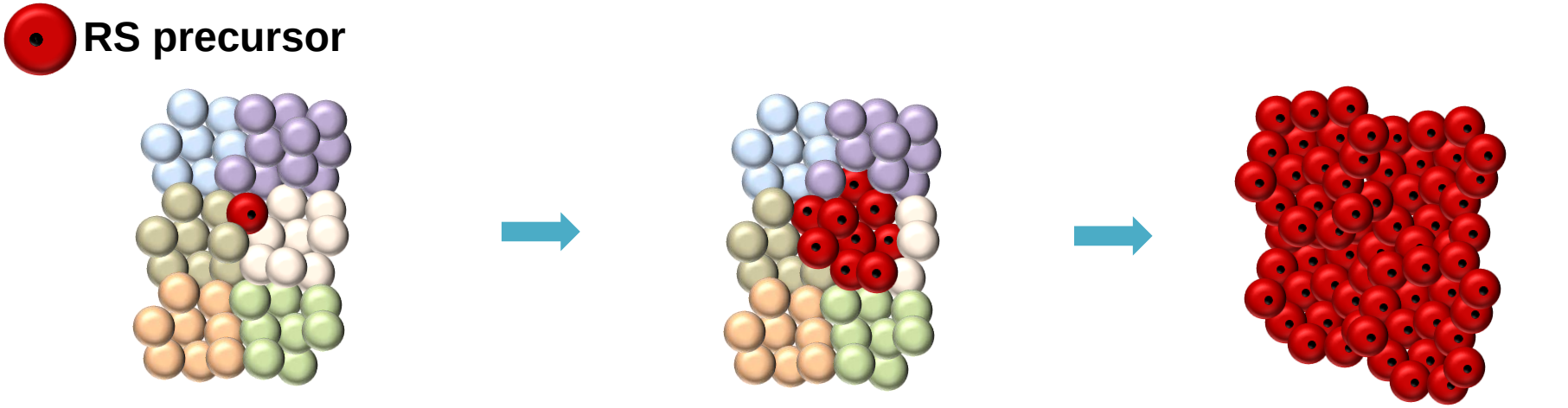
The genetic lesions of Richter syndrome are detectable at subclonal levels in the initial CLL clone

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



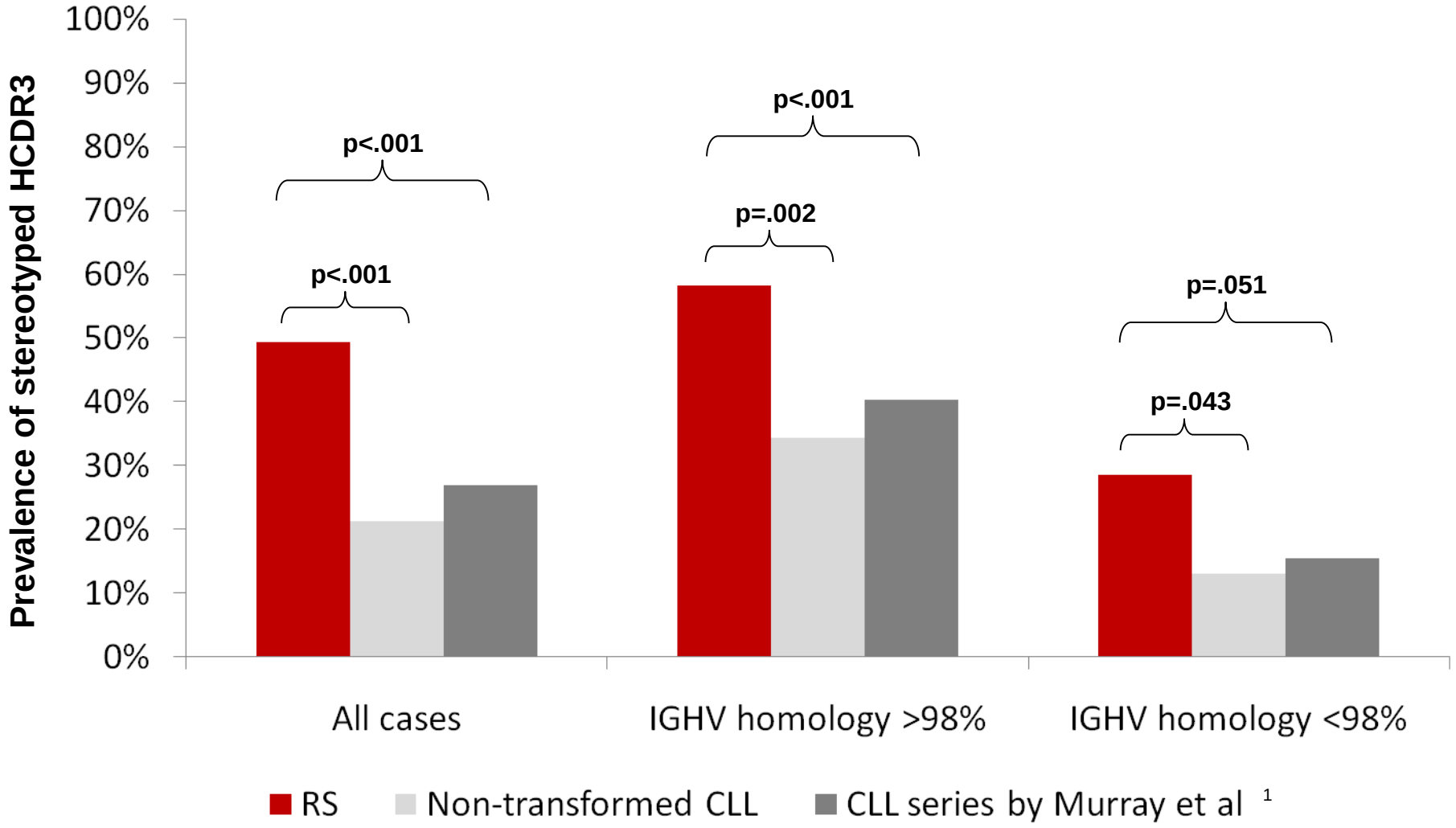
TP53 EX7: c.716A>C p.N239T (heterozygous)





Fabbri G, et al, J Exp Med 2011; 208:1389-401; **Rossi D**, et al. Blood 2012; 119: 521-9

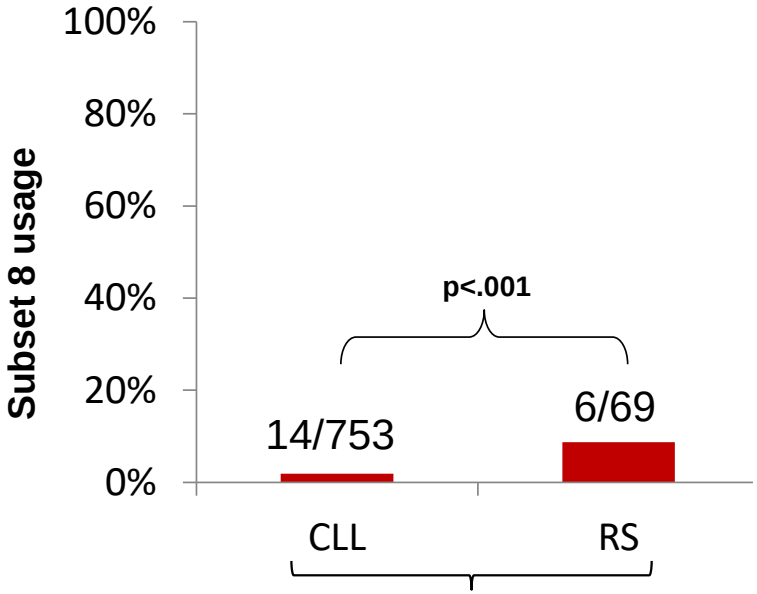
High frequency of stereotyped HCDR3s in Richter syndrome

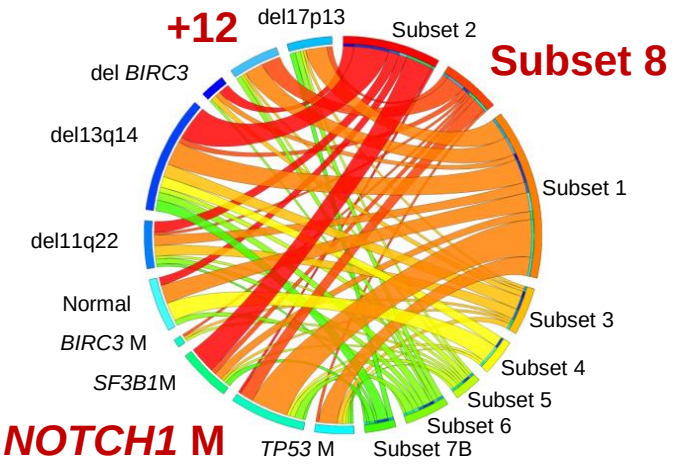


Rossi et al, Clin Cancer Res 2009

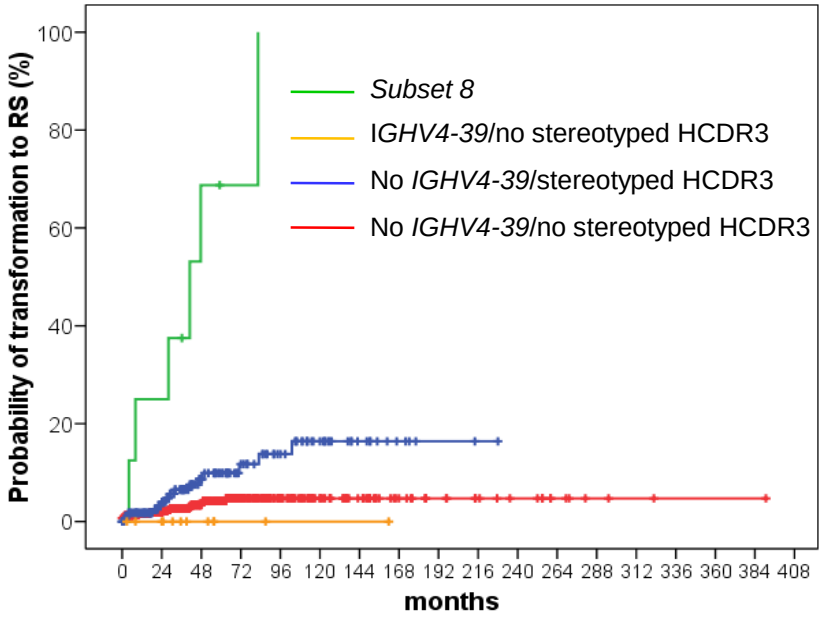
[1]Murray et al, Blood 2008

Richter syndrome show biased usage of the BCR in the subset 8 (*IGHV4-39*) configuration



