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La complessità genetica e molecolare dei linfomi diffusi a grandi cellule

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Conflict of interest

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Consultant	No
Major Stockholder	No
Speakers Bureau	No
Honoraria	Gilead, Abbvie, Janssen, Roche, AstraZeneca, Loxo
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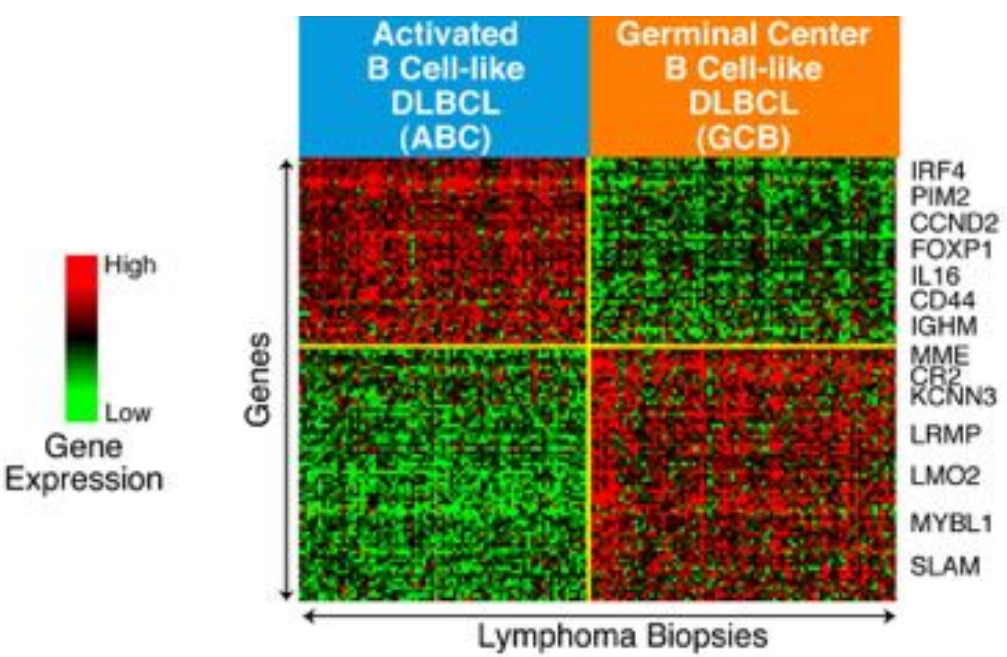
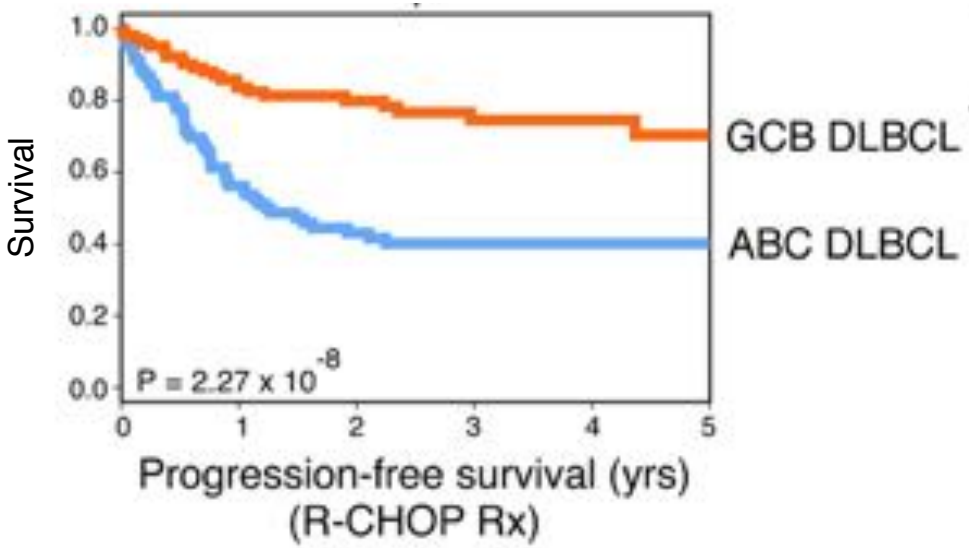
Revision to WHO Classification 2016

Diffuse large B-cell (NOS)	
	Germinal Centre B-cell type
	Activated B-cell type
T-cell/histiocyte rich large B-cell	
Primary DLBCL of central nervous system	
Primary cutaneous DLBCL leg type	
EBV+ DLBCL, NOS	
	EBV+ mucocutaneous ulcer
Primary mediastinal lymphoma	
Intravascular large B-cell lymphoma	
Primary effusion lymphoma	
Plasmablastic lymphoma	
High-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangement	
High-grade B-cell lymphoma (NOS)	

