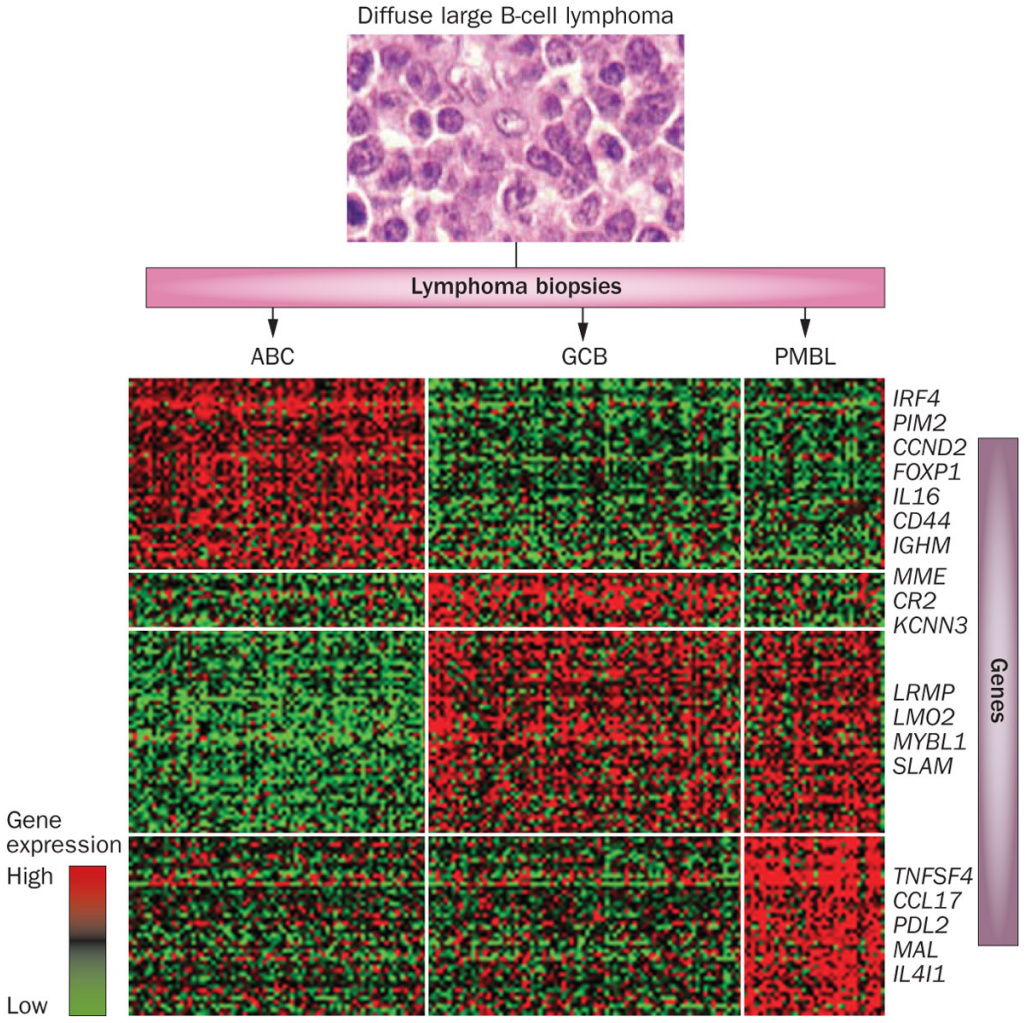
Treatment Landscape in R/R DLBCL
Novel Targets and Strategies

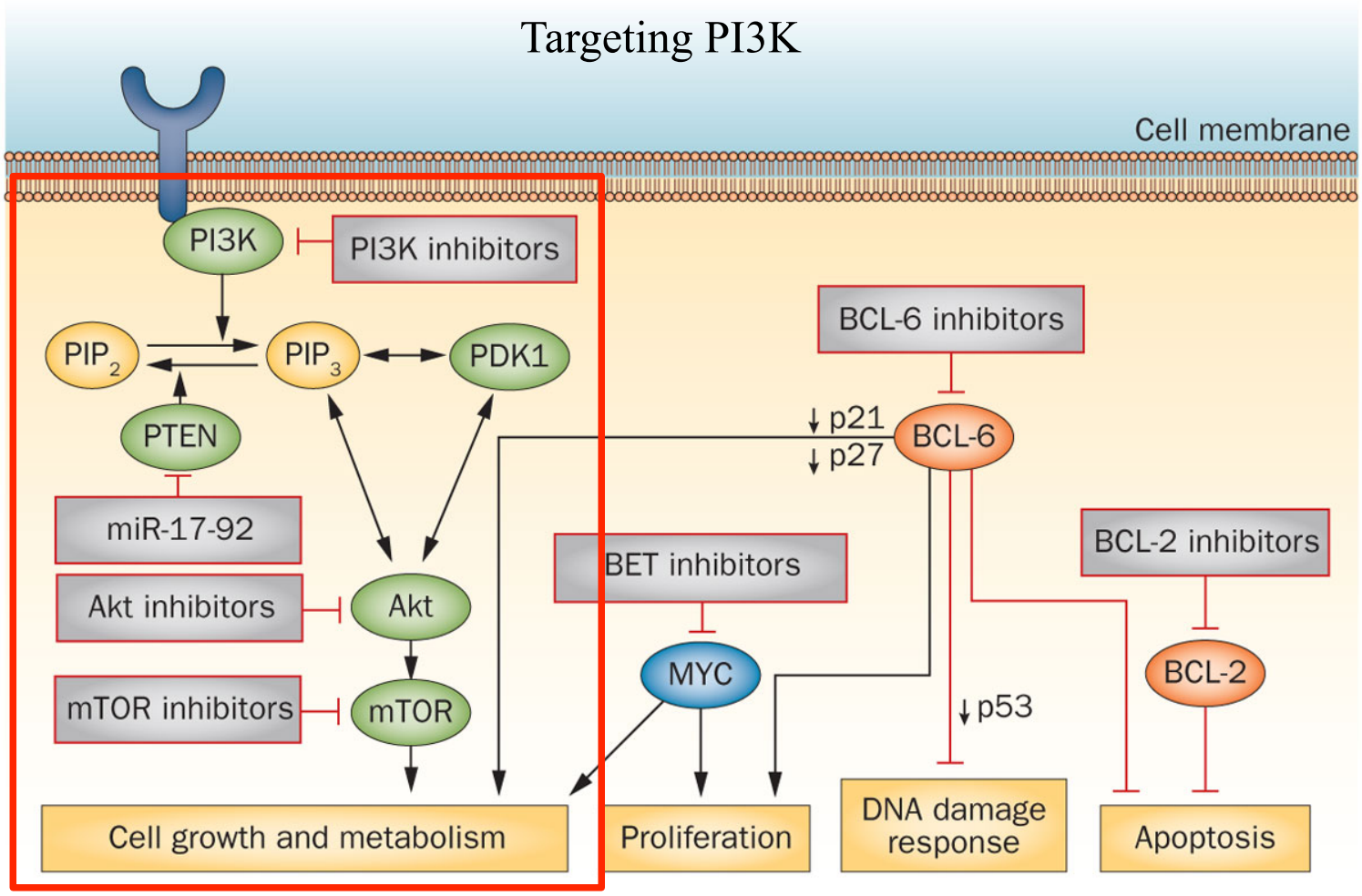
Wyndham H. Wilson, M.D., Ph.D.
Senior Investigator

Gene-expression profiling of DLBCL subtypes



Roschewski, M. *et al.* (2013) *Nat. Rev. Clin. Oncol.*

Key signaling pathways in GCB DLBCL



Roschewski, M. *et al.* (2013) *Nat. Rev. Clin. Oncol.*

Genetic aberrations activating PI3K pathway in hematologic malignancies

Disease	Node	Most common aberrations	Frequency	References
Acute myeloid leukemia	*FLT3*	FLT3-ITD and FLT3-TKD	≈40%	24
	RAS	KRAS and NRAS (codons 12, 13, and 61)	≈18%	24,25
	KIT	Mutations in exons 8 and 17; codon 816	5%-25%*	26,27
Chronic myelogenous leukemia	*BCR-ABL1*	p210 variant	≈95%	28,29
Acute lymphoblastic leukemia	*BCR-ABL1*	p190 variant	8% (T-ALL) 25% (B-ALL)	30,31
	PTEN	PTEN deletions	9%-17% (T-ALL)	21,32
		PTEN mutations	8% (T-ALL)	
Non-Hodgkin's lymphoma	*PTEN*	Loss of PTEN expression	37% (DLBCL) 19% (MCL)	33,34
	PIK3CA	Mutations in exons 9 and 20 (DLBCL)	8% (DLBCL)	33,35
		Gene amplification (MCL)	68% (MCL)	

**Higher frequency in CBF-AML. ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; CBF: core binding factor; CLL: chronic lymphocytic leukemia; CML: chronic myeloid leukemia; FLT3: Fms-like tyrosine kinase 3; FLT3-ITD: FLT3 internal tandem duplications; FLT3-TKD: FLT3 tyrosine kinase domain; HL: Hodgkin's lymphoma; MCL: mantle cell lymphoma; NHL: non-Hodgkin's lymphoma; PI3K: phosphoinositide 3-kinase; PTEN: phosphatase and tensin homolog deleted on chromosome 10; SHIP: Src homology domain–containing inositol phosphatase.*

- **Deletion PTEN 10q23 locus: 10% GCB**
- **Inactivation PTEN: 55% GCB and 14% ABC DLBCL**
- **Mutation distribution suggests relevant in GCB > ABC**

(Testoni et al. Ann Oncol 2015)

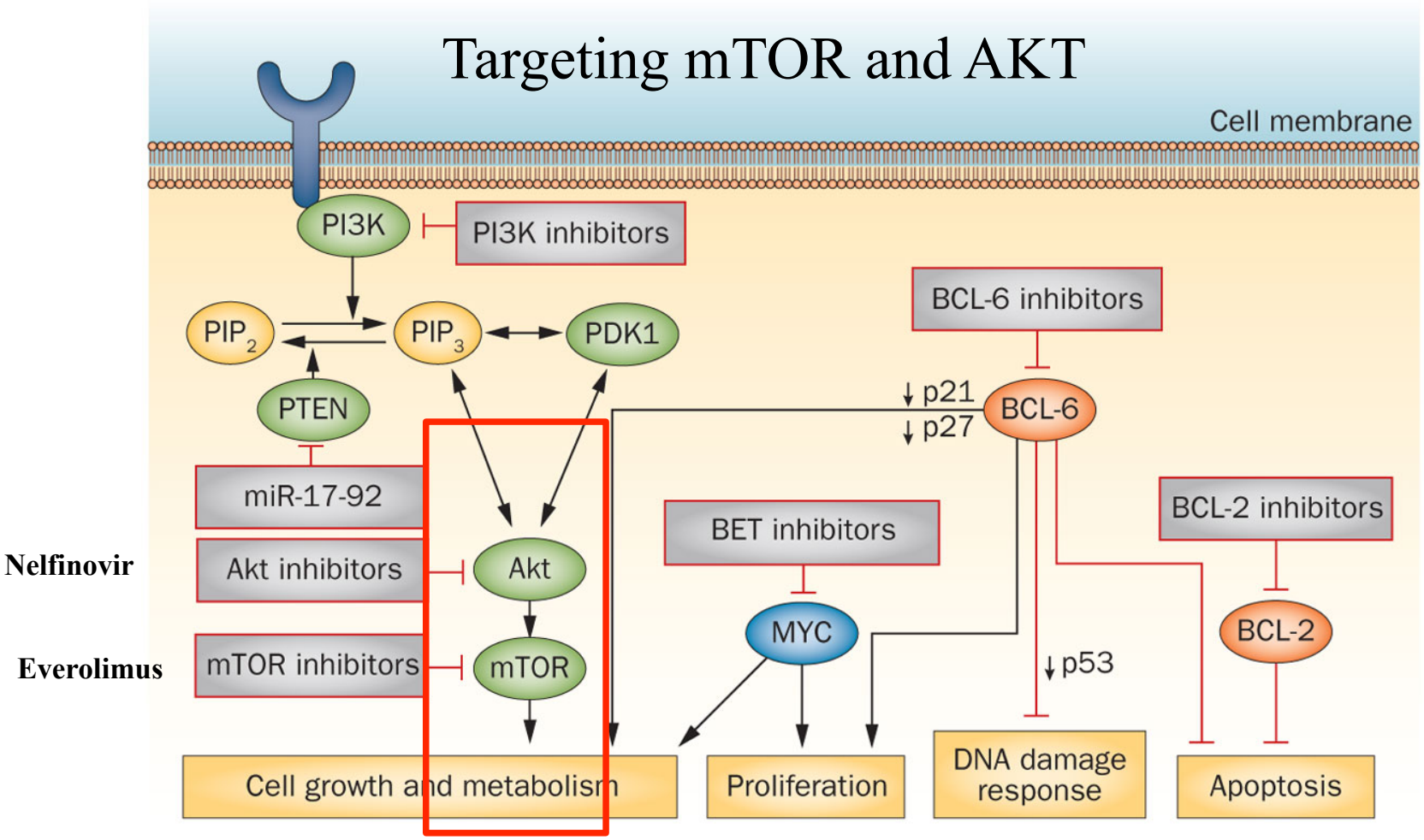
Copanlisip: PI3 Kinase pan-class I inhibitor

- 40 Relapsed/refractory DLBCL
- ORR 25%; 50% CR
- Subset by COO
  - GCB ORR 13.6%
  - ABC ORR 37.5%
- ORR not associated with mutations
  - BCL2 (54%); TP53 (41%); BCL6 (30%); MYC (22%); CD79A/B (25%); MYD88 (19%); TNFAIP3 (17%); CARD1 (13%)1

Lenz et al, ASCO Proceedings, 2017

- **Better response rate in ABC**
- **Interaction of PI3K with BCR signaling likely important**

