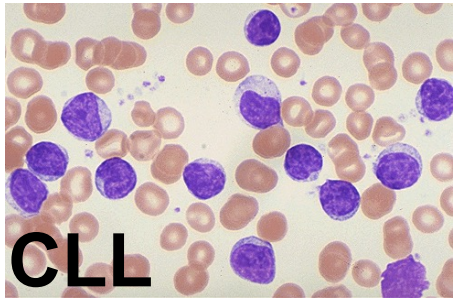
Biology of Richter's Transformation

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

Hematology
IOSI - Oncology Institute of Southern Switzerland
IOR - Institute of Oncology Research
USI – Universita' della Svizzera Italiana
Bellinzona - Switzerland

Genetics of LBCL-variant of RT

Pathologic variants of RT



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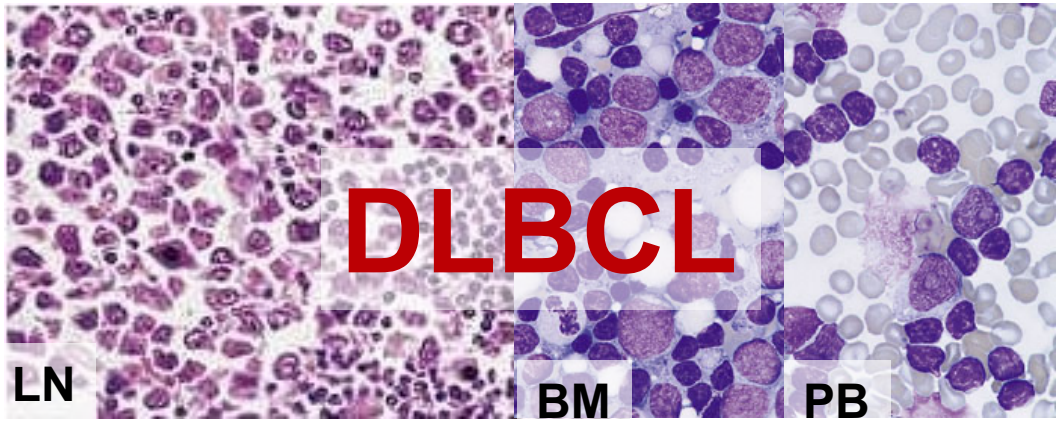
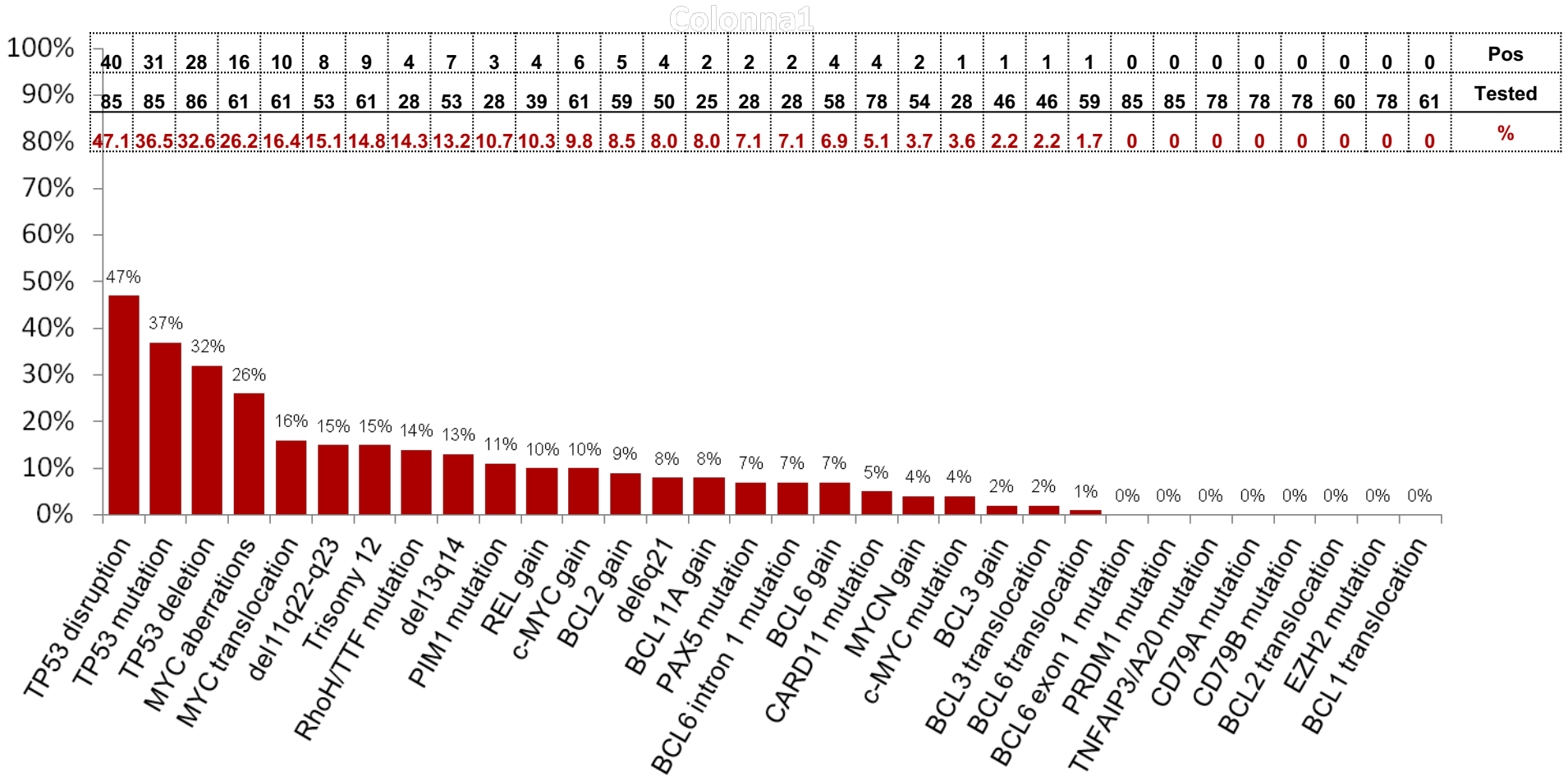


