UKM
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Biological Identification of High-Risk DLBCL

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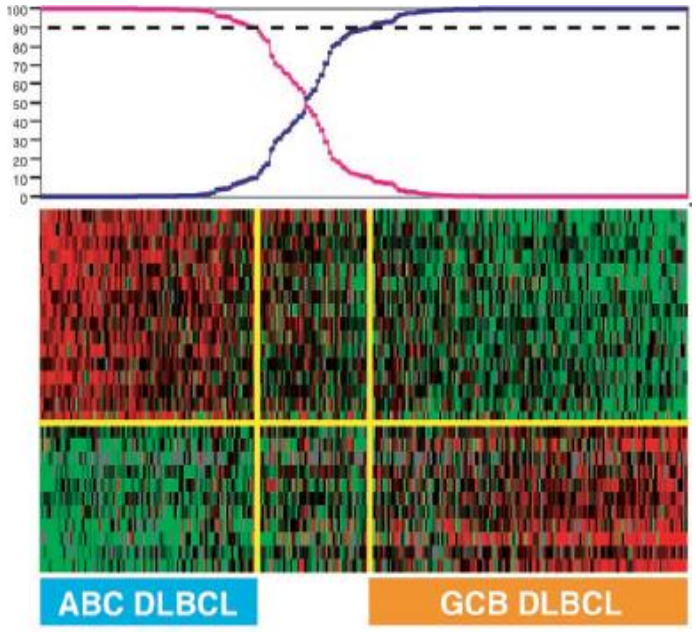
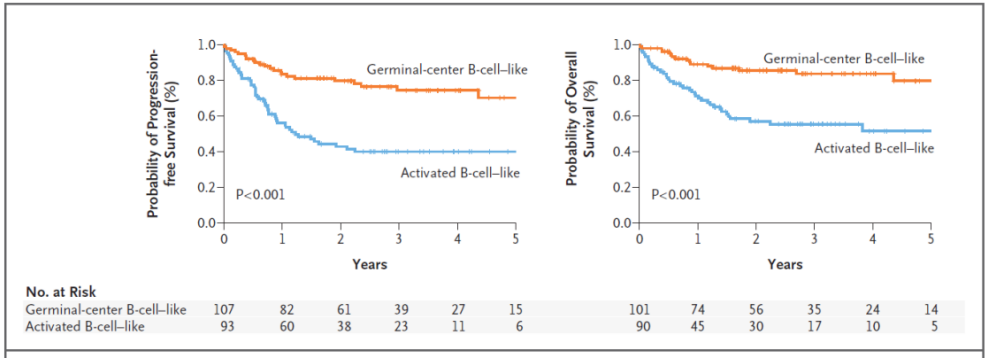
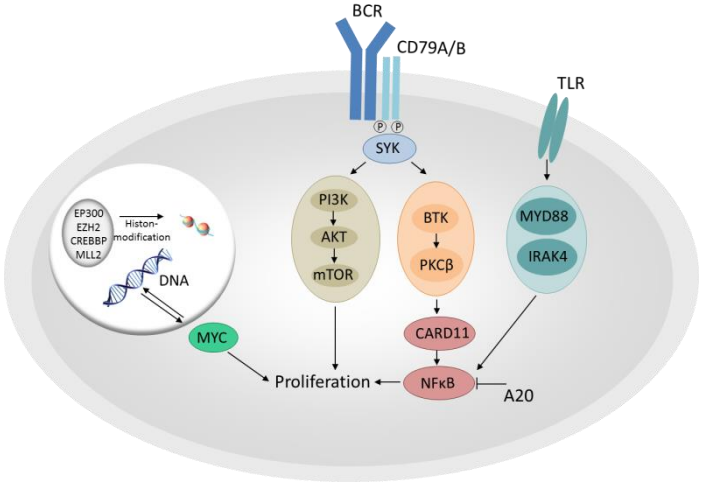
Gene Expression Profiling Reveals Distinct Molecular Subtypes





Key signaling pathways

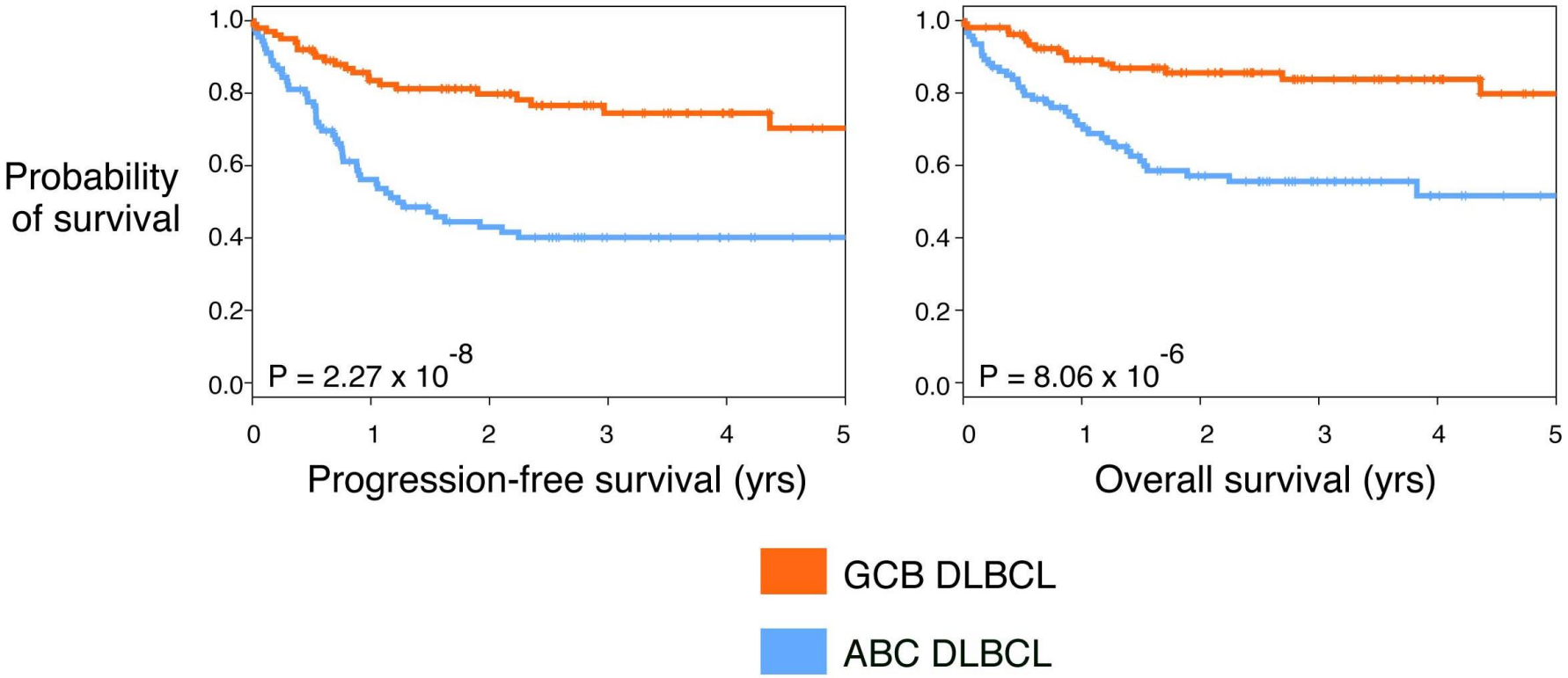
- ABC-DLBCL:
  BCR signaling



- GCB-DLBCL:
  PI3K/Akt/mTOR signaling

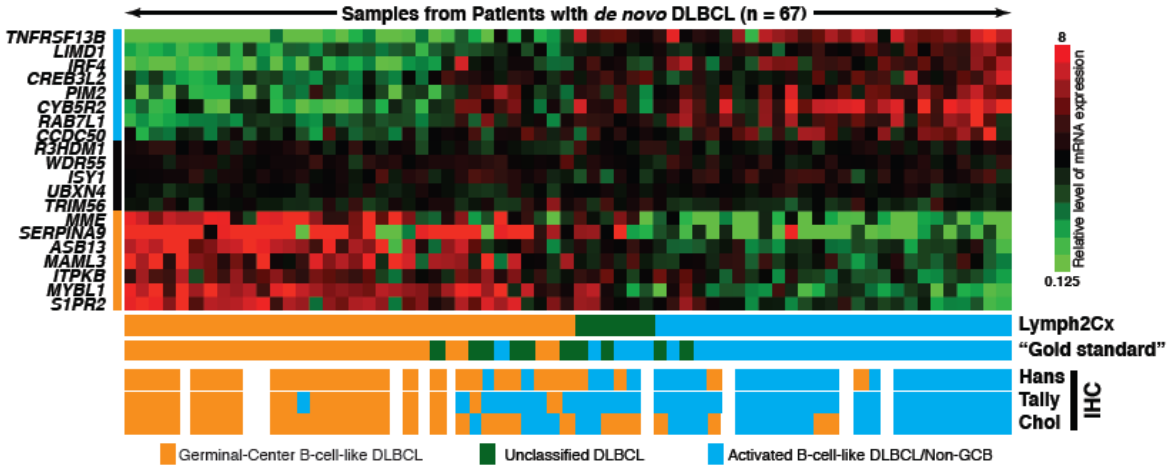
Rosenwald et al. 2002, NEJM; Wright et al. 2003, PNAS

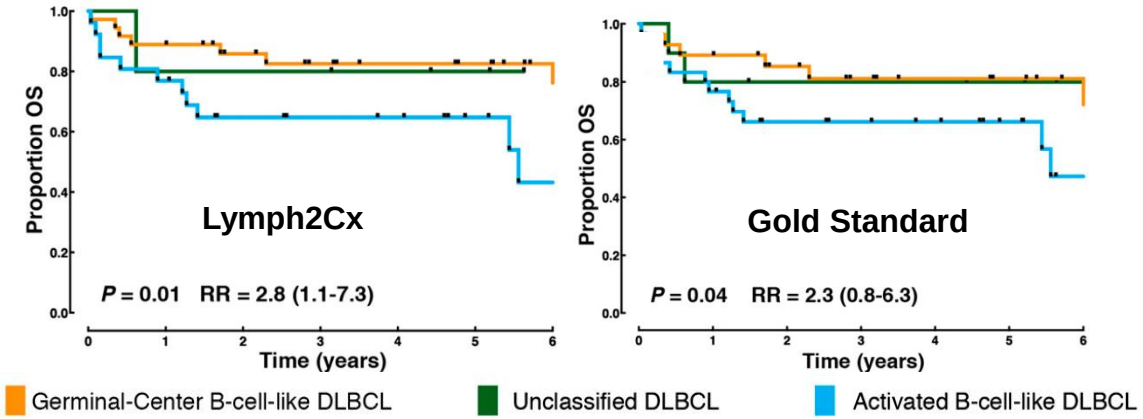
ABC and GCB DLBCL have significantly different survival rates following R-CHOP