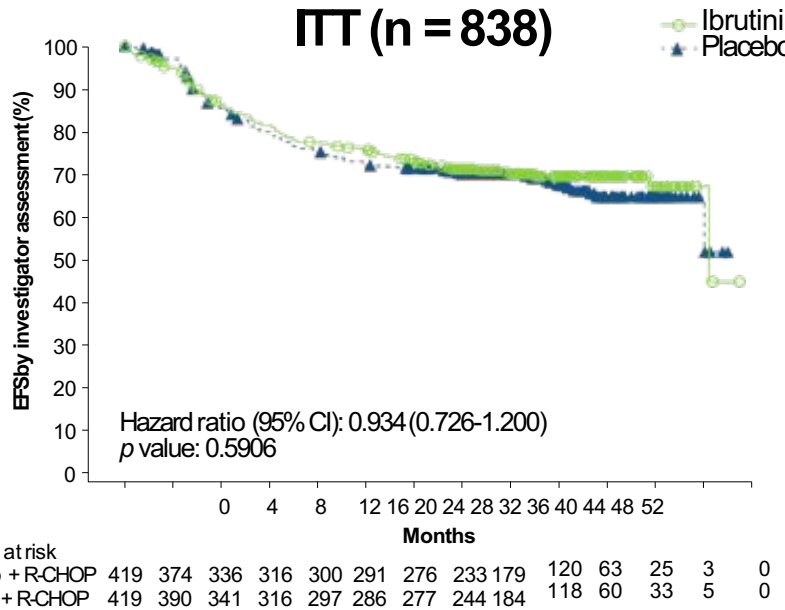
Swerdlow et al. Blood 2016

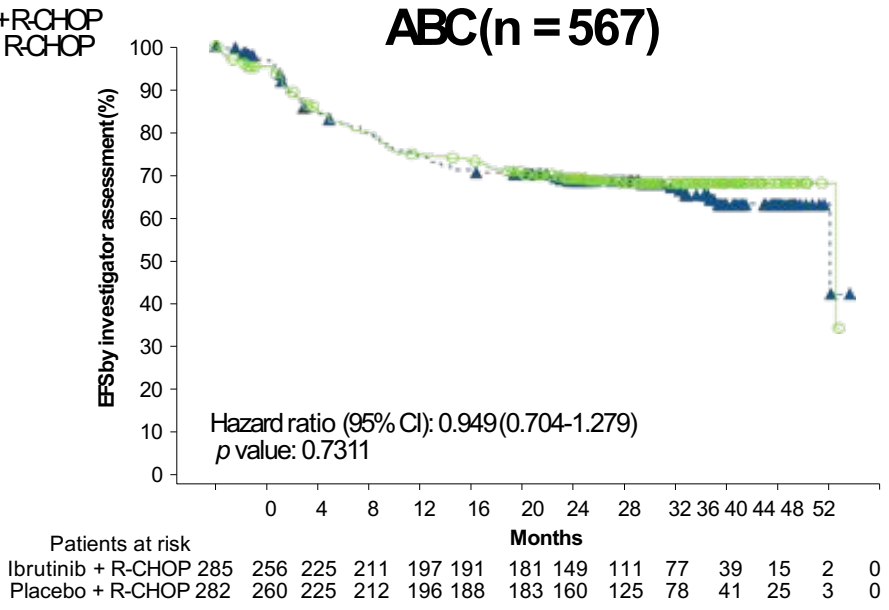
Phenotypic subtypes of DLBCL





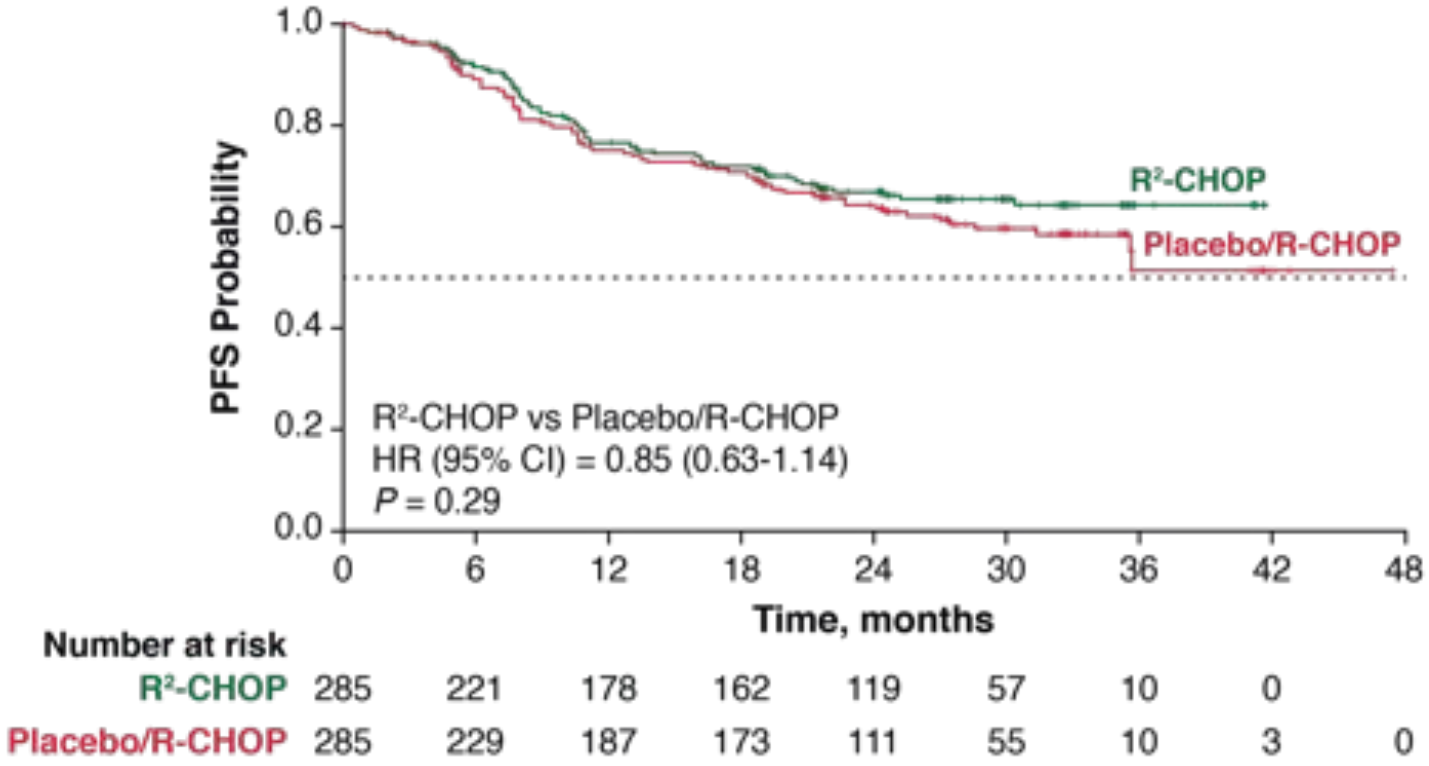
No benefit from the addition of ibrutinib to R-CHOP in non-GC DLBCL





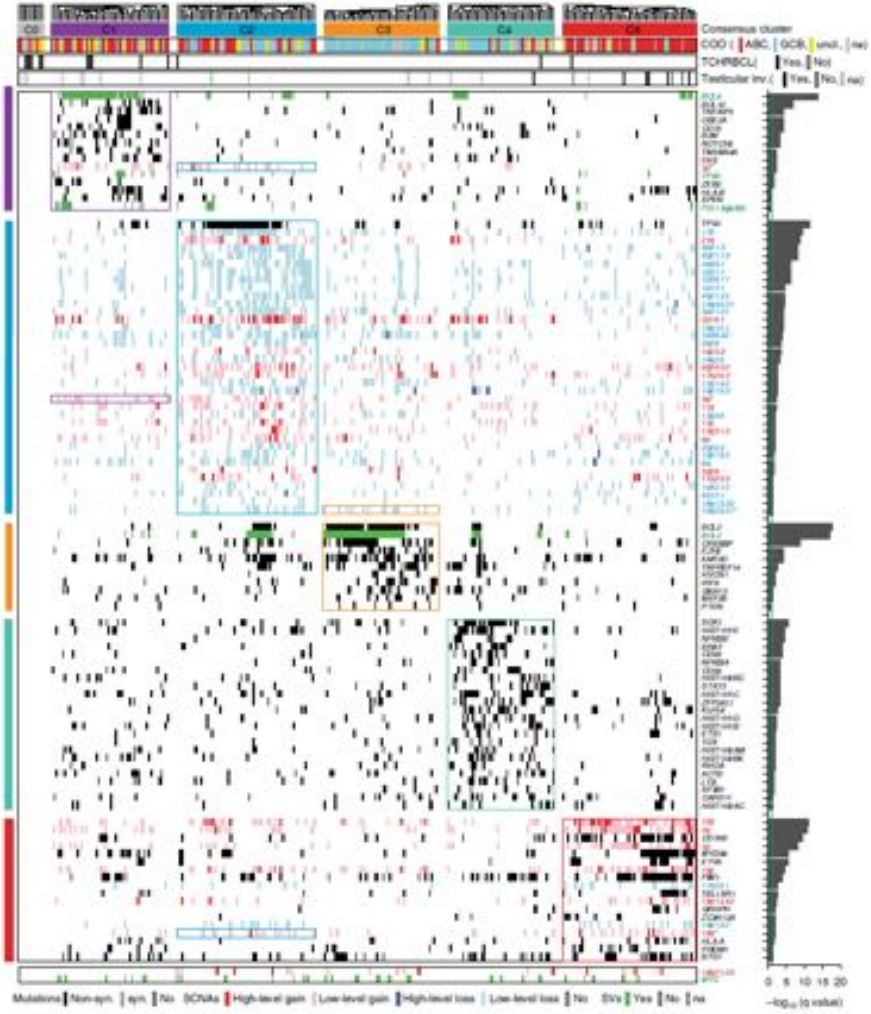
American Society of Hematology 60th Annual Meeting and Exposition, Younes A, et al. Abstract 784.

