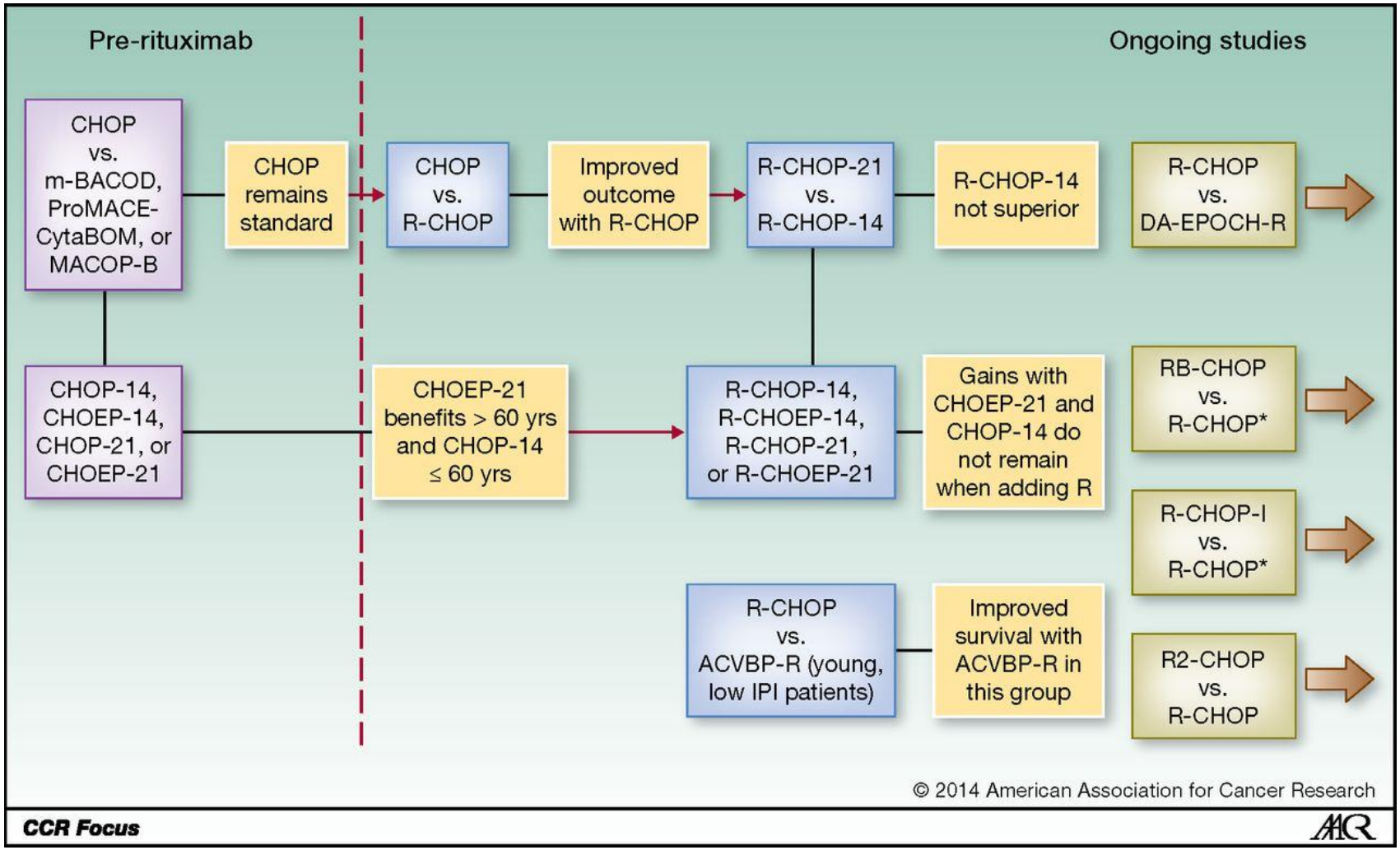
Diffuse Large B-cell Lymphomas Targeting Molecular Pathways

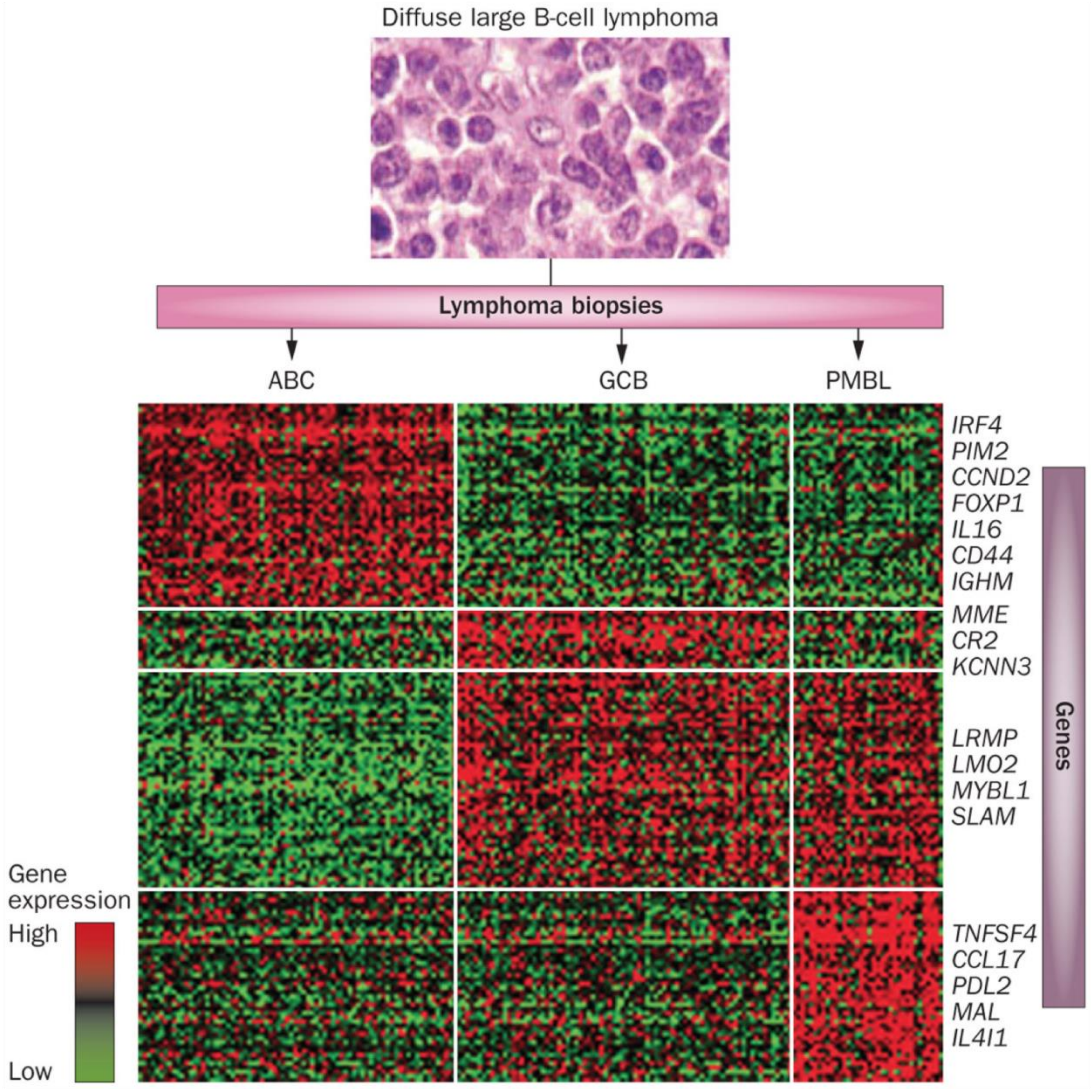
Wyndham H. Wilson, M.D., Ph.D.

Evolution of DLBCL therapeutics.