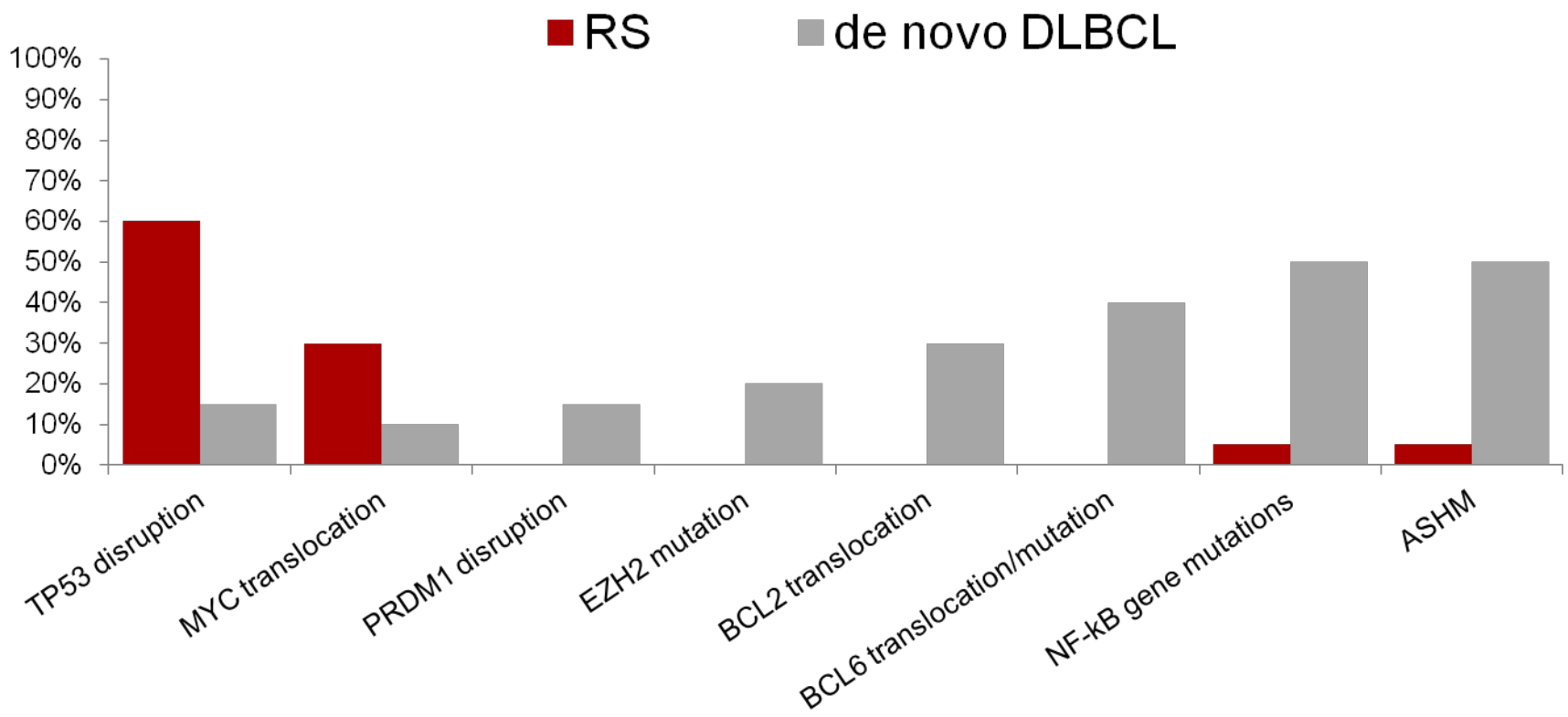
ICC and WHO-HAEM5

“Driver” genetic lesions of RT in 2013



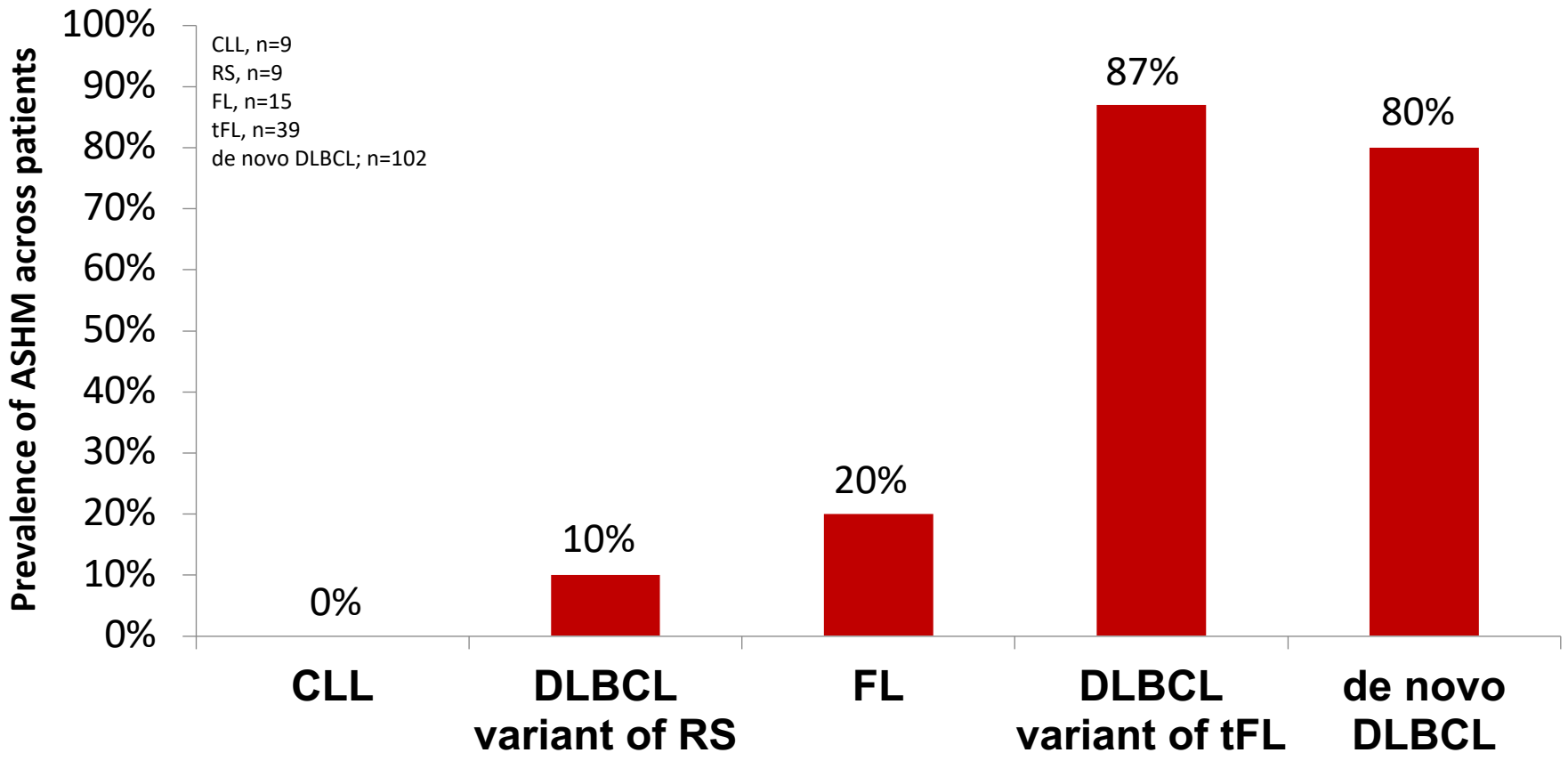
Rossi D, et al. Blood 2011

The genetic profile of clonally related RT vs DLBCL



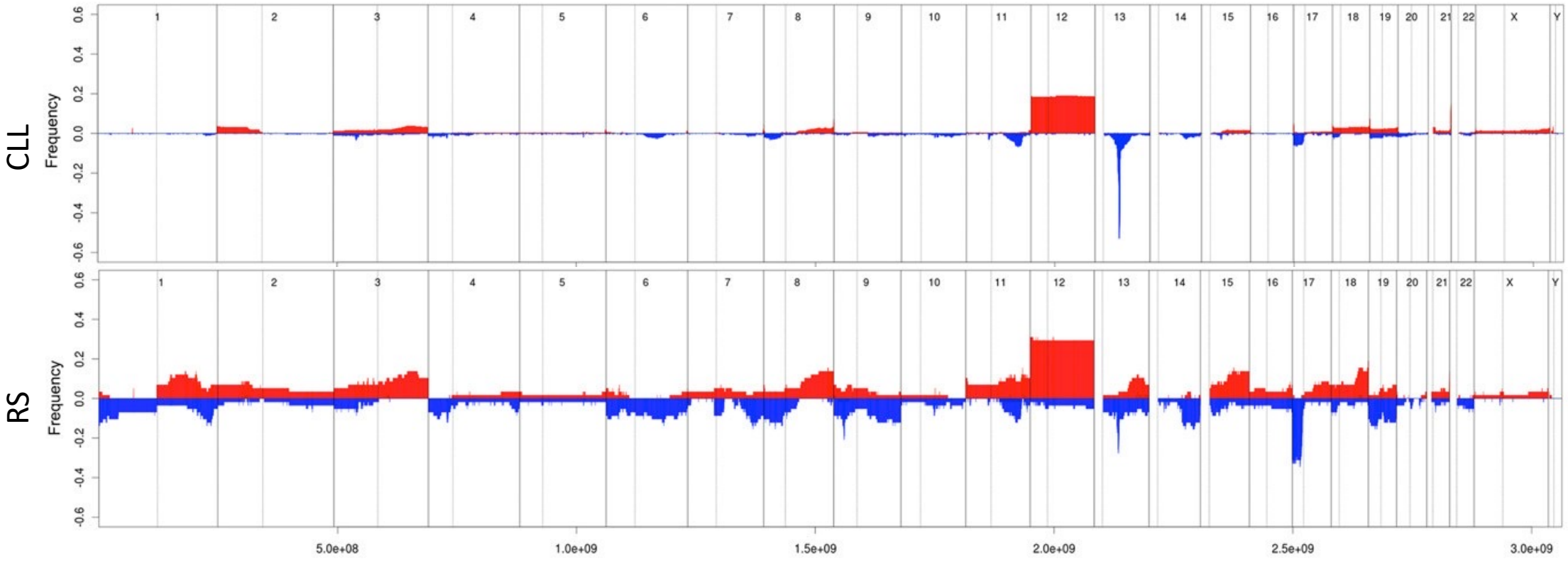
Rossi D, et al. Blood 2011

Aberrant somatic hypermutation is not a mechanism of genetic instability of RT



Rossi D, Haematologica 2006
Pasqualucci L, Cell Rep 2014

Genomic complexity of RT



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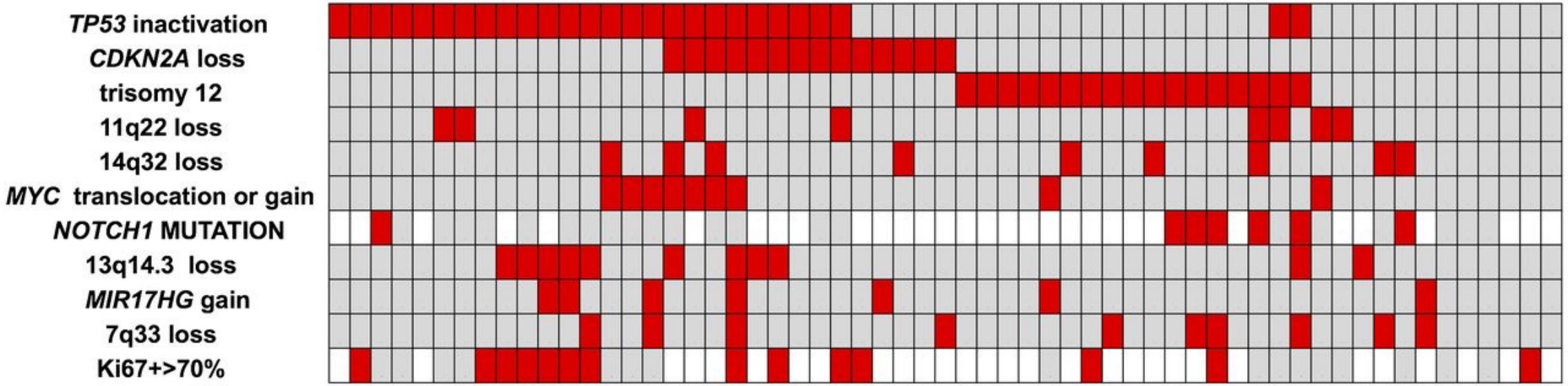