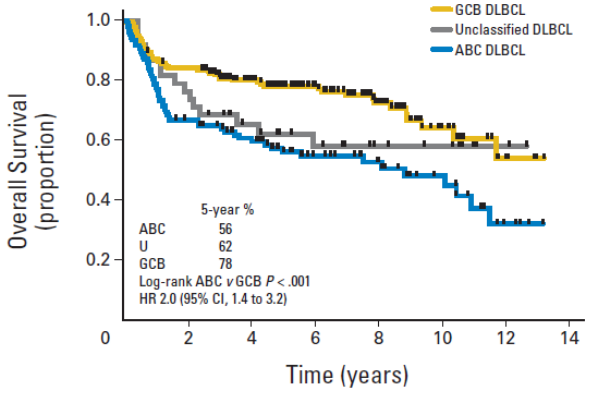


Lenz et al., NEJM 2008

Nanostring nCounter-based GE profiling LLMPP Lymph2Cx





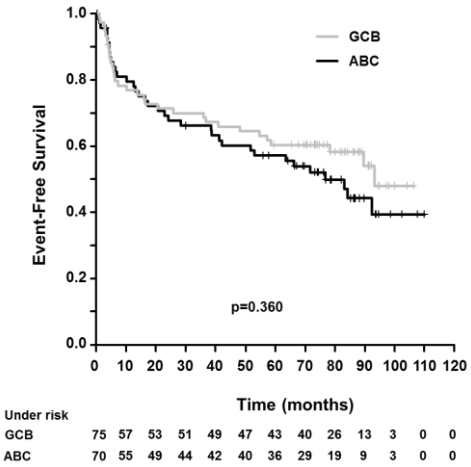


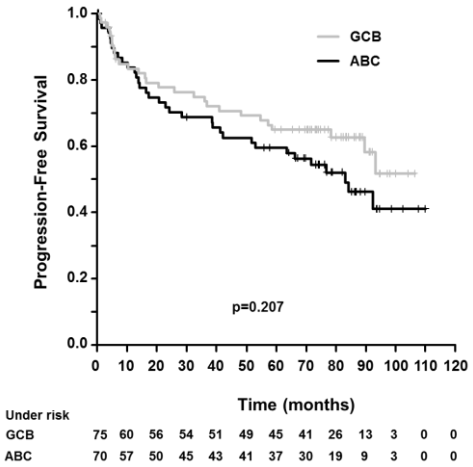
Scott et al. 2014, Blood

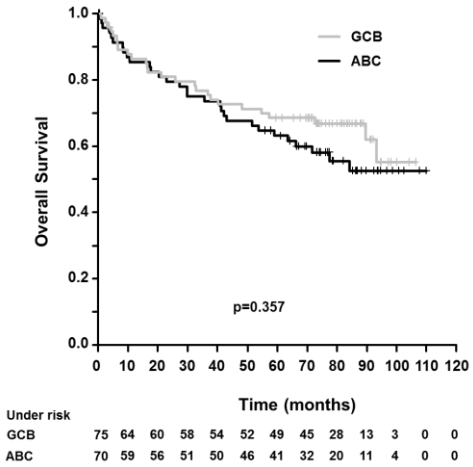
Scott et al. 2015, J Clin Oncol

Lymph2Cx-based COO Classification and Survival Analysis

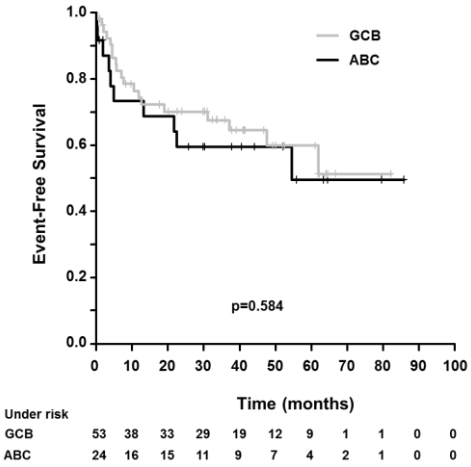
RICOVER-60 (R-CHOP-14)

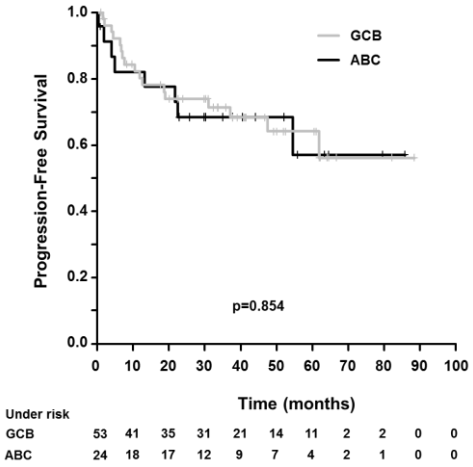


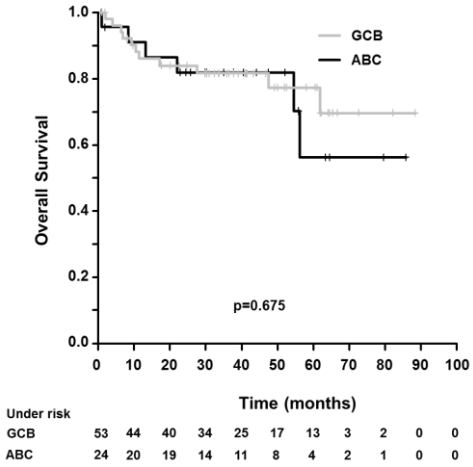




R-MegaCHOEP

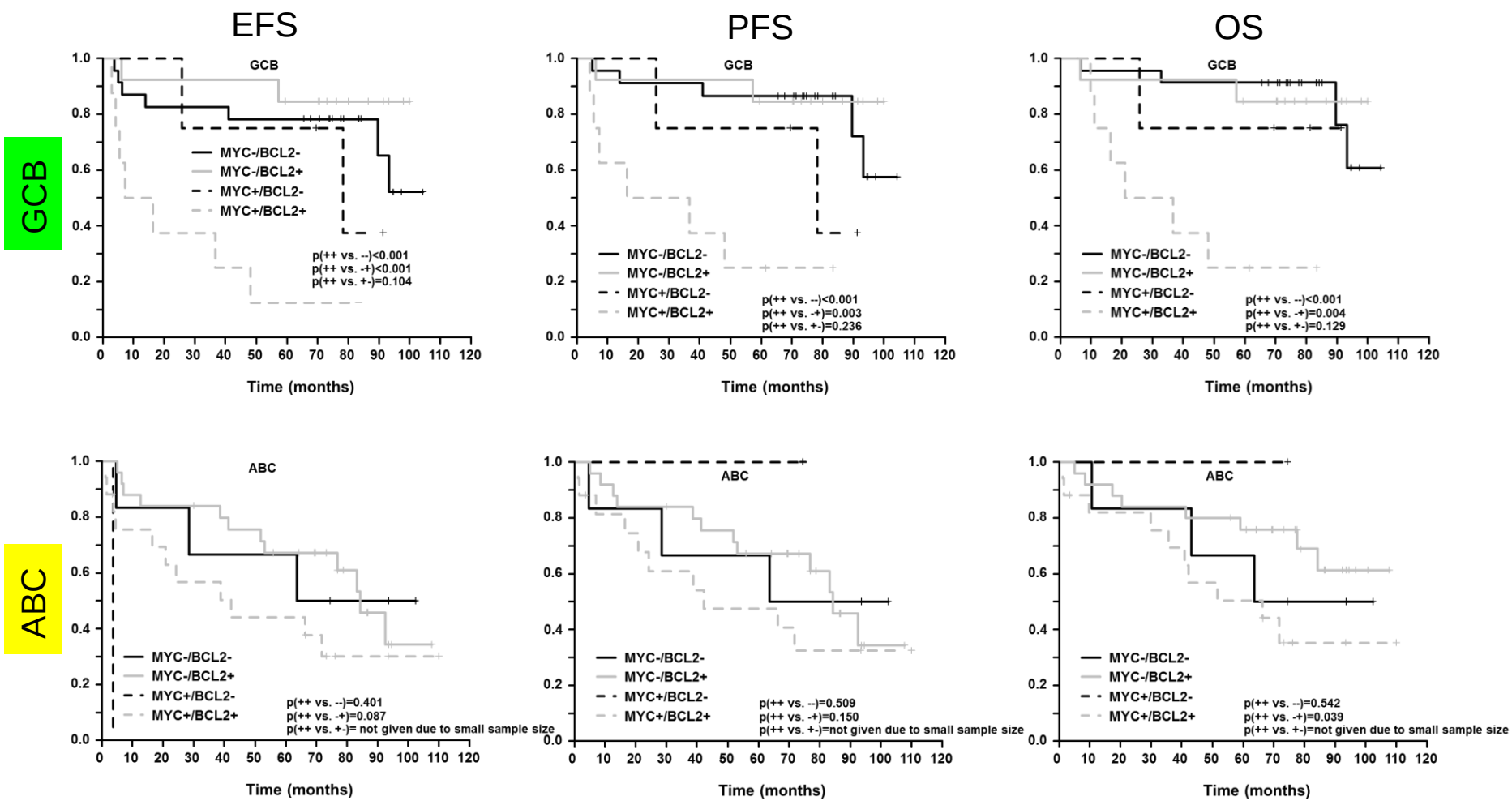






Staiger et al., submitted JCO

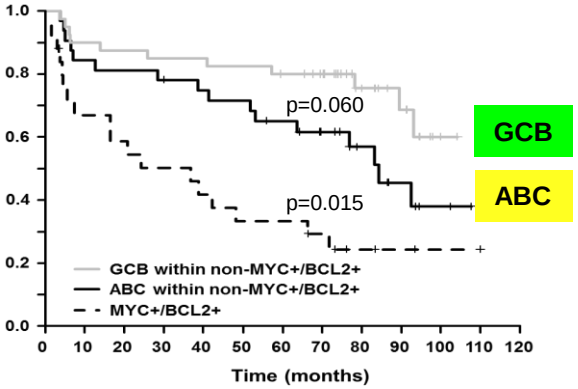
Survival Analysis of COO-Classified MYC/BCL2 Dual Expressers



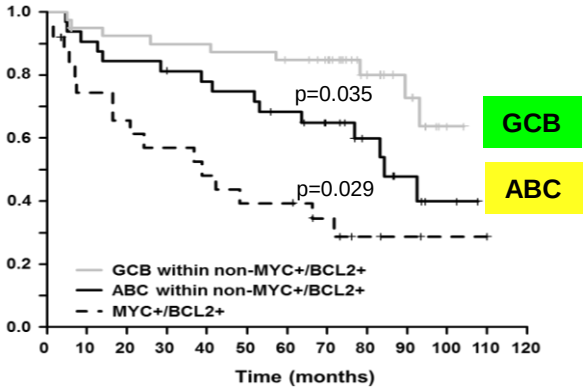
Staiger et al., submitted JCO

MYC/BCL2 Dual Expressers versus Non-Expressers

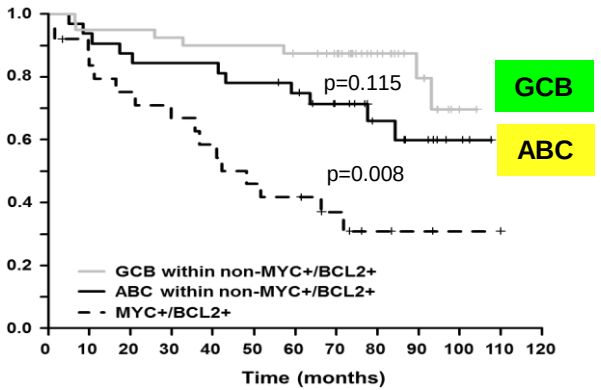
EFS



PFS



OS



MYC/BCL2 DE status is a risk factor independent of COO classification

→ Corroborating data from Scott and colleagues 2015

Staiger et al., submitted JCO

Risk of CNS relapse in dual expresser MYC+BCL2+.