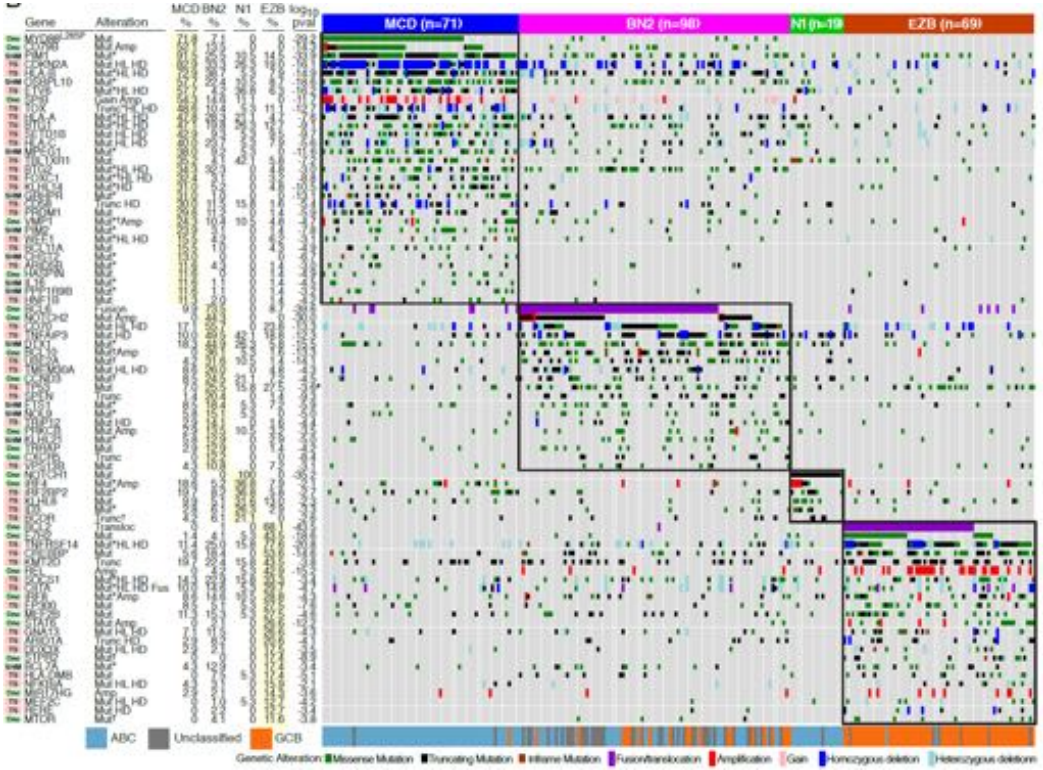
No benefit from the addition of lenalidomide to R-CHOP in ABC DLBCL