Key signaling pathways in GCB DLBCL

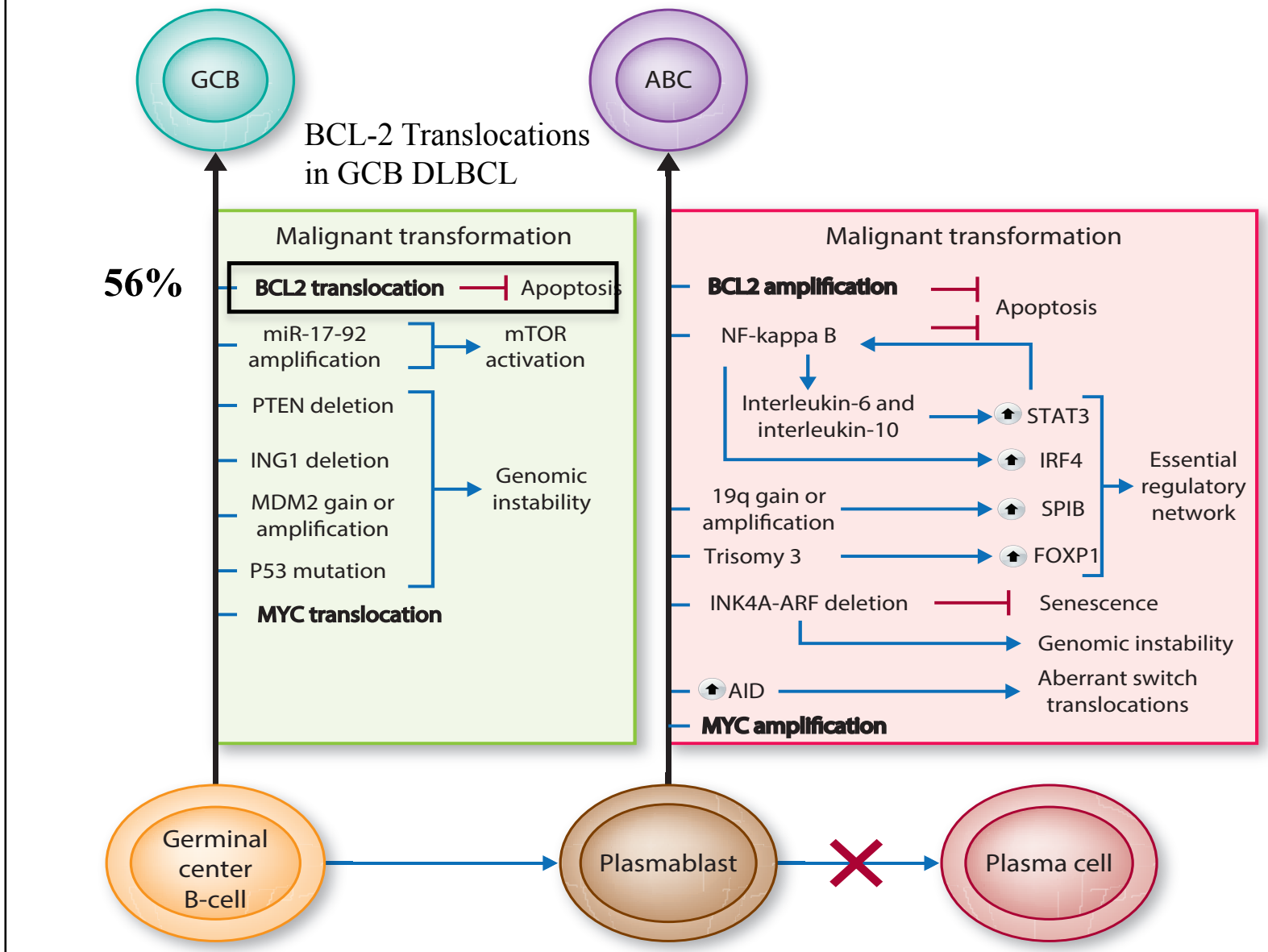


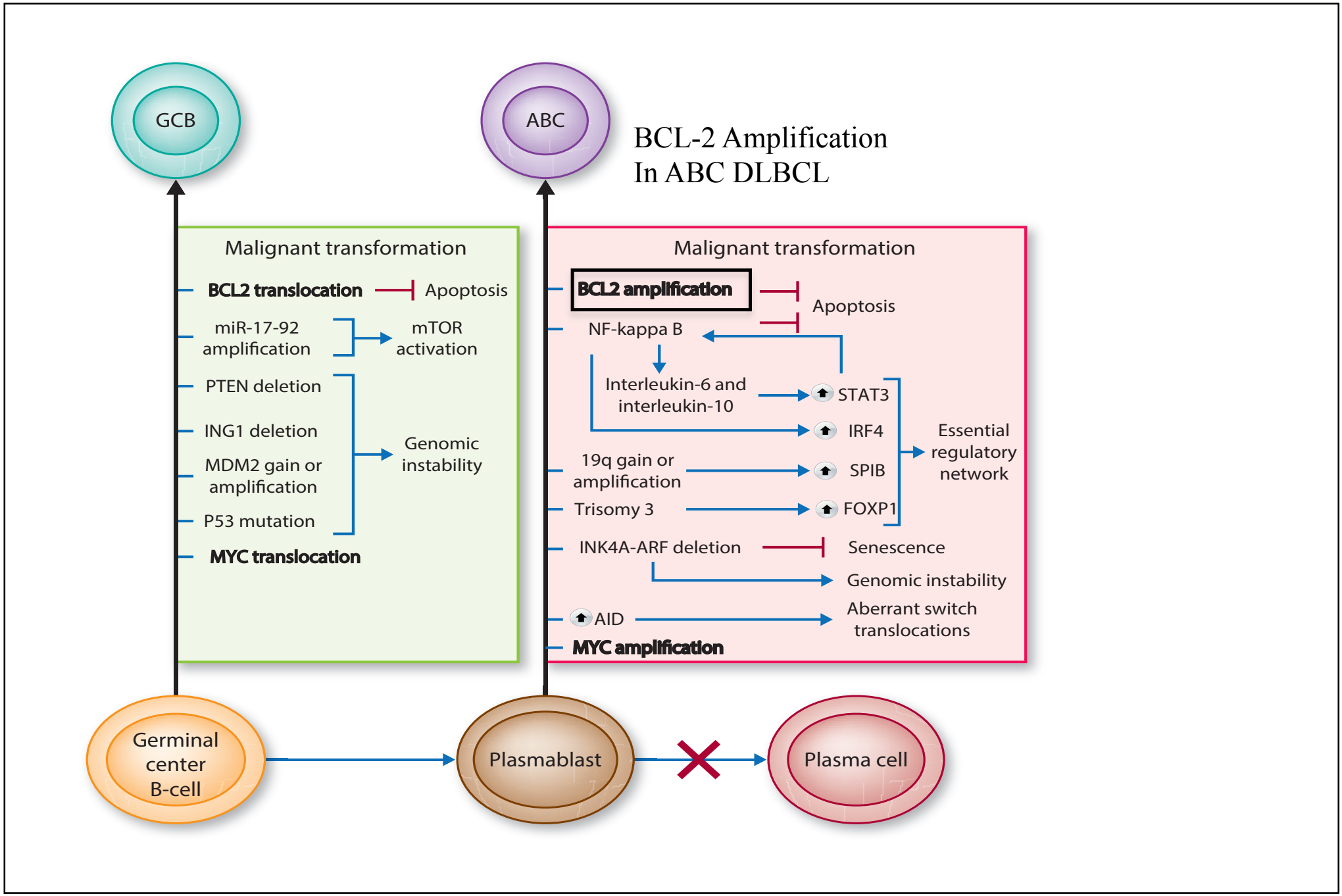
Roschewski, M. *et al.* (2013) *Nat. Rev. Clin. Oncol.*

Everolimus in R/R Aggressive Lymphoma

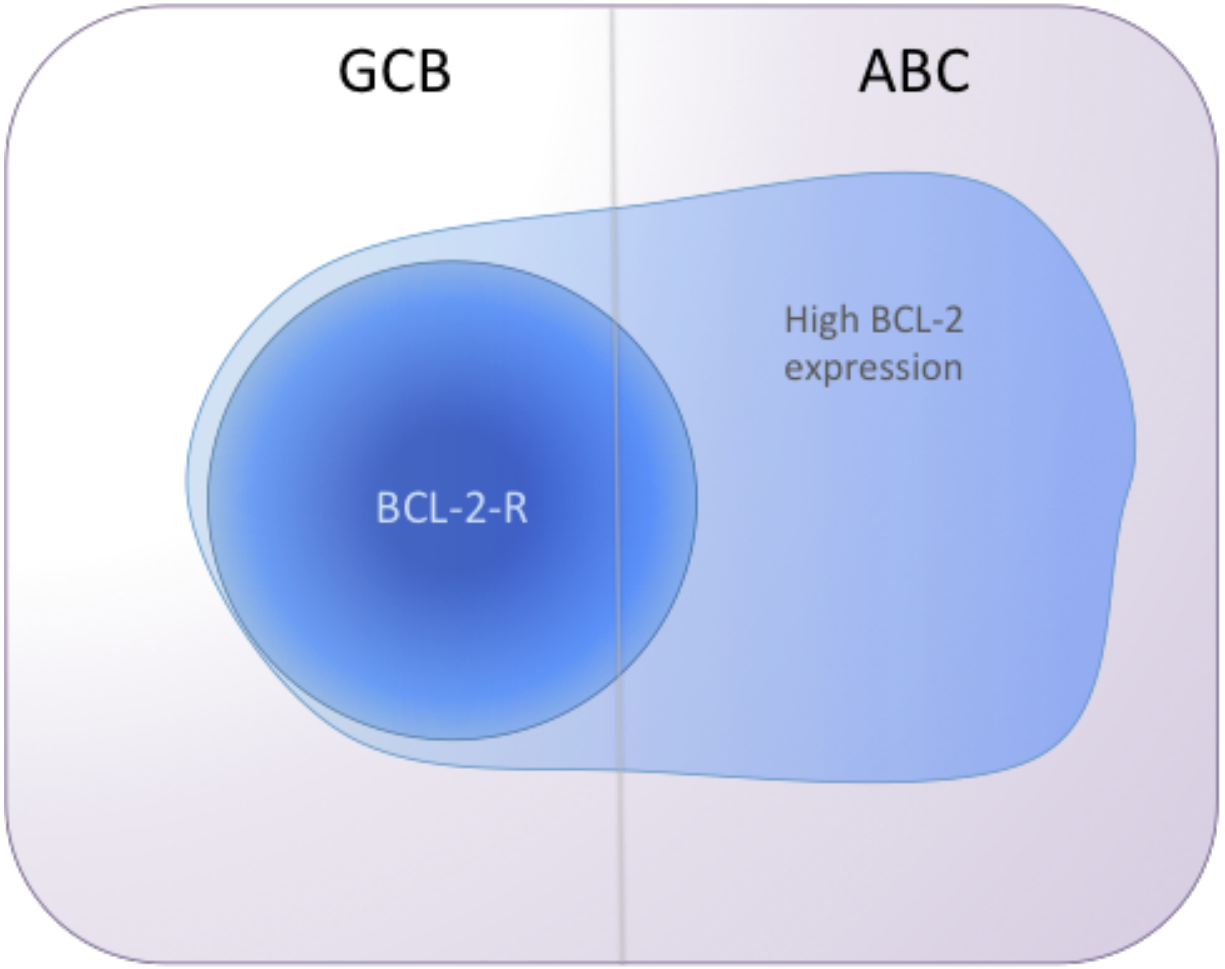
Disease type	**N**	***ORR (95% CI)***	***CR***	***PR***
Total	77	30% (20–41)	3	20
DLBCL	47	30% (17–45)	0	14
MCL	19	32% (13–57)	2	4
FL-III	8	38% (9–76)	1	2
Other	3	0	0	0