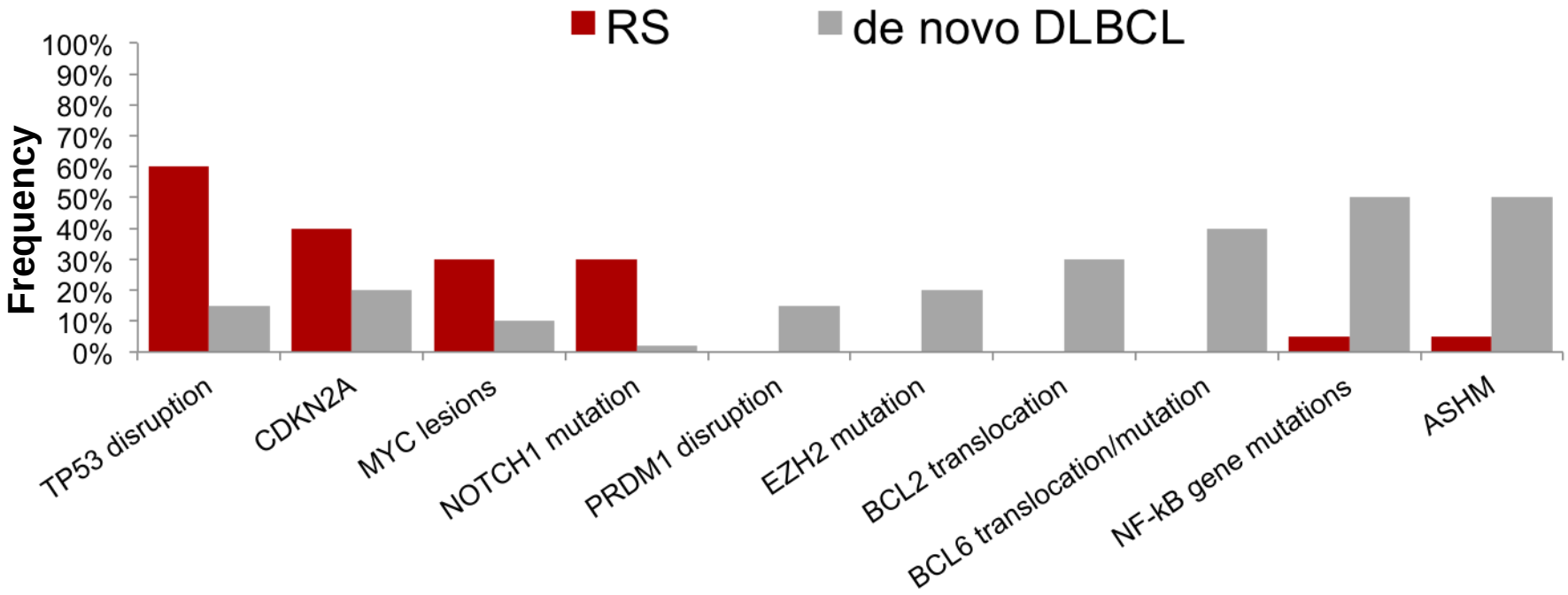


- BCR from subset 8 CLL display extreme antigen polyreactivity
- Subset 8 CLL clones respond avidly to stimulation by multiple antigens

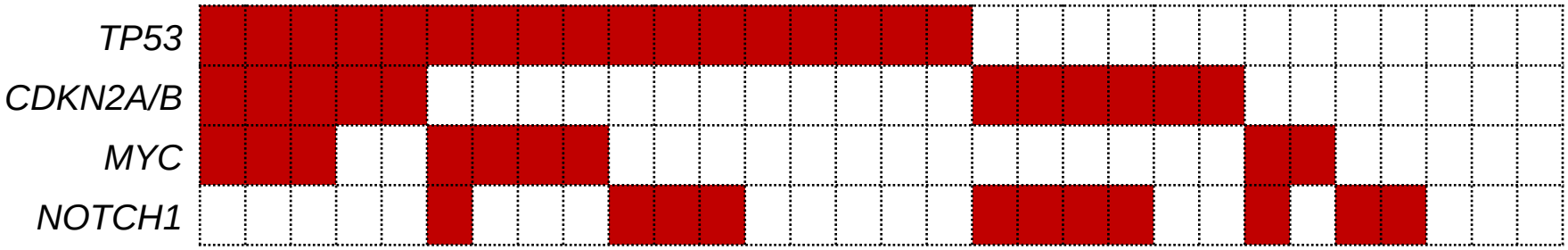


Rossi D, et al, Clin Cancer Res 2009; 15: 4415-22
Chu, et al, Blood 2011; 117:2227-36
Rossi D, et al, Blood 2013; 121: 4902-5
Gounari M, et al, Blood 2015; 125: 3580-7

The genetic profile of Richter sydrome differs from that of *de novo* DLBCL

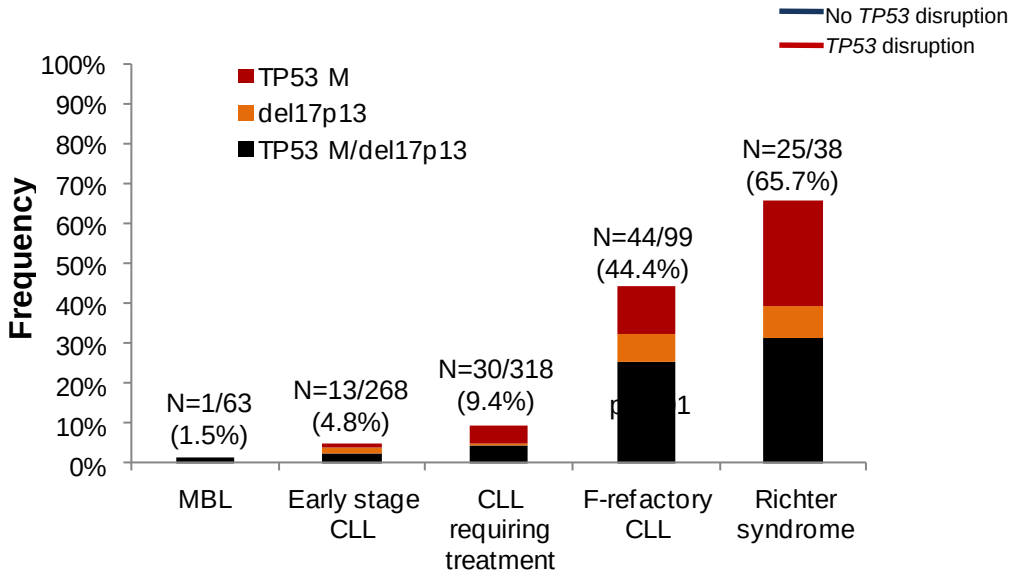


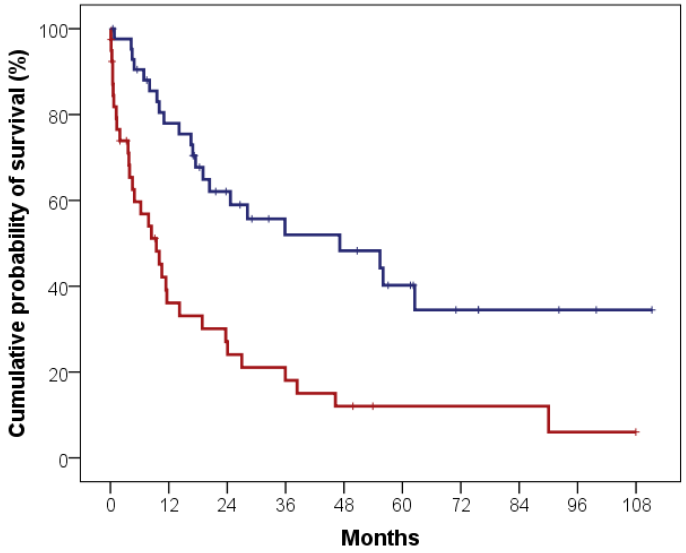
Lesions of *TP53*, *NOTCH1*, *MYC* and *CDKN2A* recapitulates 90% RS