Kieron Dunleavy et al. Clin Cancer Res 2014;20:5182-5193

Gene-expression profiling of DLBCL subtypes



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

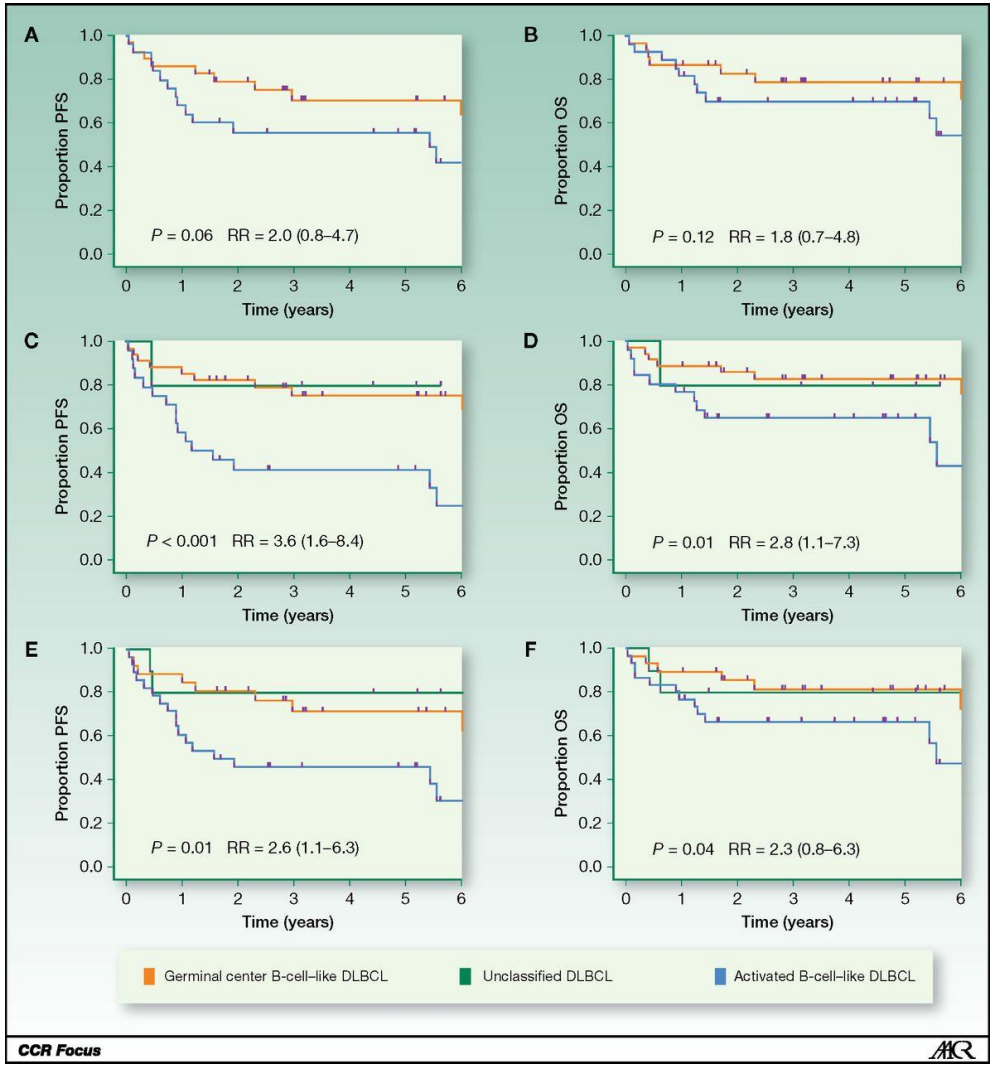
DLBCL outcomes following R-CHOP by Cell of Origin