Vitolo U et Al, ICML 2019

Molecular subtypes of DLBCL

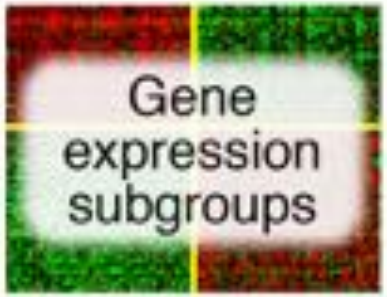


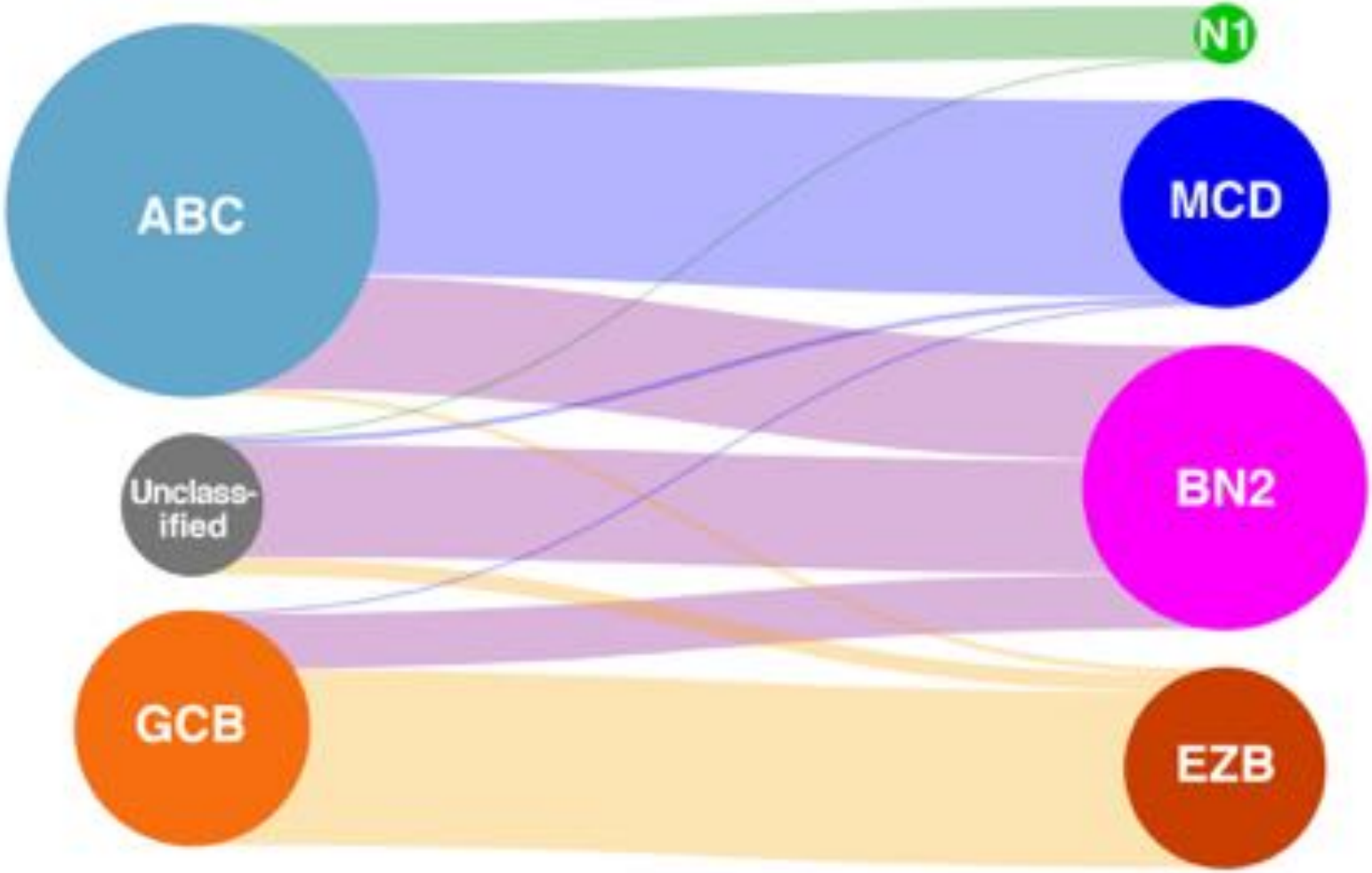


Chapuy et al., Nat. Med 2018

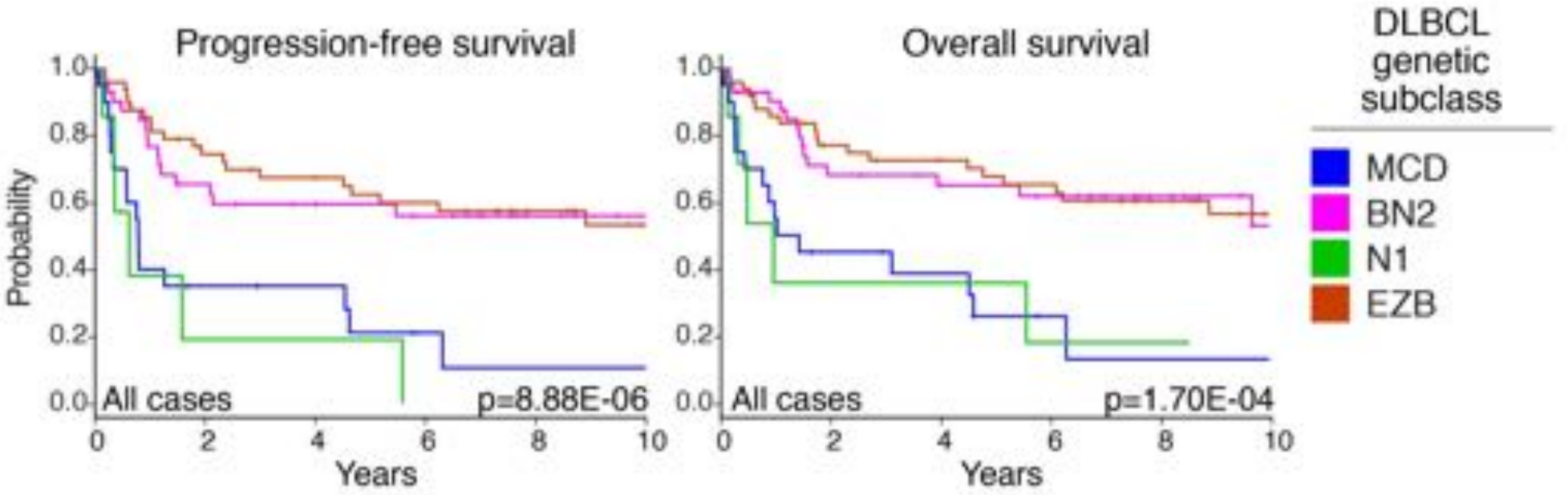
Schmitz et al., New Engl J Med 2018

The Molecular Diagnosis of Diffuse Large B Cell Lymphoma v.2.0

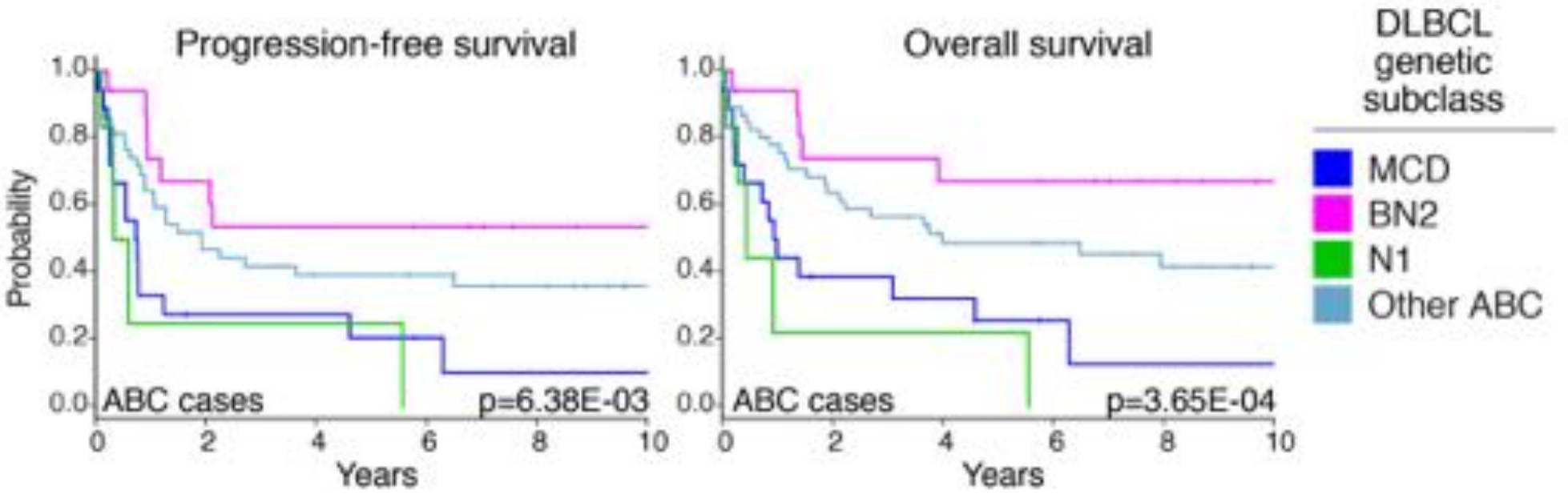