Rossi D, et al. Blood 2011; 117: 3391-401 **Fabbri G**, et al. J Exp Med 2011; 208:1389-401 **Fabbri G**, et al. J Exp Med 2013; 210: 2273-88 **Chirginova** et al. Blood 2013; 122: 2673-82 **Monti**, et al. Hematol Oncol 2014; 32: 155-7

TP53 abnormalities in Richter syndrome

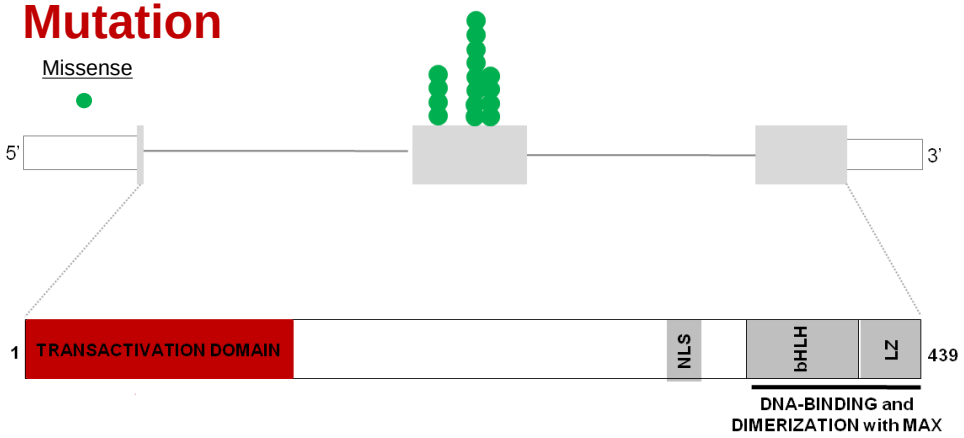


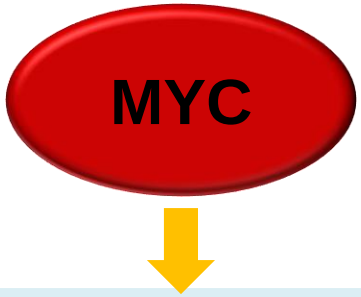


Döhner H, et al. New Engl J Med 2000;343:1910–6;**Rasi S,** et al. Haematologica 2012;97:153–4; **Zainuddin N**, et al. Leuk Res 2011;35:272–4; **Zenz T**, et al J Clin Oncol 2010;28:4473–9; **Rossi D,** et al. Blood 2011;117:3391–401; **Stilgenbauer S,** et al. Blood 2014;123:3247–54; **Fabbri G**, et al. J Exp Med 2013;210:2273-88

MYC abnormalities in Richter syndrome

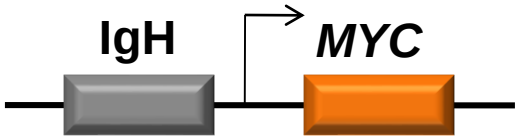
Mutation



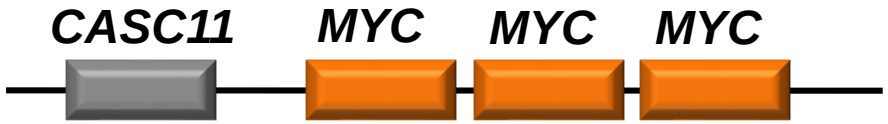


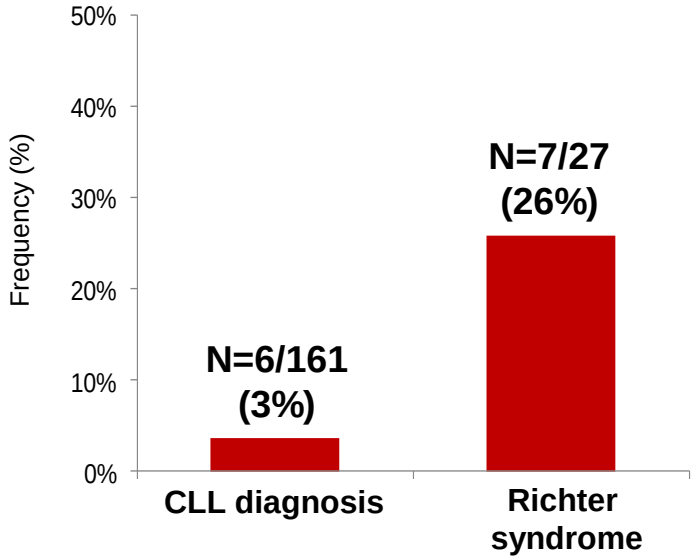
Aberrant cell proliferation
Metabolic reprogramming
Genomic instability

Translocation



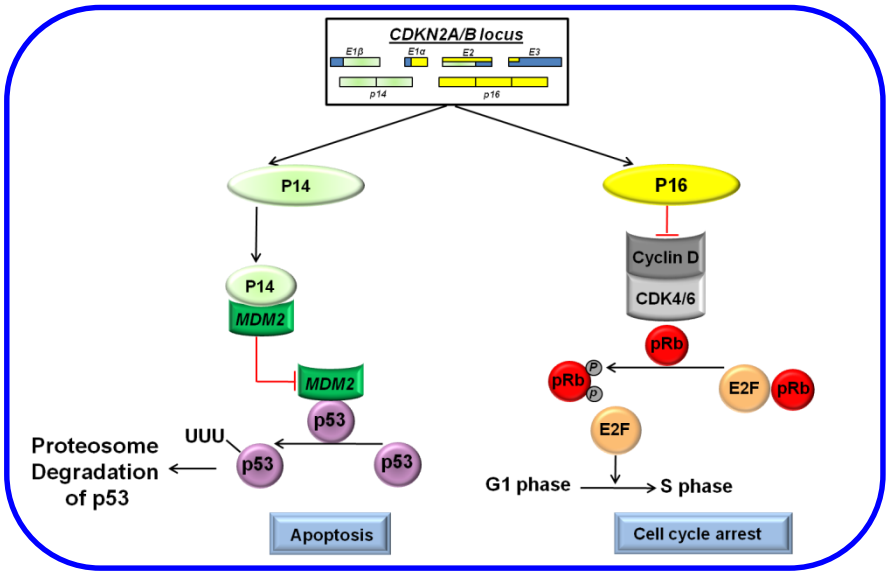
Amplification

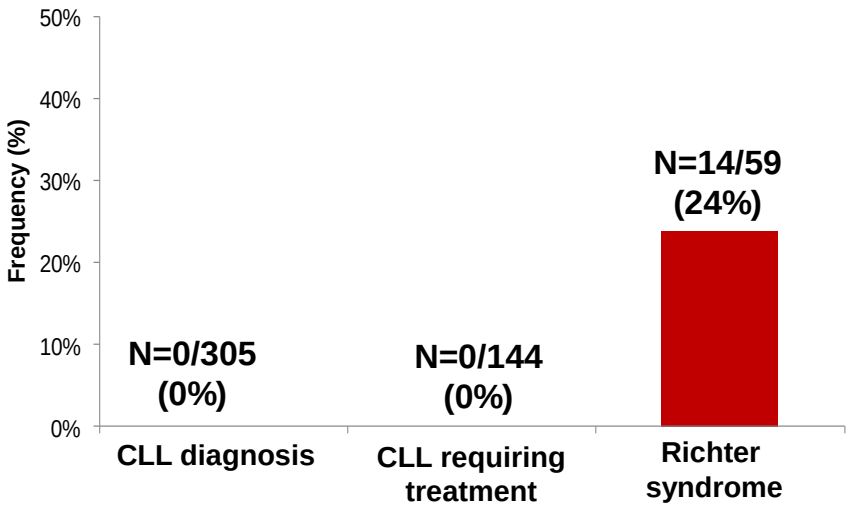




Rossi D, et al. Blood 2011;117:3391–401; **Brown J,** et al. Clin Cancer Res 2012;18:3791-802; **Fabbri G,** et al. J Exp Med 2013;210:2273-88; **Monti S,** et al. Hematol Oncol 2014;32:155-7

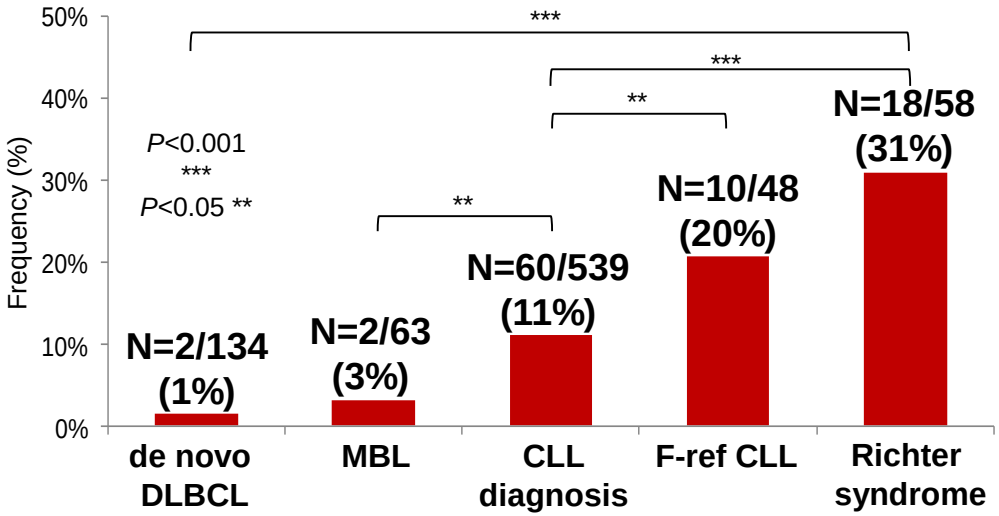
CDKN2A/B abnormalities in Richter syndrome