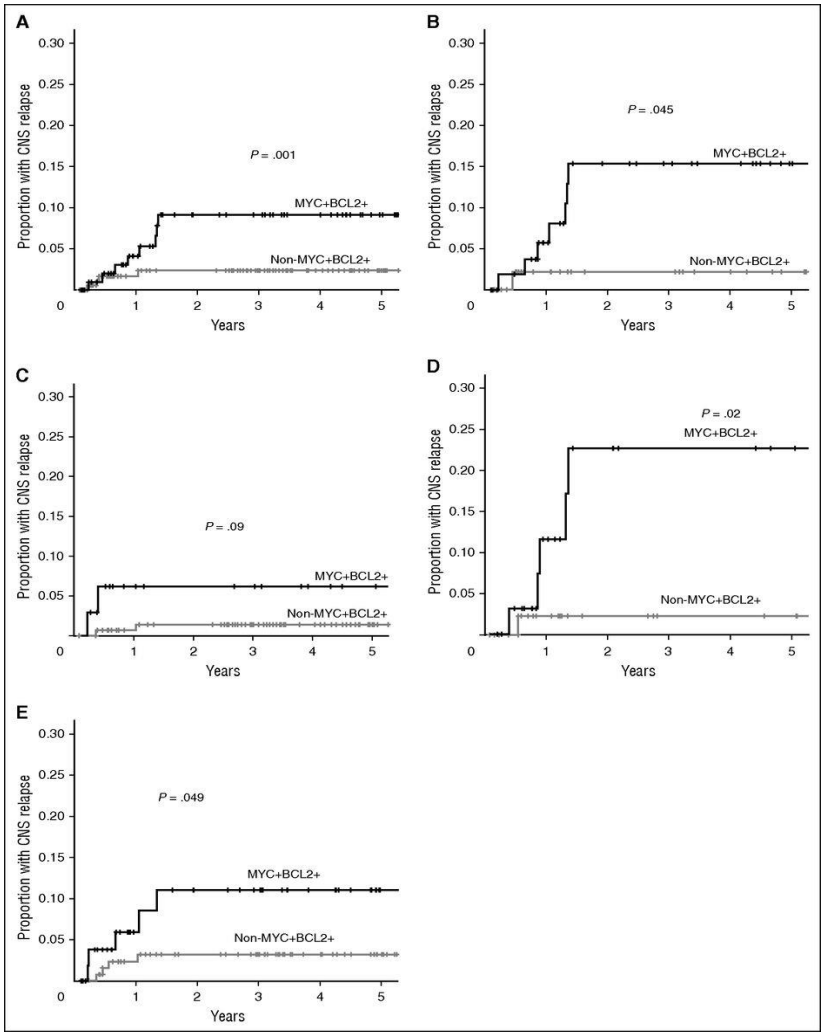
A. All DLBCL

B. ABC-subtype

C. GCB-subtype

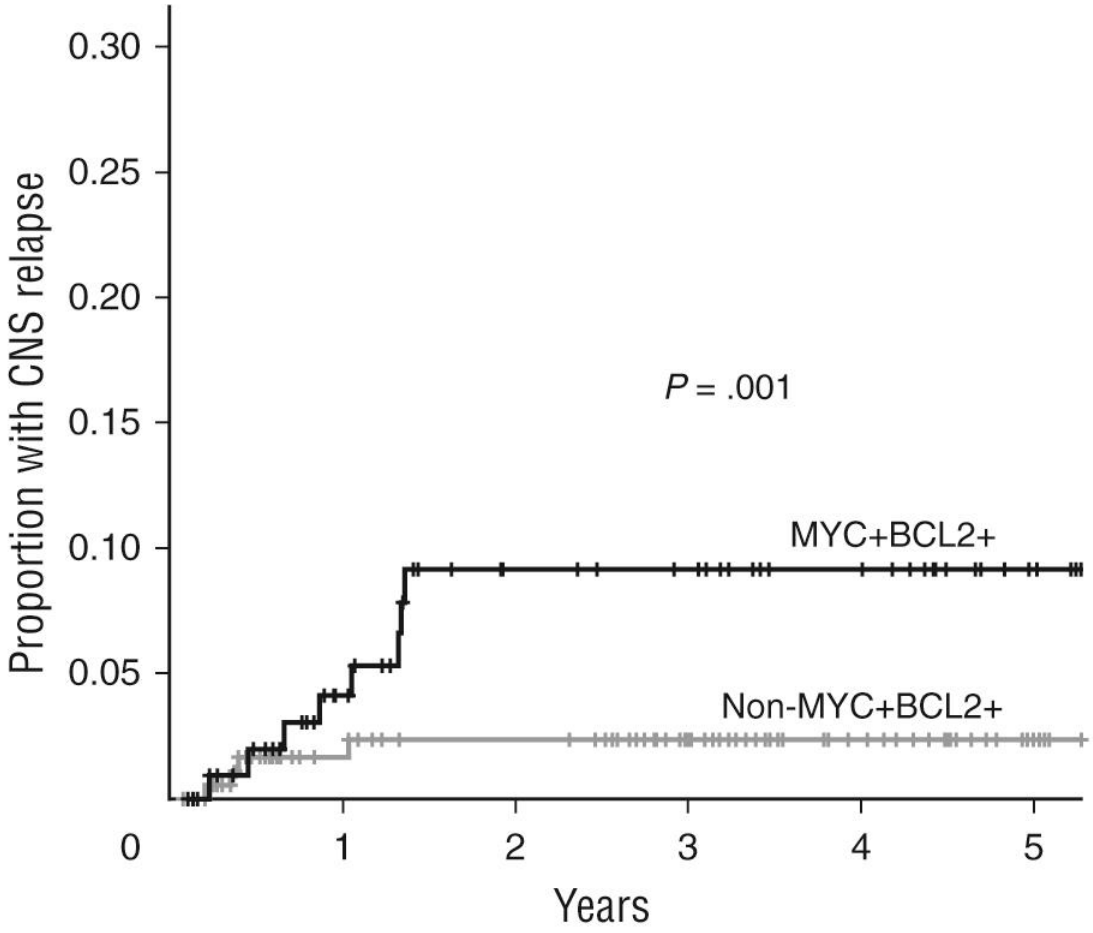
D. CNS-IPI high

E. CNS-IPI



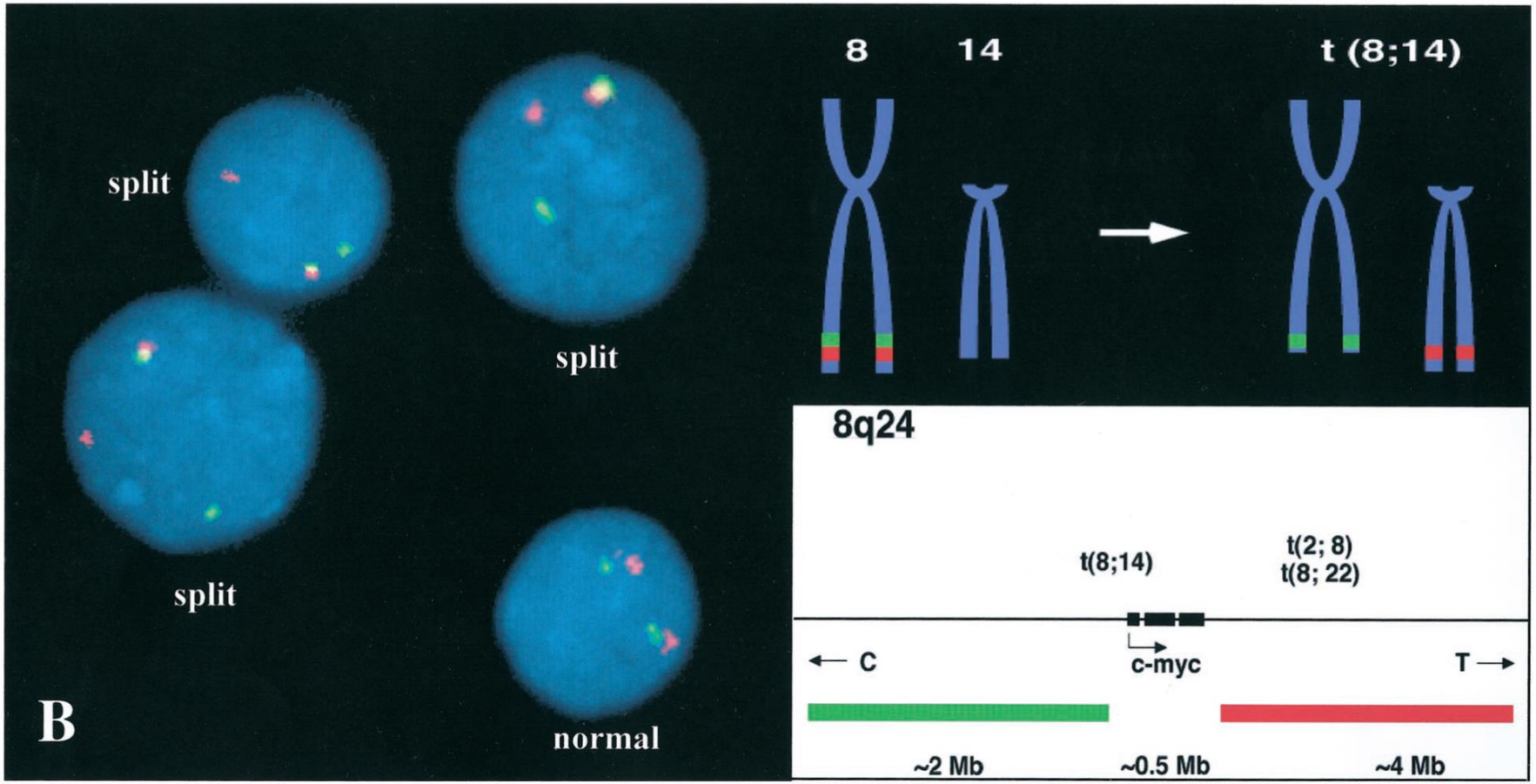
Savage et al. Blood 2016;127:2182-2188

Double expressers are characterized by increased CNS relapse risk



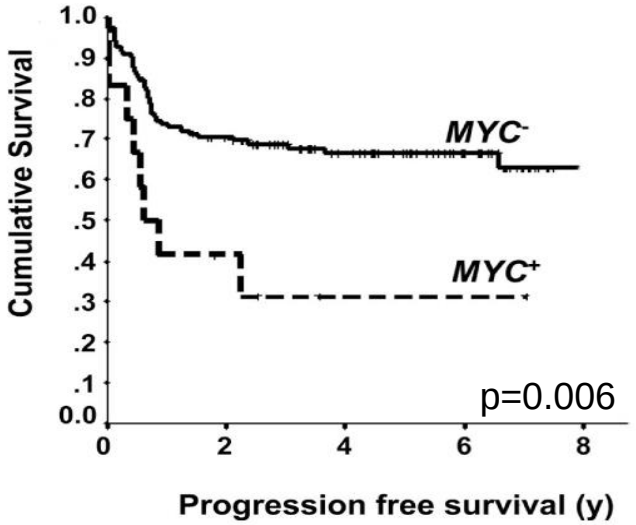
Savage et al., Blood, 2016

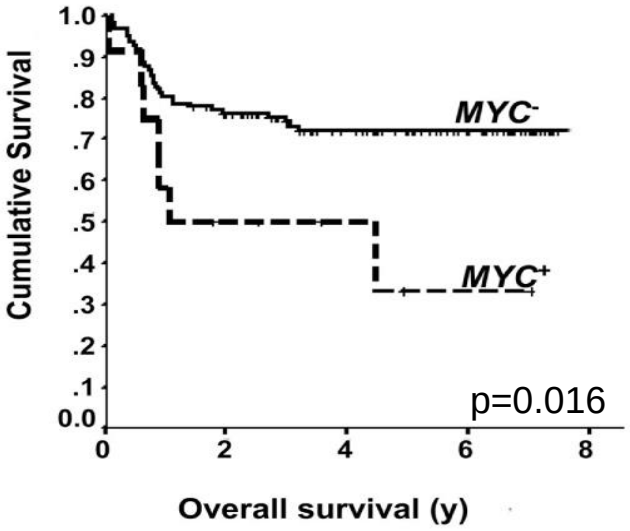
8–10% of all DLBCLs are characterized by *MYC* translocations



Hecht and Aster, JCO, 2000; 18(21):3707-21