Method

Hans IHC

Lymph2cx nanostring

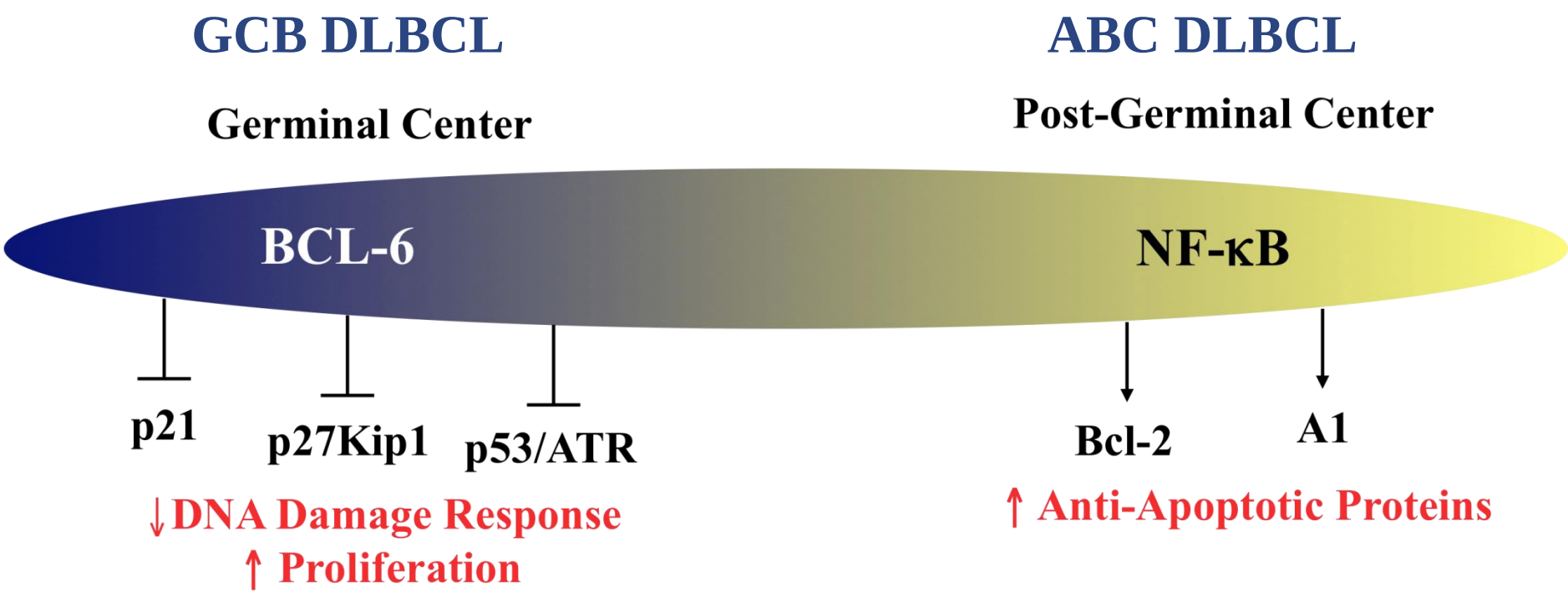
Frozen GEP Gold standard



Kieron Dunleavy et al. Clin Cancer Res 2014;20:5182-5193

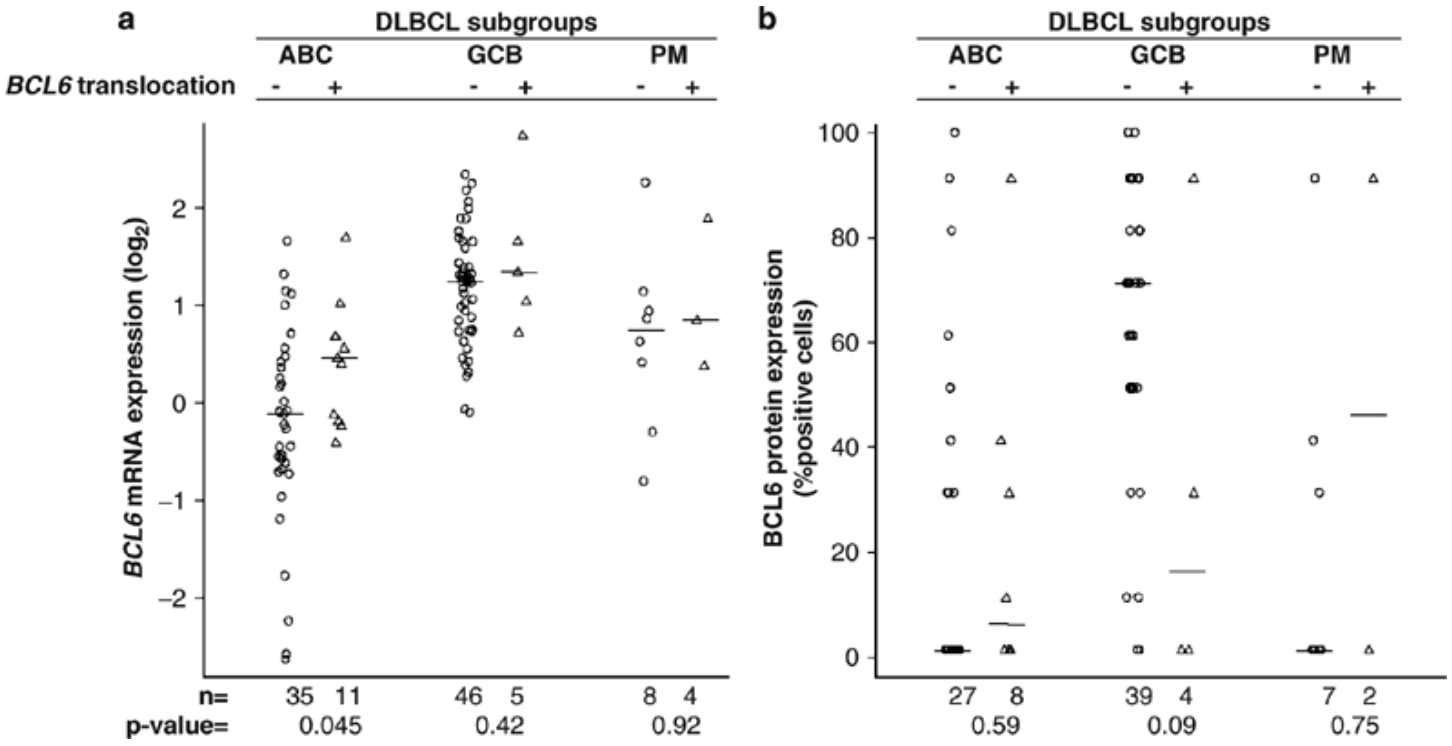
Germinal Center B-cell DLBCL

Key Transcription Factors



Proto-Oncogene BCL-6 is a Transcriptional Repressor

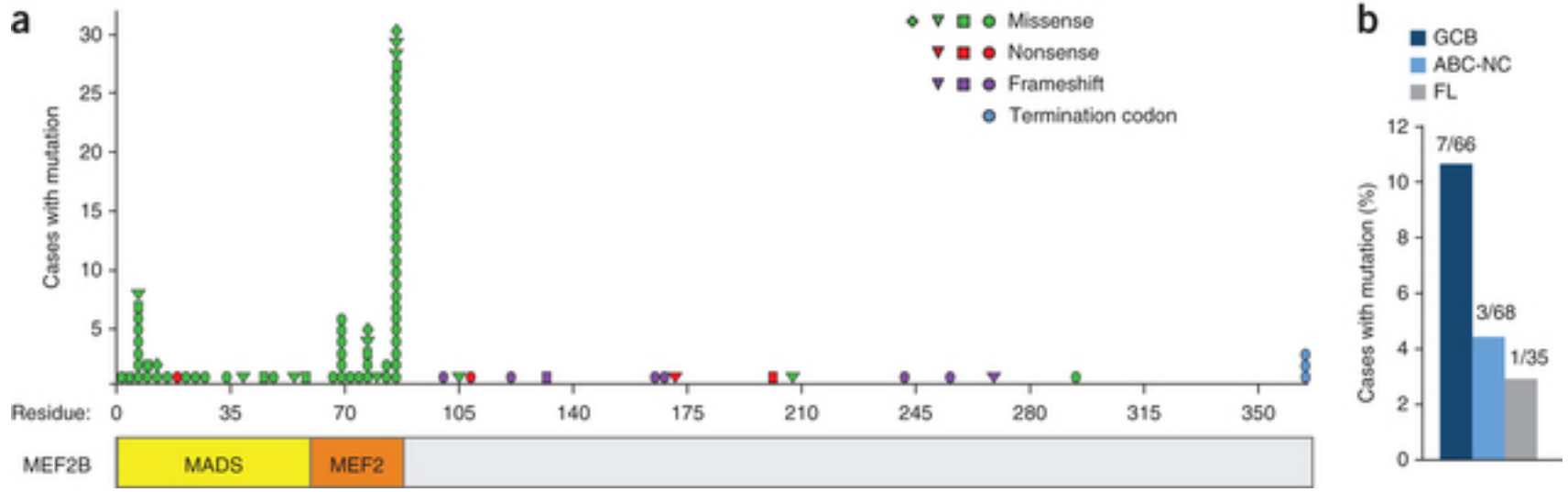
BCL-6 translocations associated with increased mRNA and protein levels



Iqbal et al. Leukemia (2007) 21, 2332–2343

Proto-Oncogene BCL-6 is a Transcriptional Repressor

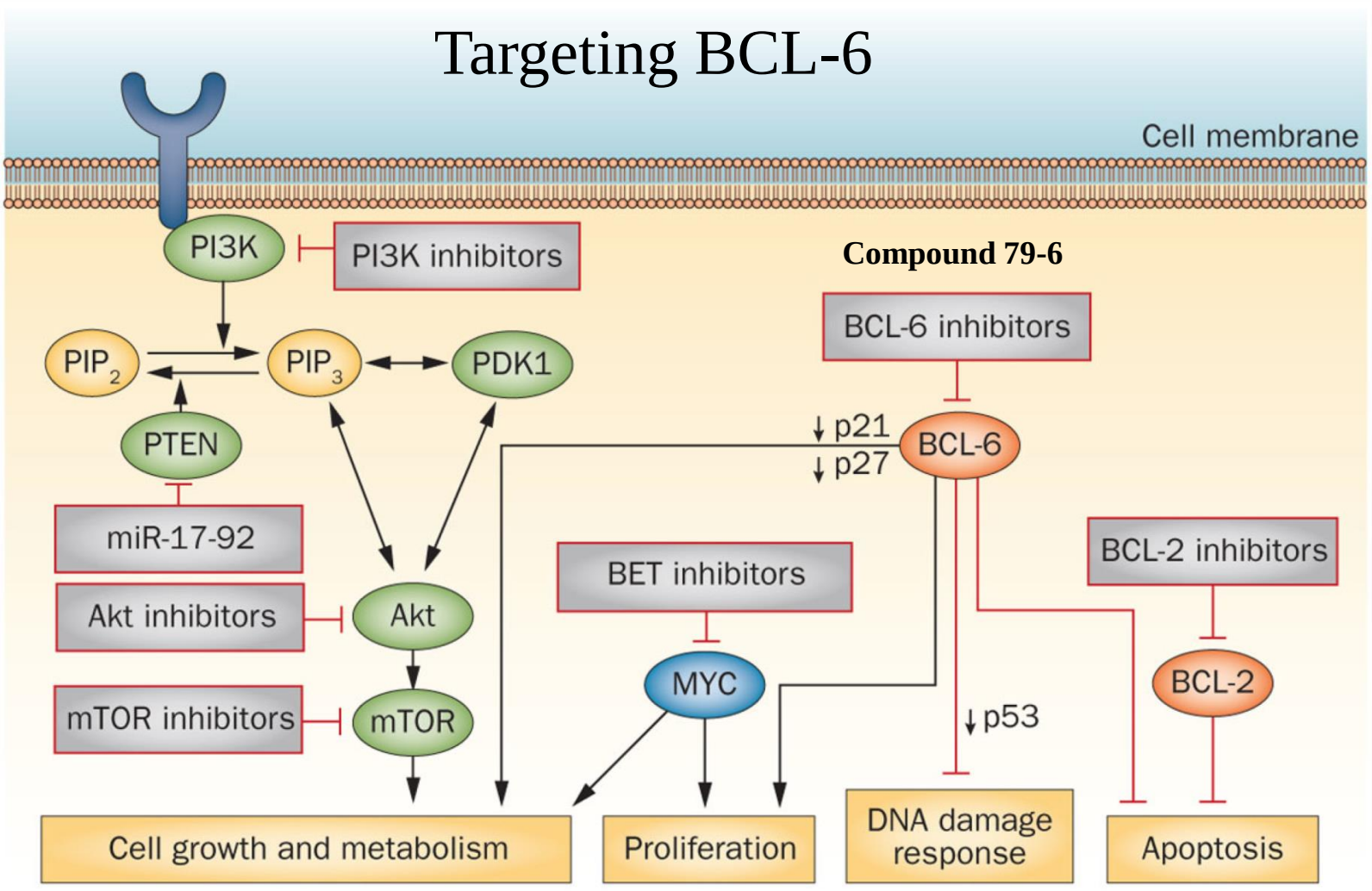
Mutations MEF2B (transcriptional activator) Activates BCL-6 (11% DLBCL)