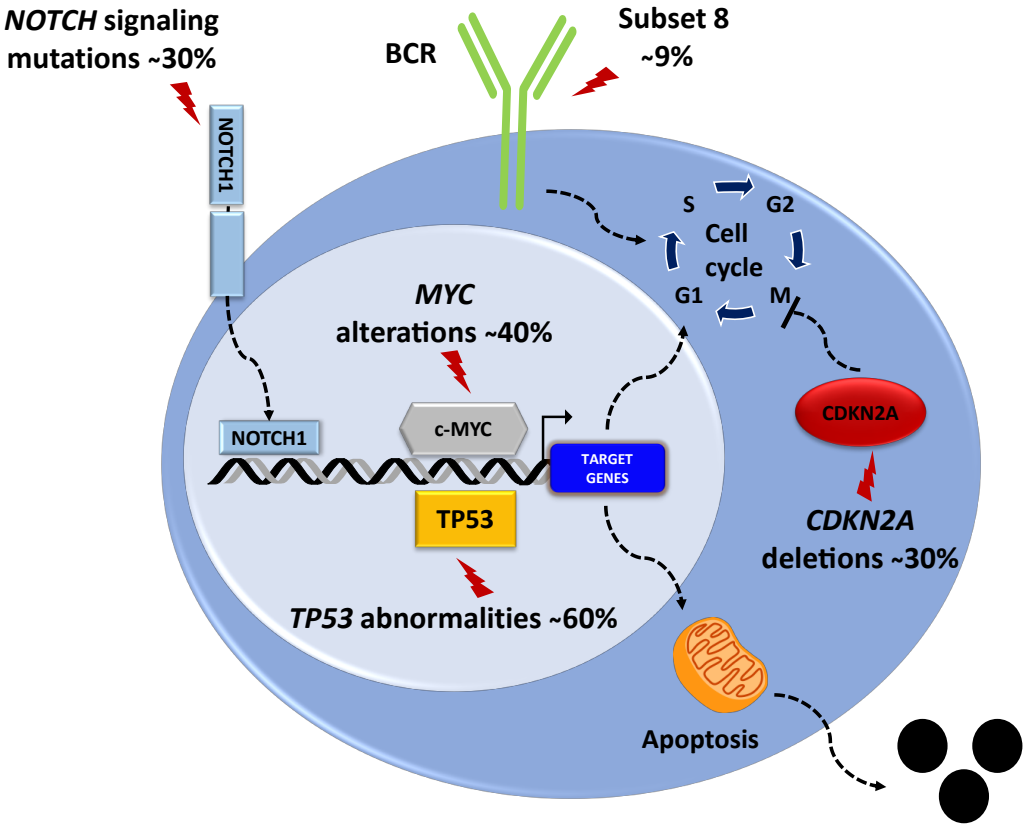
Chigrinova E, et al. Blood. 2013;122:2673-2682; Fabbri G, et al. J Exp Med. 2013;210:2273-2288

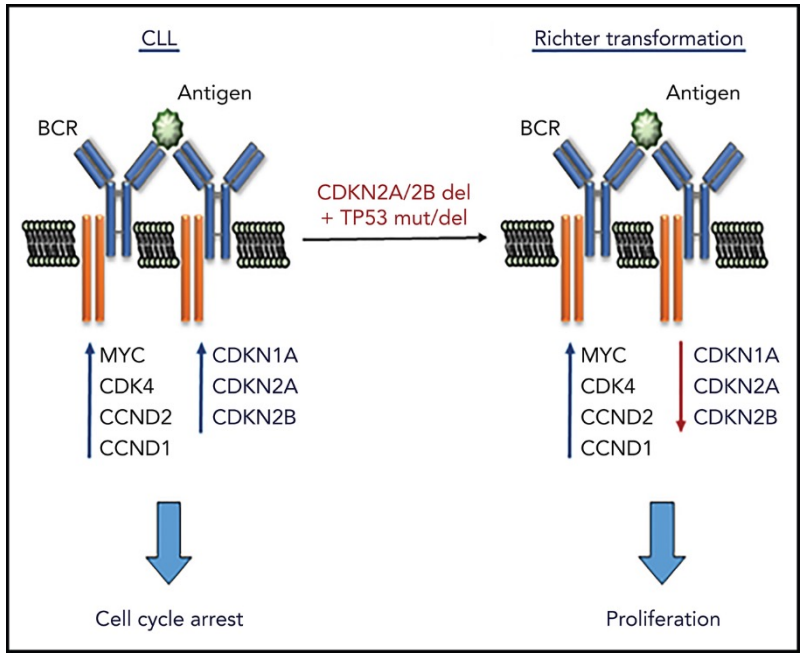
TP53 and *CNKN2A* disruption and *MYC* activation



Rossi D, et al. Blood 2011
Chigrinova et al, Blood 2013

Proliferation and apoptosis are the master cellular programs deregulated in RT





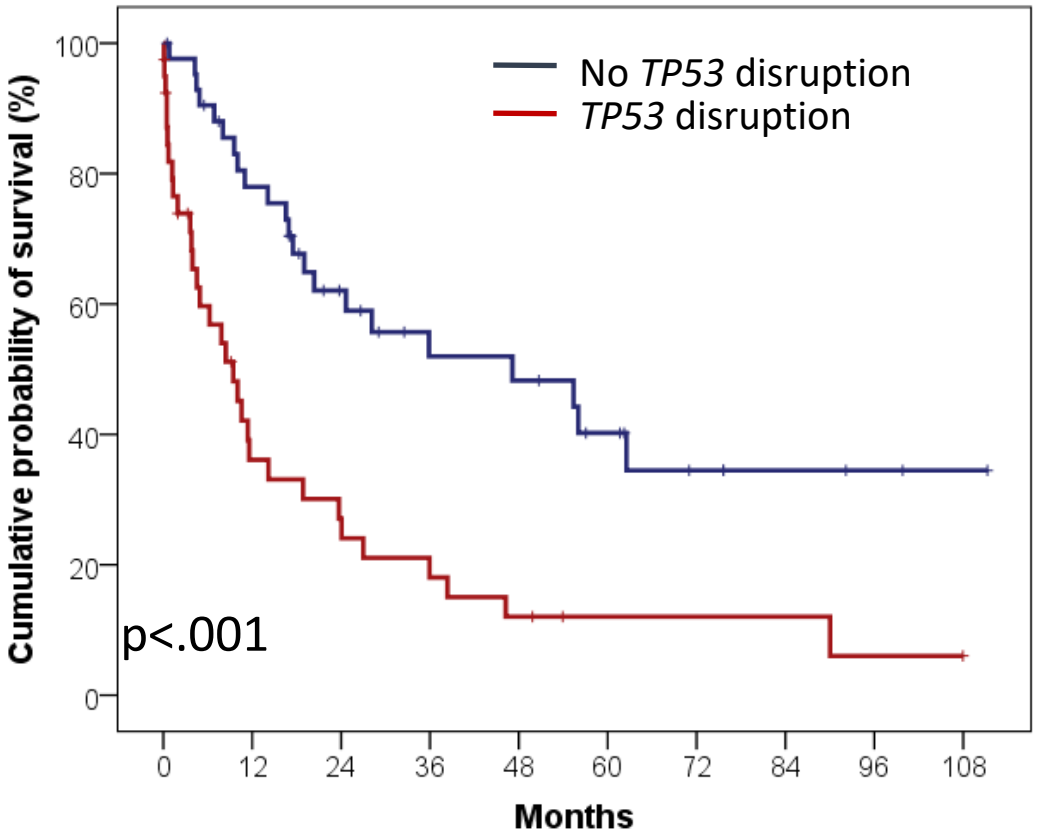
Chakraborty S, Blood. 2021

Rapidly progressive kinetics
Chemorefractoriness

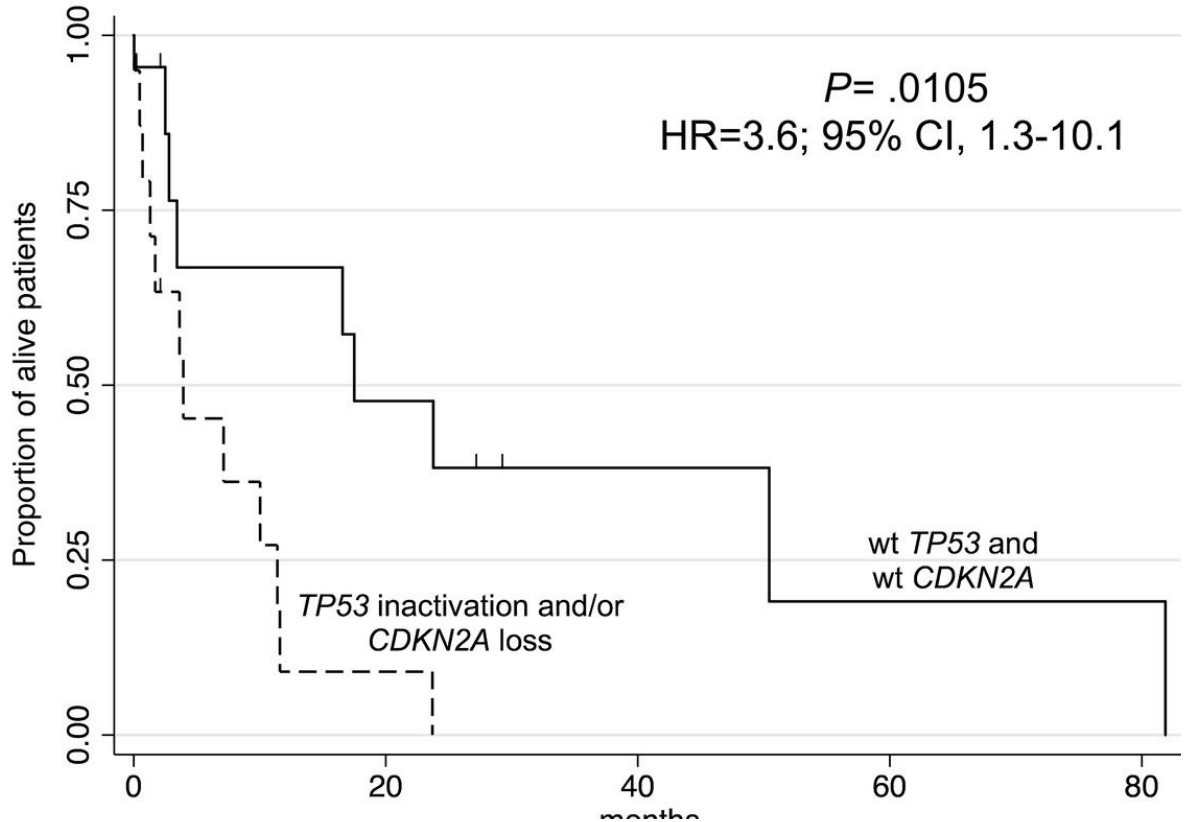
Adapted from Rossi D, *et al. Semin Oncol* 2016; 43:311–319.