DLBCLs with *MYC* rearrangement are characterized by inferior survival after R-CHOP

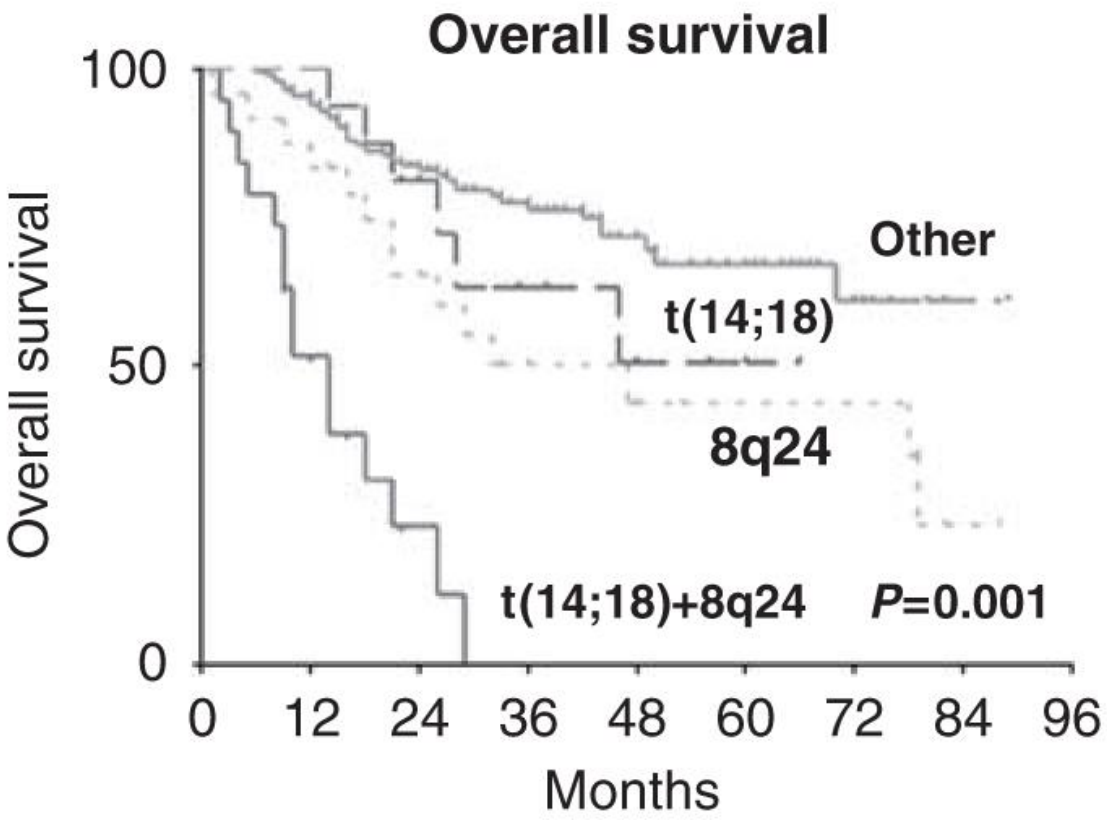




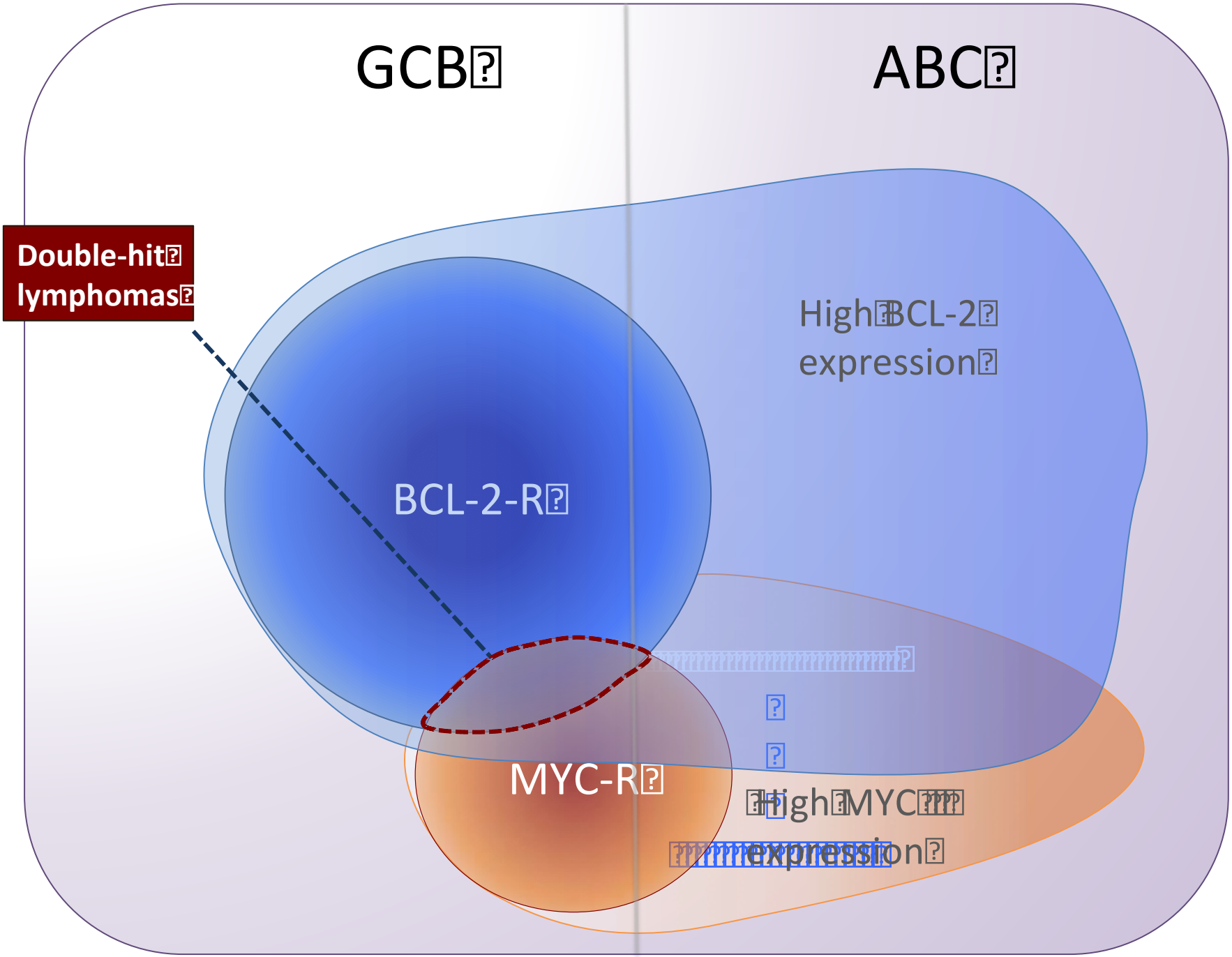
- Incidence 8.8%
- Characterized by high proliferation
- Increased risk of CNS relapse
- 3/12 cases with *MYC* rearrangement had concurrent t(14;18)

Savage et al., Blood, 2009

DLBCLs with *MYC* and *BCL2* translocations are characterized by inferior survival



Niitsu et al., Leukemia 2009


GCB
ABC
Double-hit lymphomas
High BCL-2 expression
BCL-2-R
MYC-R
High MYC expression