Ying et al. Nature Immunology ***14, 1084–1092 (2013)***

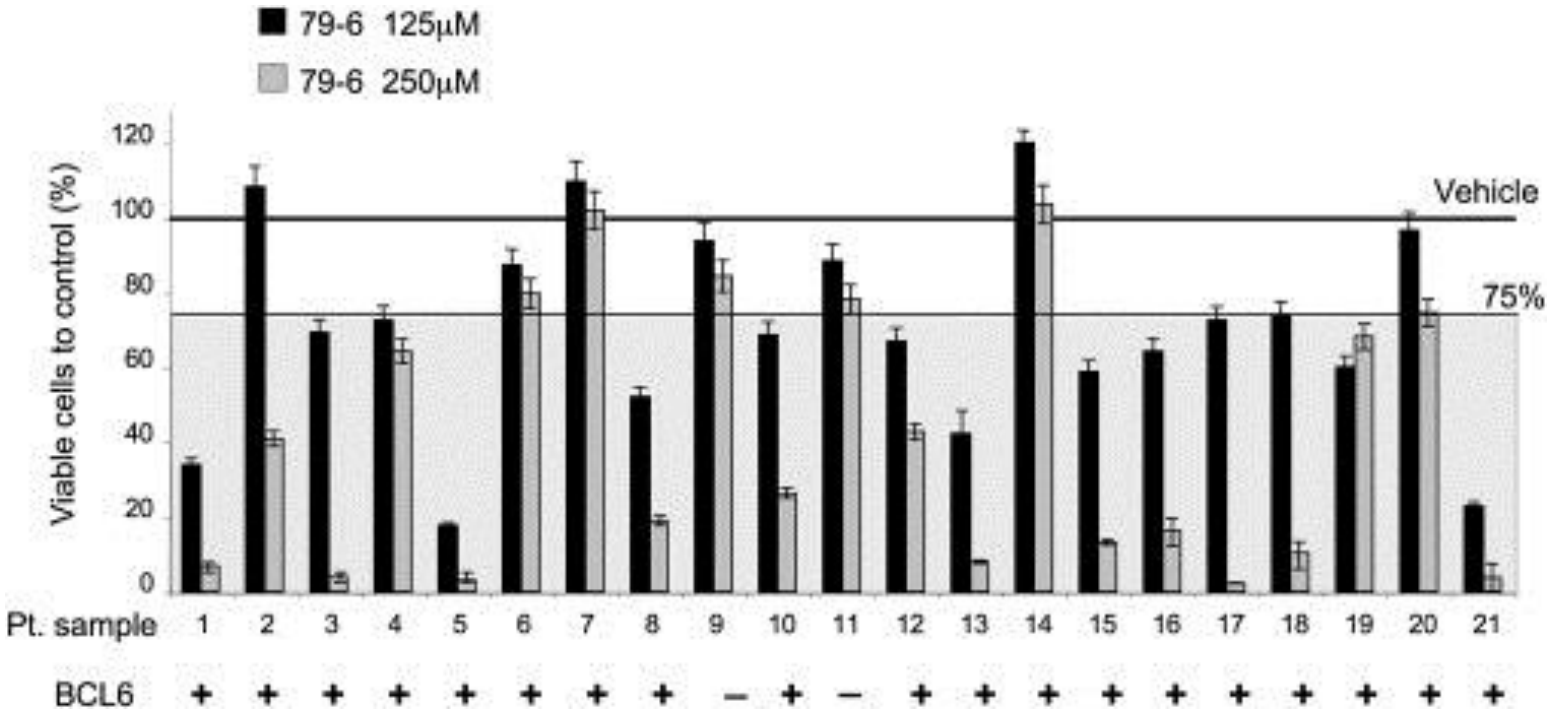
Key signaling pathways in GCB DLBCL

Targeting BCL-6



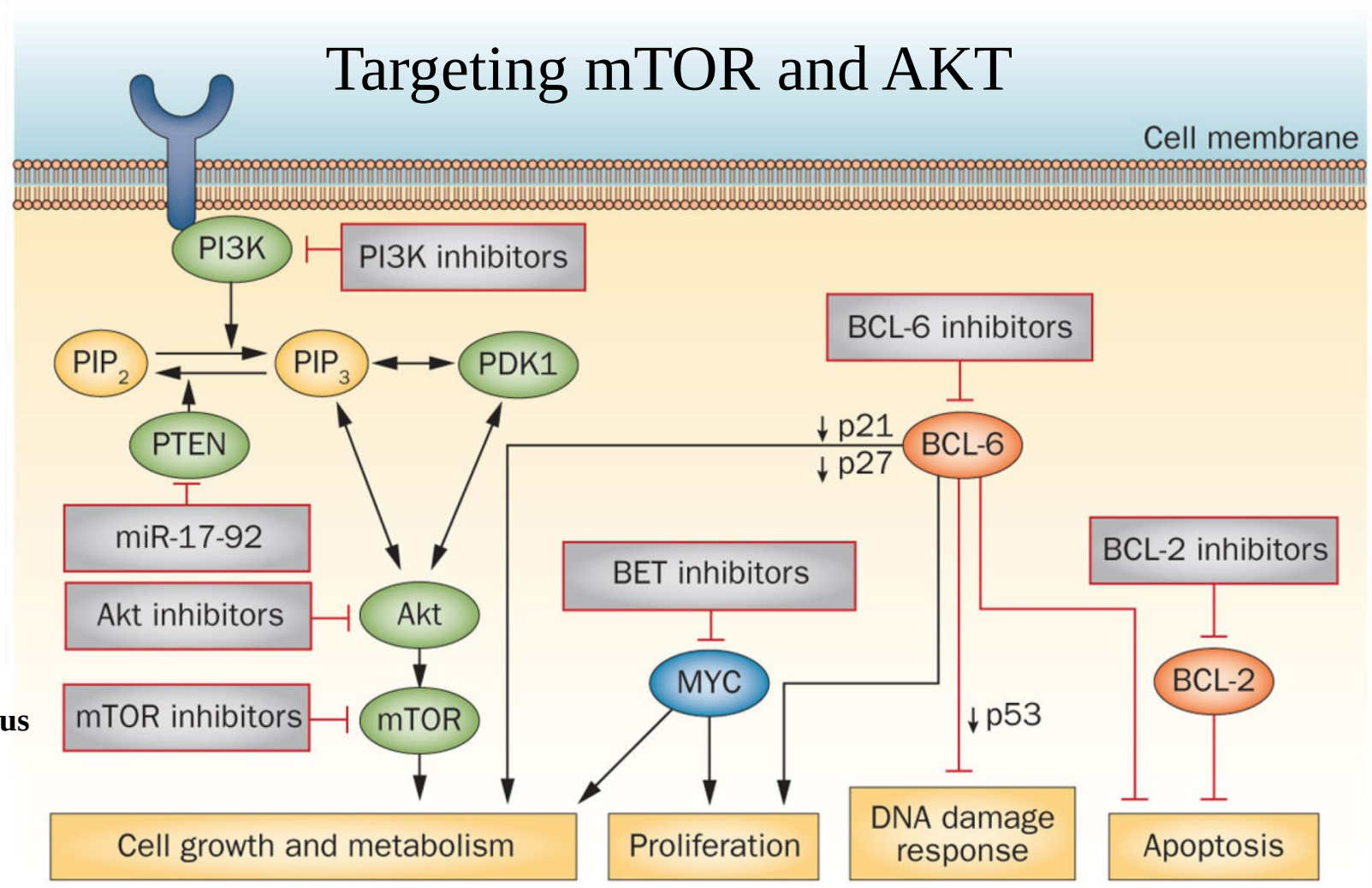
Roschewski, M. *et al.* (2013) *Nat. Rev. Clin. Oncol.*

BCL-6 Small Molecular Inhibitor (79-6)



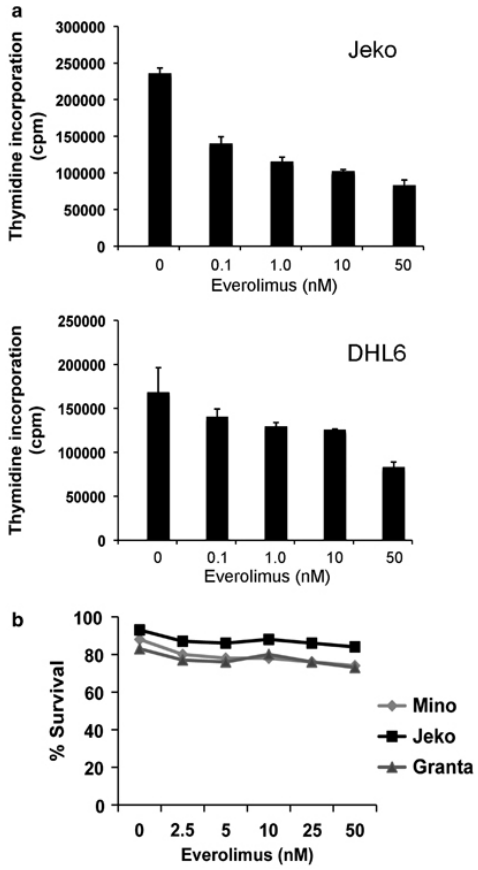
Cherietti et al Cancer Cell, Volume 17, Issue 4, 13 April 2010, Pages 315-316

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

Everolimus, Rituximab, and Combination Chemotherapy in Treating Patients With Newly Diagnosed Untreated Diffuse Large B-Cell Lymphoma

Basic Trial Information Trial Description Summary Further Trial Information Eligibility Criteria Trial Contact Information