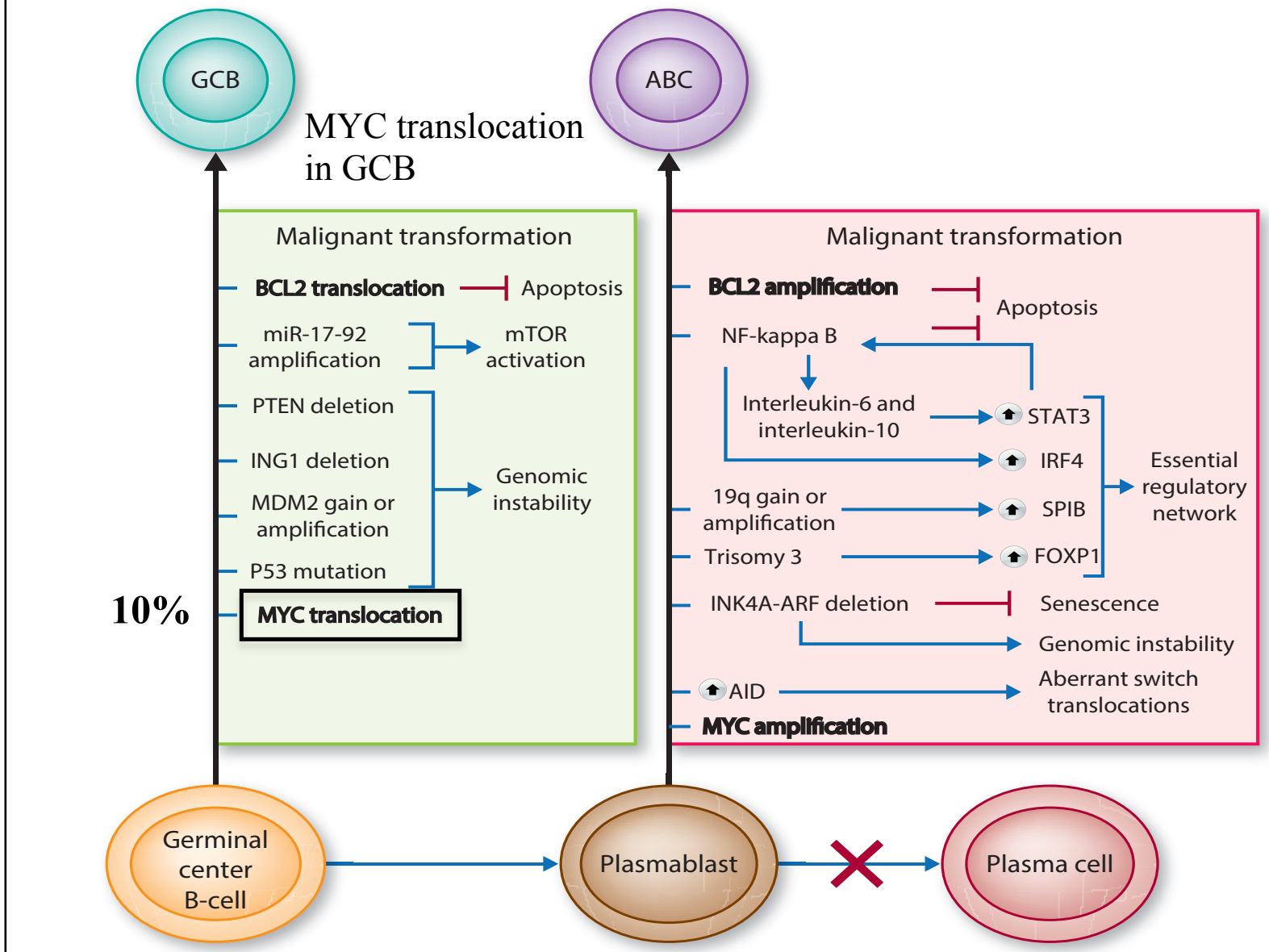
Witzig et al. Leukemia (2011) 25, 341–347

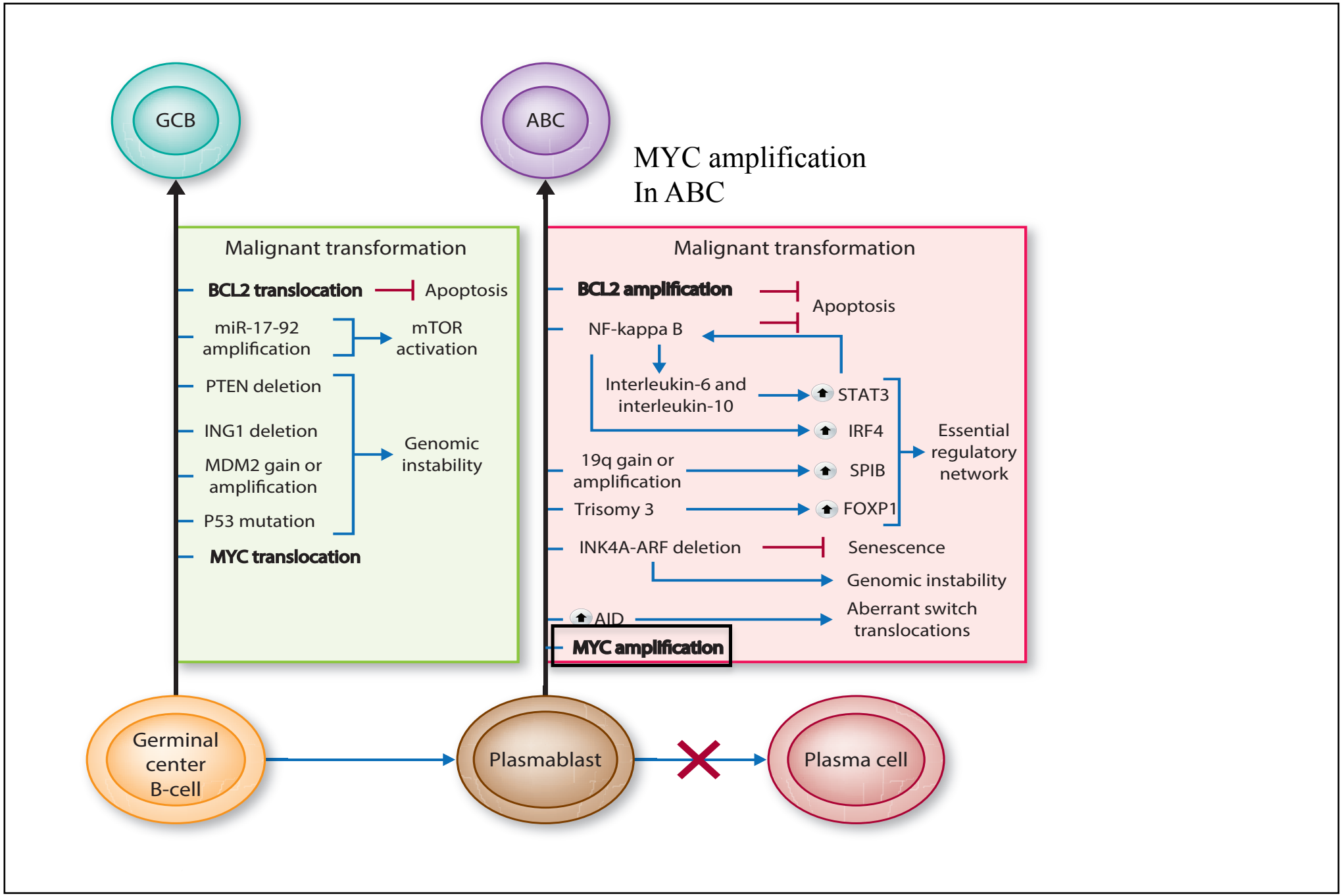

GCB
ABC
BCL-2 Translocations in GCB DLBCL
56%
Malignant transformation
BCL2 translocation
Apoptosis
miR-17-92 amplification
mTOR activation
PTEN deletion
ING1 deletion
MDM2 gain or amplification
P53 mutation
Genomic instability
MYC translocation
Malignant transformation
BCL2 amplification
Apoptosis
NF-kappa B
Interleukin-6 and interleukin-10
STAT3
IRF4
19q gain or amplification
SPIB
Trisomy 3
FOXP1
Essential regulatory network
INK4A-ARF deletion
Senescence
Genomic instability
AID
Aberrant switch translocations
MYC amplification
Germinal center B-cell
Plasmablast
Plasma cell

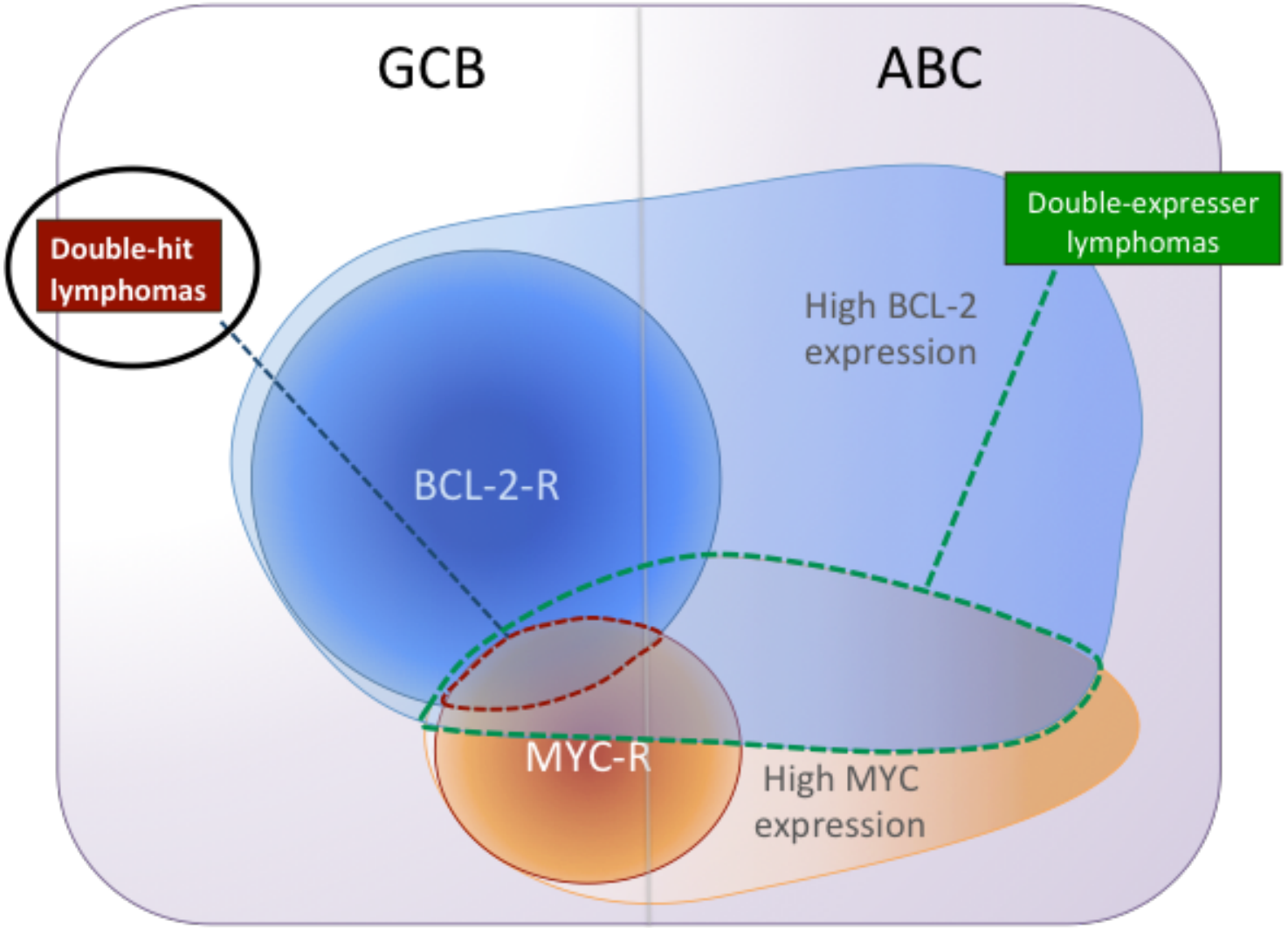

GCB
ABC
BCL-2 Amplification
In ABC DLBCL
Malignant transformation
BCL2 translocation
Apoptosis
miR-17-92 amplification
mTOR activation
PTEN deletion
ING1 deletion
MDM2 gain or amplification
P53 mutation
Genomic instability
MYC translocation
Malignant transformation
BCL2 amplification
Apoptosis
NF-kappa B
Interleukin-6 and interleukin-10
STAT3
IRF4
19q gain or amplification
SPIB
Trisomy 3
FOXP1
Essential regulatory network
INK4A-ARF deletion
Senescence
Genomic instability
AID
Aberrant switch translocations
MYC amplification
Germinal center B-cell
Plasmablast
Plasma cell

BCL-2-Rearrangement versus Expression

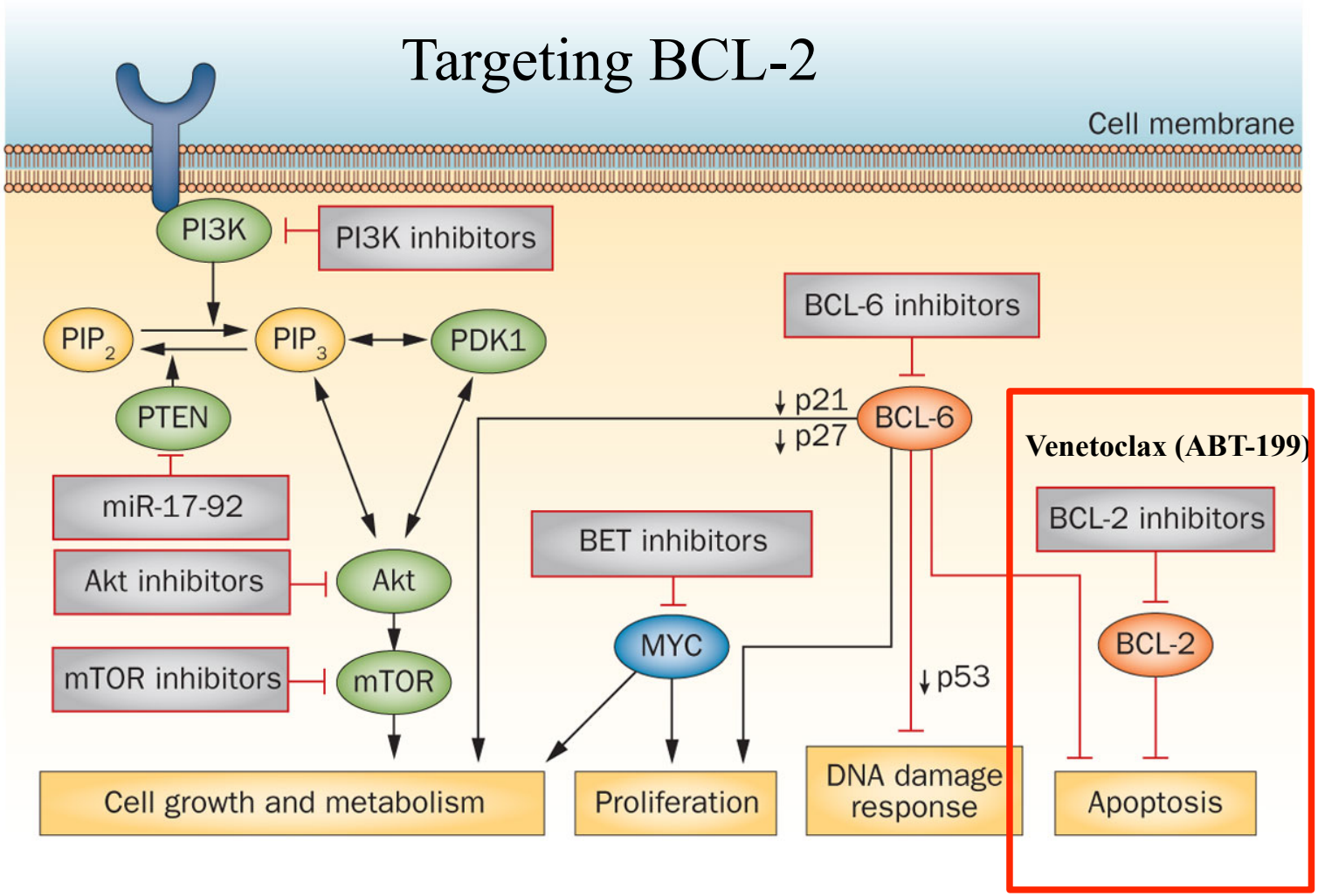



GCB
ABC
MYC translocation in GCB
Malignant transformation
BCL2 translocation
Apoptosis
miR-17-92 amplification
mTOR activation
PTEN deletion
ING1 deletion
MDM2 gain or amplification
P53 mutation
Genomic instability
MYC translocation
10%
Malignant transformation
BCL2 amplification
Apoptosis
NF-kappa B
Interleukin-6 and interleukin-10
STAT3
IRF4
19q gain or amplification
SPIB
Trisomy 3
FOXP1
Essential regulatory network
INK4A-ARF deletion
Senescence
Genomic instability
AID
Aberrant switch translocations
MYC amplification
Germinal center B-cell
Plasmablast
Plasma cell