Prognostic implications of biological markers

partly controversial

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partly controversial

BUT

Molecular DLBCL subtypes are addicted to different oncogenic pathways

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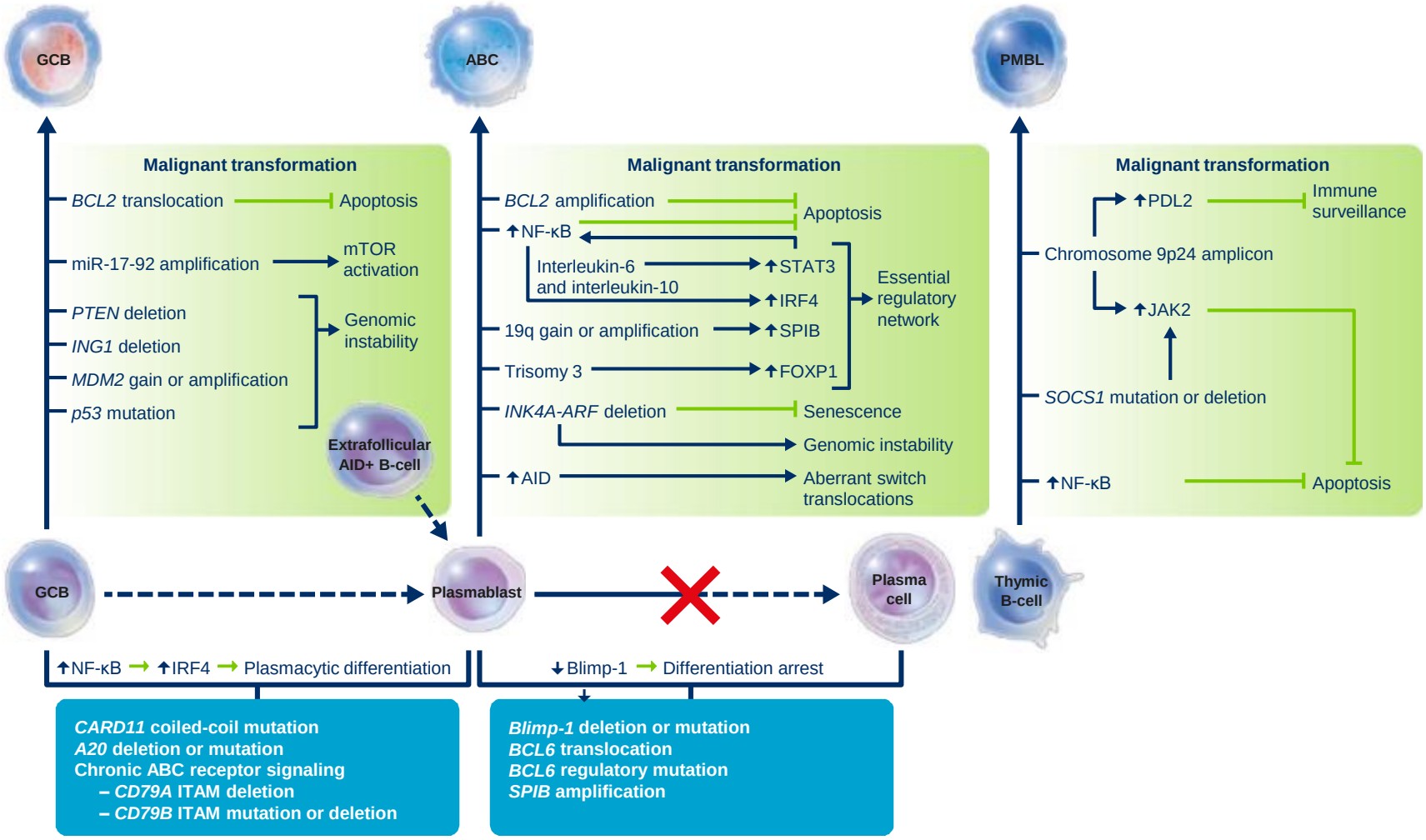
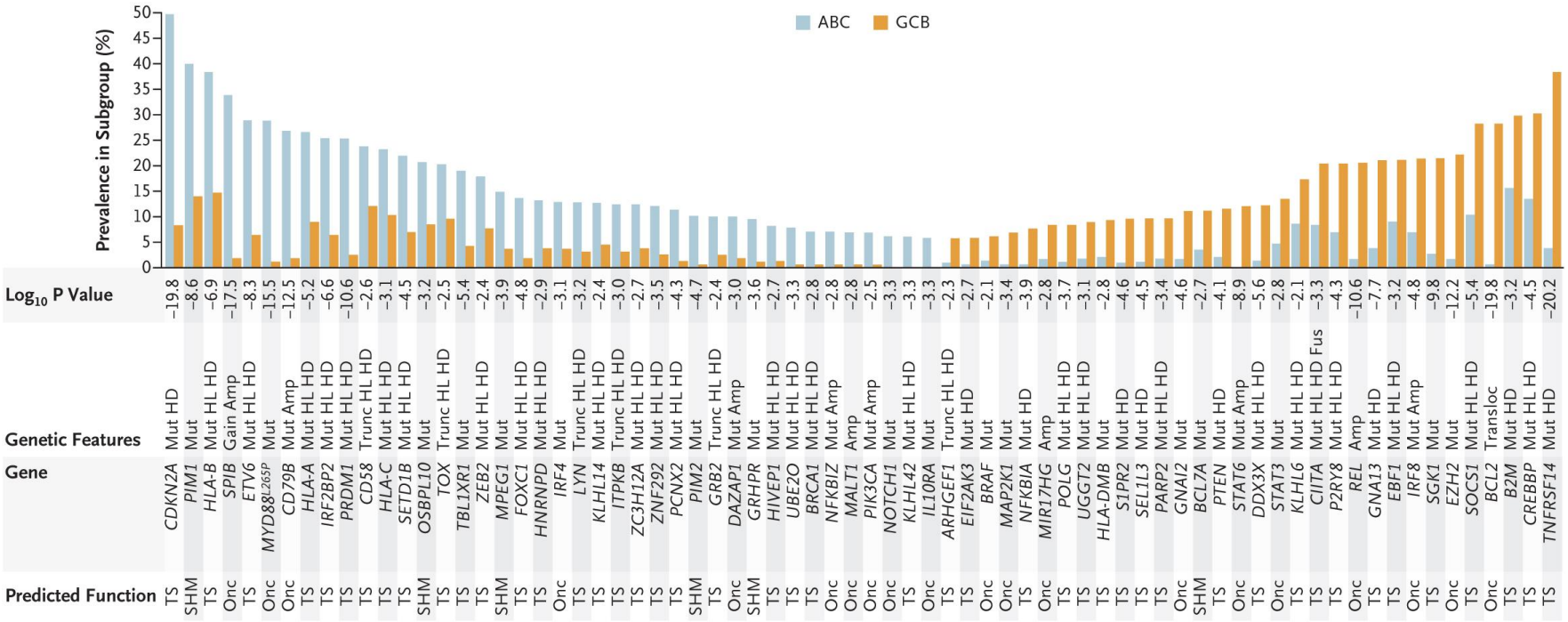