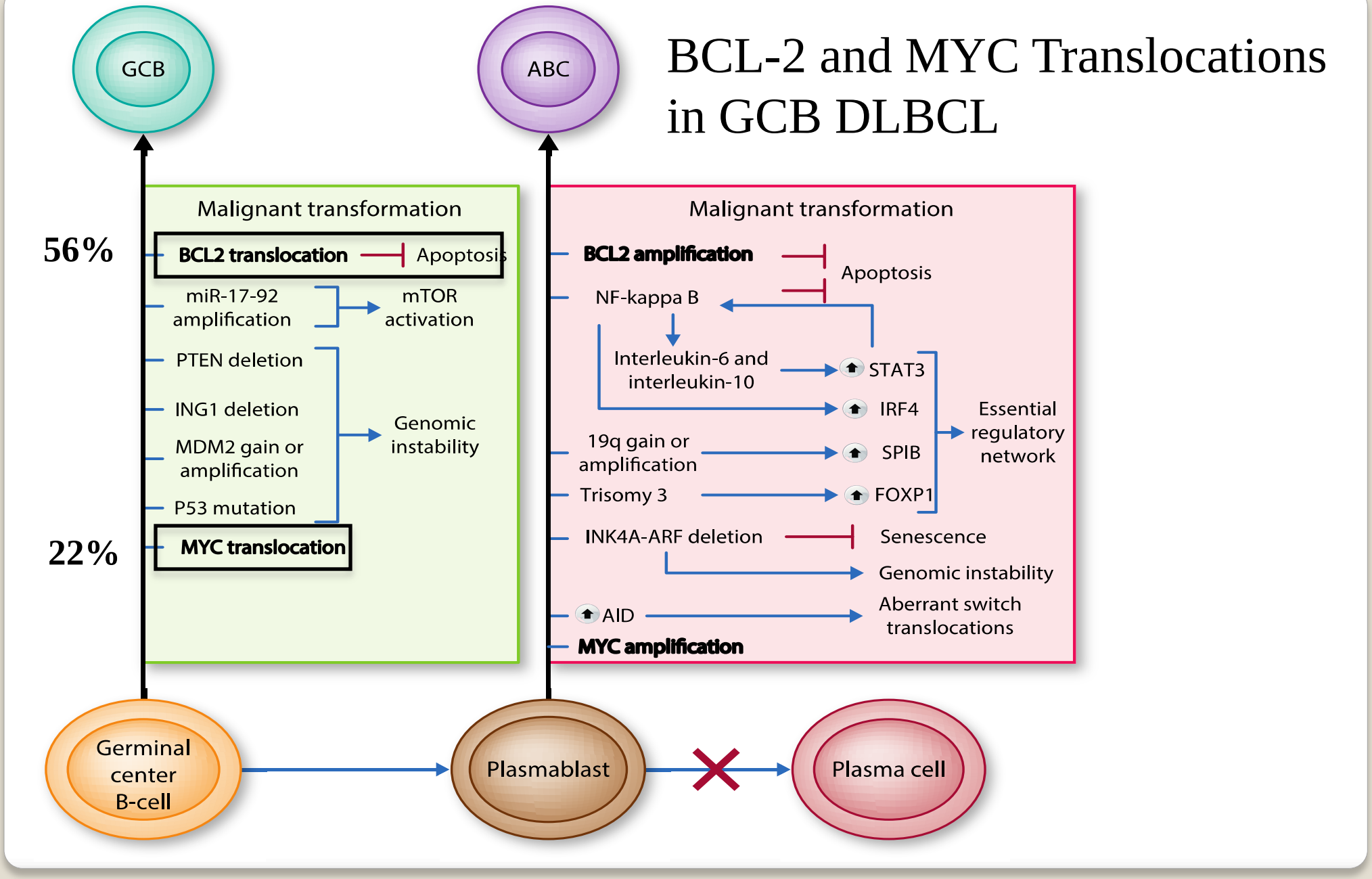
Summary

RATIONALE: Everolimus may stop the growth of cancer cells by blocking some of the enzymes needed for cell growth. Monoclonal antibodies, such as rituximab, can block cancer cells in different ways. Some block the ability of cancer cells to grow and spread. Others find cancer cells and help kill them or carry cancer-killing substances to them. Drugs used in chemotherapy, such as cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone, work in different ways to stop the growth of cancer cells, either by killing the cells or stopping them from dividing. Giving everolimus together with rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone may kill more cancer cells.

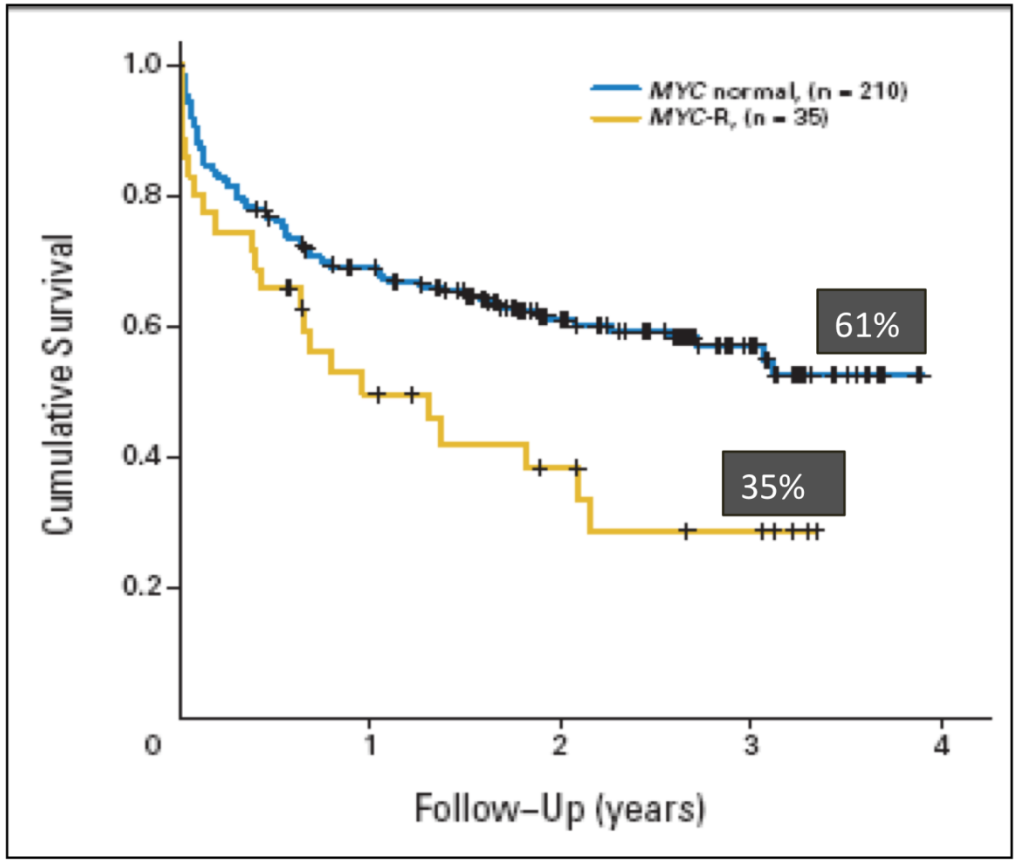
OBJECTIVES:

Primary

- To establish the maximum-tolerated dose (MTD) of everolimus in combination with R-CHOP (rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate and prednisone) chemotherapy.
- To assess the feasibility of everolimus in combination with standard R-CHOP chemotherapy in patients with newly diagnosed diffuse large B-cell lymphoma.


GCB
ABC
BCL-2 and MYC Translocations in GCB DLBCL
Malignant transformation
56%
BCL2 translocation
Apoptosis
miR-17-92 amplification
mTOR activation
PTEN deletion
ING1 deletion
MDM2 gain or amplification
P53 mutation
Genomic instability
22%
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