GCB
ABC
MYC amplification
In ABC
Malignant transformation
BCL2 translocation
Apoptosis
miR-17-92 amplification
mTOR activation
PTEN deletion
ING1 deletion
MDM2 gain or amplification
P53 mutation
Genomic instability
MYC translocation
Malignant transformation
BCL2 amplification
Apoptosis
NF-kappa B
Interleukin-6 and interleukin-10
STAT3
IRF4
19q gain or amplification
SPIB
Trisomy 3
FOXP1
Essential regulatory network
INK4A-ARF deletion
Senescence
Genomic instability
AID
Aberrant switch translocations
MYC amplification
Germinal center B-cell
Plasmablast
Plasma cell

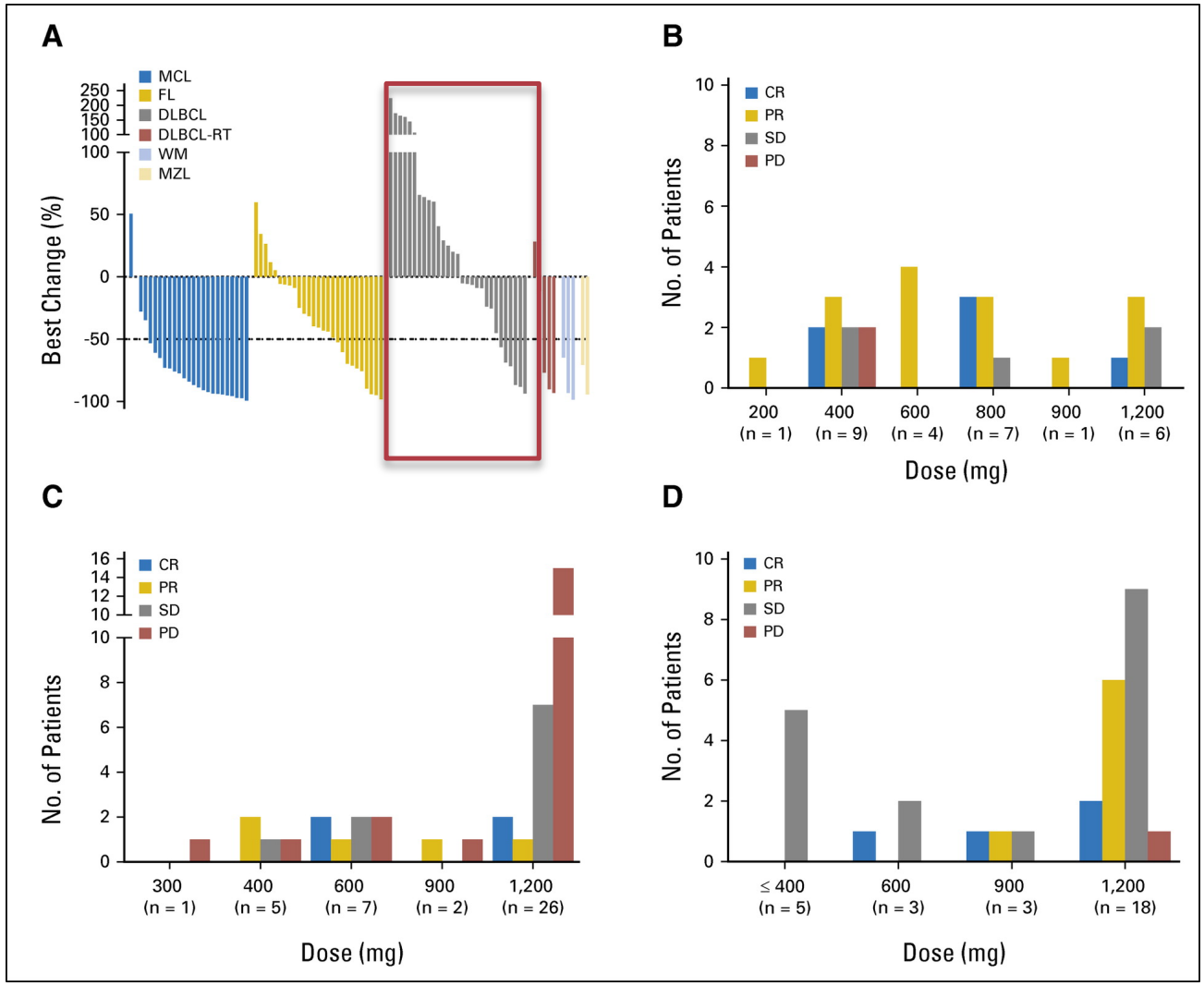

GCB
ABC
Double-hit lymphomas
Double-expresser lymphomas
High BCL-2 expression
BCL-2-R
MYC-R
High MYC expression

Key signaling pathways in GCB DLBCL



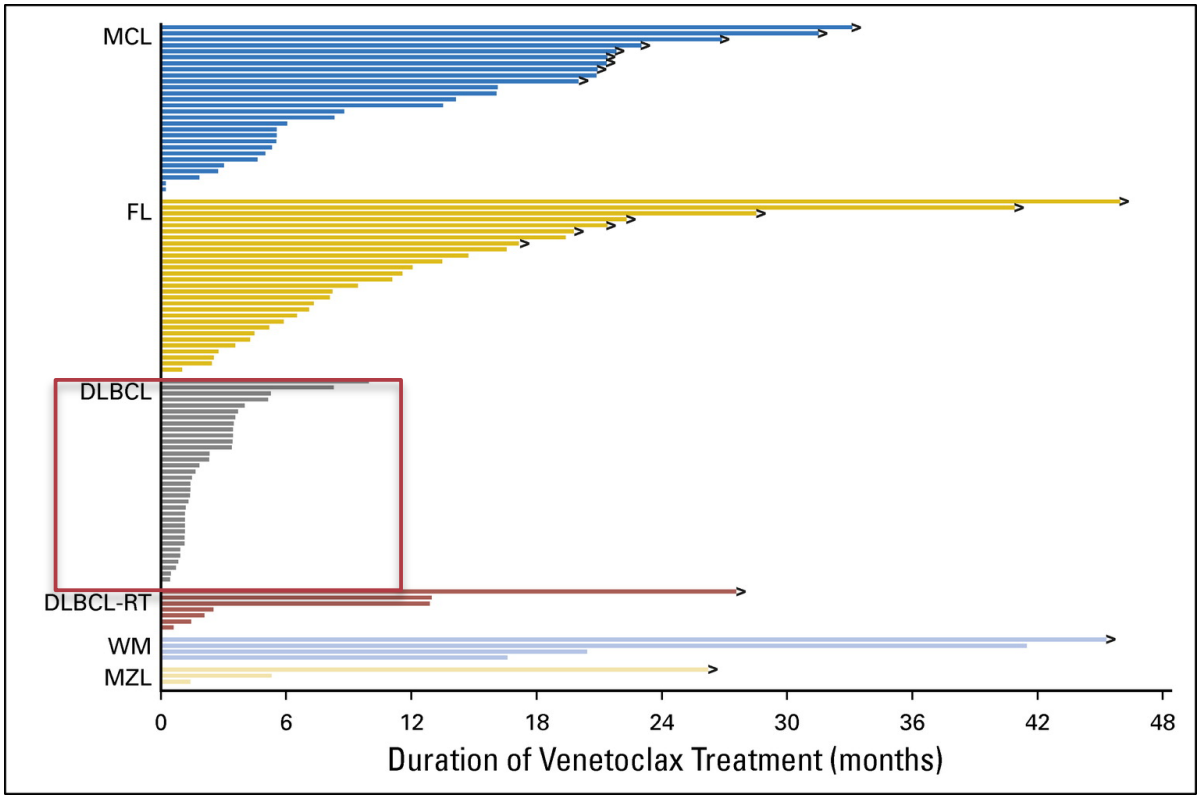
Roschewski, M. *et al.* (2013) *Nat. Rev. Clin. Oncol.*

Phase 1 Study of Venetoclax (ABT-199 / GDC-0199) in Patients with Relapsed/Refractory Non-Hodgkin Lymphoma



Davids et al JCO 2016

Phase 1 Study of Venetoclax (ABT-199 / GDC-0199) in Patients with Relapsed/Refractory Non-Hodgkin Lymphoma



Davids et al JCO 2016

Phase 1 Study of Venetoclax (ABT-199 / GDC-0199) in Patients with Relapsed/Refractory Non-Hodgkin Lymphoma

Table A4. Objective Responses by BCL-2 and MYC DE Subtype

Patient	Histology	IHC		Subtype	Best Objective Response
		BCL-2*	MYC (%)†		
1	DLBCL-RT	3+	40	DE	PR
2	DLBCL	3+	100	DE	PD
3	DLBCL	3+	80	DE	PD
4	DLBCL	3+	90	DE	CR
5	DLBCL	3+	30	Non-DE	SD
6	DLBCL	1+	20	Non-DE	PD

Abbreviations: BCL-2, B-cell leukemia/lymphoma-2; CR, complete response; DE, double expressor; DLBCL, diffuse large B-cell lymphoma; IHC, immunohistochemistry; PD, progressive disease; PR, partial response; RT, Richter transformation; SD, stable disease.

*BCL-2 staining was scored on a 0 to 3 intensity scale, and samples were coded BCL-2 high if ≥ 50% of tumor cells showed a cytoplasmic intensity score of 2+ or 3+. An IHC score of 2+ was assigned if lymphoma cells had a staining intensity equal to the predominant intensity of cytoplasmic staining in the mantle zone B cells and paracortical T cells found in tonsils, which served as positive control tissue. Specimens with a signal weaker or stronger than the latter 2+ score were assigned an intensity of 1+ or 3+, respectively.

†Samples were coded MYC positive if ≥ 40% of tumor cells showed any level of MYC nuclear staining above background.

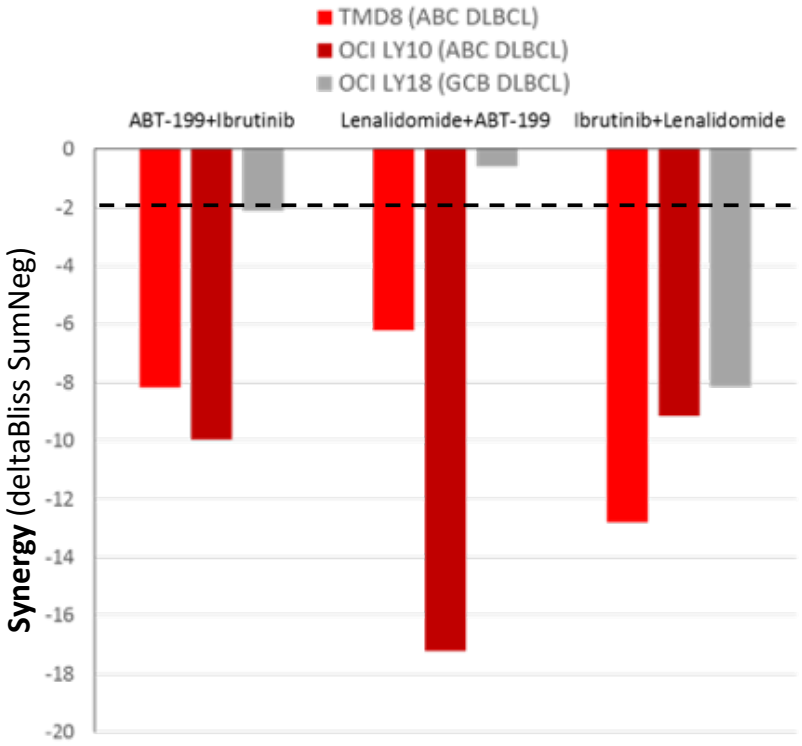
- **Unimpressive response rate in DLBCL**
- **DE does not appear to increase ORR**