Nadeu F, Nat Med. 2022

TP53 and *CDKN2A* disruption prognosticate survival of RT

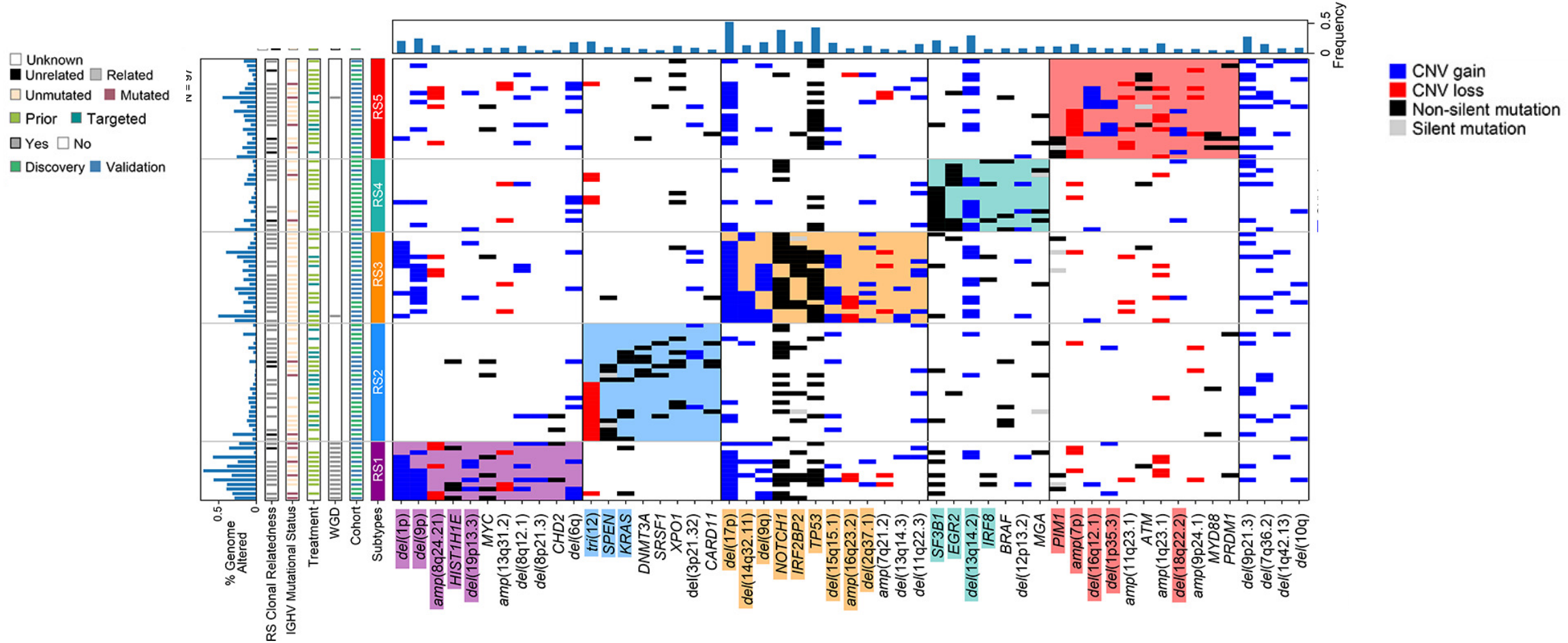


Rossi D, et al, Blood 2011



Chigrinova et al, Blood 2013

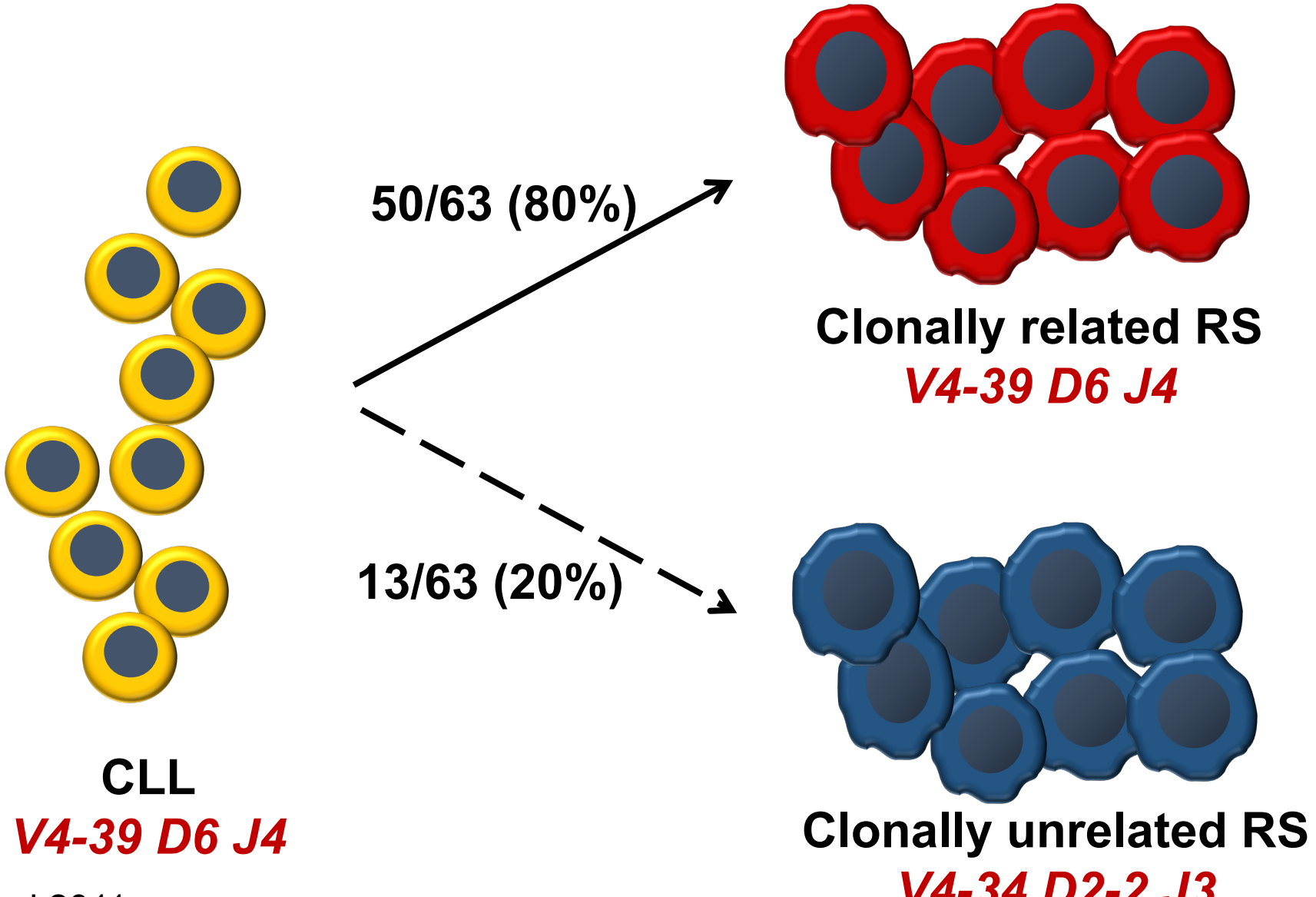
Genetics of RT in 2023



Parry EM, Nat Med. 2023

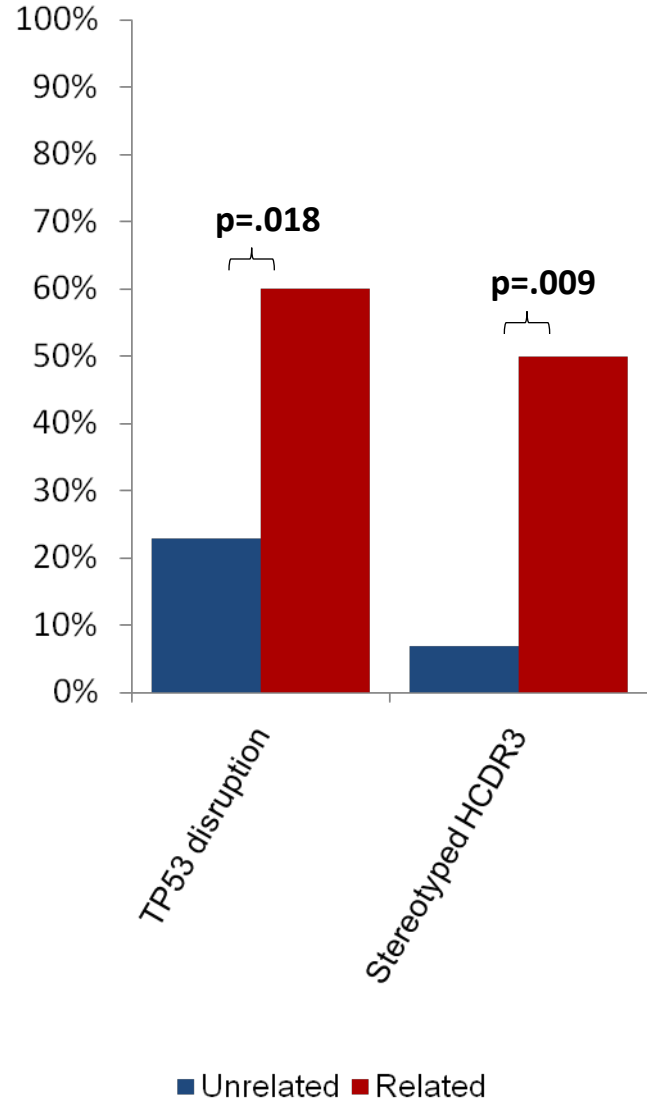
Genetics of de novo LBCL in CLL