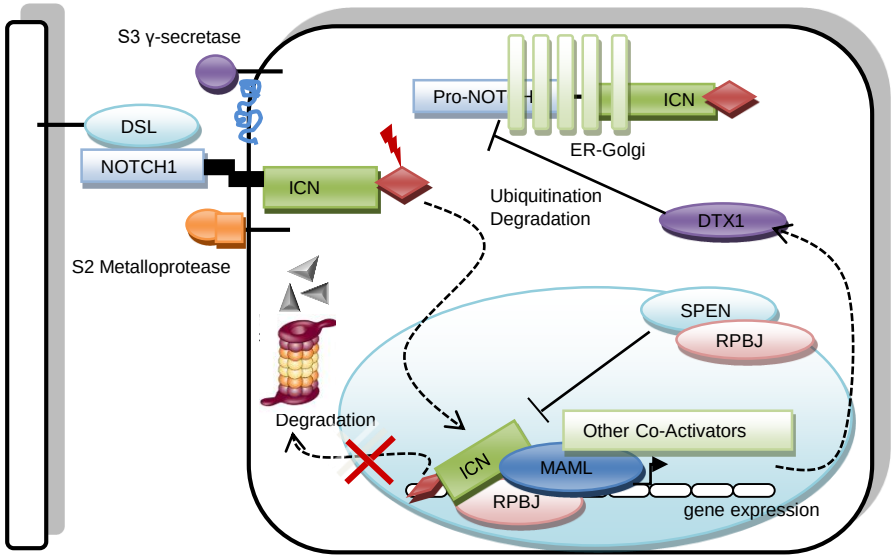




Rinaldi A, et al, Br J Haematol 2011; 154: 590-9 **Edelmann J** et al, Blood 2012; 120: 4783-94
Fabbri G et al, J Exp Med 2013; 210: 2273-88 **Chirginova** et al, Blood 2013; 122: 2673-82