Davids et al JCO 2016

Venetoclax in DLBCL

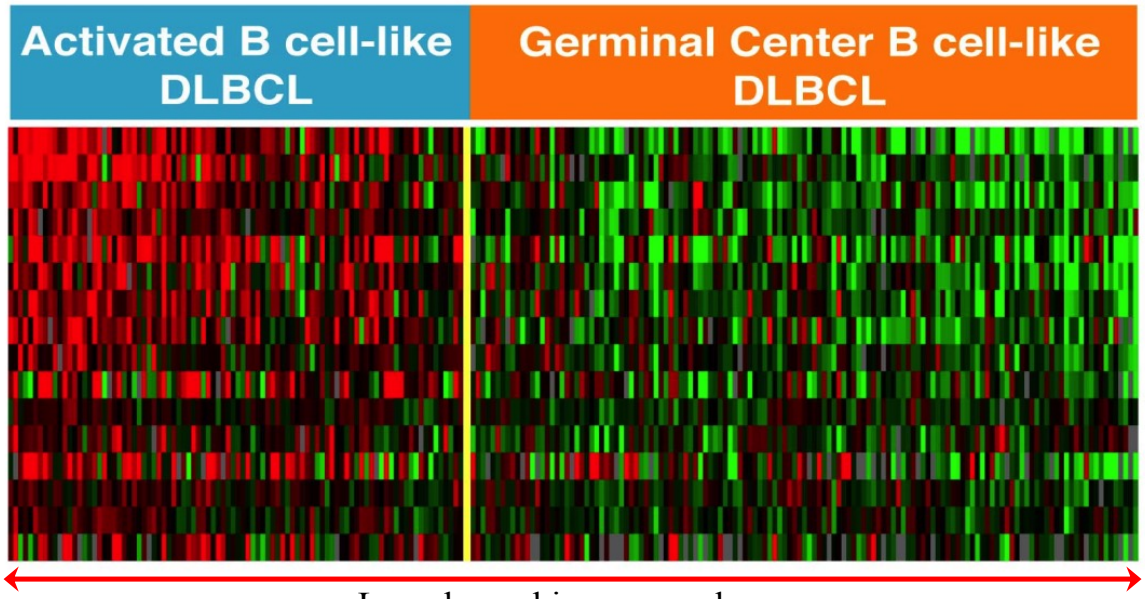
- **How do you select patients?**
- **Role of combination treatment?**

ABT-199, Ibrutinib and Lenalidomide: drug *vs* drug interactions



Thomas et al NCI data

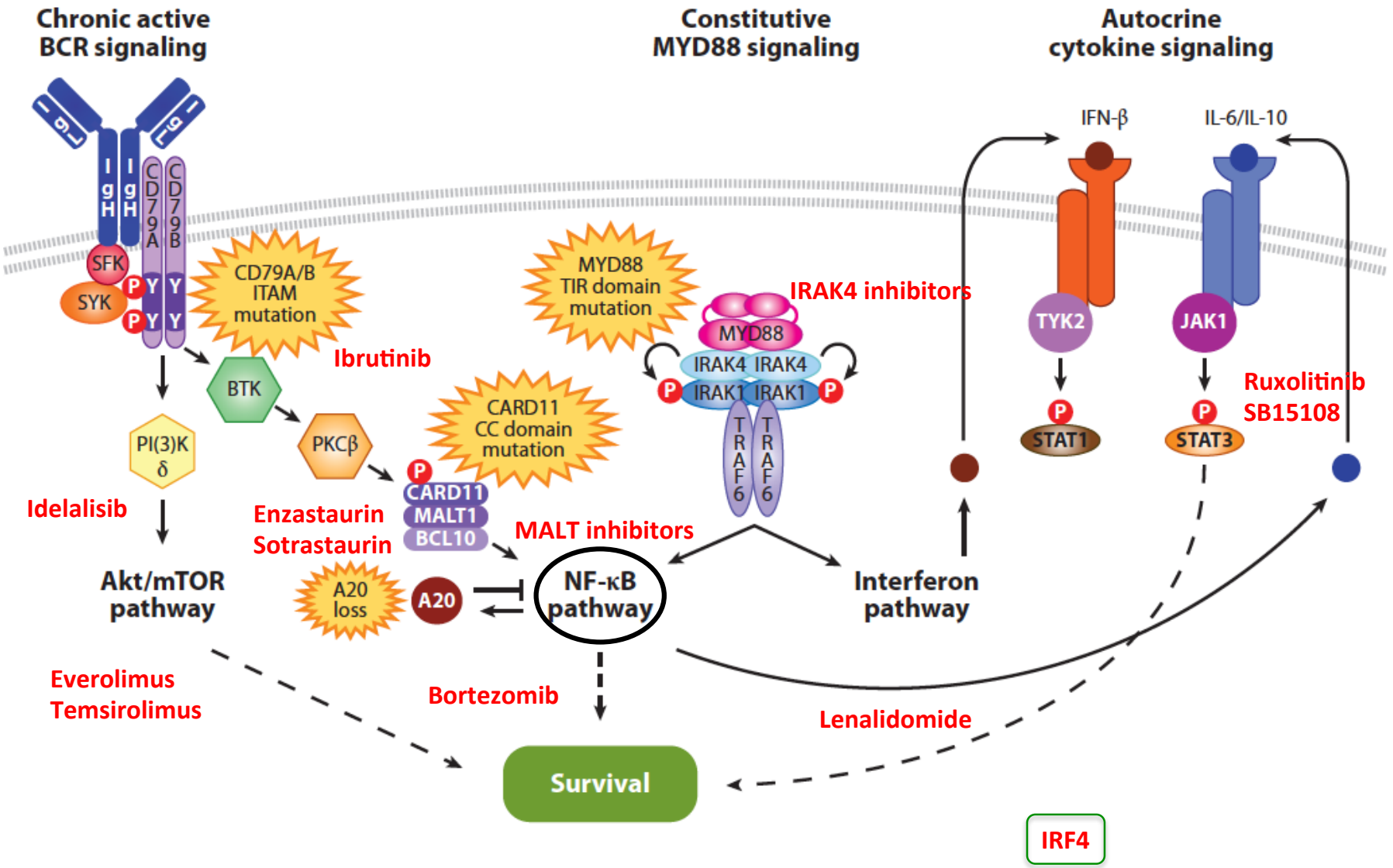
Targeting NFKB in ABC DLBCL

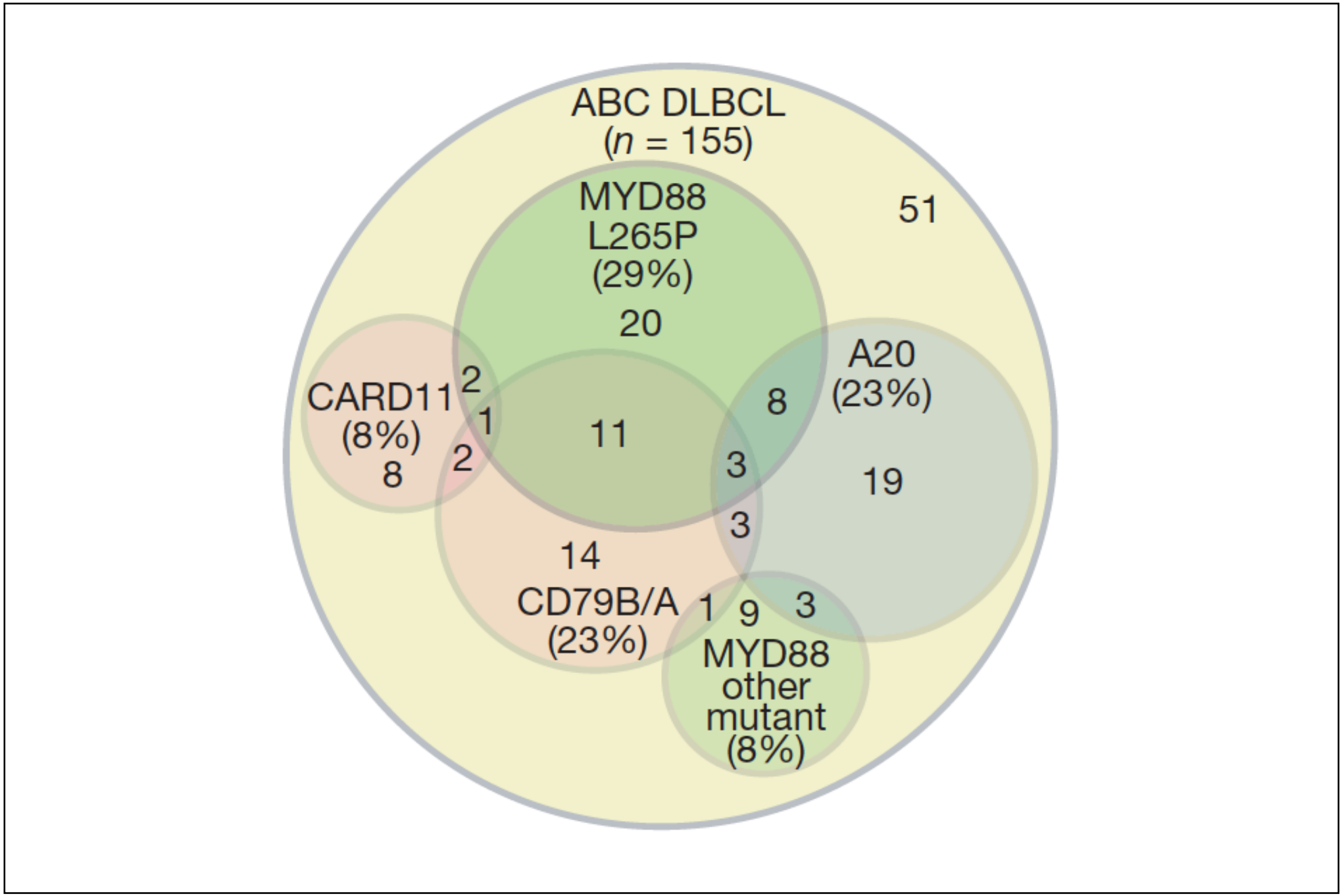


NF-kB target gene	p value
IRF-4	6.23 E-29
Cyclin D2	1.28 E-16
Pim-1	2.69 E-19
Lyn	5.34 E-19
BIC	6.49 E-18
CD44	2.35 E-13
FLICE	3.30 E-14
IM684838	8.74 E-14
IkB ε	7.64 E-09
EBI2	2.77 E-07
NCF2	6.67 E-07
DIFF48	2.86 E-06
CCR7	1.55 E-05
SNF2L2	1.16 E-05
NFkB1	6.68 E-05
IL-6	4.01 E-04

Staudt et al NCI data

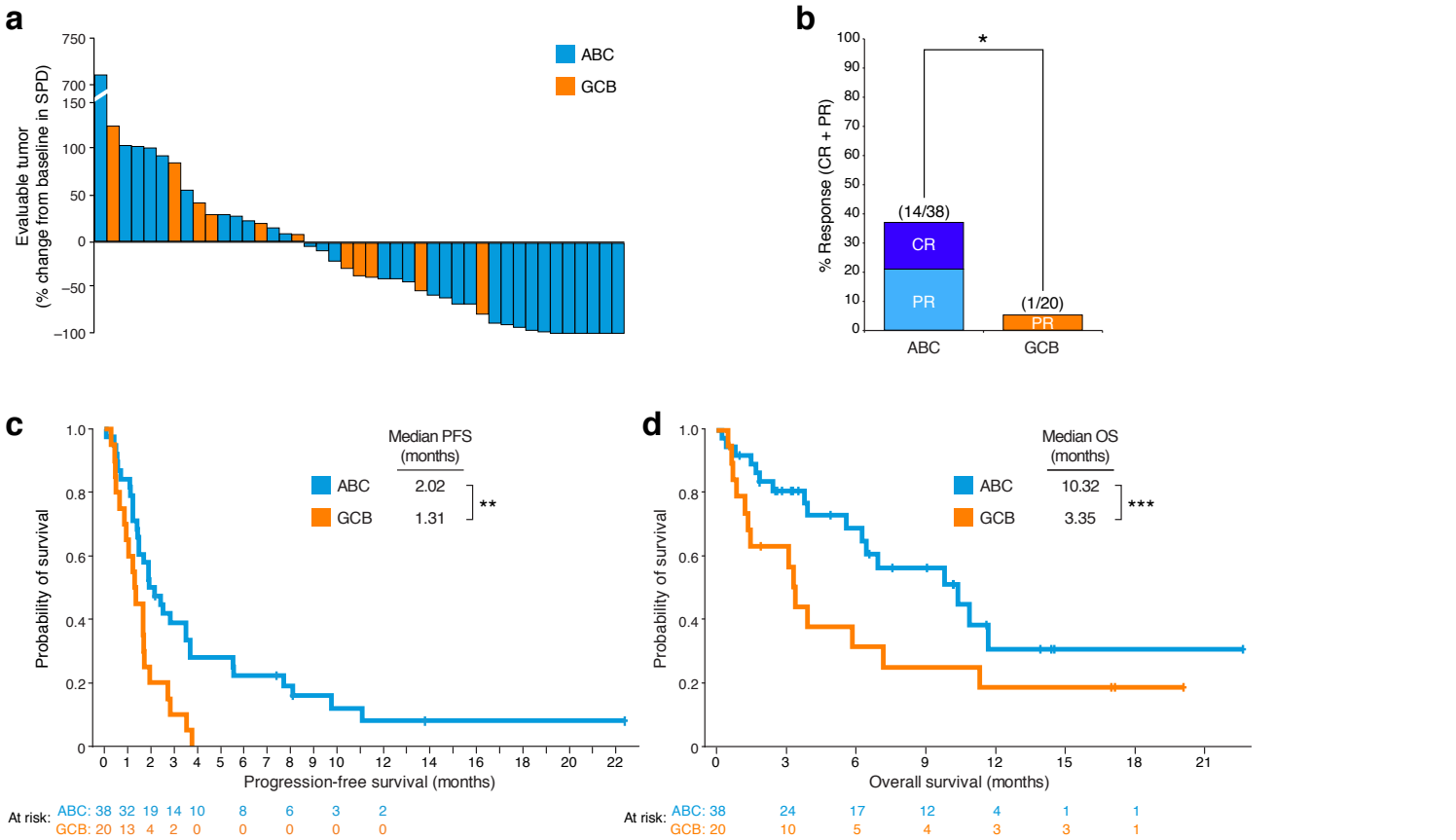
BCR and MYD88 Pathways




ABC DLBCL
(n = 155)
MYD88
L265P
(29%)
20
51
CARD11
(8%)
8
2
1
2
11
8
A20
(23%)
3
19
3
14
CD79B/A
(23%)
1
9
3
MYD88
other
mutant
(8%)