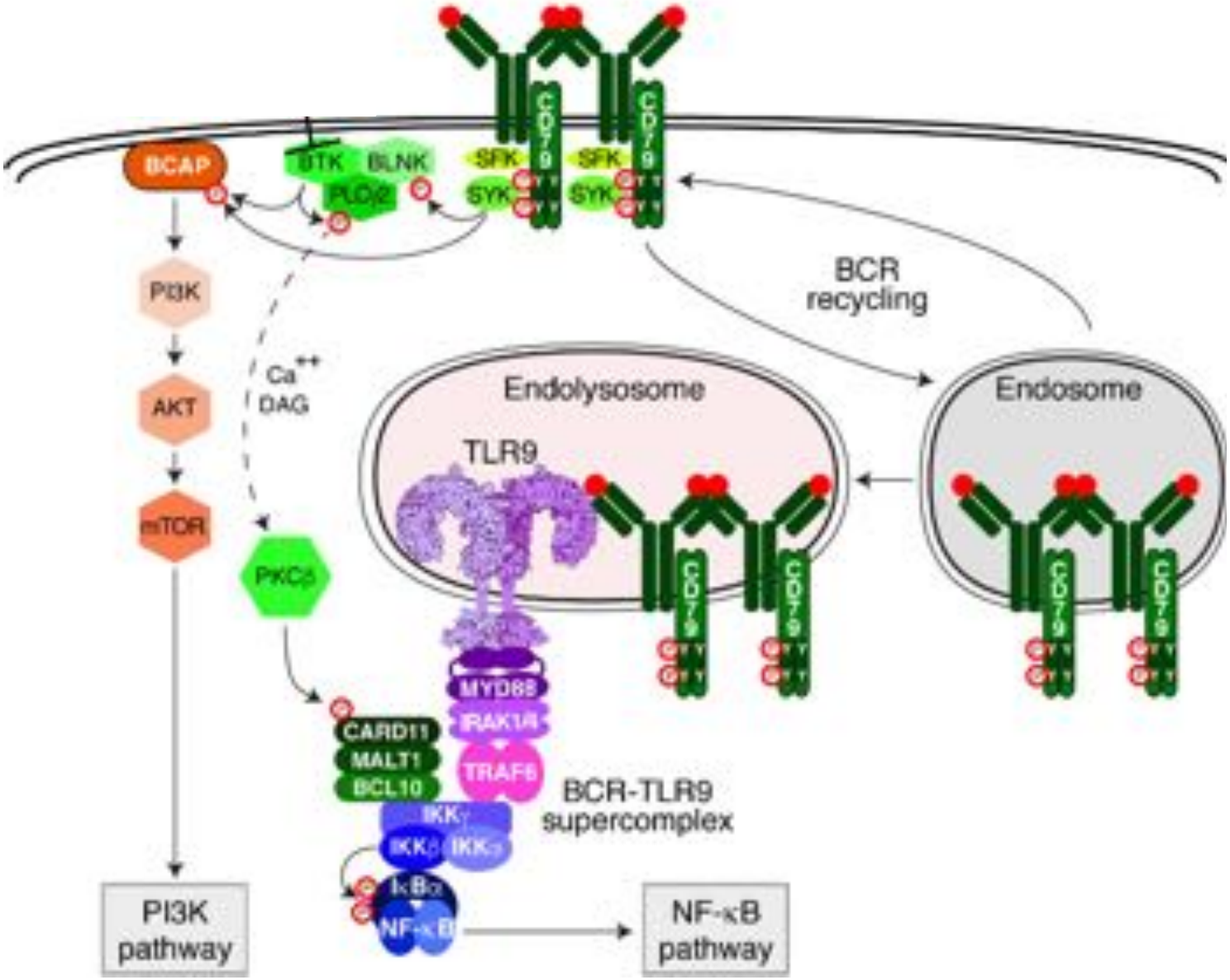
DLBCL Genetic Subtypes Predict Survival Following R-CHOP



DLBCL Genetic Subtypes Predict Survival Within ABC DLBCL

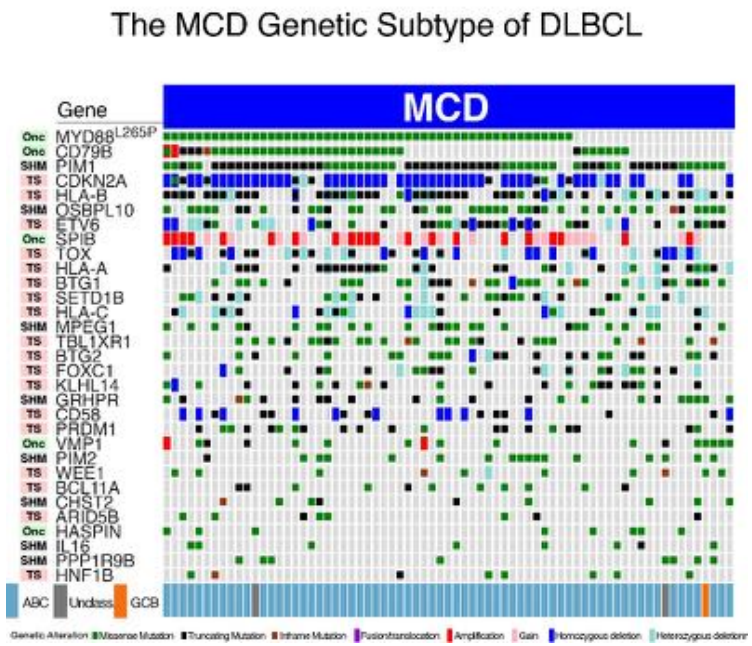


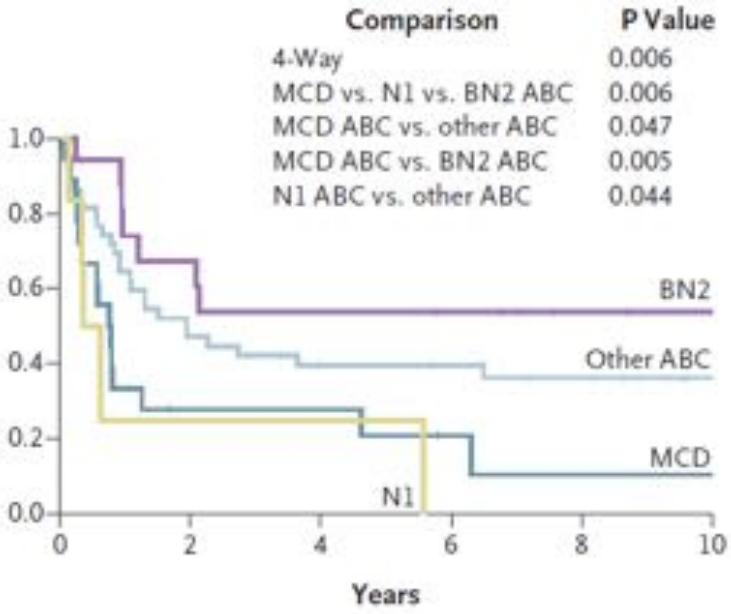
MYD88 co-localizes with the BCR to for a signaling supercomplex in ABC DLBCL