MYC-R DLBCL –Inferior Outcome with R-CHOP



303 patients with DLBCL
- 245 with FISH data

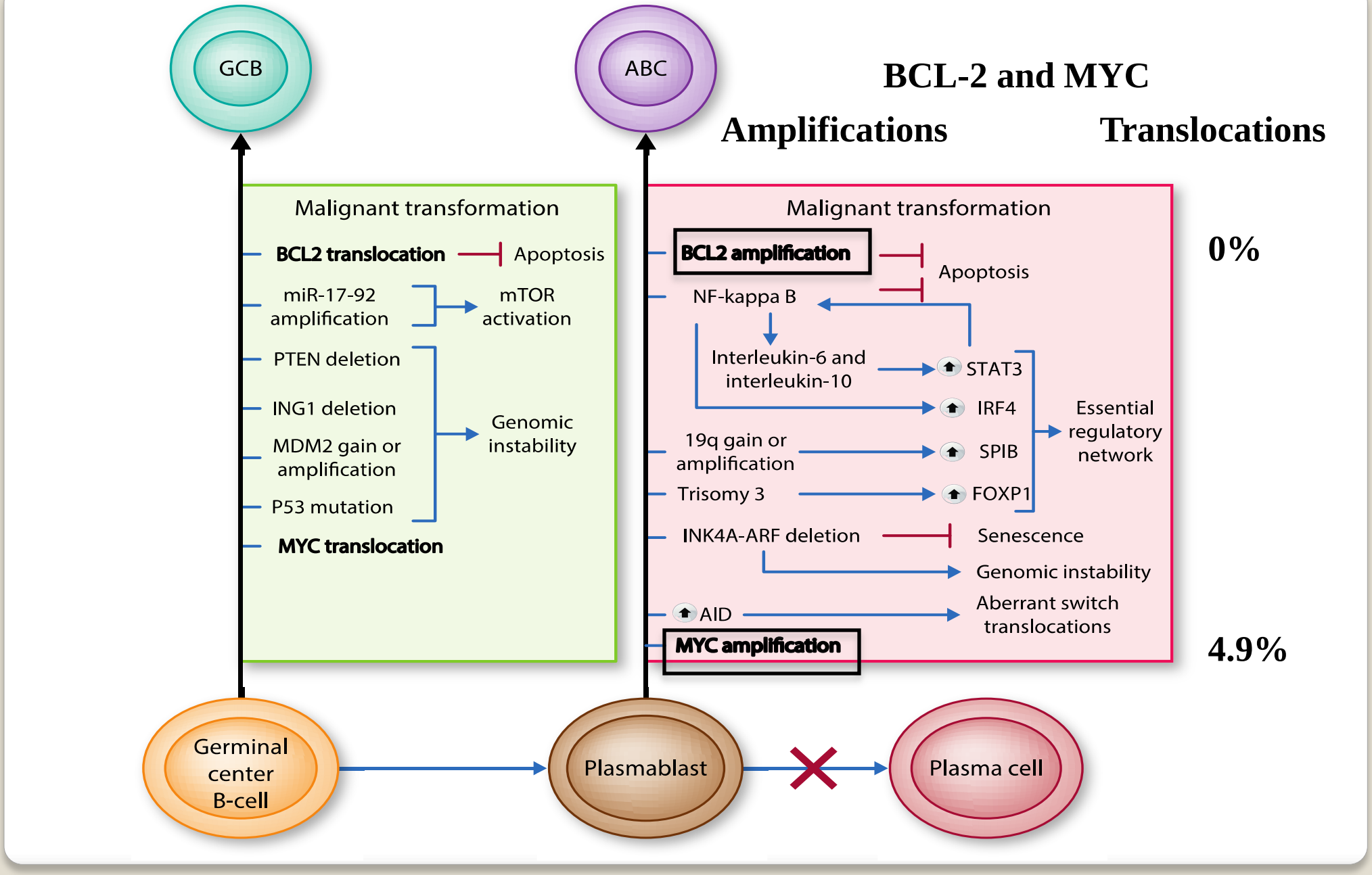
35 (14%) with c-MYC R

19 (54%) also with BCL2 R
3 (8%) also with BCL6 R
7 (20%) had MYC, BCL2 & BCL6

6 (17%) MYC as the sole abnormality

MYC-R cases: high IPI and GCB origin

Barrans S et al. JCO 2010


GCB
ABC
BCL-2 and MYC
Amplifications
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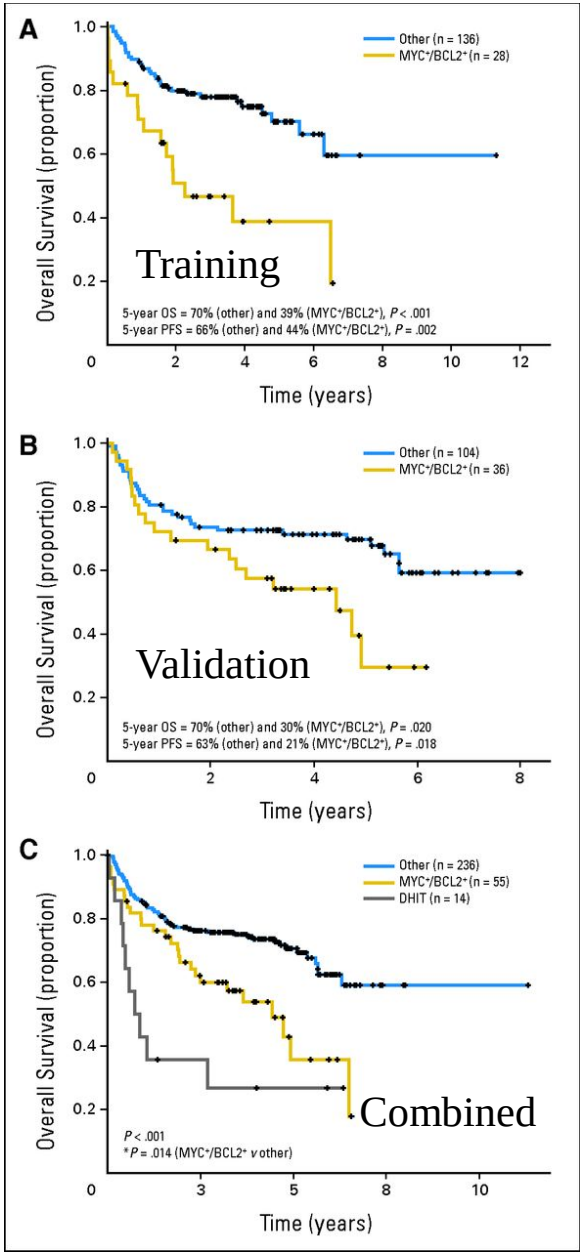
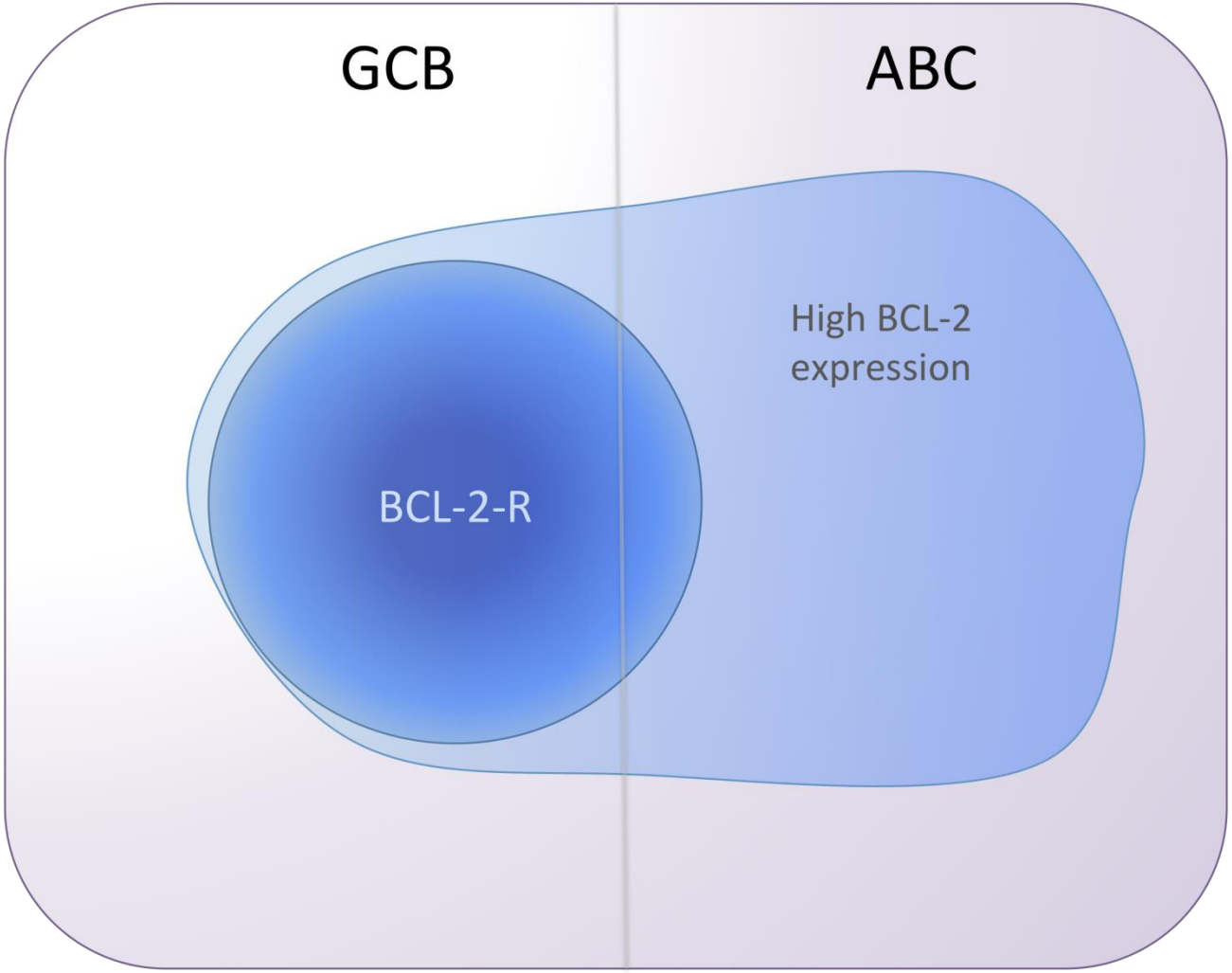
SPIB
Trisomy 3
FOXP1
Essential regulatory network
INK4A-ARF deletion
Senescence
Genomic instability
AID
Aberrant switch translocations
MYC amplification
0%
4.9%
Germinal center B-cell
Plasmablast
Plasma cell