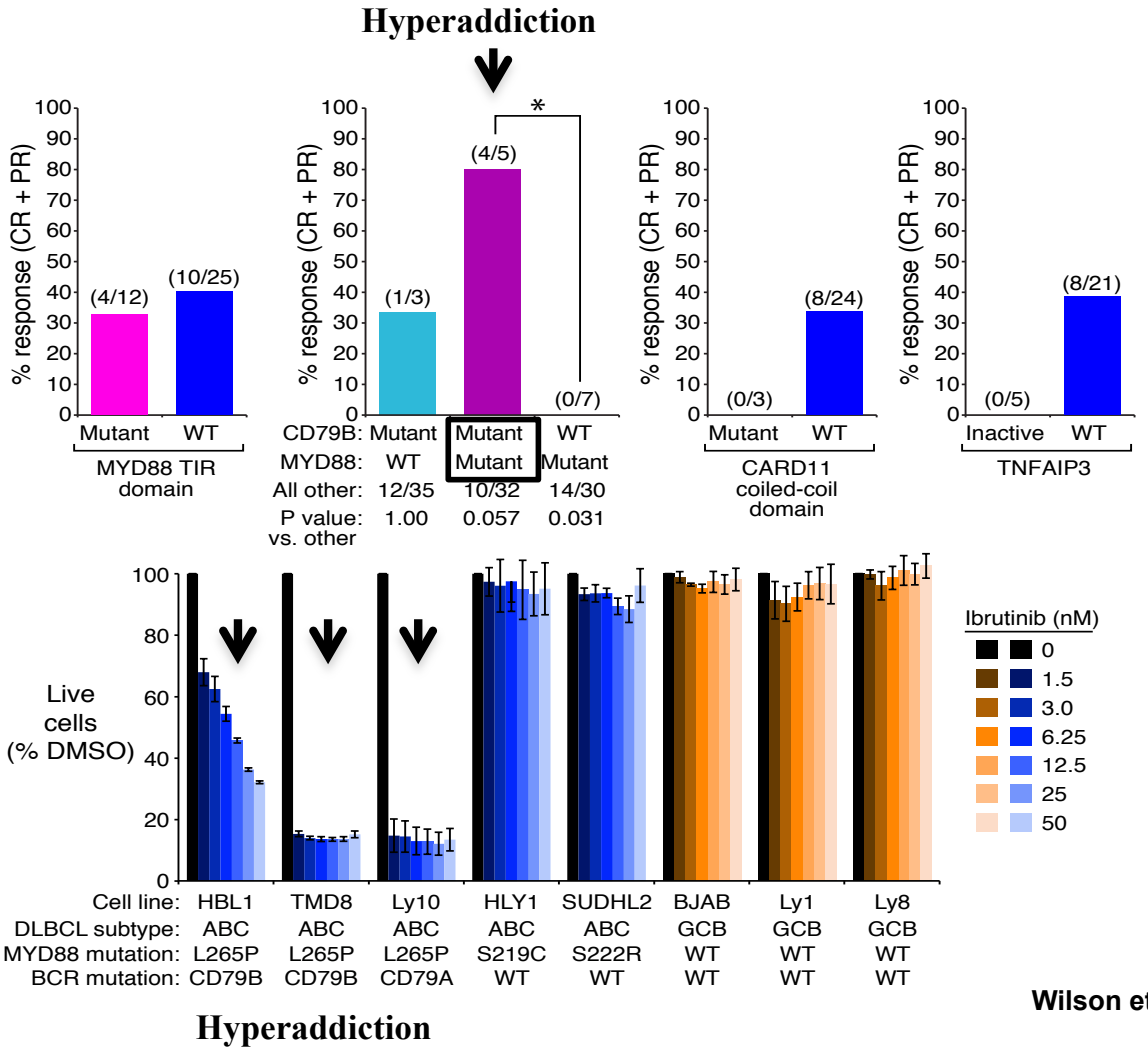
Ibrutinib in ABC DLBCL

Figure 1



Wilson et al Nat Med 2015

Ibrutinib in ABC DLBCL



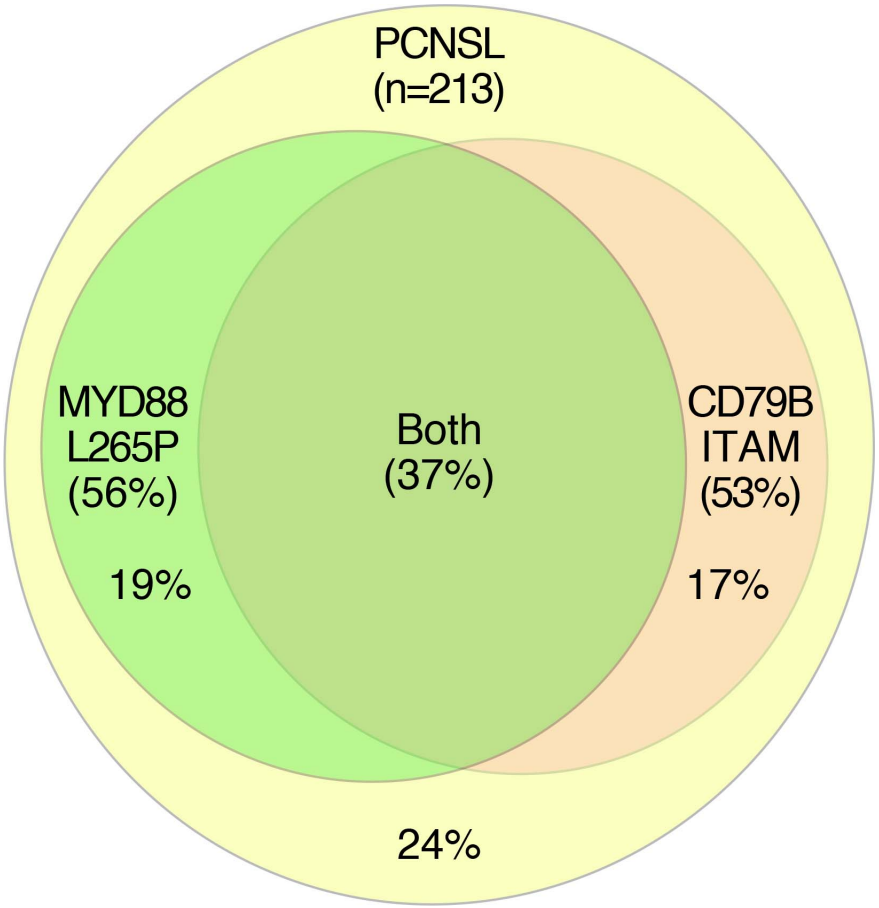
Wilson et al Nat Med 2015

Phoenix Trial

Targeting BTK in Untreated ABC DLBCL

- Phase III double blind randomized study R-CHOP ± Ibrutinib
  - International Registration trial 800 patients (Janssen sponsor)
  - Study Completed Accrual 2015
  - Tumors analyzed for molecular subtype and NGS (Staudt et al)