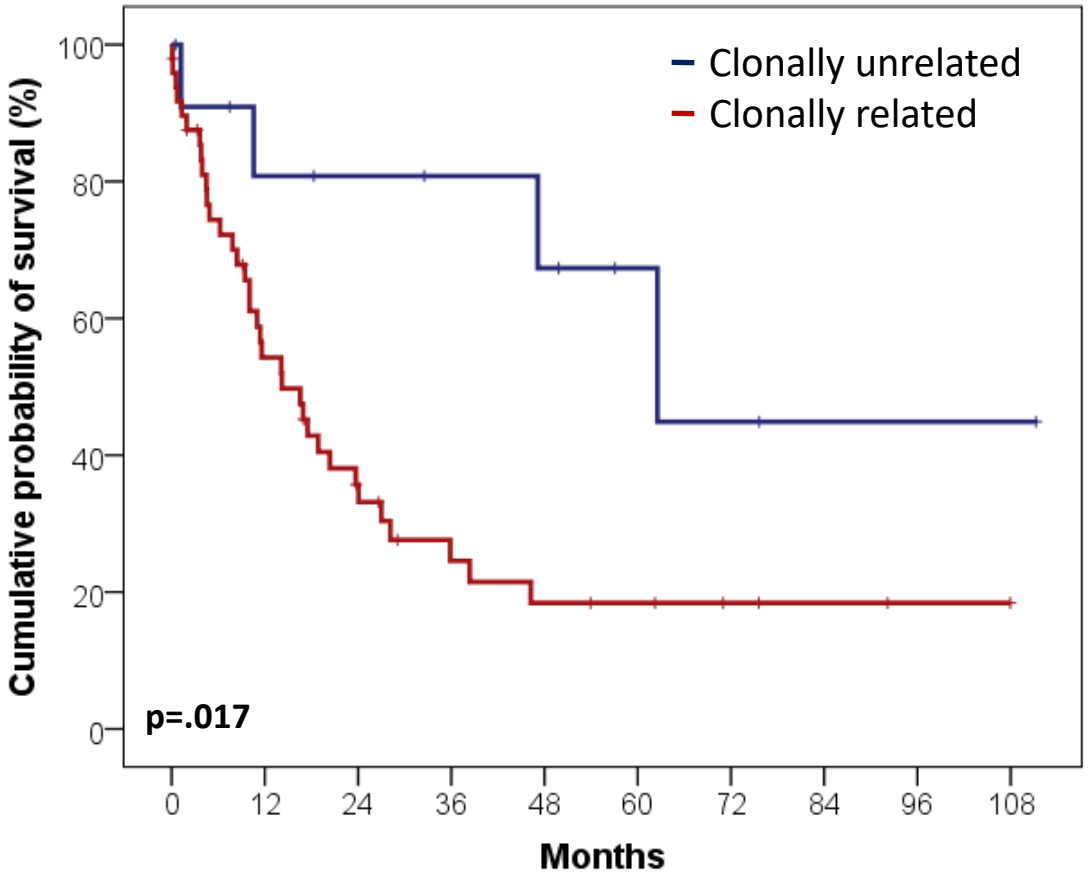
Clonally related vs unrelated variants of RT



Rossi et al, Blood 2011

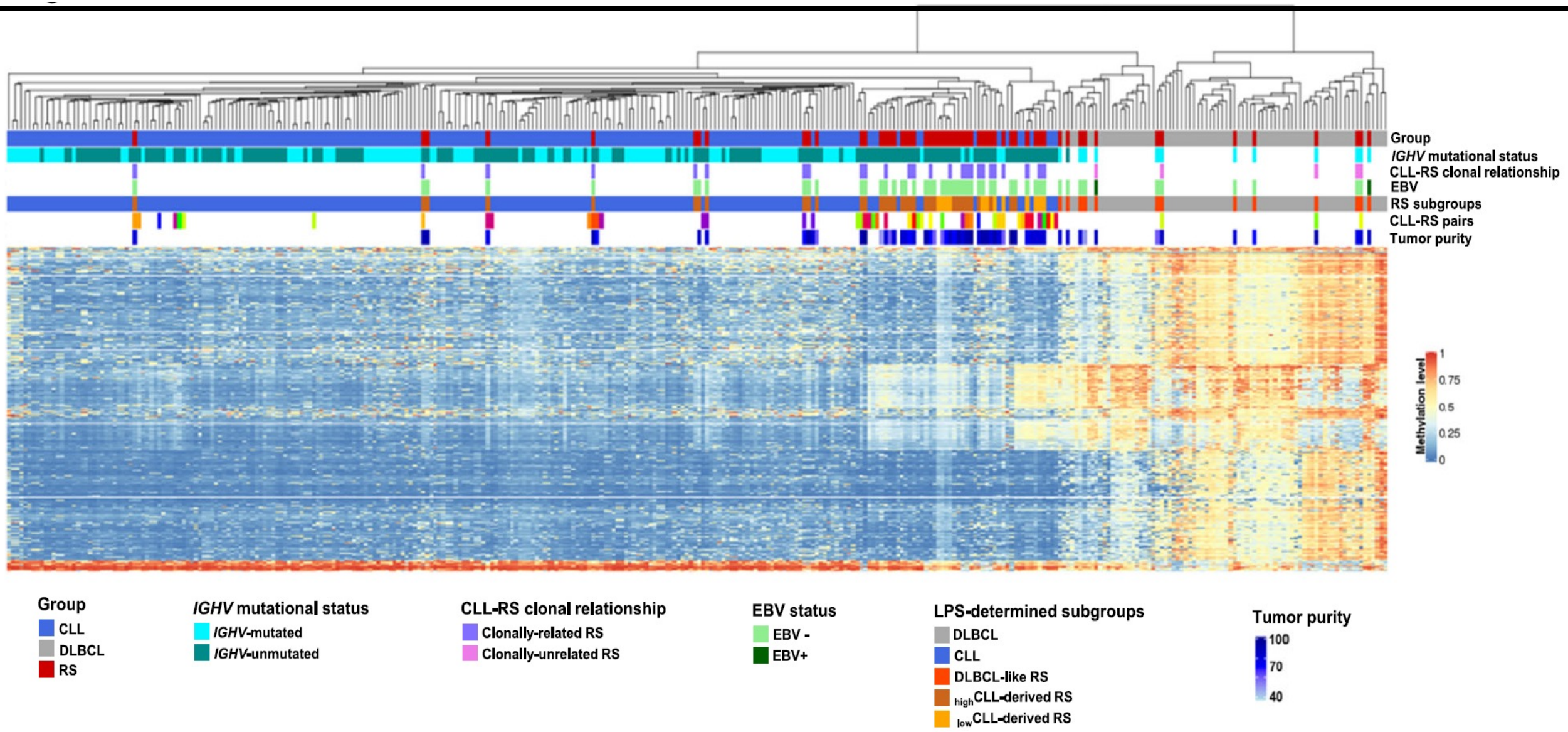
Clonally relared and unrelated Richter's syndrome





Rossi et al, Blood 2011

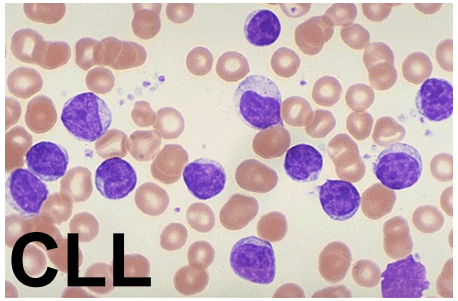
Epigenetically, de novo LBCL arising in patients with CLL cluster apart from RT