NOTCH1 mutations in Richter syndrome

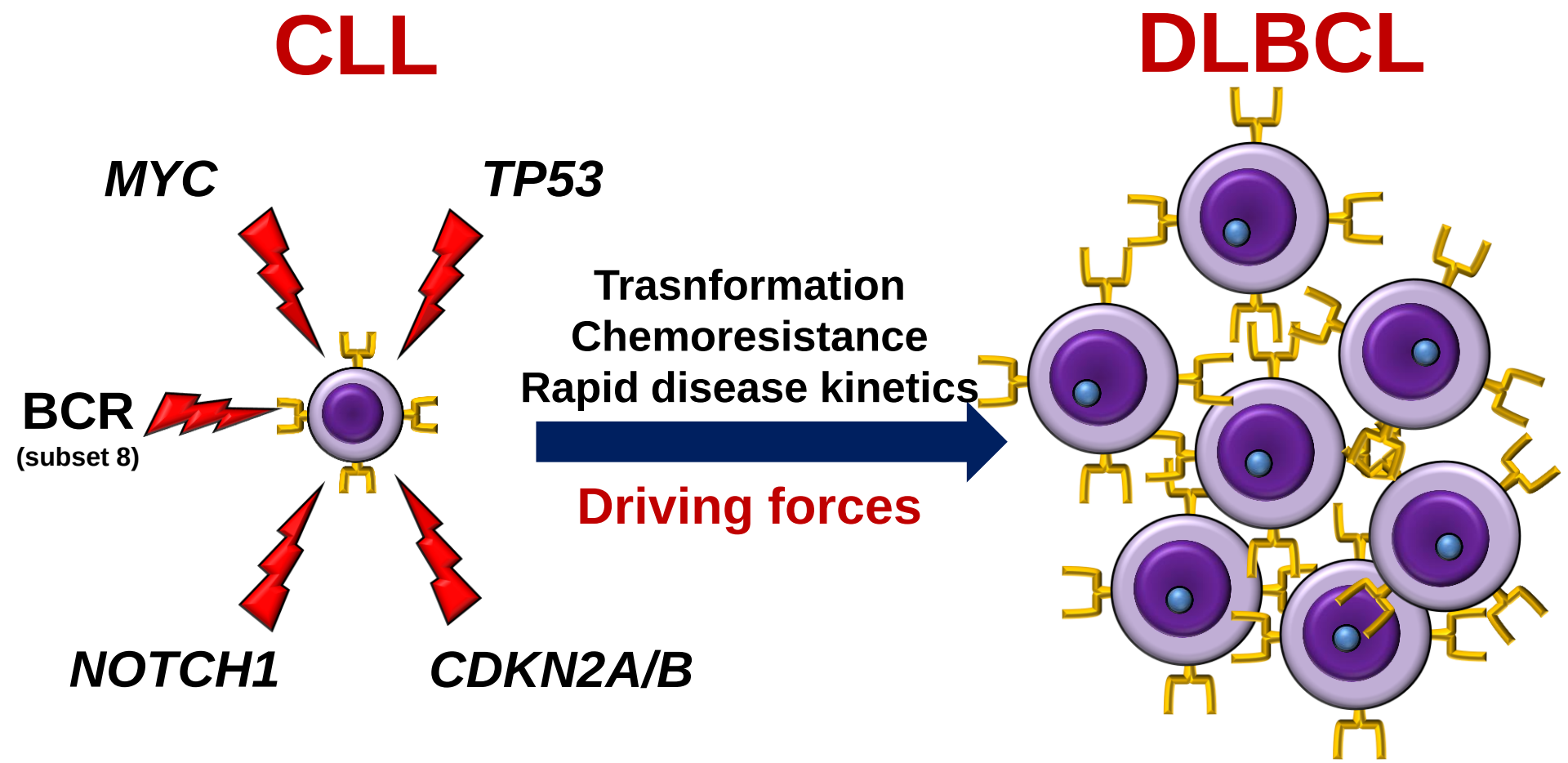




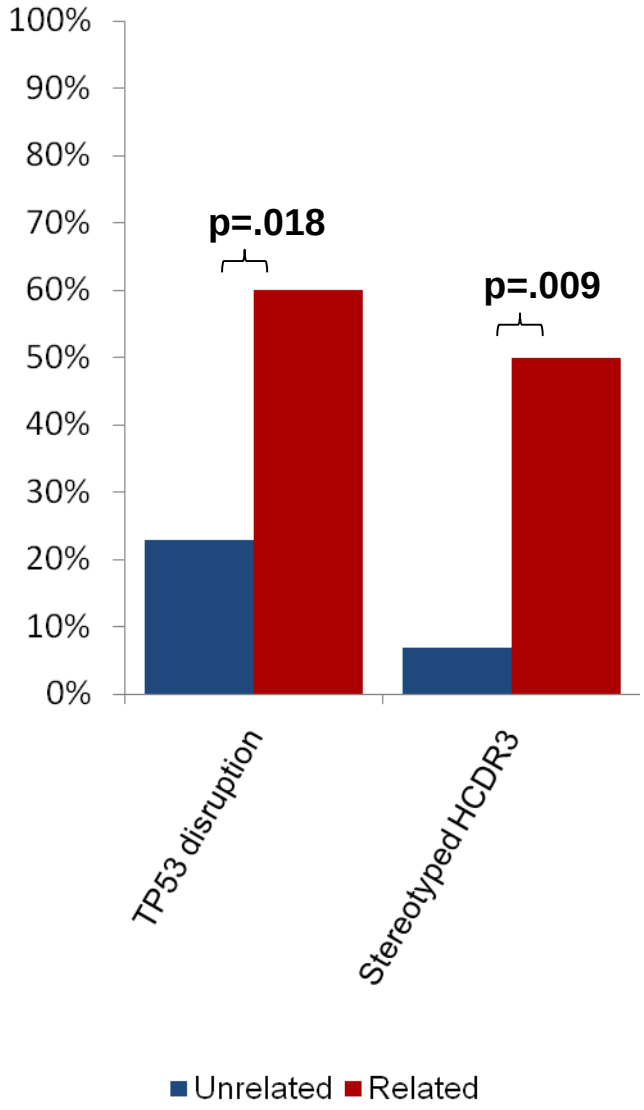
Arruga, et al. Leukemia 2013

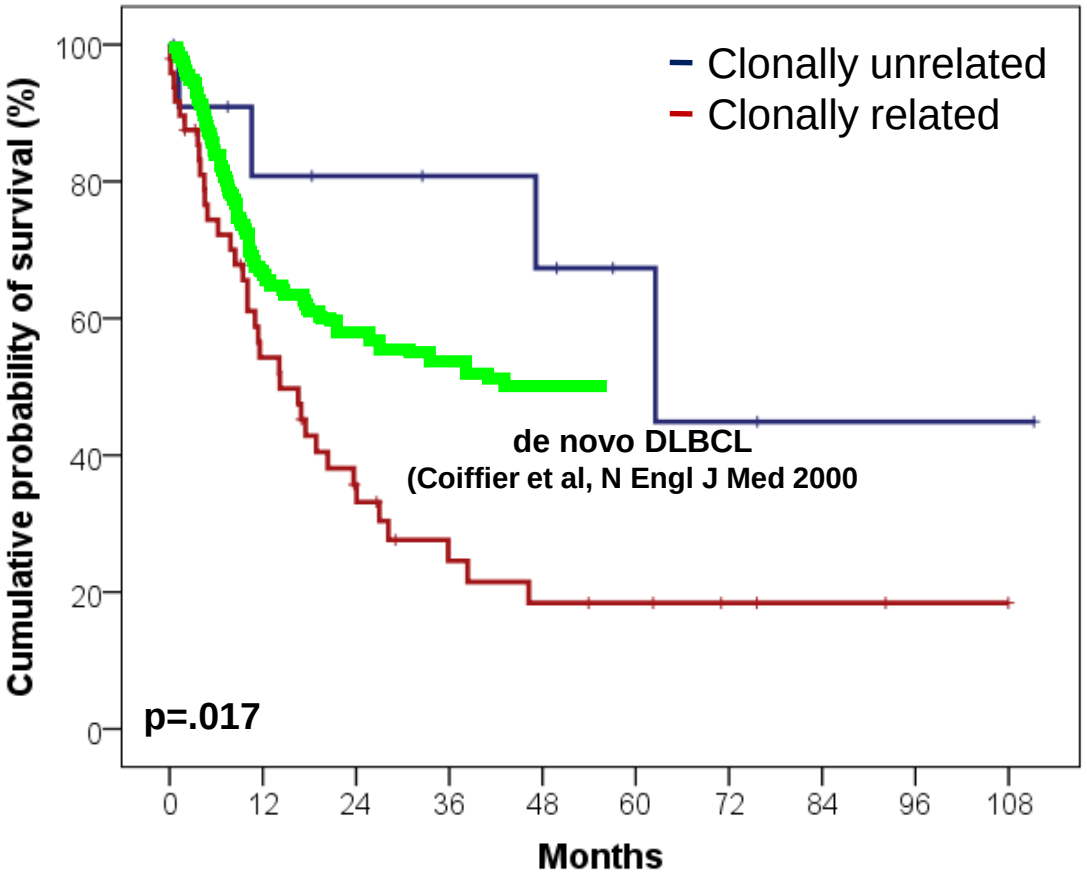
Fabbri G, et al, J Exp Med 2011; 208:1389-401
Puente X, et al. Nature 2011; 475: 101-5
Rossi D, et al. Blood 2012; 119: 521-9
Rasi S, et al. Haematologica 2012; 97: 153-4
Fabbri G et al, J Exp Med 2013; 210: 2273-88

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



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

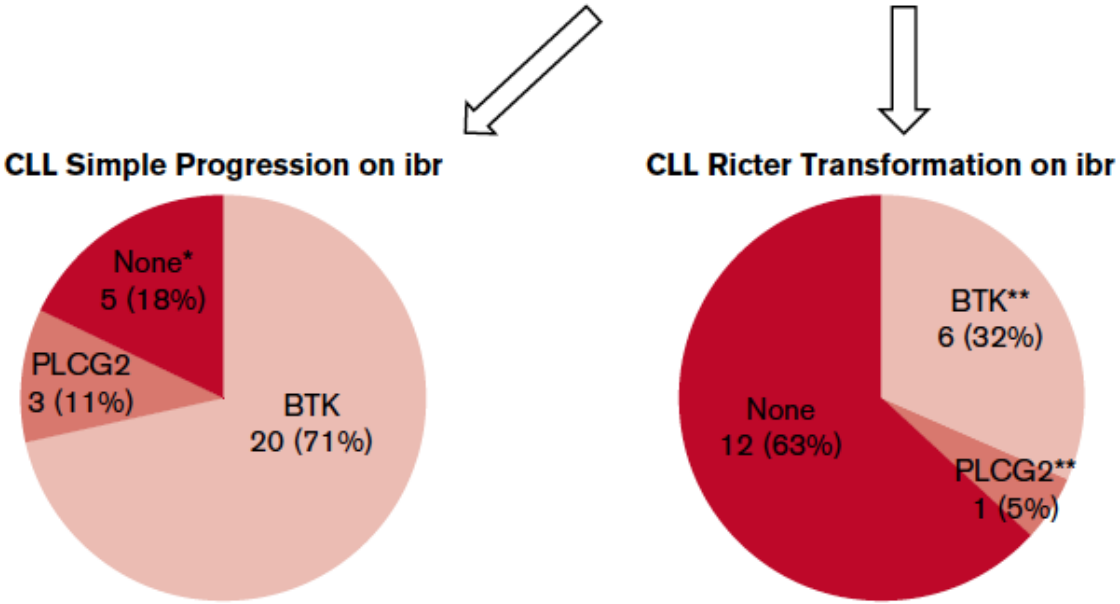




Rossi et al, Blood 2011

BTK and PLCG2 mutations in Richter syndrome developing 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

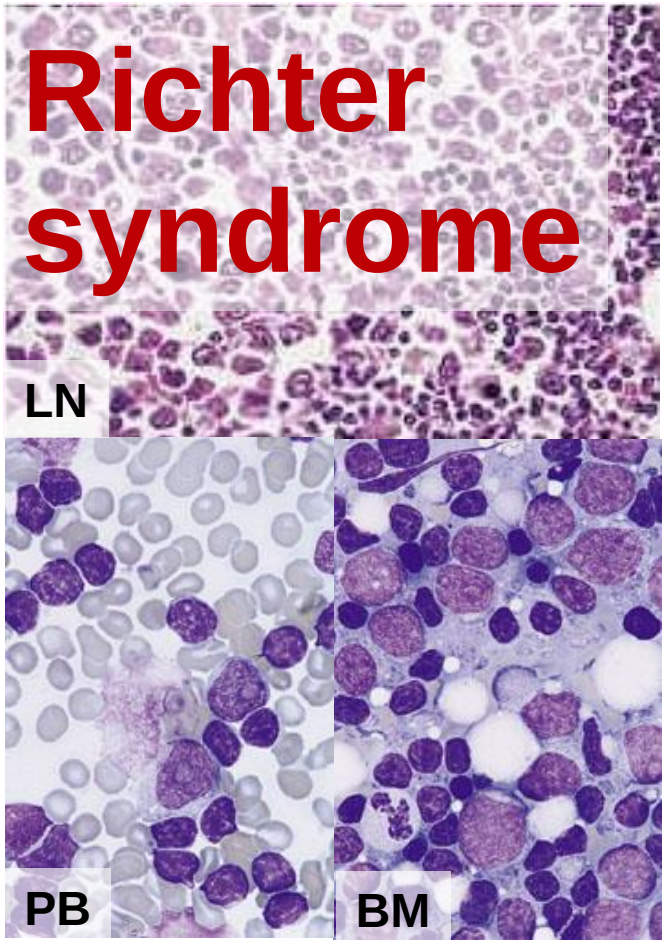


Kadri et al, Blood Adv 2017

Outline

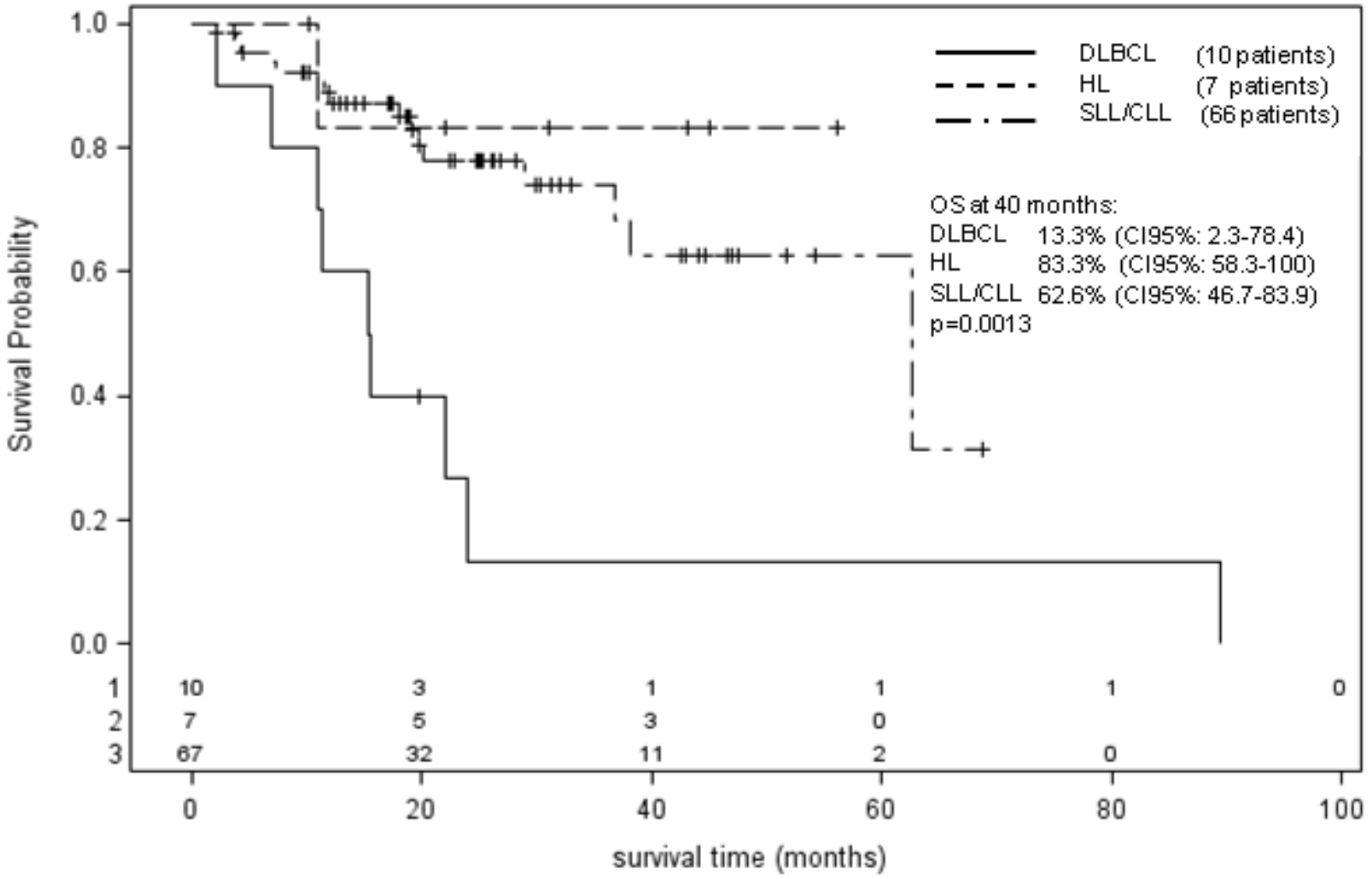
- Definition of Richter syndrome
- Frequency of Richter syndrome
- Genetics of Richter syndrome
- **Reasons for treatment failure in Richter syndrome**
- Investigational treatment approaches for Richter syndrome