Primary CNS Lymphoma Mutations in MYD88 and CD79



Mutation Summary

Any: 76%

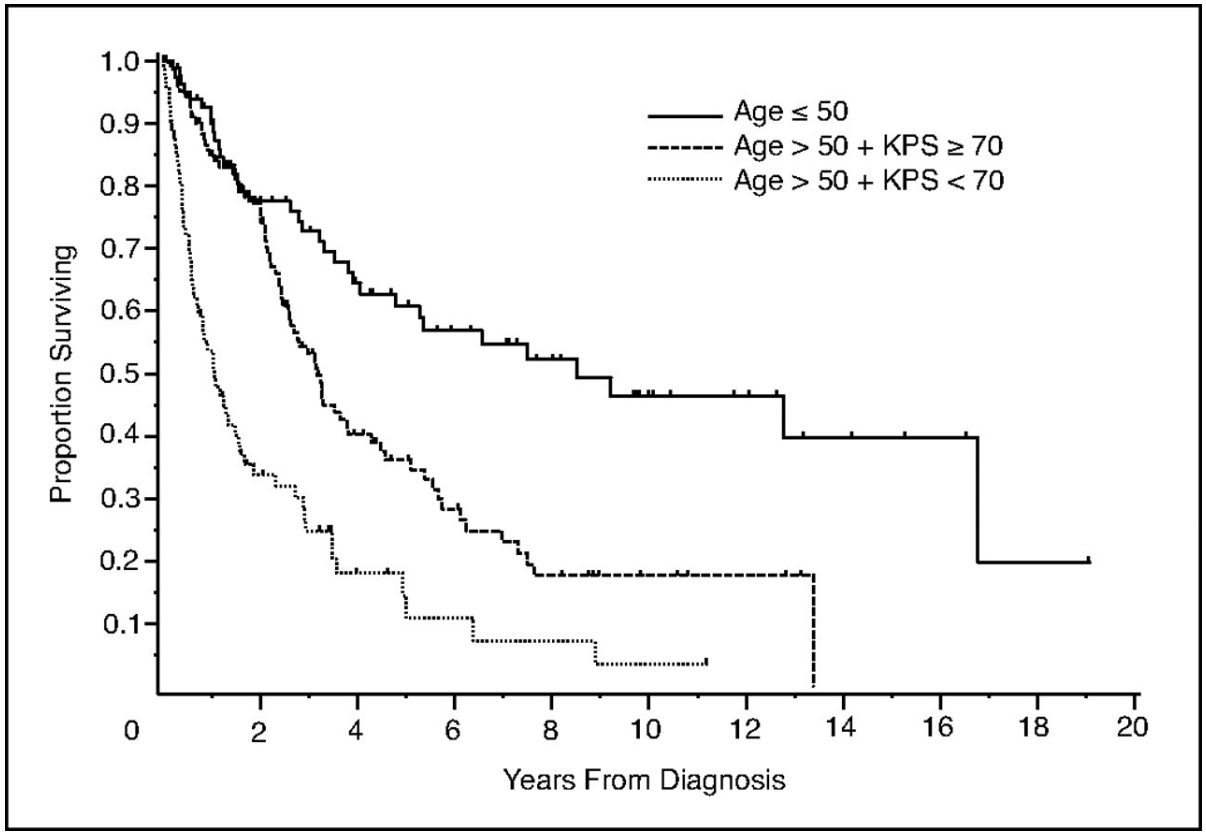
CD79B: 53%

MYD88: 56%

Both: 37%

Suggest "hyper" addiction to BCR signaling

Primary CNS Lymphoma
282 Untreated Patients MSKCC



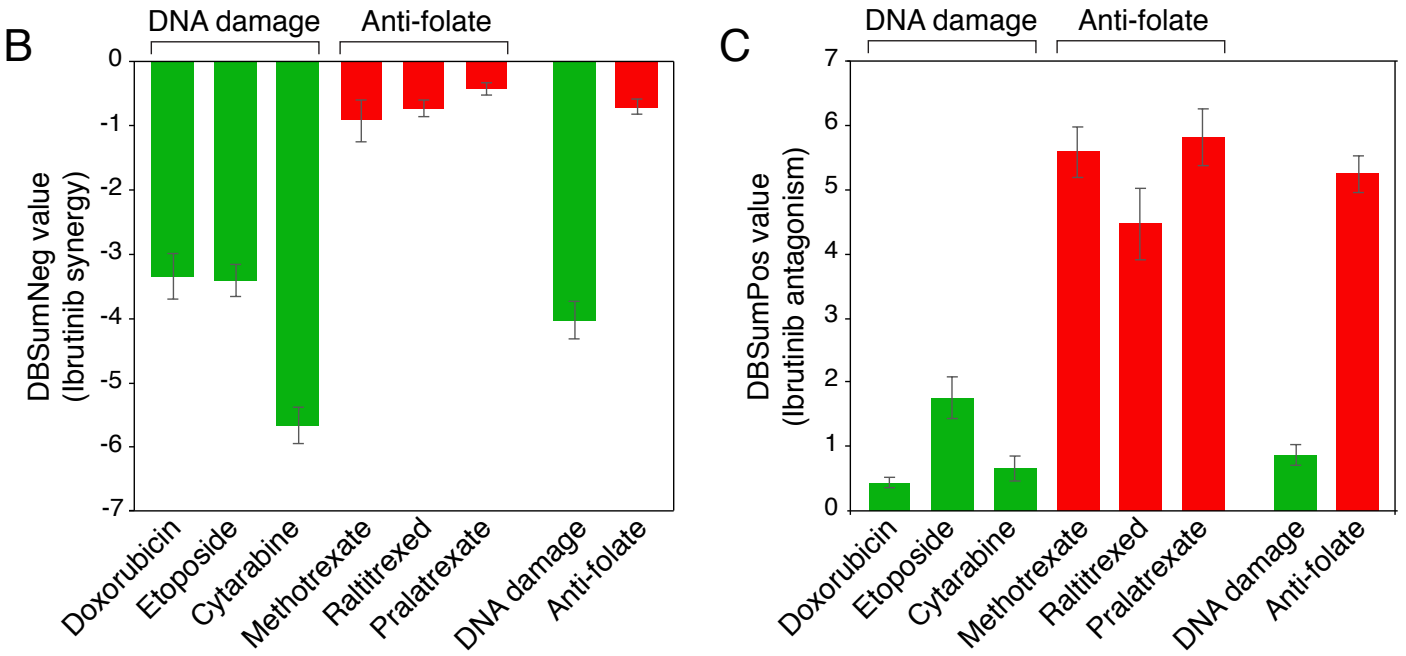
Abrey et al. JCO 2006, 24:5711

Phase I Study of Ibrutinib and TEDDi-R Objectives

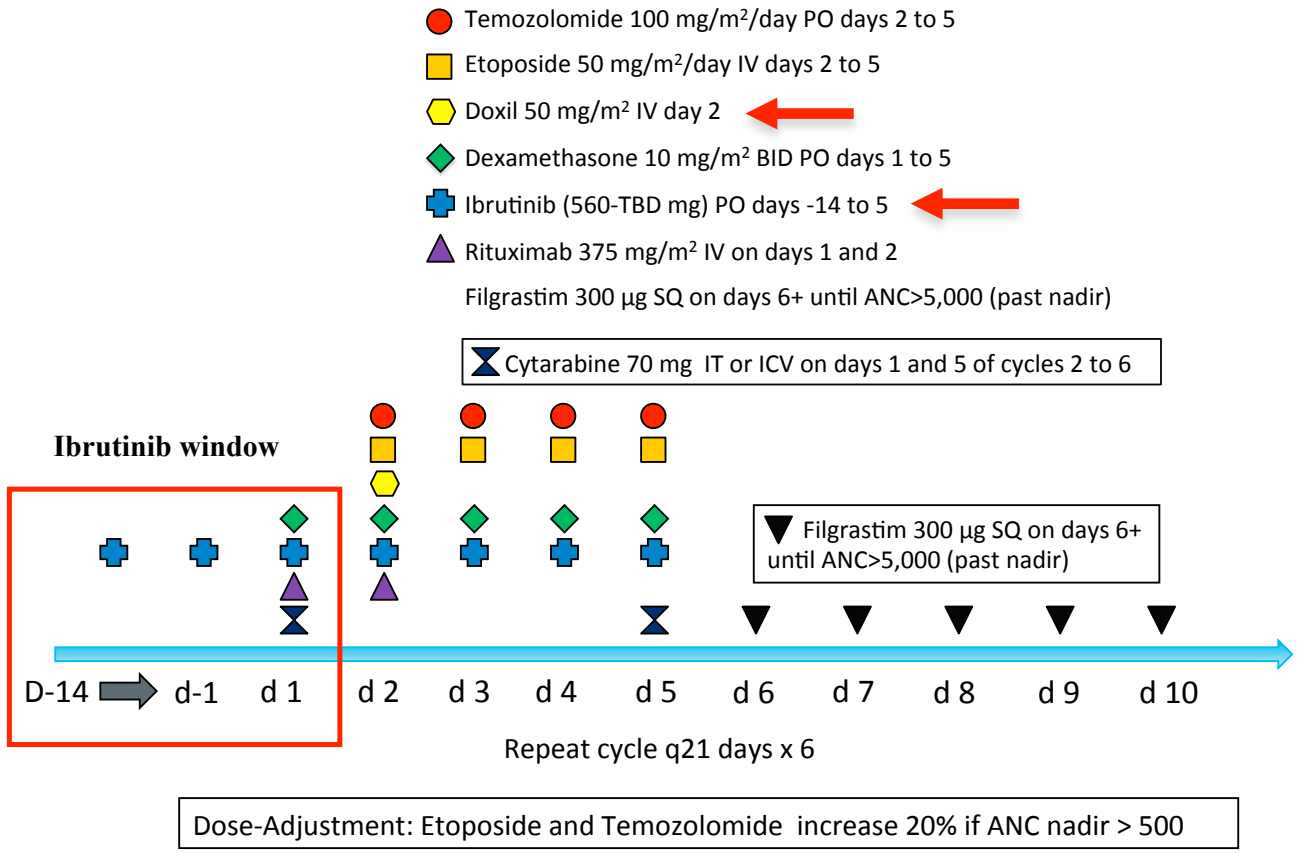
- Ibrutinib response rate
- Ibrutinib safe tolerated dose with DA-TEDDI-R
- DA-TEDDi-R response and duration
- Tumor mutations in CD79 and MYD88

DA-TEDDi-R Development

TMD8 Cell Line Ibrutinib-Cytotoxic Drug Killing



Dose Adjusted-TEDDI-R



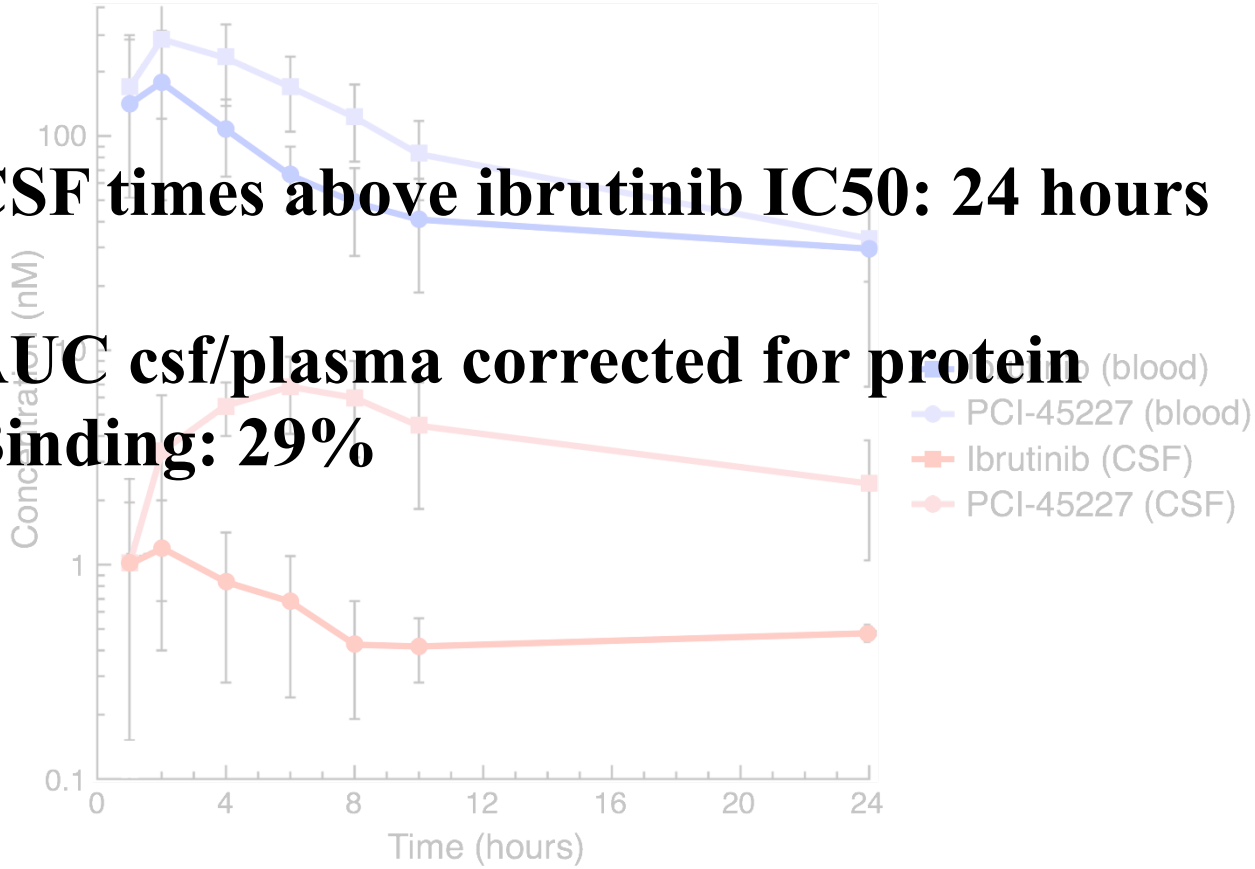
Dose-Adjustment: Etoposide and Temozolomide increase 20% if ANC nadir > 500

Patient Characteristics

Characteristics	N= 18
Age (median)	66 years (49-87)
Age > 60 years	67%
Male gender	61%
Untreated	28% (5/18)
Refractory to standard treatment	77% (10/13)
Relapsed	23% (3/13)
Prior Rx (median) Prior Autologous Transplant	2 (1-6) 4 (31%)
IELSG risk >=2	83%

Wilson et al. Cancer Cell 2017

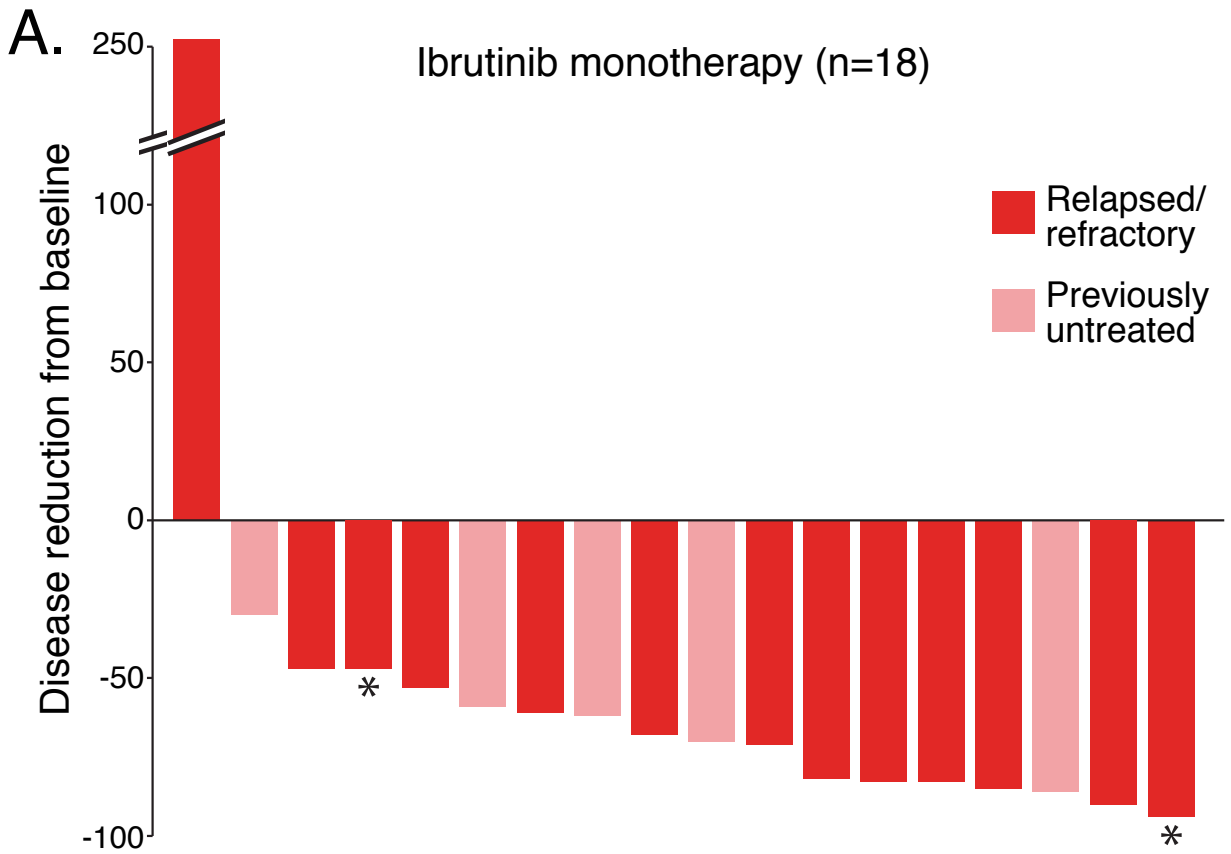
Pharmacokinetics of Ibrutinib 840 mg and PCI-45227 (active metabolite)



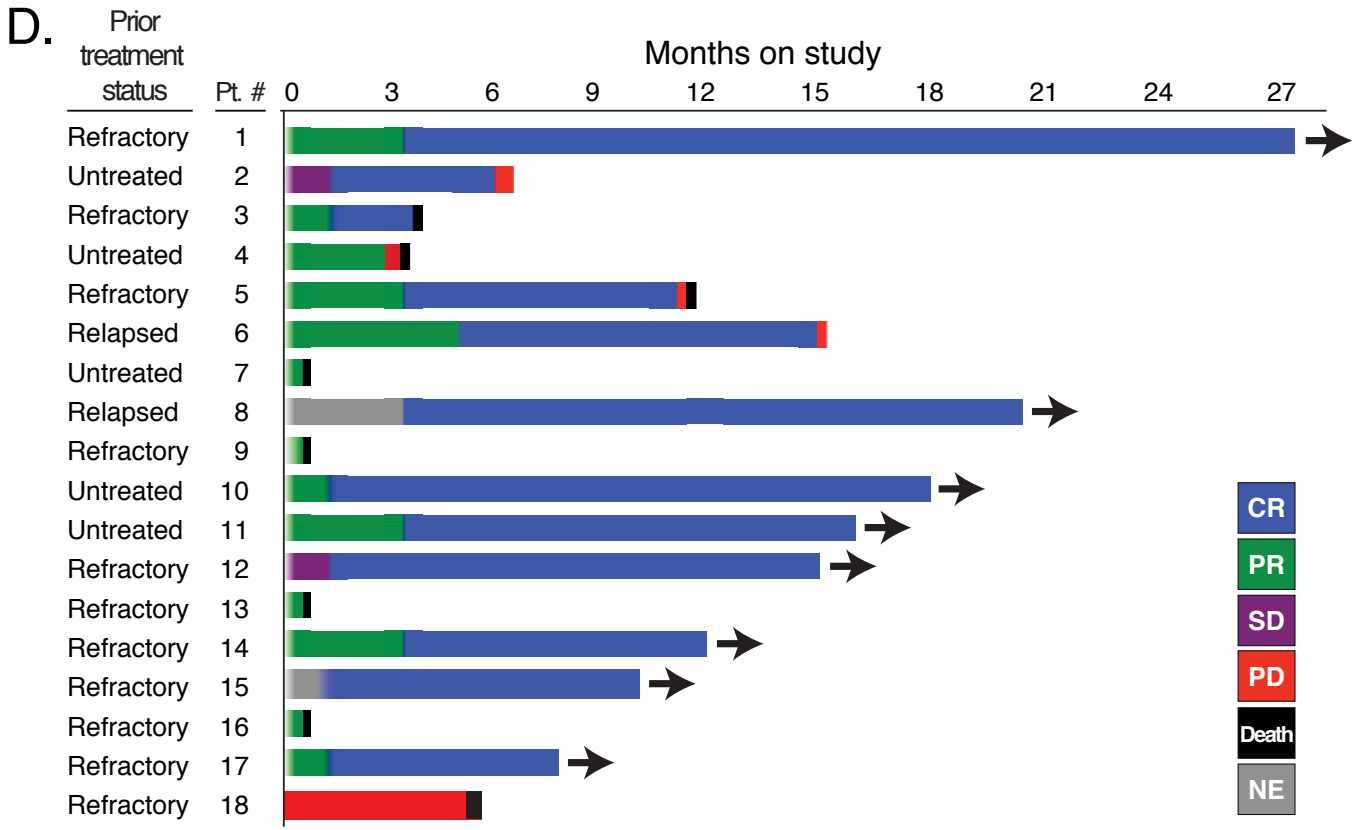
CSF times above ibrutinib IC50: 24 hours