Broseus et al, Nat Comm 2023

Genetics of cHL variant of RT

Pathologic variants of RT



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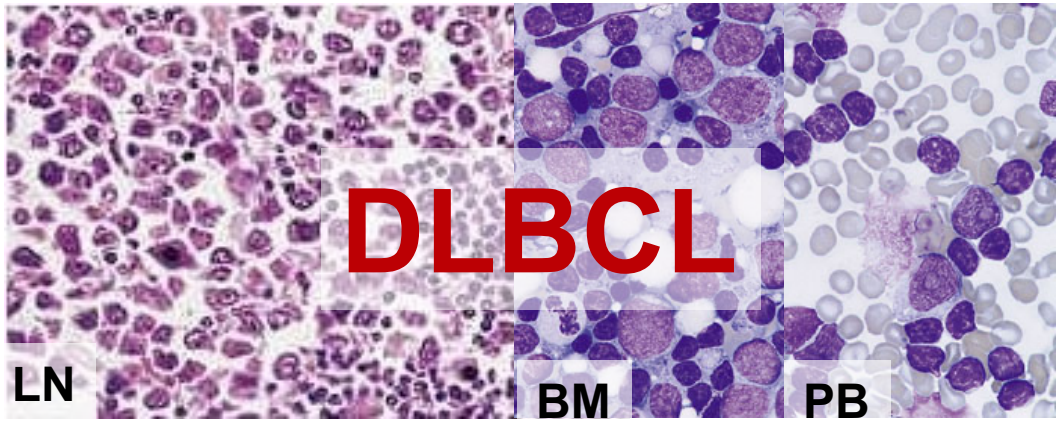
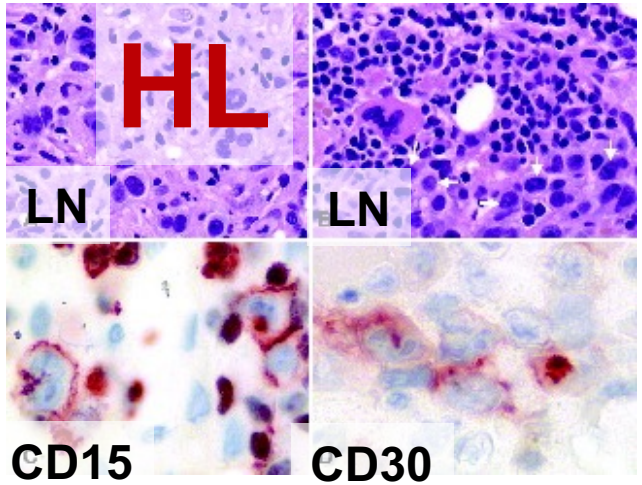
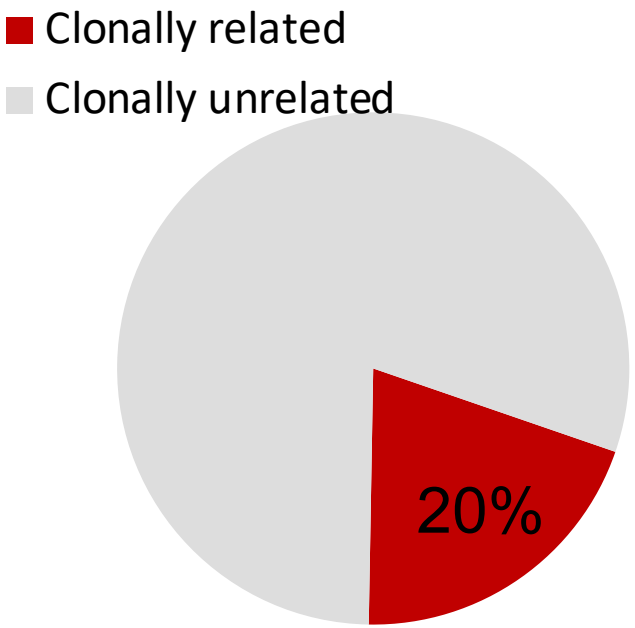