Reasons for treatment failure in Richter syndrome



- Biology of the tumor
- Lack of dedicated treatments
- Patient frailty
- Late recognition

Overall survival of Richter syndrome by histology



Mauro et al, Leukemia 2014

Poor prognosis of Richter transformation after BCRi

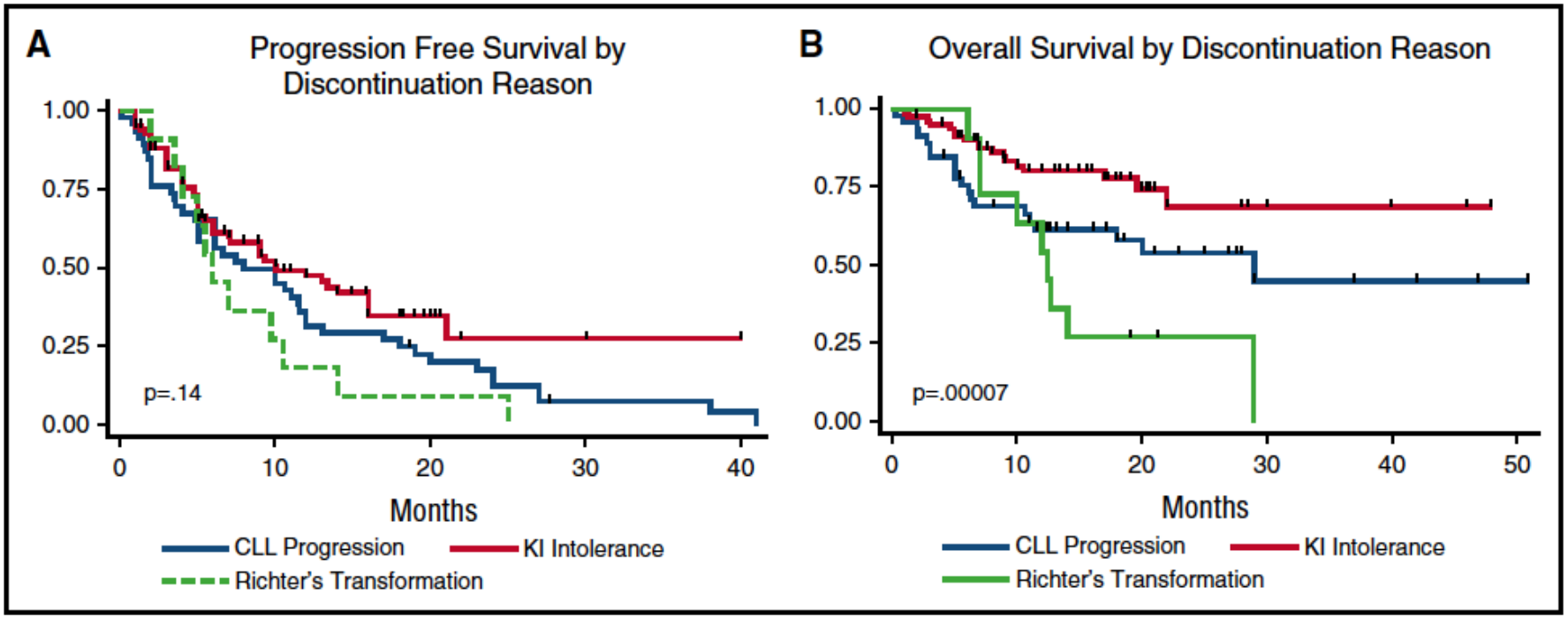
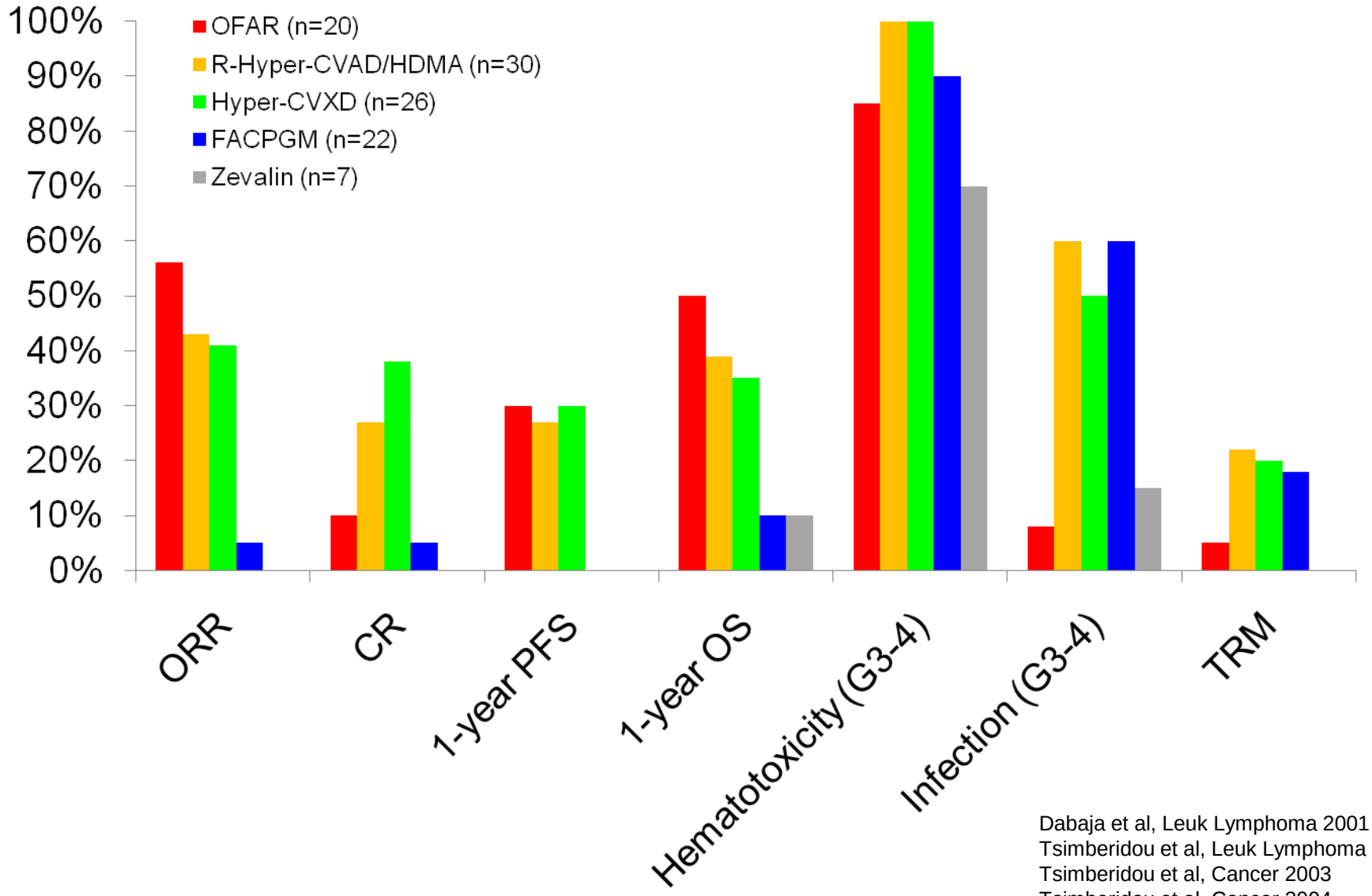


Figure 2. PFS and OS by discontinuation reason. (A-B) PFS and OS of patients after KI discontinuation, stratified by reason for discontinuation.