Lenz and Staudt, NEJM, 2010

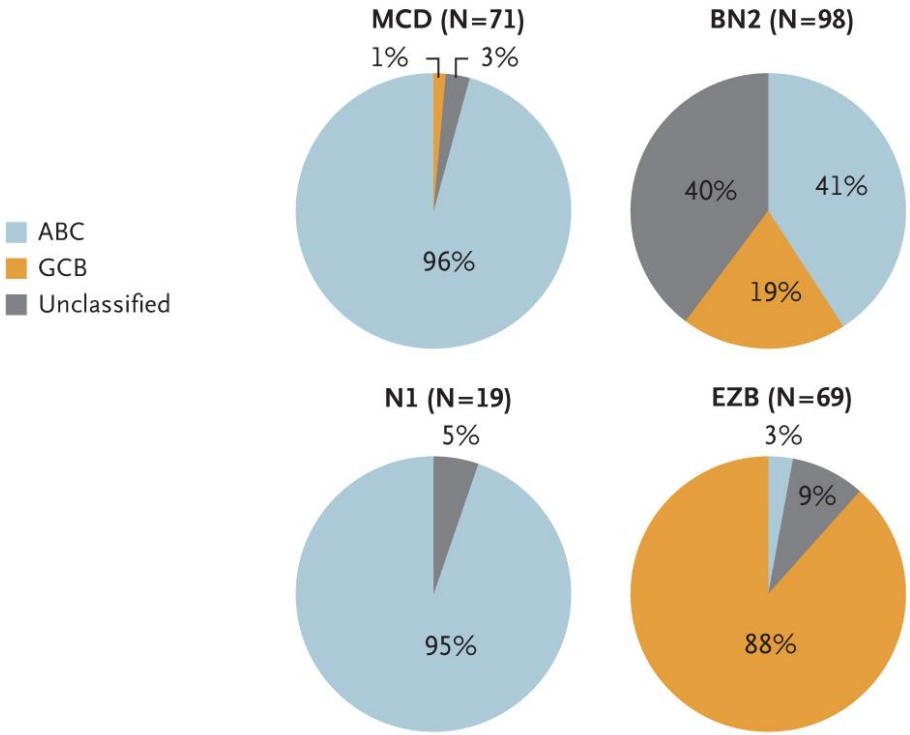
Future developments

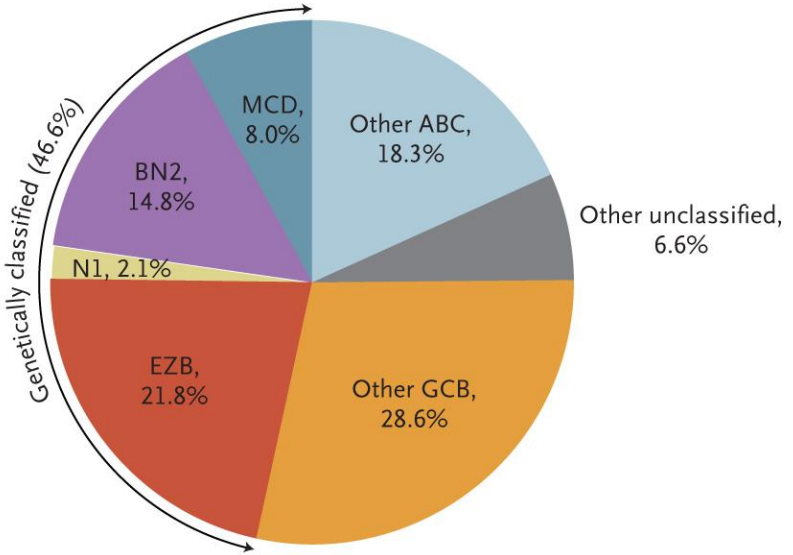
Novel subtypes have been identified



Schmitz et al., NEJM, 2018

Novel subtypes have been identified





Schmitz et al., NEJM, 2018

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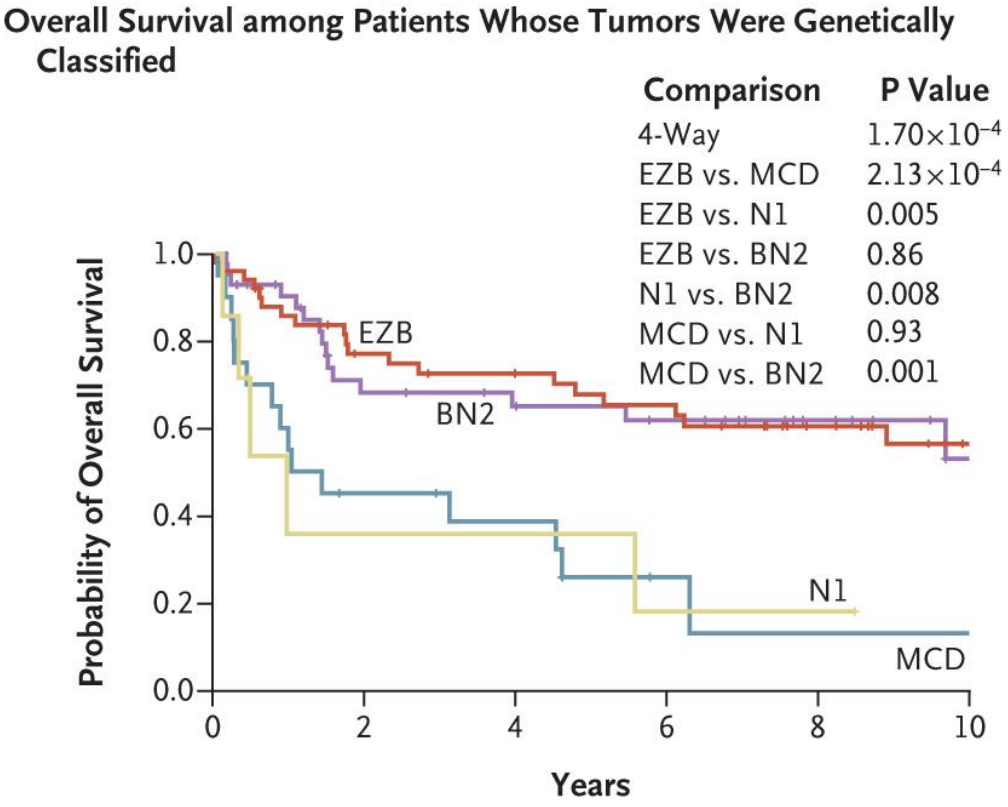


No. at Risk

MCD	20	8	6	2	1	1
BN2	42	24	20	18	11	5
N1	7	2	2	1	1	0
EZB	50	34	30	27	19	11

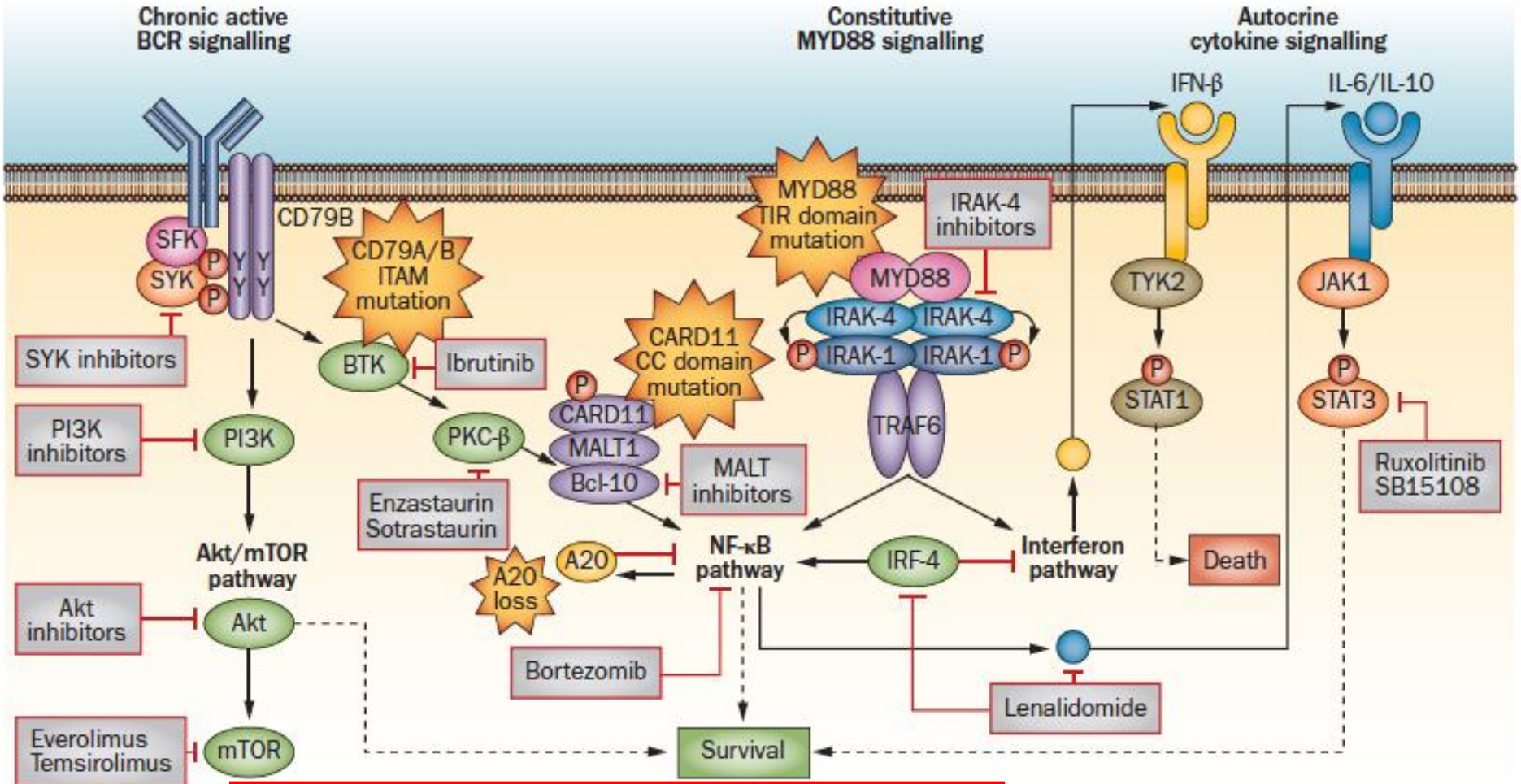
Schmitz et al., NEJM, 2018

Therapeutic implications

Molecular Characterisation: Implications for targeted therapy

20% of ABC DLBCL
Chronic active BCR signalling with intact NFkB genes *CD79B/A*

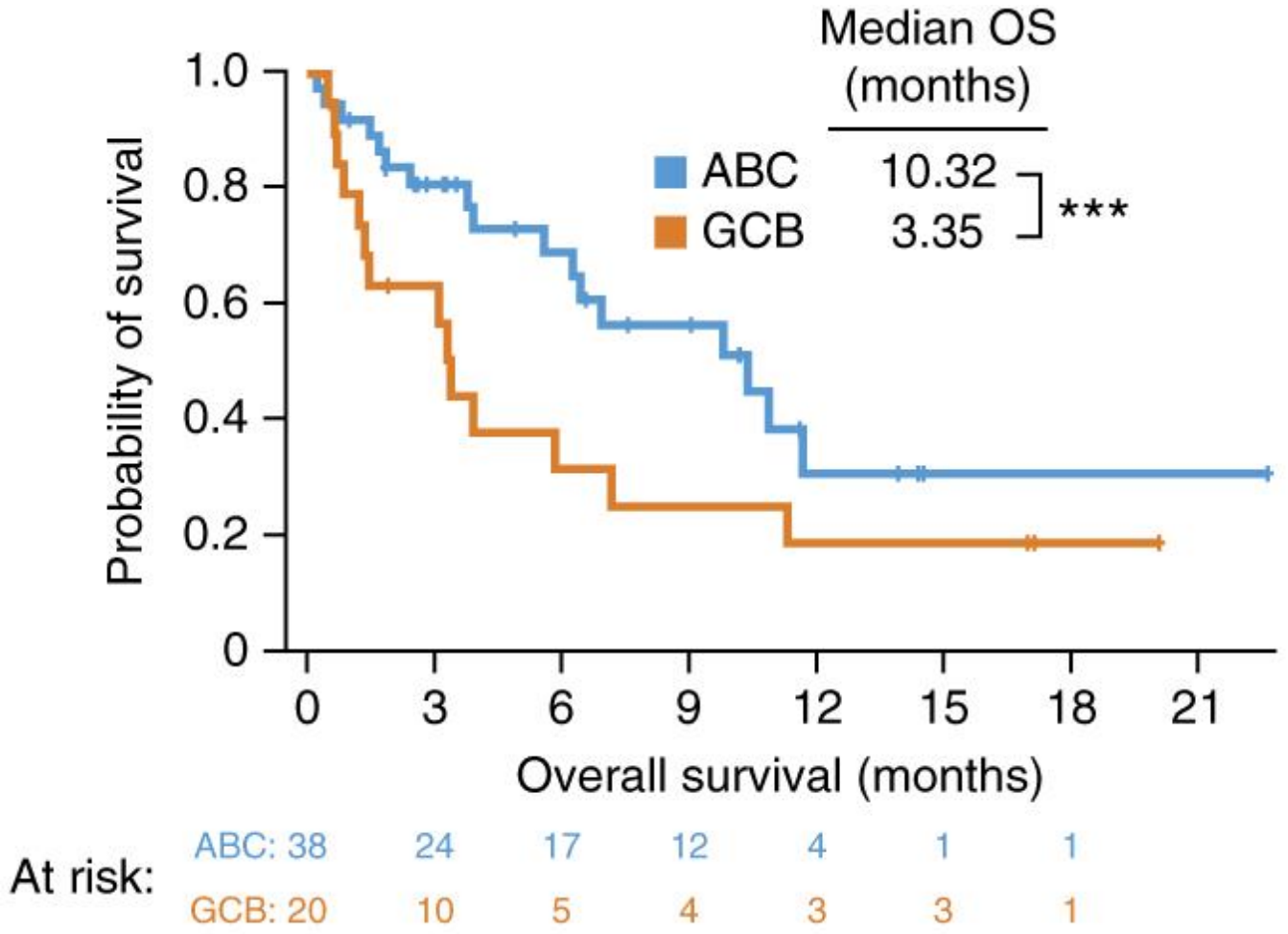
30% of ABC DLBCL
Activating mutations of *MyD88*
Association with *CD79* mutations