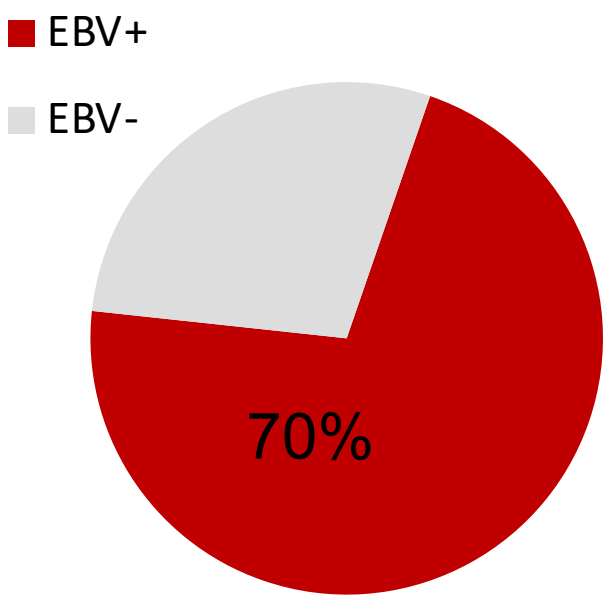
1-5%



ICC and WHO-HAEM5

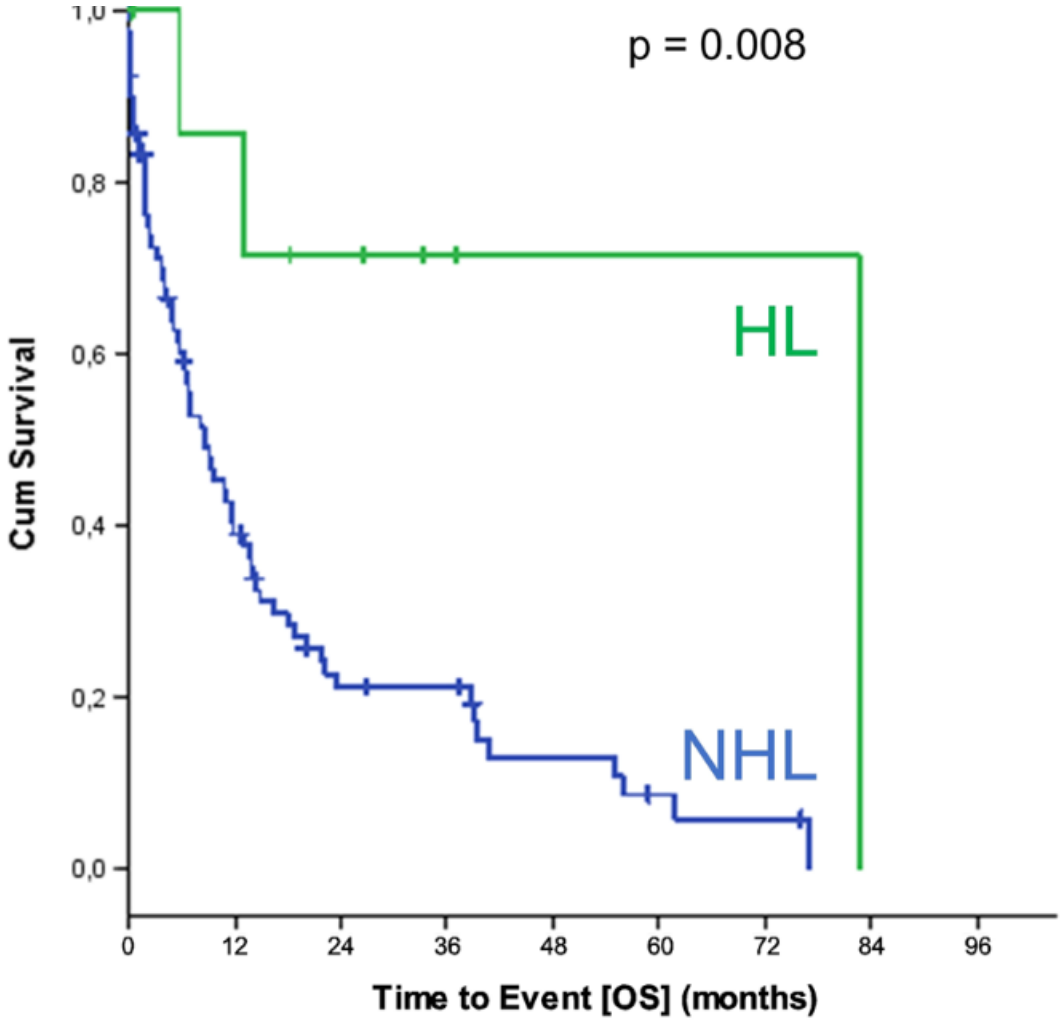
Classic Hodgkin lymphoma variant of RT





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

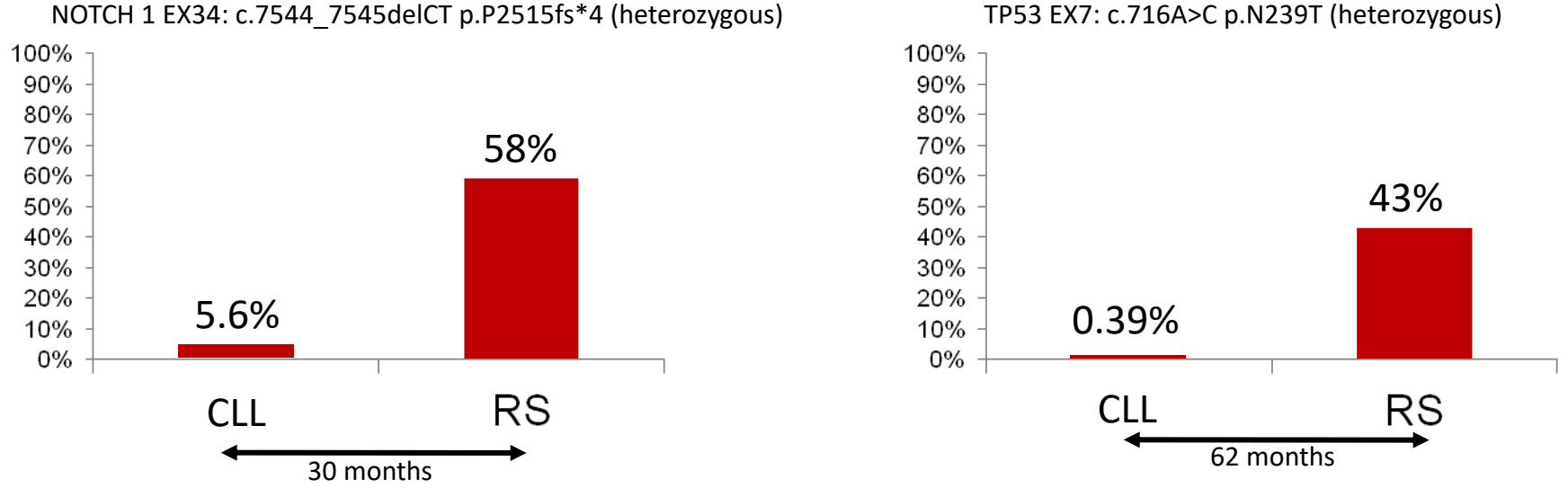
Post-transformation survival of cHL arising in patients with CLL

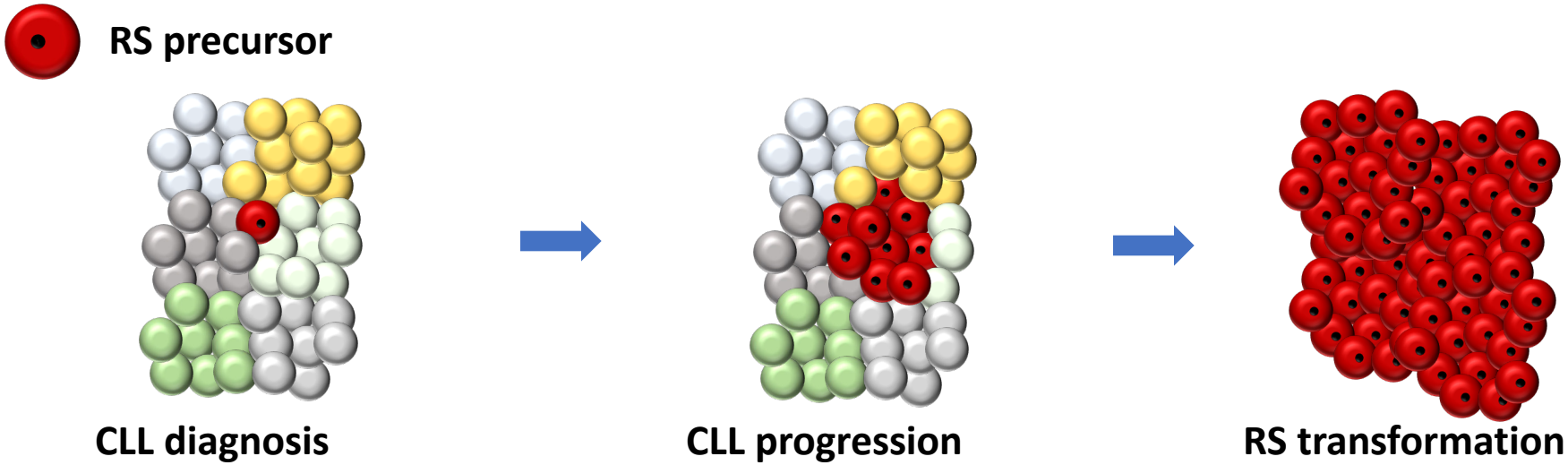


Al-Sawaf O et al. Leukemia 2021

Early seeding of transformed clones

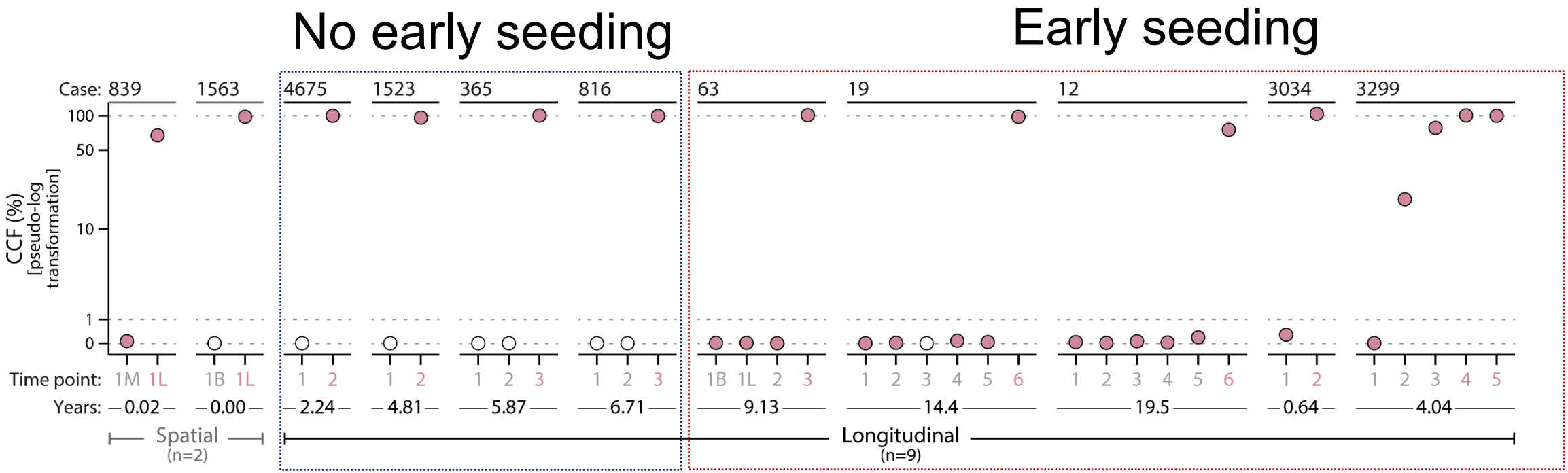
Early seeding of the RT clones





Fabbri G, et al, J Exp Med 2011

Early seeding of the RT clone is frequent (ca. 50%)