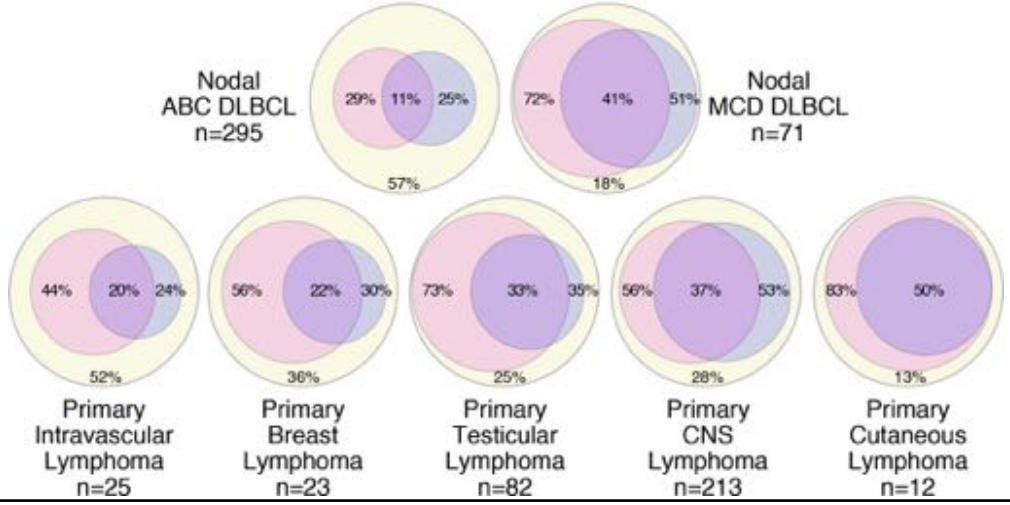
Young RM, Nature 2018

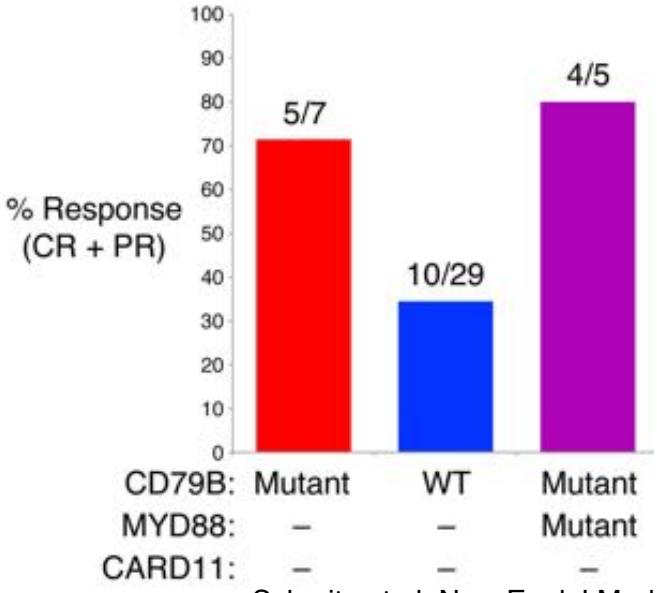
The MCD subtype of DLBCL





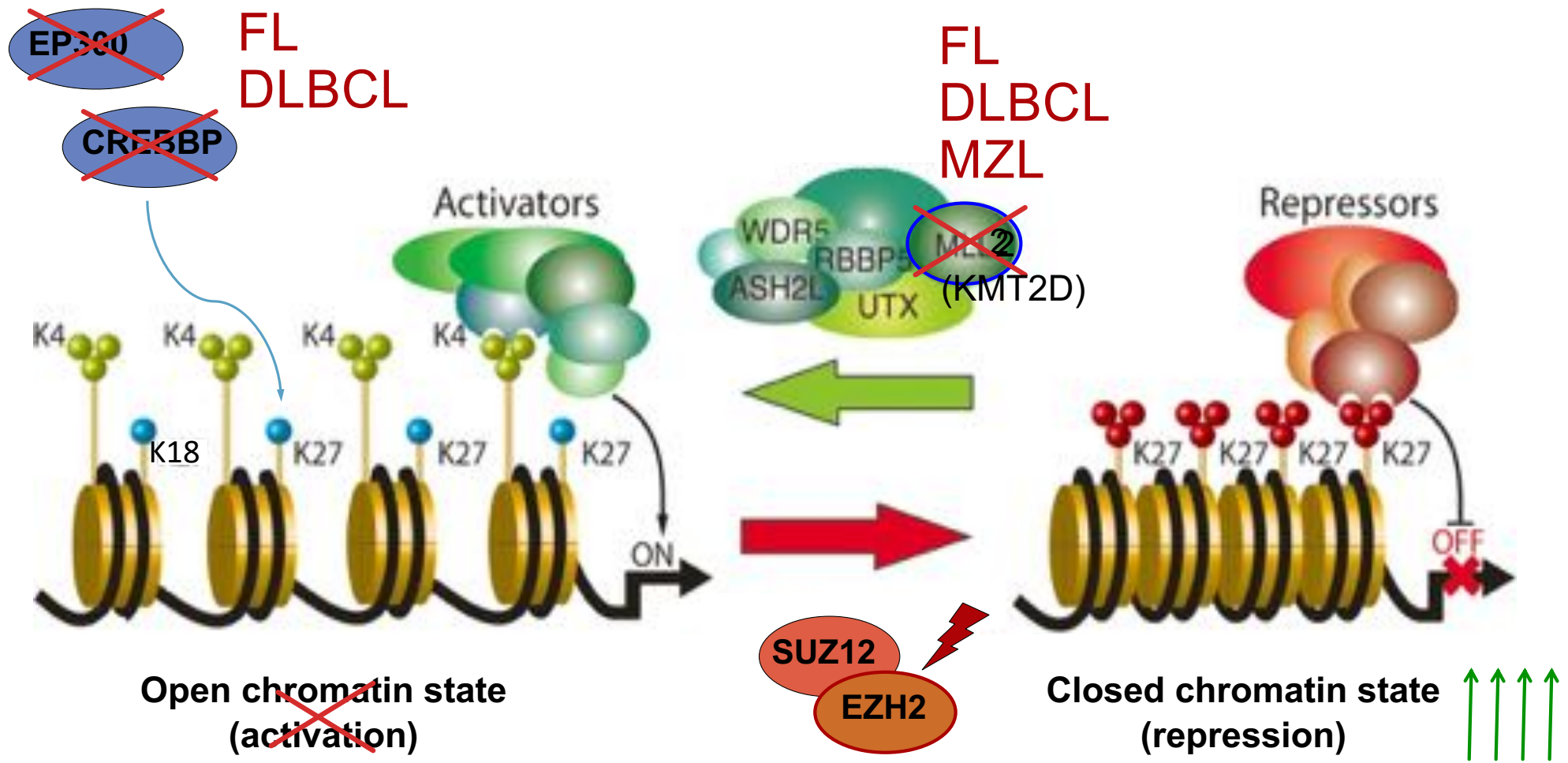
Enrichment for CD79B and MYD88^{L265P} Mutations in MCD DLBCL and in Extranodal Lymphomas