Concurrent Myc and Bcl-2 Protein Expression Adverse with R-CHOP treated DLBCL

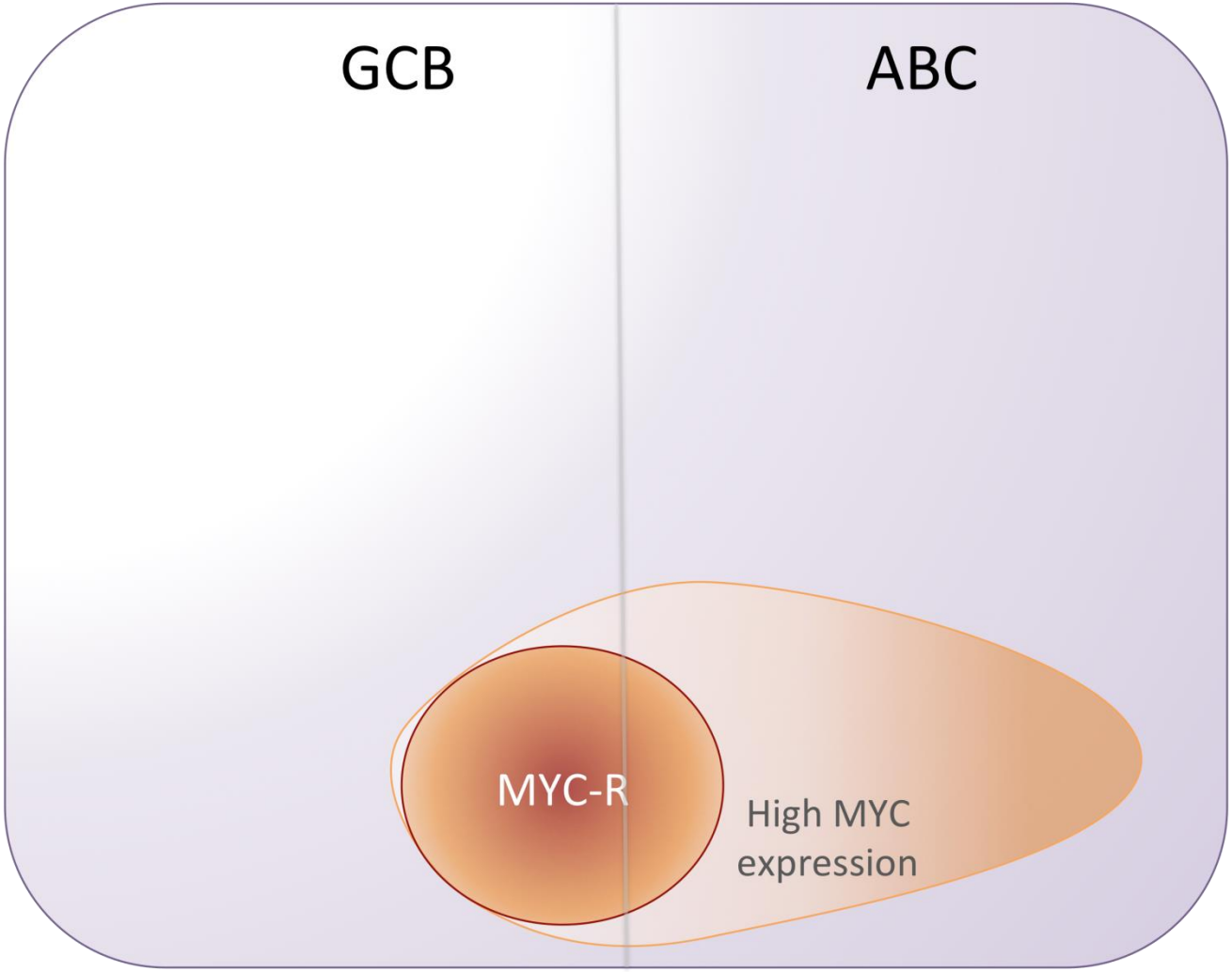


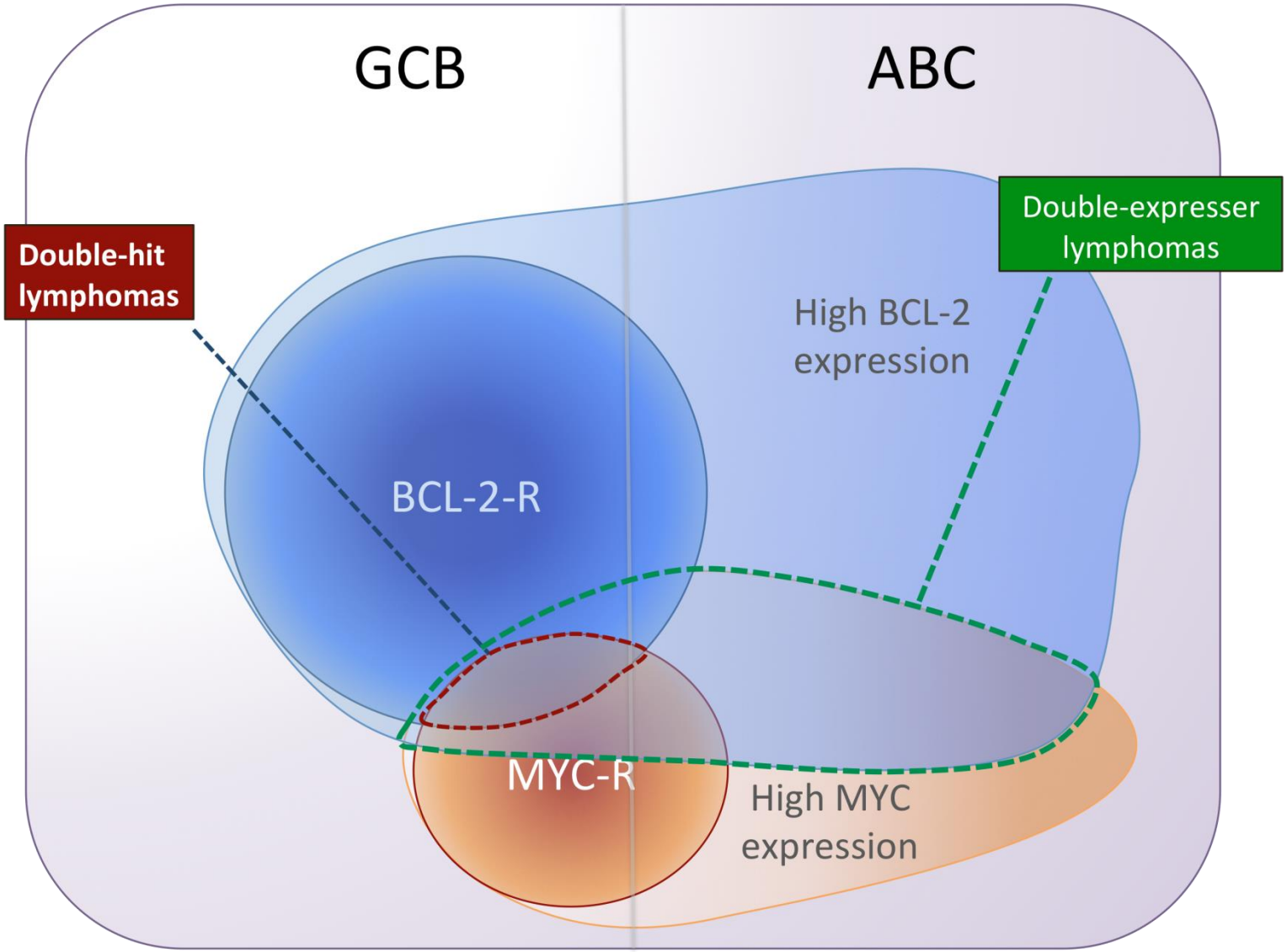
Johnson N A et al. JCO 2012;30:3452-3459

BCL-2-Rearrangement versus Expression

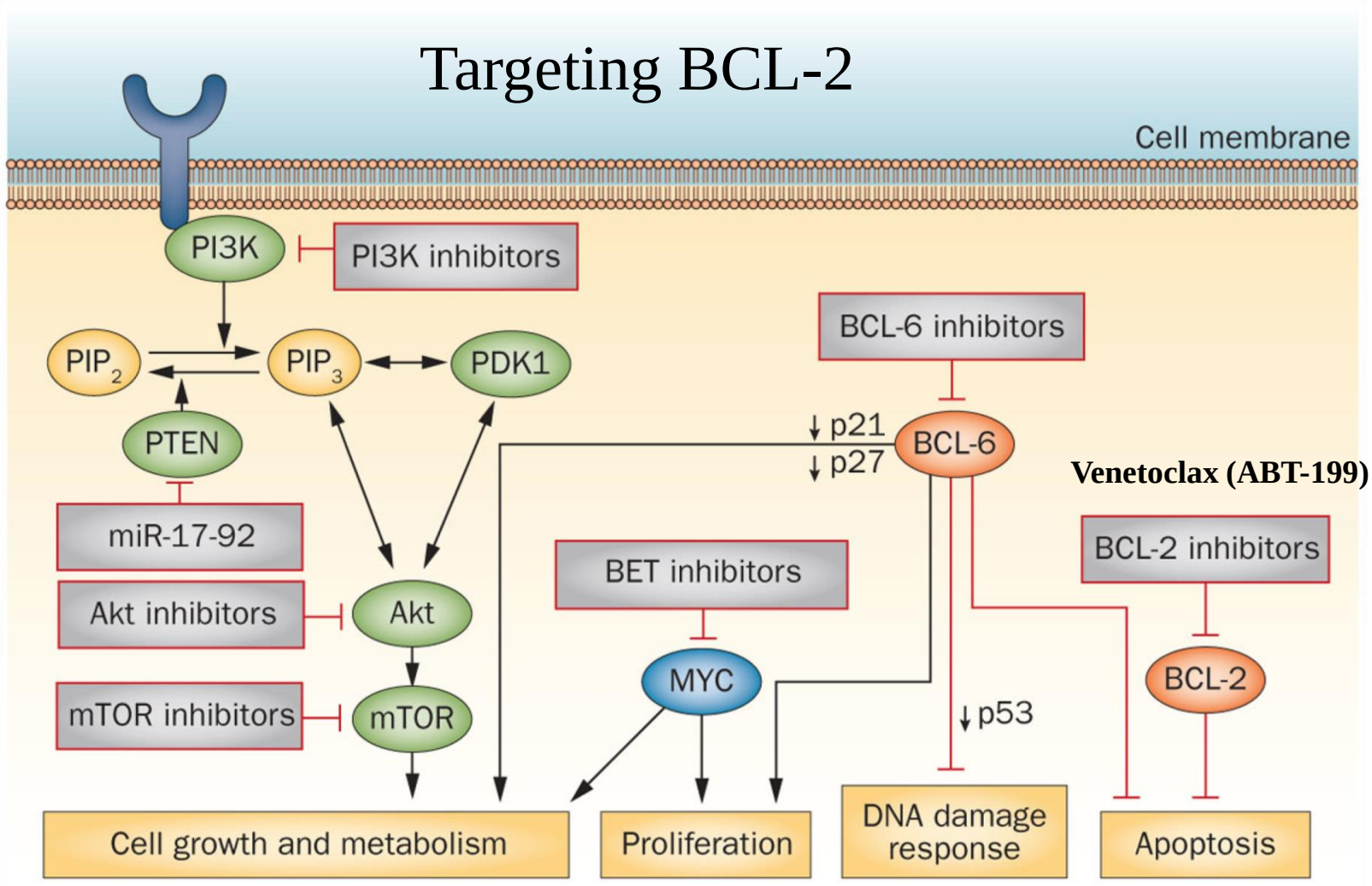


MYC-Rearrangement versus Expression




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.*

A Safety and Pharmacokinetics Study of GDC-0199 (ABT-199) in Patients With Non-Hodgkin's Lymphoma