AUC csf/plasma corrected for protein Binding: 29%

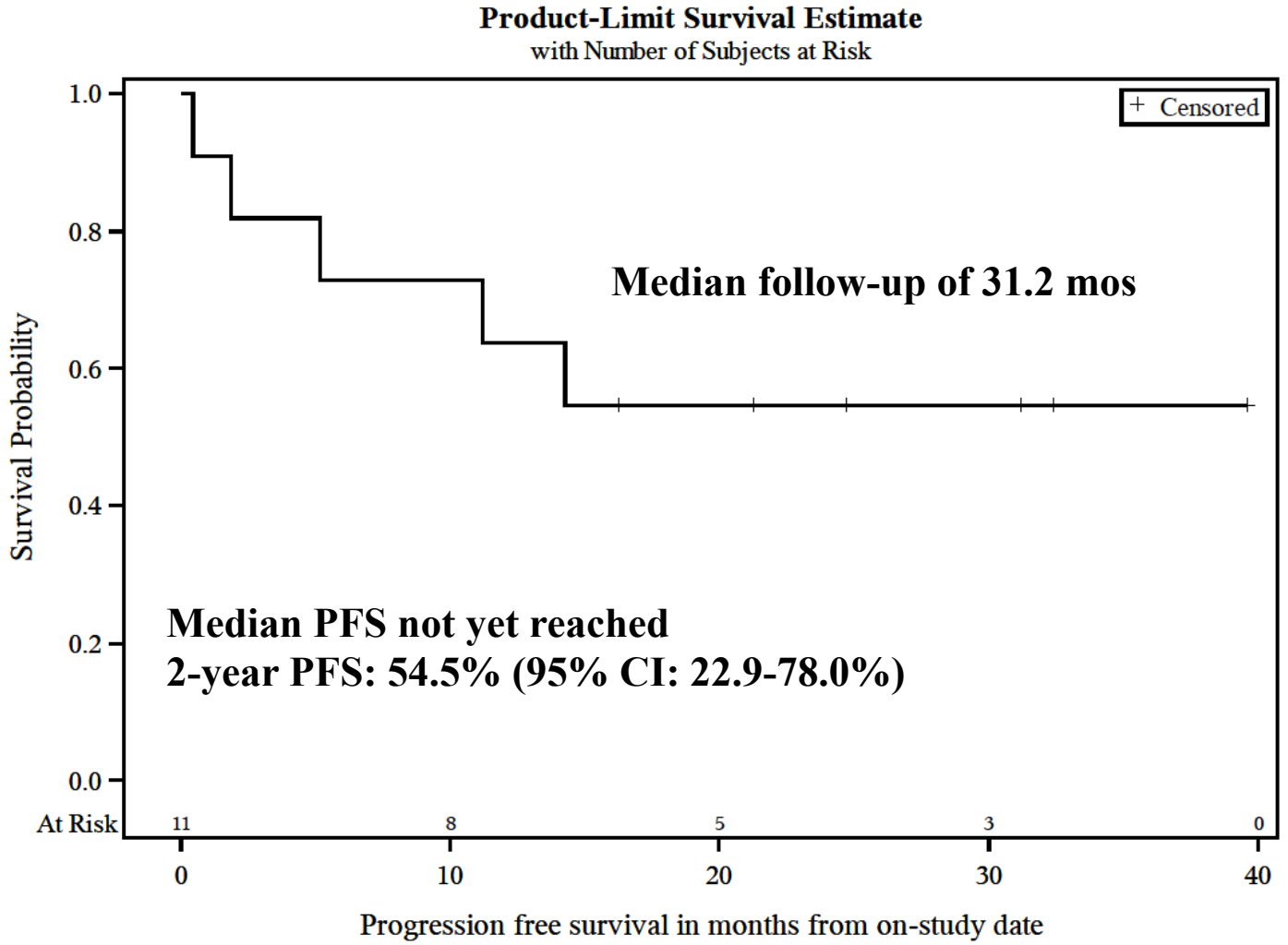
Ibrutinib Response in 14-day Window



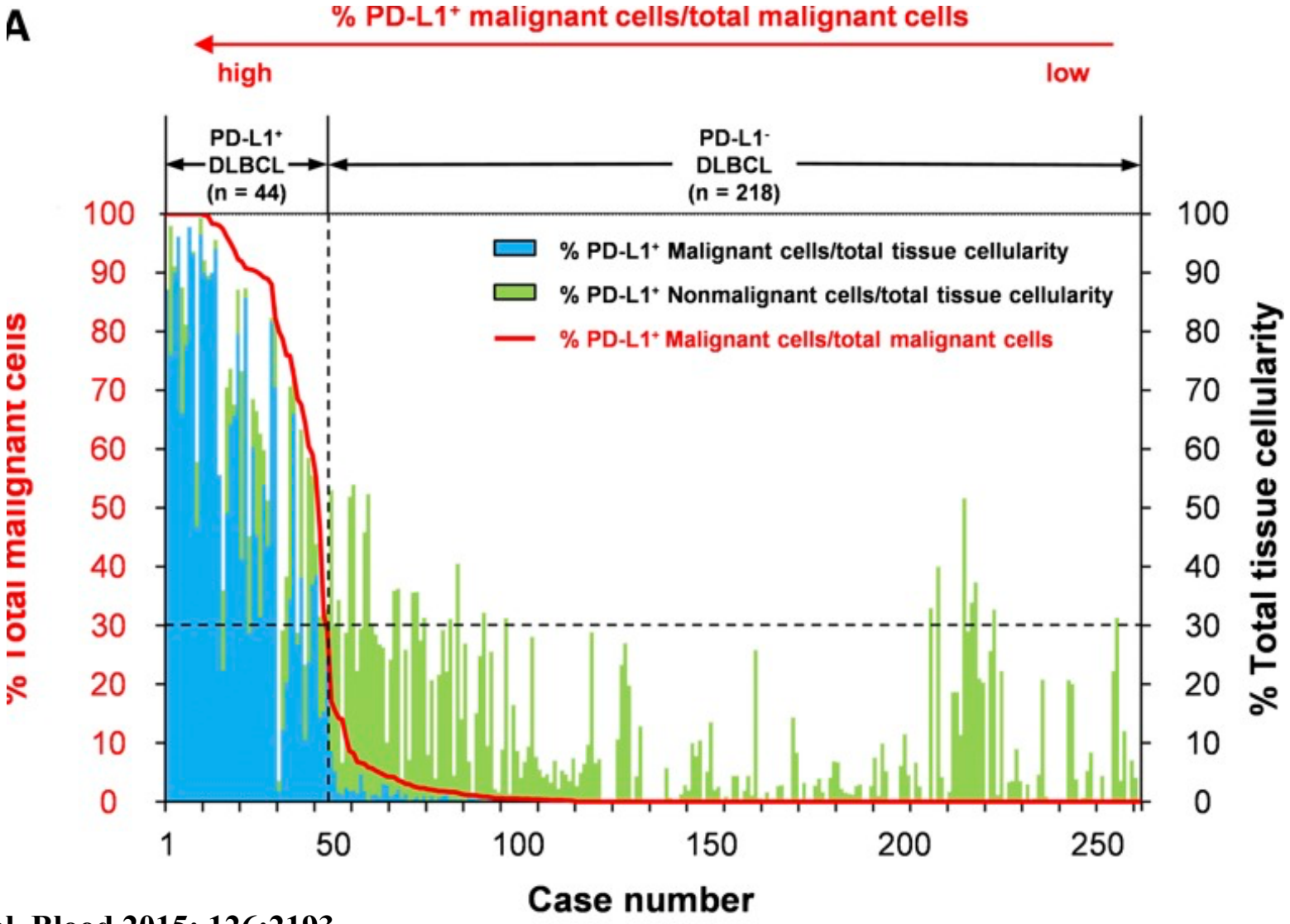
TEDDi-R Response



DA-TEDDi-R PFS R/R PCNSL

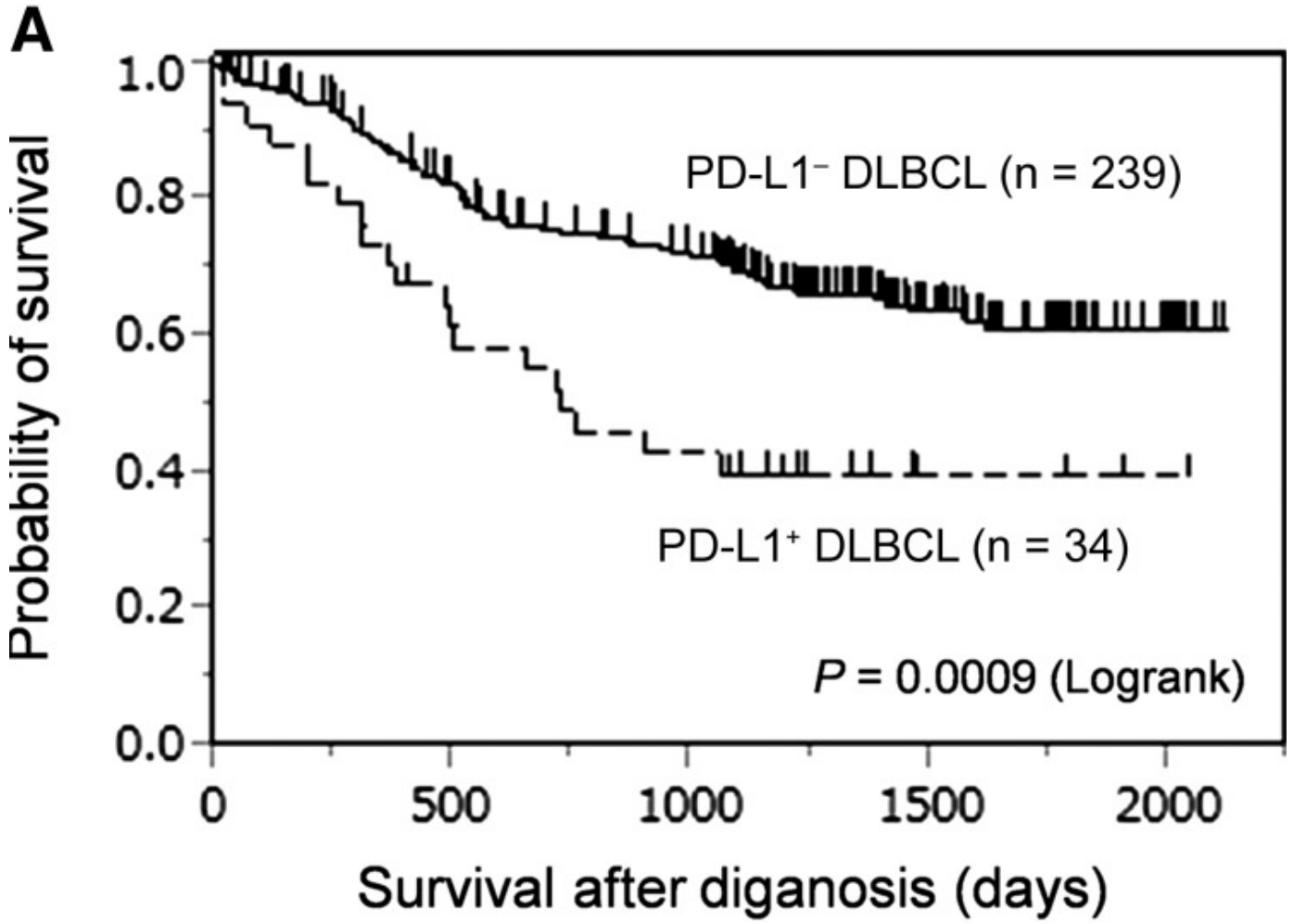


PD-L-1 Expression in 262 DLBCL Samples



Kiyasu et al. Blood 2015; 126:2193

PD-L-1 Expression Associated with Lower Survival



Kiyasu et al. Blood 2015; 126:2193

PD-1 Blockade with Nivolumab in R/R PCNSL

- PCNSL Patients: N= 5
- Refractory N=1; Relapsed N=4
- CR N=4; PR N=1
- PFS 13+; 14; 14+; 17; 17+

Nayak et al. Blood 2017; 129:3071

Novel Targets in R/R DLBCL

- **Targeting PI3K/AKT-mTOR in GCB and ABC**
- **Targeting Bcl-2 in ABC and GCB**
  - **Single agent activity poor-Synergy with BTK targets**
  - **Role in double hit versus double expressor unknown**
- **Ibrutinib targets BCR in ABC**
  - **High activity in PCNSL**
- **PD-1 inhibition in PCNSL and extranodal ABC**