50% of ABC DLBCL
Mutations in NFKB regulators : *A20, CARD11, others*

Roschewski M, Nat Rev 2014

Ibrutinib is preferentially active in ABC DLBCL

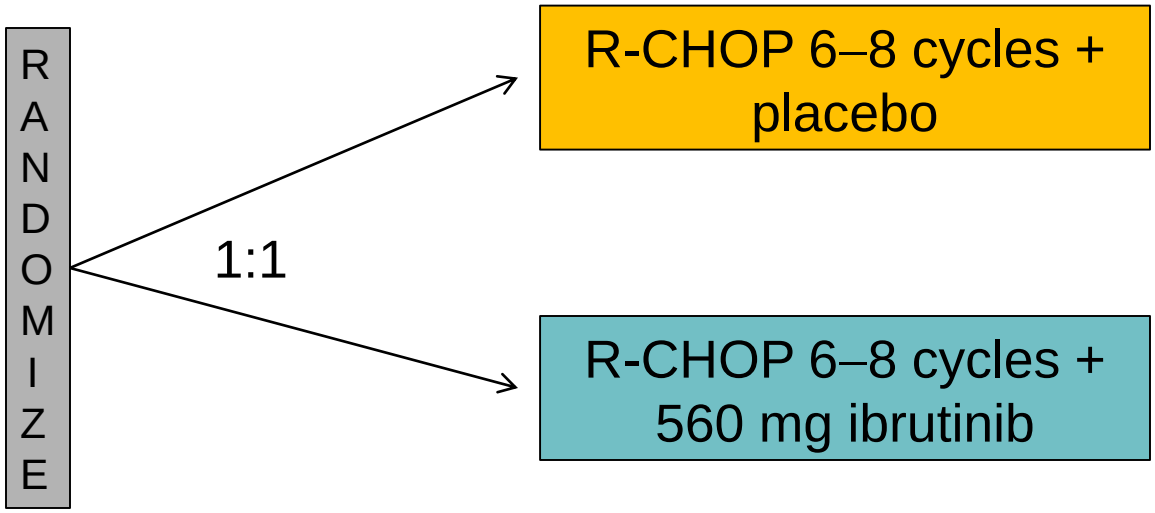


Wilson et al., Nat Med, 2015

Ibrutinib + R-CHOP in newly diagnosed non-GCB DLBCL

PHOENIX (NCT01855750): study design

Phase III trial



Stratified by R-IPI 1–2 vs 3–5, region and number of prespecified cycles

Primary endpoint: EFS
Secondary endpoint: PFS, OS, CR, time to worsening (LYM subscale), pharmacokinetics, safety
Exploratory endpoint: quality of life, biomarkers related to resistance

Key Inclusion Criteria
Newly diagnosed histologically confirmed non-GCB DLBCL
Stage II–IV disease
At least one measurable site of disease
Age ≥ 18 years
R-IPI ≥ 1
ECOG PS 0–2

R-IPI, revised international prognostic index.

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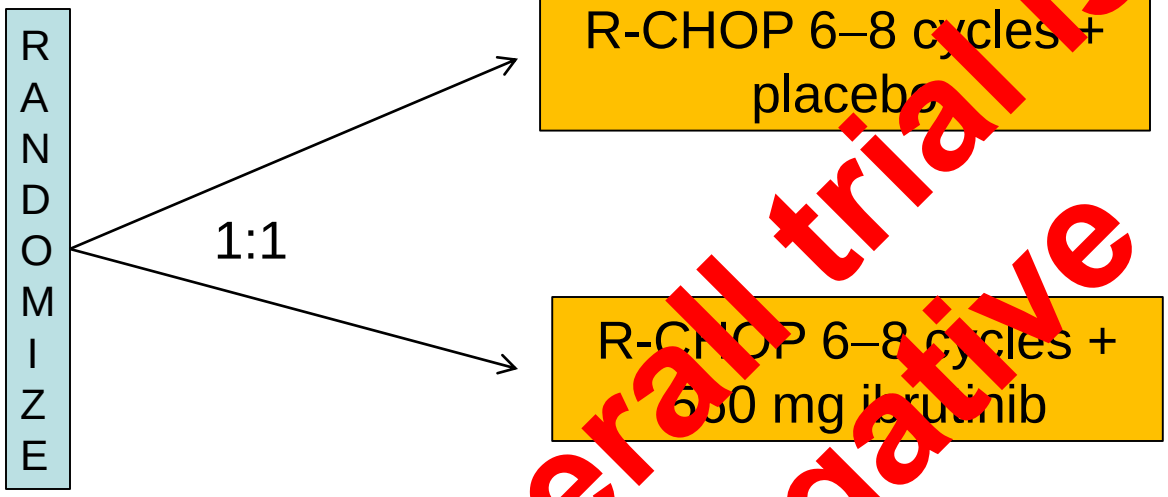

Overall trial is negative

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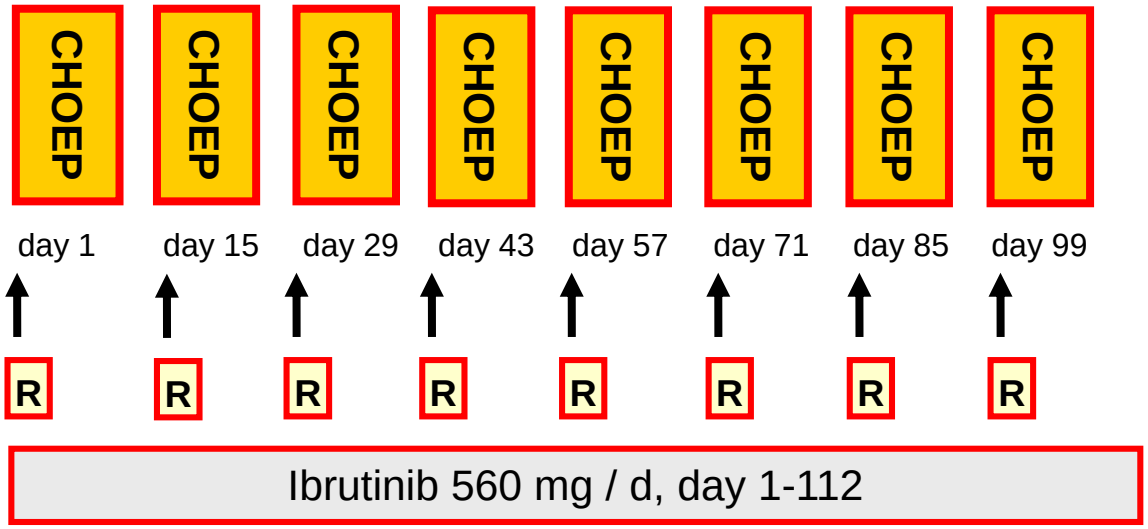
R-IPI, revised international prognostic index.

Younes A, et al. J Clin Oncol. 2014;32:abstract TPS8615.
(Updated data presented in poster at ASCO annual meeting.)

R-CHOEP-brut

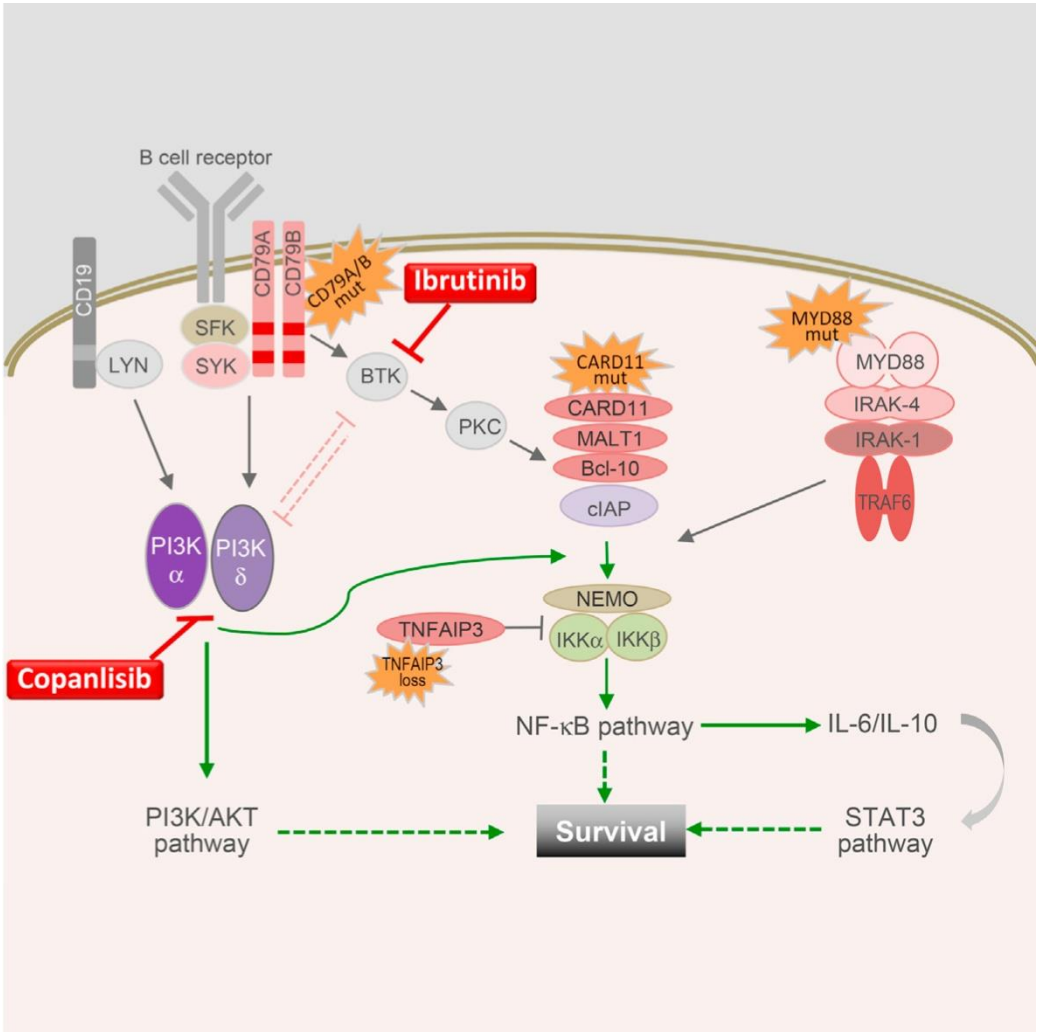
Indication	First-line therapy of diffuse large B-cell lymphoma Younger patients (18-60 years) Age-adjusted International Prognostic Index 2-3
Design	Prospective, multicenter, phase II study
No. of patients	75



Patients with bulky disease/extranodal involvement:
radiotherapy (dose 39.6 Gy)

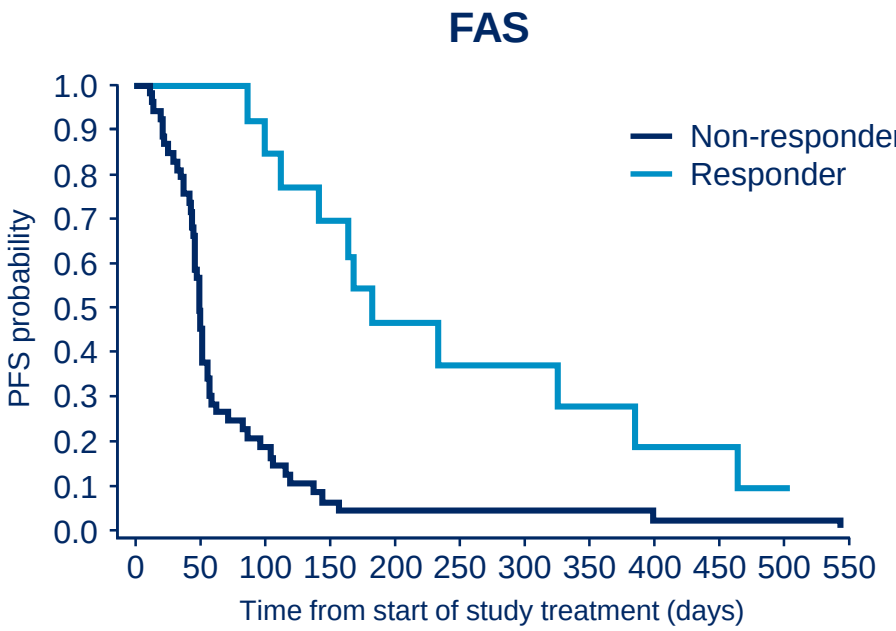
Molecular DLBCL subtypes are addicted to different components of the PI3K/AKT pathway