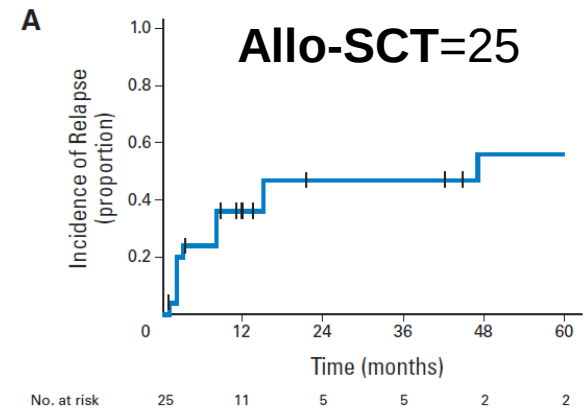
Mato et al, Blood 2016

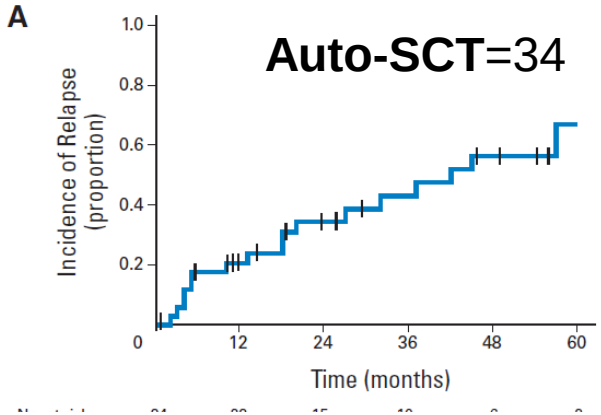
Chemo(immuno)-therapy approaches other than R-CHOP in in Richter syndrome

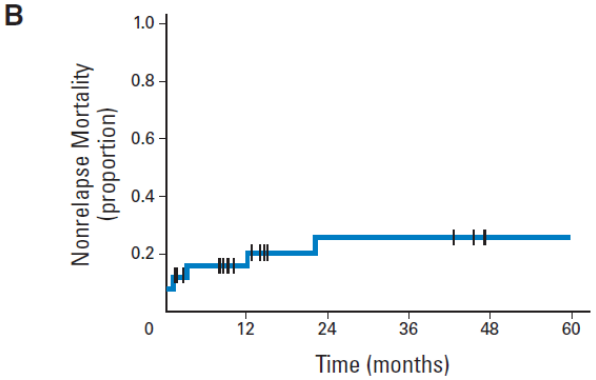


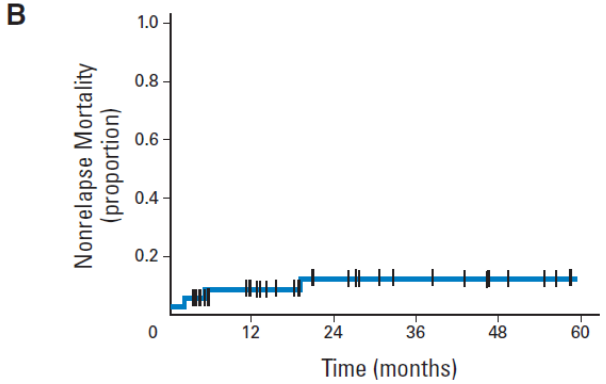
Dabaja et al, Leuk Lymphoma 2001
Tsimberidou et al, Leuk Lymphoma 2002
Tsimberidou et al, Cancer 2003
Tsimberidou et al, Cancer 2004
Tsimberidou et al, J Clin Oncol 2008

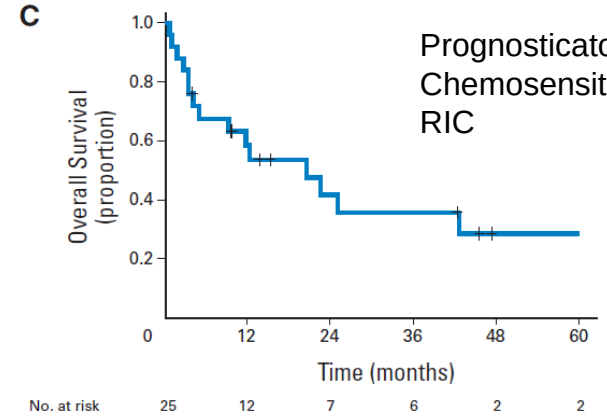
Post remission SCT is a potentially curative approach for Richter syndrome (EBMT)