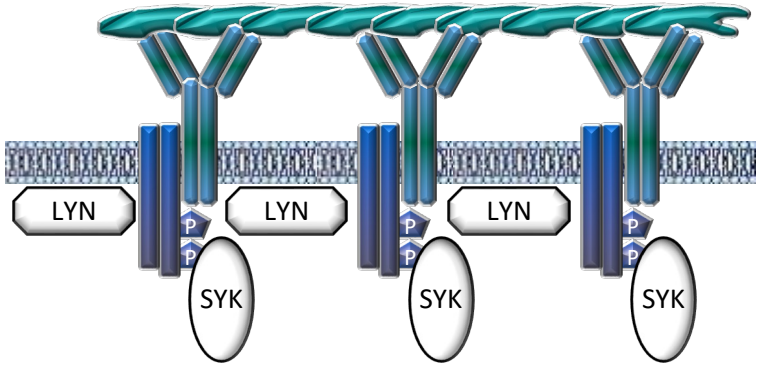
Nadeu F et al Nat Med 2022

BCR signaling

Usage of subset 8 configuration of the BCR is biased in RT

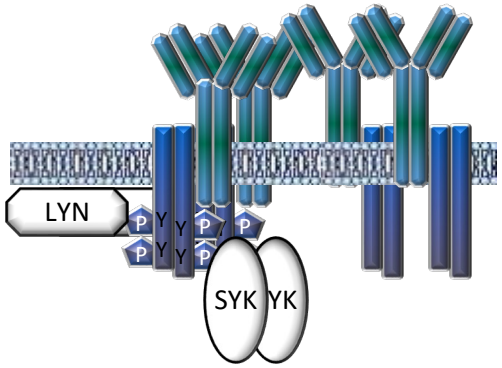
External antigens

Autoantigens exposed on apoptotic cells



Cell autonomous BCR signal

Interaction between of one BCR with another BCR that functions as an autoantigen



BTK

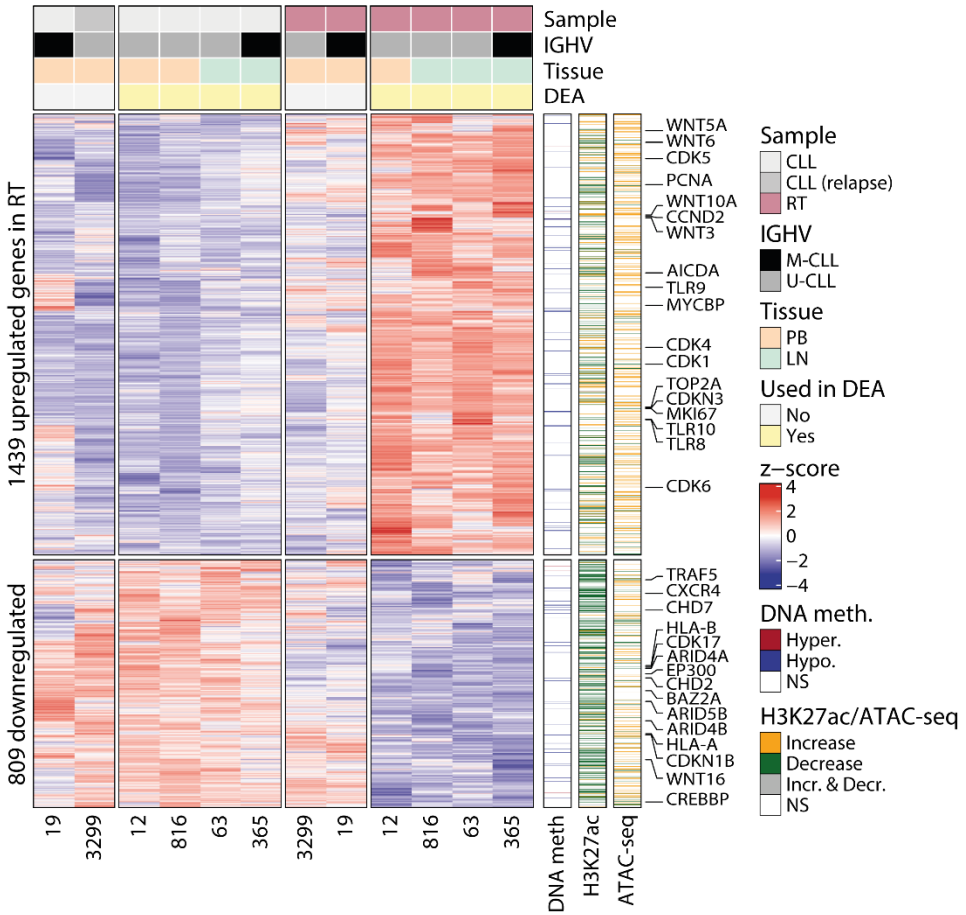
PI3K

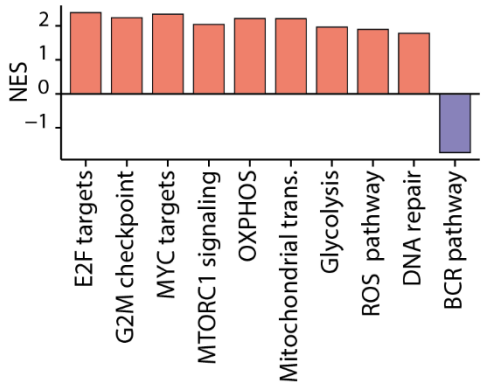
Substet #8

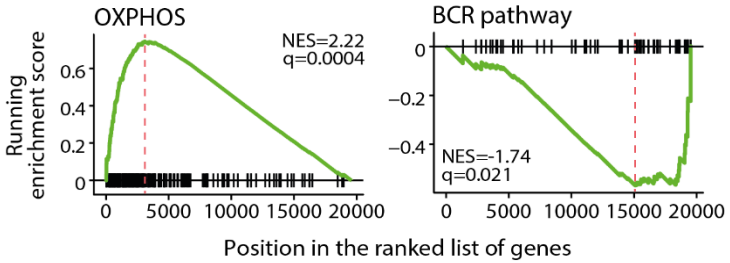
- 0.5% of CLL
- 10% of Richter syndrome
- IGHV unmutated
- Low affinity homotypic interactions
- Extreme antigen polyreactivity
- Strong phosphorylation of PLCγ2 and ERK1/2

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; Minici C, Nat Commun. 2017;8:15746; Jaramillo S, Haematologica. 2019; doi:10.3324/haematol.2019.231027

The OXPHOS^{high}-BCR^{low} transcriptional axis of RT



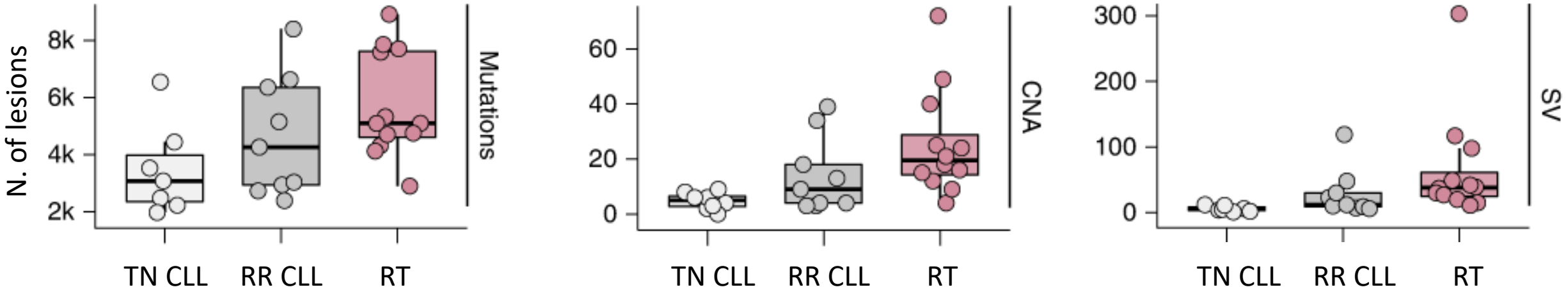




Nadeu F et al Nat Med 2022

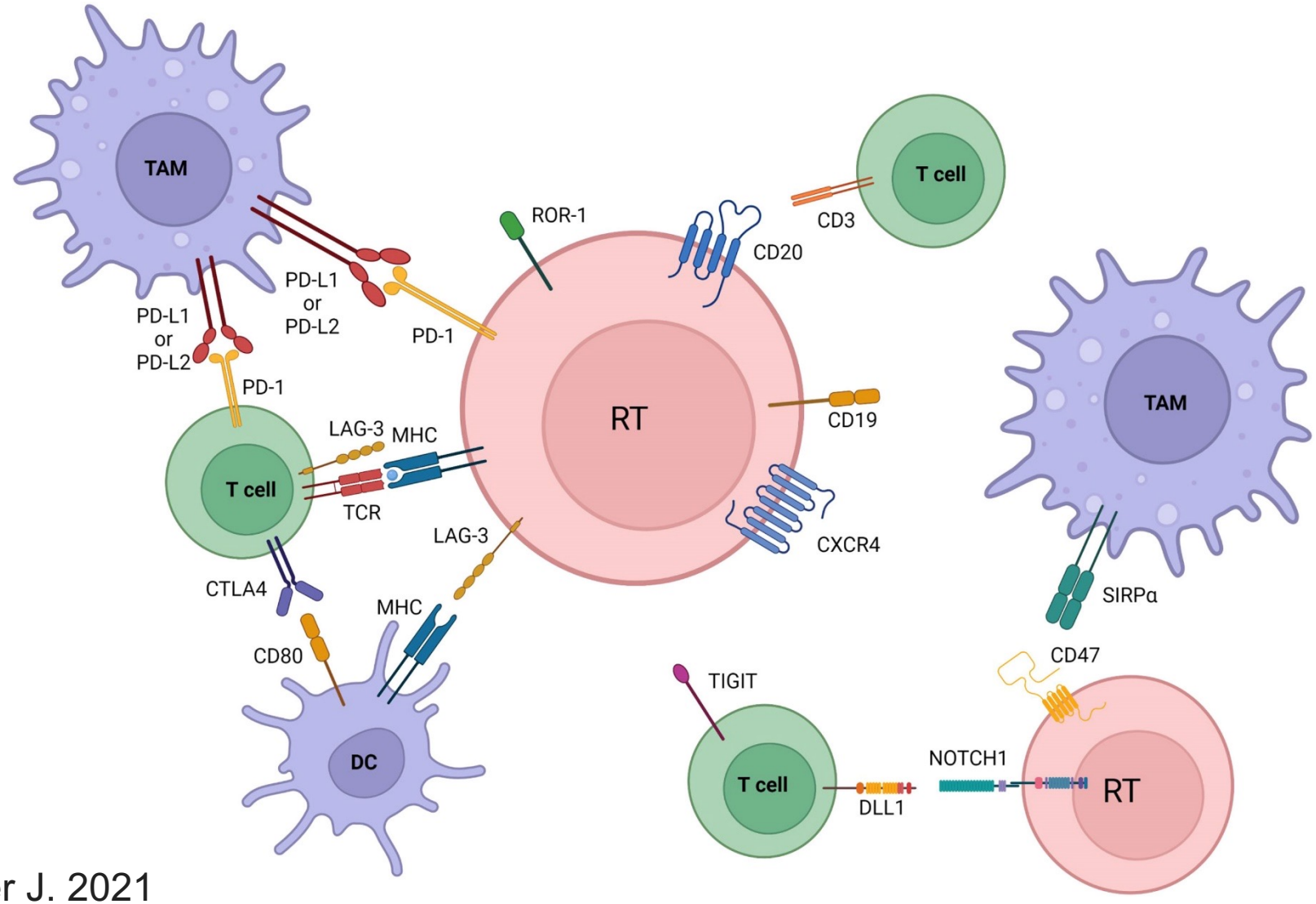
Immune escape

Genomic complexity of RT (implication for neoantigens?)



Nadeu F, Nat Med. 2022

RT has an immune suppressive microenvironment



Wang Y, Blood Cancer J. 2021
Gould C, Br J Haematol. 2021

Implications for management

- RT should be carefully differentiated from de novo LBCL and de novo cHL an
- Treatment of RT should include agents that circumvents the block of DNA damage response (e.g. venetoclax)
- Treatment of RT should leverage on immunotherapy
- Early seeding of RT clones prompts the development of diagnostic tests for their detection during the CLL phase