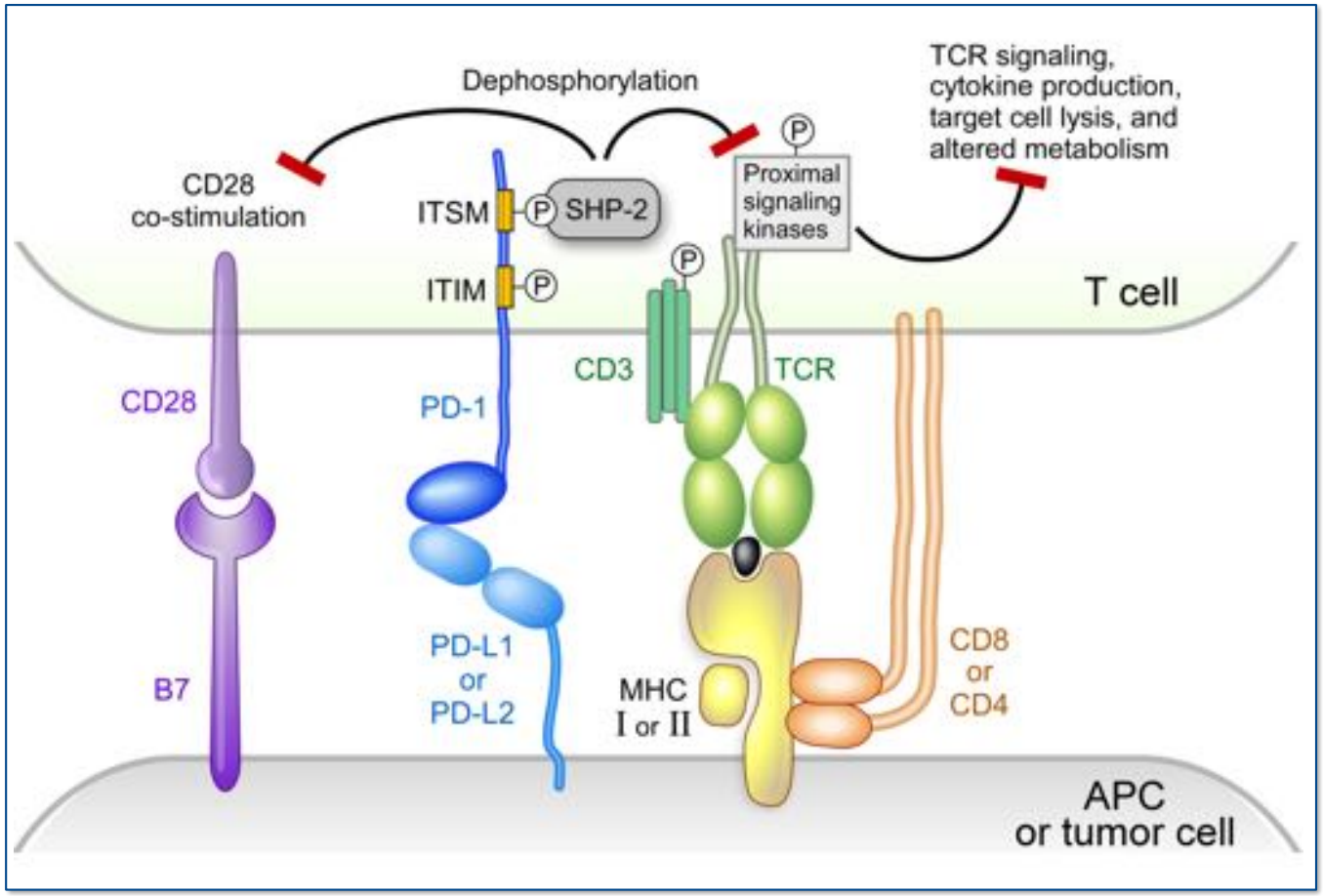
Schmitz et al. New Engl J Med 2018

Lymphoma driver genes in the chromatin organization pathway



Lymphoma driver genes in the immune evasion pathway

- 9p24.1/ *PD-L1/ PD-L2* alterations
- *β2M* inactivating mutations/ deletions (perturb MHC class I)
- *CIITA* inactivating alterations (perturb MHC class II)
- Evaluate expression of antigen presentation pathway components in cHL



DLBCL
PMBL
cHL

Modified from Baumeister, S.H. *et al.* 2016; *Annu. Rev. Immunol.* 34:539-73

Reichel *et al., Blood* 2015; 125:1061-72
Steidl *et al., Nature* 2011; 471:377-81

Oncogenic TLR and BCR Signaling and PD-1 Ligand Deregulation in PTL and EBV$^-$ PCNSL

Oncogenic TLR and BCR Signaling	PTL	EBV$^-$ PCNSL
MYD88^{L265P}	78% (38/49)[a]	60% (33/55)[b]
CD79B^{Y196mut}		
Total	49% (22/45)[c]	38% (19/50)[d]
With *MYD88* ^{L265P}	91% (20/22)	89% (17/19)

PD-1 Ligand Deregulation		
9p24.1/ *PD-L1* and/or *PD-L2* gain	54% (26/50)[e]	52% (33/63)[f]
PD-L1 or *PD-L2* translocation	4% (2/50)[g]	6% (4/66)[h]

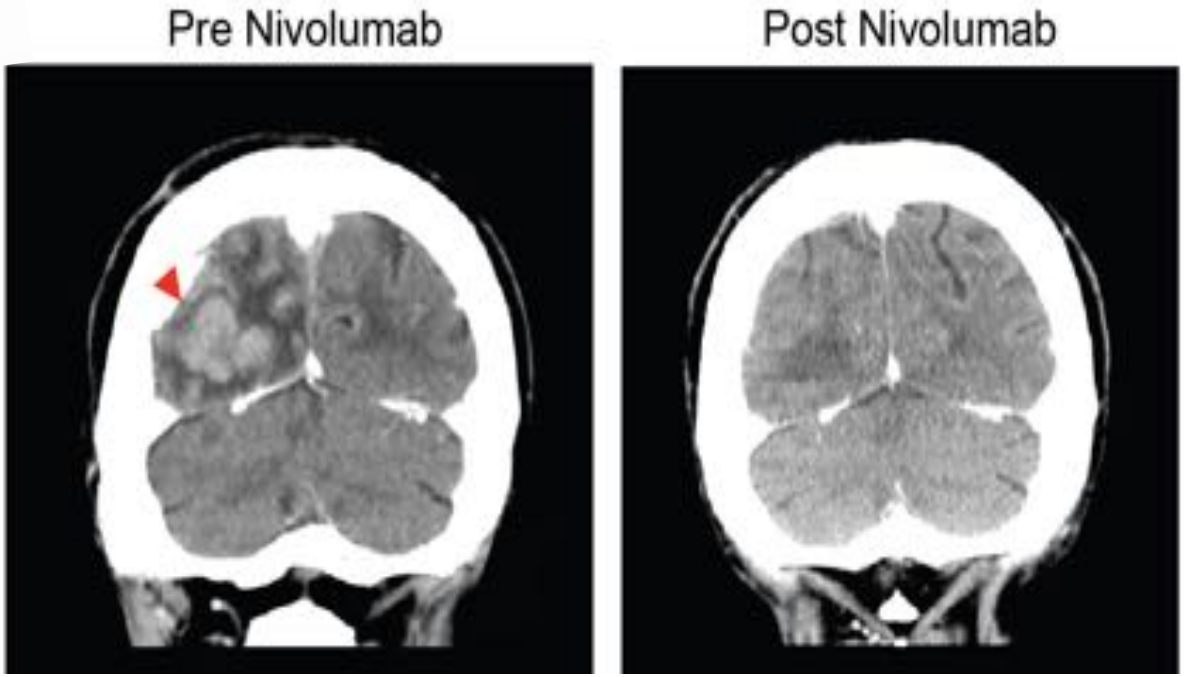
Chapuy and Roemer *et al., Blood* 2016; 127:869-81

PCNSL/ SCNSL Case Series

- N= 5 pts (2 women, 3 men)
  - Recurrent PCNSL 3
  - Primary refractory PCNSL 1
  - Recurrent PTL (SCNSL) 1
- Median Age = 64 yrs (range, 54-85 yrs)
- Median KPS = 70% (range, 40-80 %)