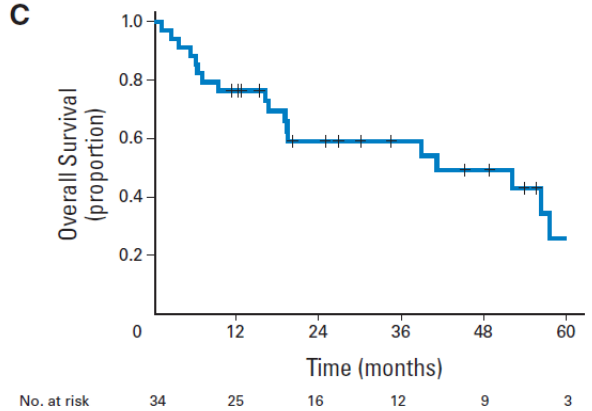






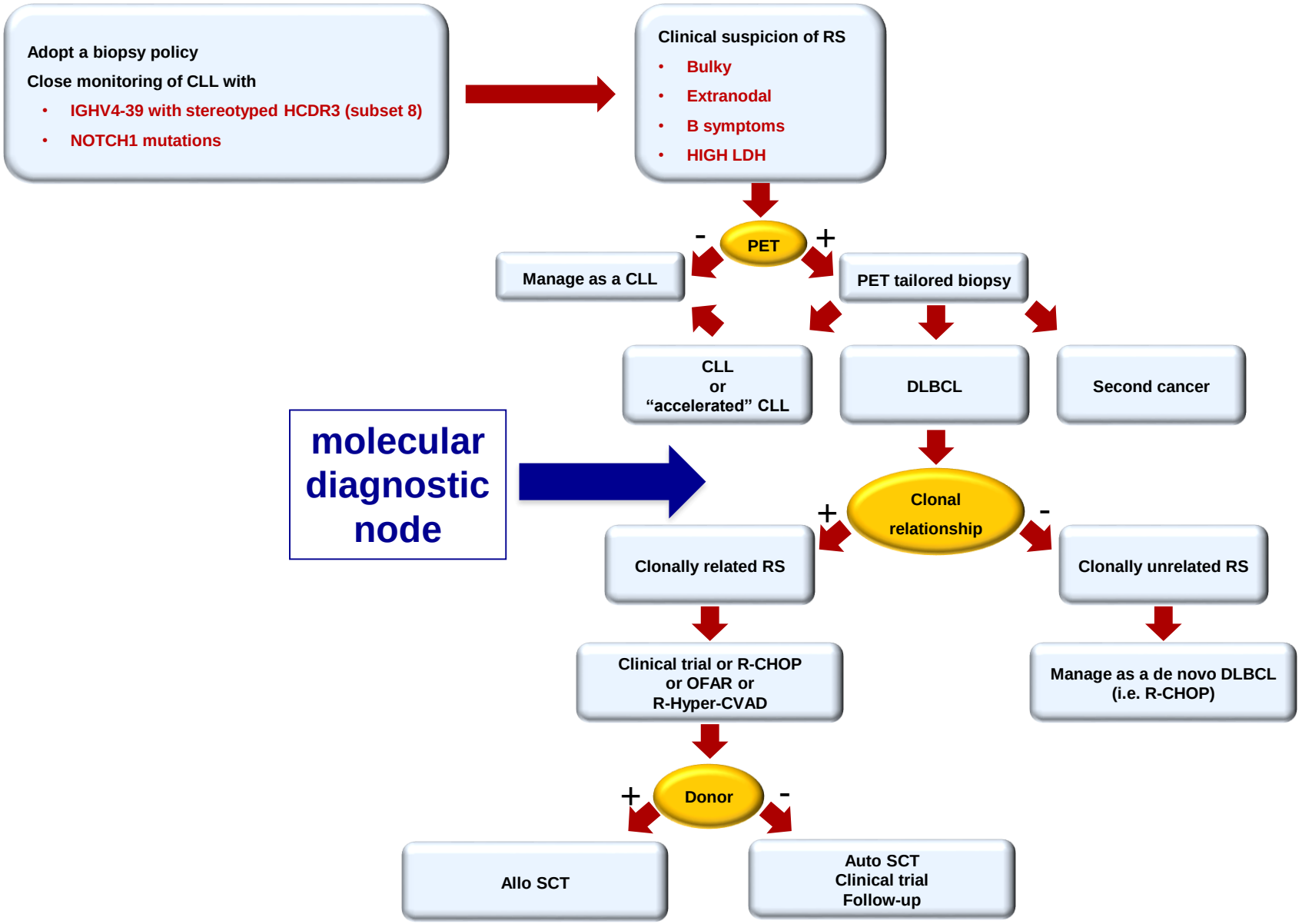


Prognosticators:
Chemosensitive disease
RIC



Cwynarski et al, JCO 2012

Molecular diagnosis for the clinical management of RS



Outline

- Definition of Richter syndrome
- Frequency of Richter syndrome
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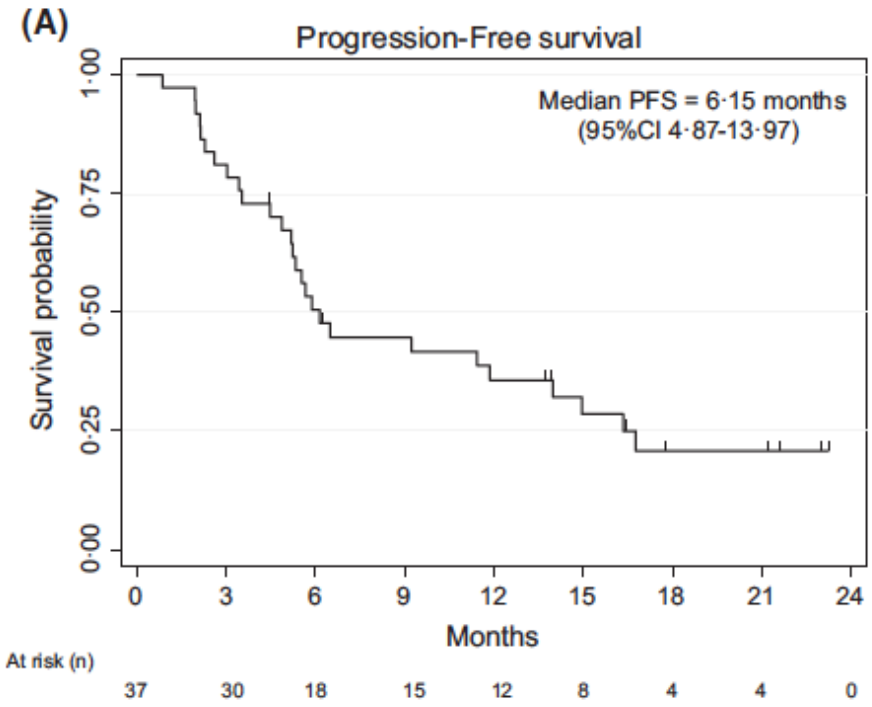
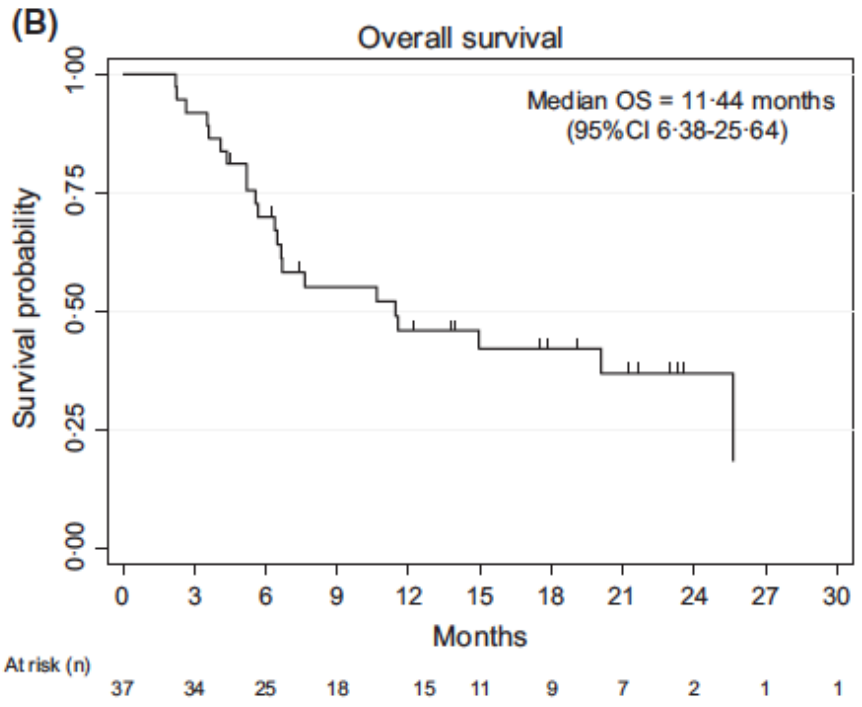
- Reasons for treatment failure in Richter syndrome
- **Investigational treatment approaches for Richter syndrome**

CHOP in combination with ofatumumab in induction and maintenance in newly diagnosed Richter syndrome





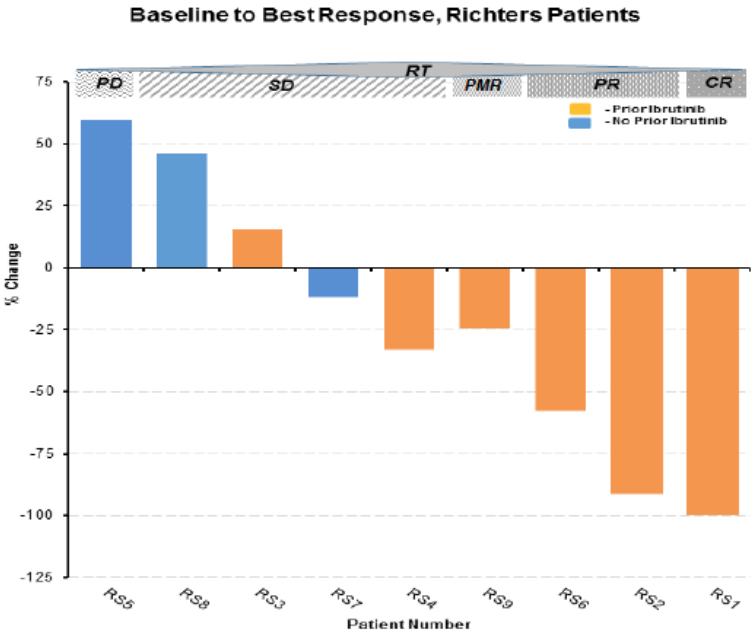
- CHOP-O with ofatumumab maintenance provides minimal benefit over CHOP plus rutuximab.
- Standard immunochemotherapy for RS remains wholly inadequate for unselected RS.

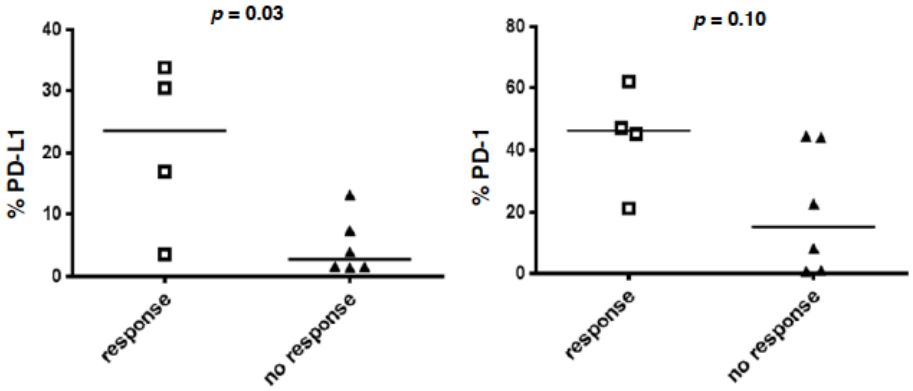
Eyre et al, Br J Haematol, 2016

Pembrolizumab in Richter syndrome

Table 3. Clinical Activity of Pembrolizumab in Trial Patients.

Response	RT (n=9)	CLL (n=16)	Total (n=25)
Complete Response – no. (%)	1 (11)	0	1 (4)
Partial Response – no. (%)	2 (22)	0	2 (8)
Partial Metabolic Response – no. (%)	1 (11)	0	1 (4)
Stable Disease – no. (%)	4 (44)	5 (31)	9 (36)
Progressive Disease#-- no. (%)	1 (11)	8 (50)	9 (36)
Could not be evaluated*-- no. (%)	0	3 (19)	3 (12)
Overall Response Rate -- % (95% CI)	44 (14 - 79)	0	16 (5 - 36)
Median PFS in months (95% CI)	5.4 (2.8 to 12.2)	2.4 (1.2 to 3.3)	3.0 (2.1 to 5.4)
Median OS in months (95% CI)	10.7 (4.4 - NR)	11.2 (2.8 - NR)	10.7 (4.4 - NR)





Ding et al, Blood 2017

- Pembrolizumab exhibits selective activity in CLL patients with RT
- Active after Ibrutinib exposure
- Higher levels of PD-L1 in pts with confirmed responses

Other investigational drugs

Reference	Study design	Patients	RS type	Regimen	ORR	CR	PFS/FFS
Kuruvilla 2014	Clinical trial	6	DLBCL	Selinexor	33%	0%	na
Hillmen, 2016	Clinical trial	29	DLBCL	Acalabrutinib	38%	14%	3 months
Tsang, 2016	Retrospective	4	DLBCL	Ibrutinib	75%	25%	na
Ding, 2016	Clinical trial	9	DLBCL	Pembrolizumab	44%	11%	na
Davids, 2017	Clinical trial	7	DLBCL	Venetoclax	43%	0%	na

Ongoing trials

- venetoclax combination with dose-adjusted EPOCH-R (NCT03054896)
- ibrutinib and obinutuzumab alone or in combination with CHOP (NCT03145480)
- pembrolizumab alone (NCT02576990) or in combination with ublituximab (NCT02535286)
- nivolumab in combination with ibrutinib (NCT02420912)
- blinatumumab monotherapy (NCT03121534)

Summing up

- The genotype of Richter syndrome sustains the clinical aggressiveness and chemorefractoriness of the disease
- A molecular workup to distinguish clonally related vs clonally unrelated cases may be useful
- In R/R CLL treated with BCR and BCL2 inhibitors, development of Richter syndrome occurs early and may reflect an aggressive clone selected by previous chemotherapy
- The outcome of Richter syndrome is still very poor and mandates the investigation of new treatment modalities
- The incidence, biology and clinical behavior of Richter syndrome in patients receiving only chemo-free regimens need to be defined