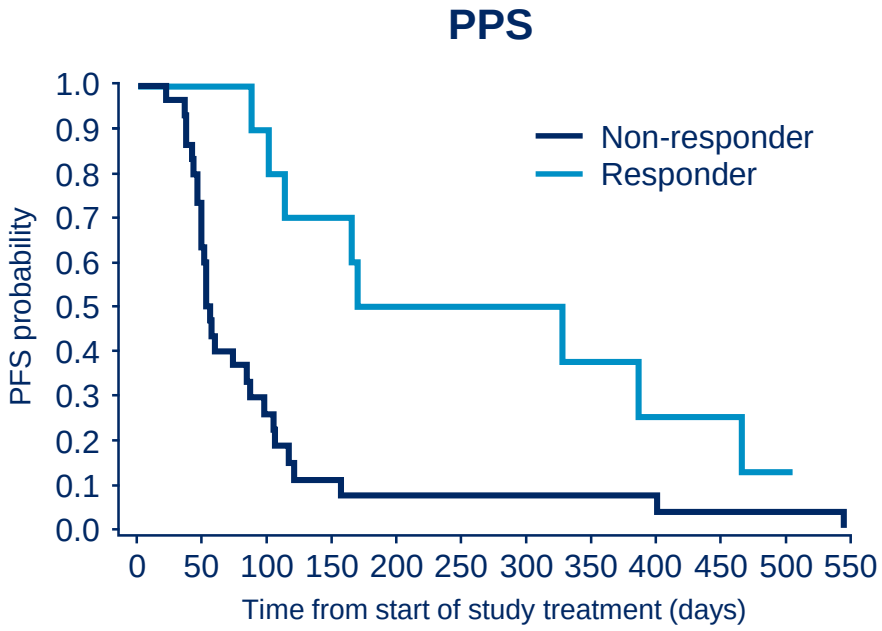
Copanlisib is active in preclinical models of ABC DLBCL



Paul et al., Cancer Cell, 2017

COPANLISIB: Progression-free survival for patients with objective responses

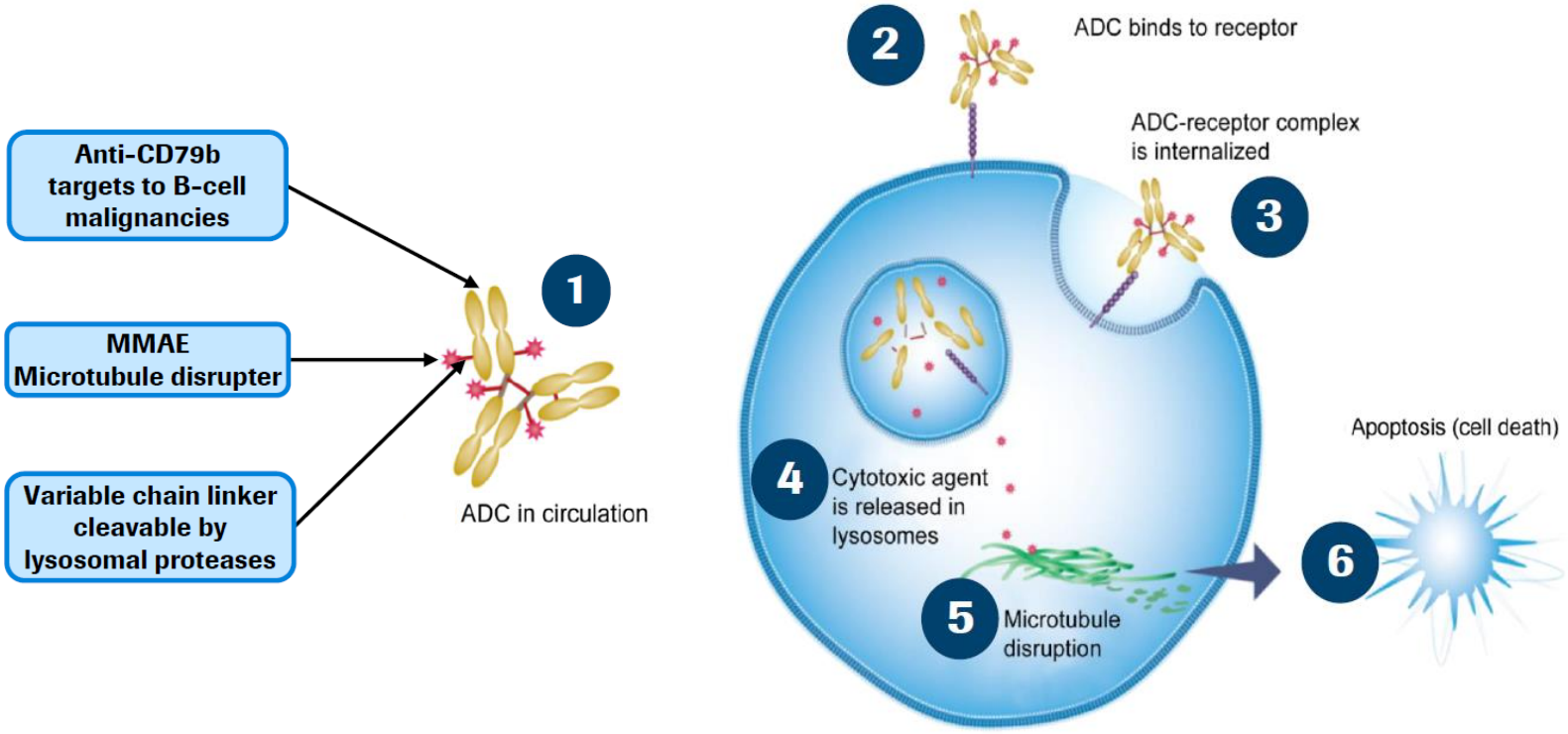




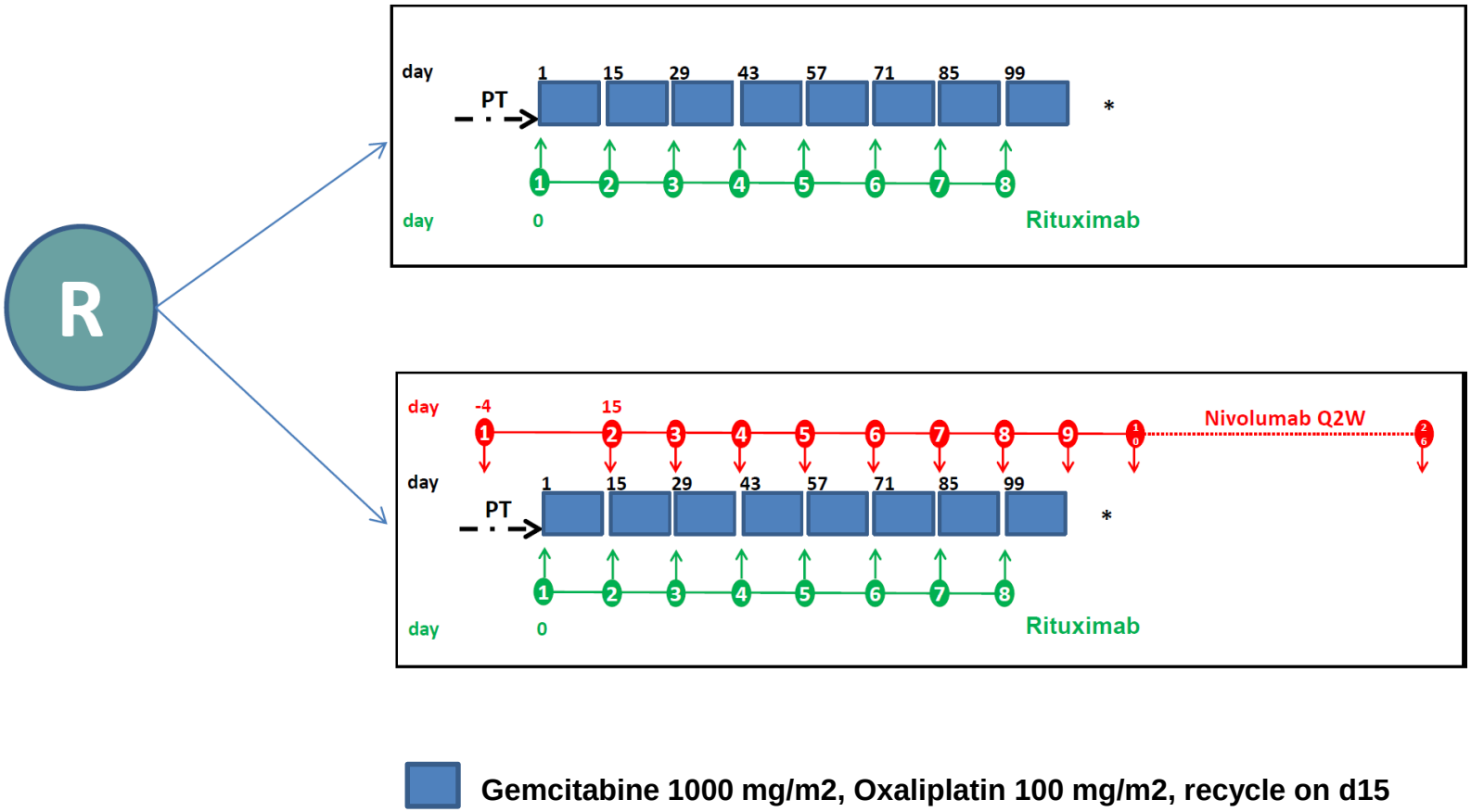
	Overall FAS (*n*=67)	Responder (*n*=13)	Non-responder (*n*=54)
Median PFS, days (95% CI)	54 (50-84)	183 (113-385)	50 (46-56)

	Overall PPS (*n*=40)	Responder (*n*=10)	Non-responder (*n*=30)
Median PFS, days (95% CI)	84 (52-106)	248 (88-465)	54 (50-84)

Polatuzumab Vedotin:
anti-CD79b ADC (Antibody drug conjugate)



Design



Gemcitabine 1000 mg/m2, Oxaliplatin 100 mg/m2, recycle on d15

DSHNHL