Nayak *et al., Blood* 2017; 129:3071-73

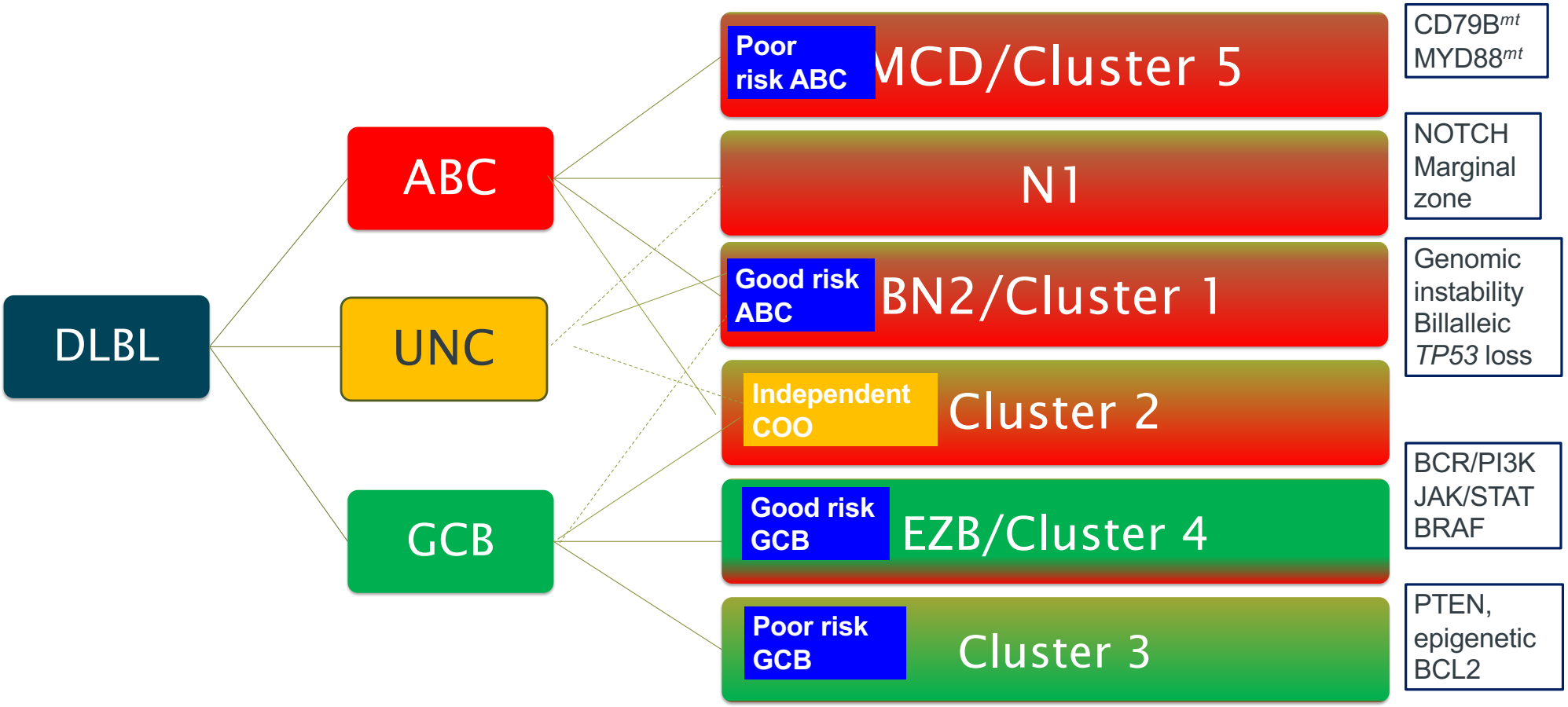
Nivolumab in PCNSL and PTL



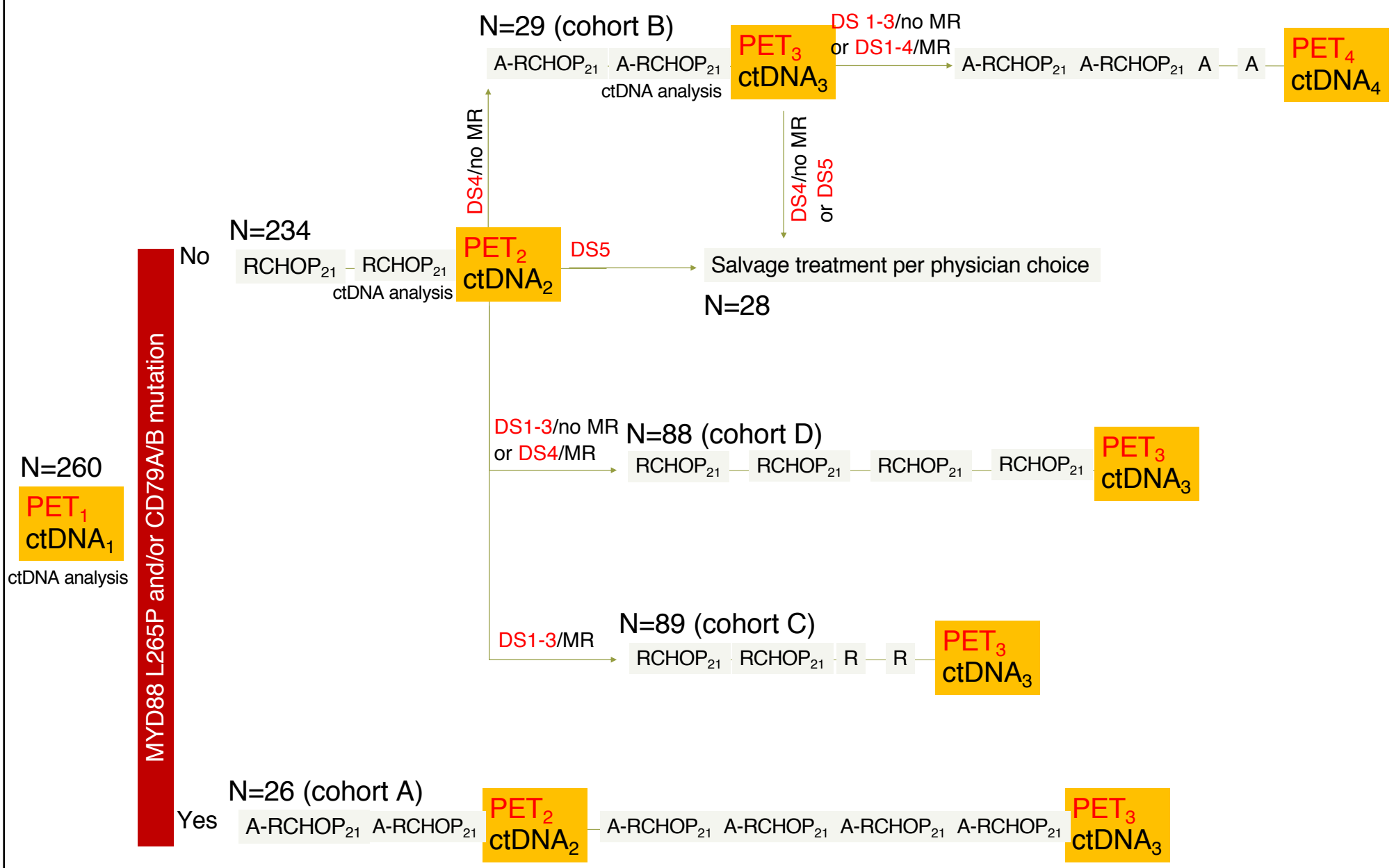
- All 5 pts had clinical and radiographic responses to PD-1 blockade – 4 CRs and 1 PR
- 3 pts remain progression – free (PF) at 13+-17+mos; 2 pts PF for 14 and 17 mos.
- National/ international trial of PD-1 blockade (Nivolumab therapy) in relapsed/refractory PCNSL and PTL underway – CA209-647

Nayak *et al., Blood* 2017; 129:3071-73

A new taxonomy and new targets



ctDNA-driven therapy of DLBCL: SAKK 38



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