This study is currently recruiting participants. (see **Contacts and Locations**)

Verified March 2015 *by Hoffmann-La Roche*

Sponsor:

Hoffmann-La Roche

Collaborator:

AbbVie

Information provided by (Responsible Party):

Hoffmann-La Roche

ClinicalTrials.gov Identifier:

NCT02055820

First received: February 4, 2014

Last updated: March 9, 2015

Last verified: March 2015

History of Changes

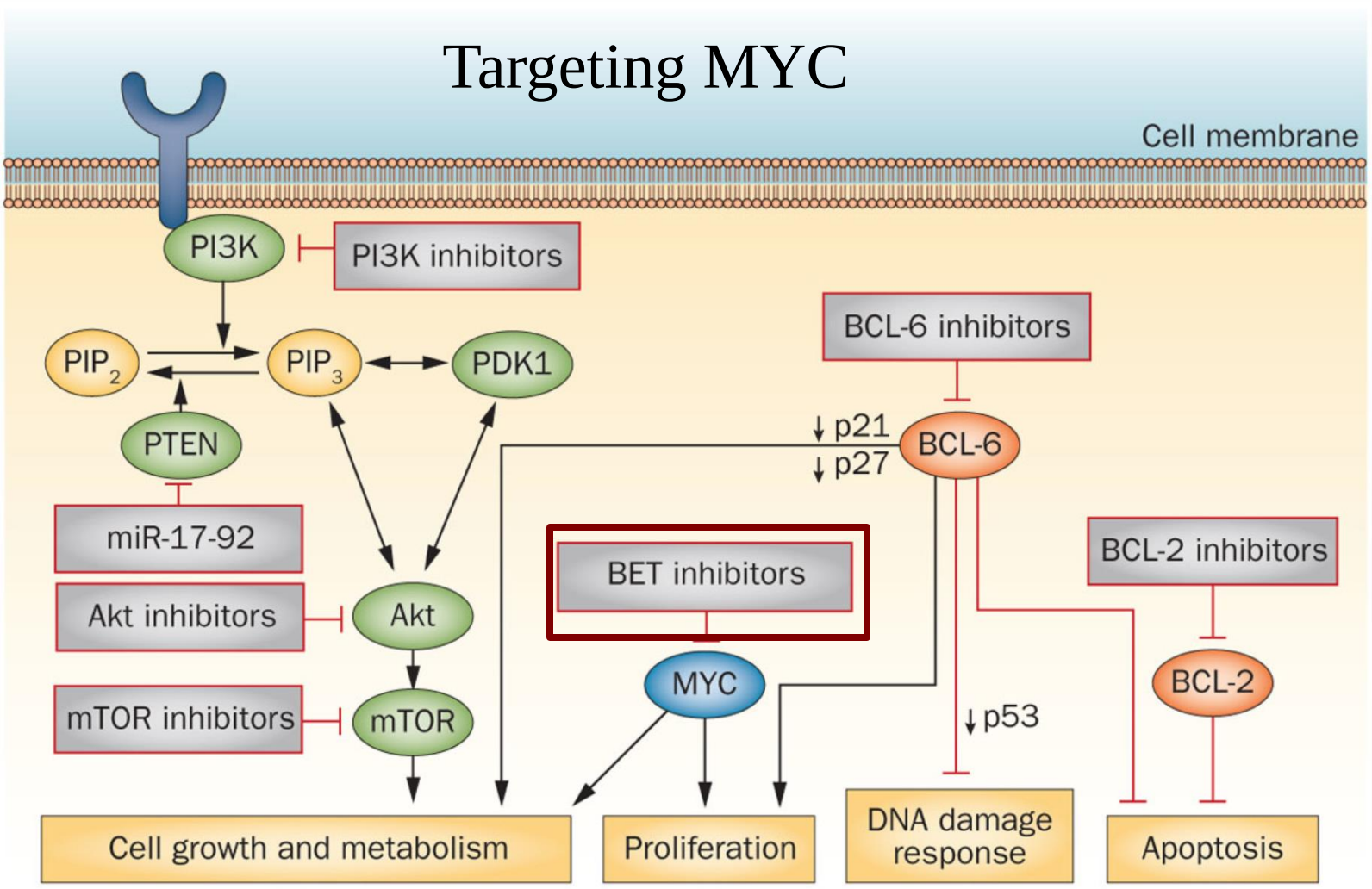
- **Full Text View**
- **Tabular View**
- **No Study Results Posted**
- Disclaimer
- How to Read a Study Record

Purpose

This is a multicenter, open-label, dose-finding study of GDC-0199 administered orally in combination with MabThera/Rituxan (R) or obinutuzumab (G) and standard doses of cyclophosphamide, doxorubicin, vincristine and oral prednisone (CHOP) in patients with Non-Hodgkins Lymphoma (NHL). Patients will be randomized to one of two treatment arms of GDC-0199 in combination with R-CHOP and G-CHOP. The study will consist of two stages, a dose-finding stage and an expansion stage. The maximum tolerated dose (MTD) of GDC-0199 in combination with R-CHOP and G-CHOP will be determined during the dose-finding stage.

Condition	Intervention	Phase
Non-Hodgkin's Lymphoma	Drug: CHOP Drug: GDC-0199 Drug: obinutuzumab Drug: rituximab [MabThera/Rituxan]	Phase 1

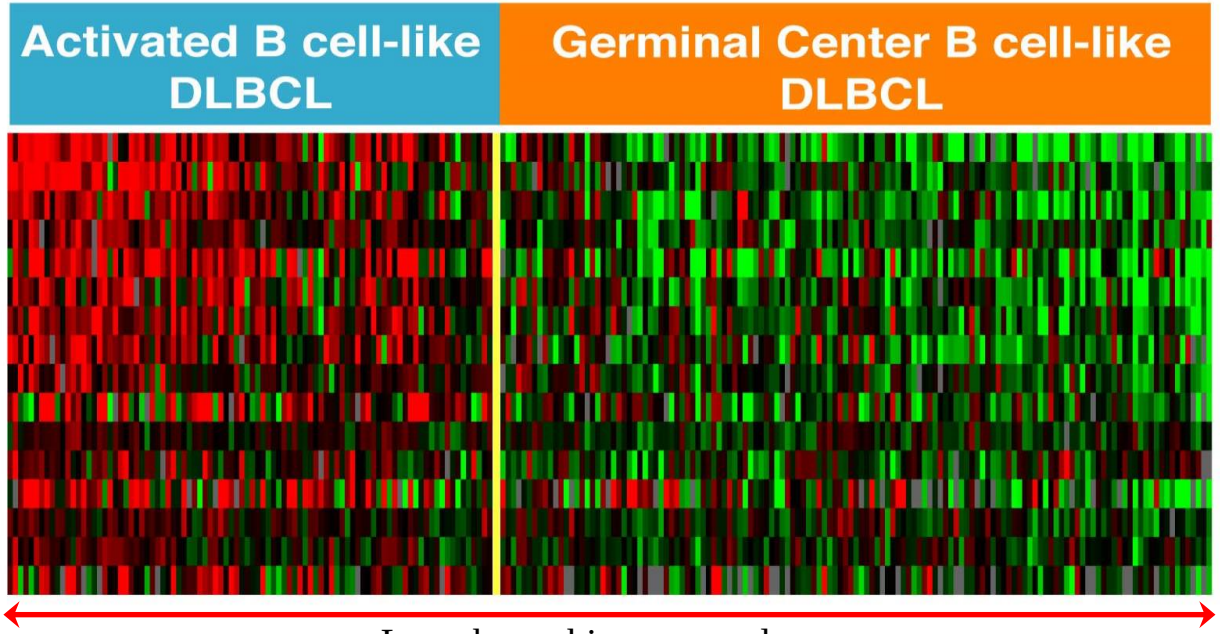
Key signaling pathways in GCB DLBCL



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

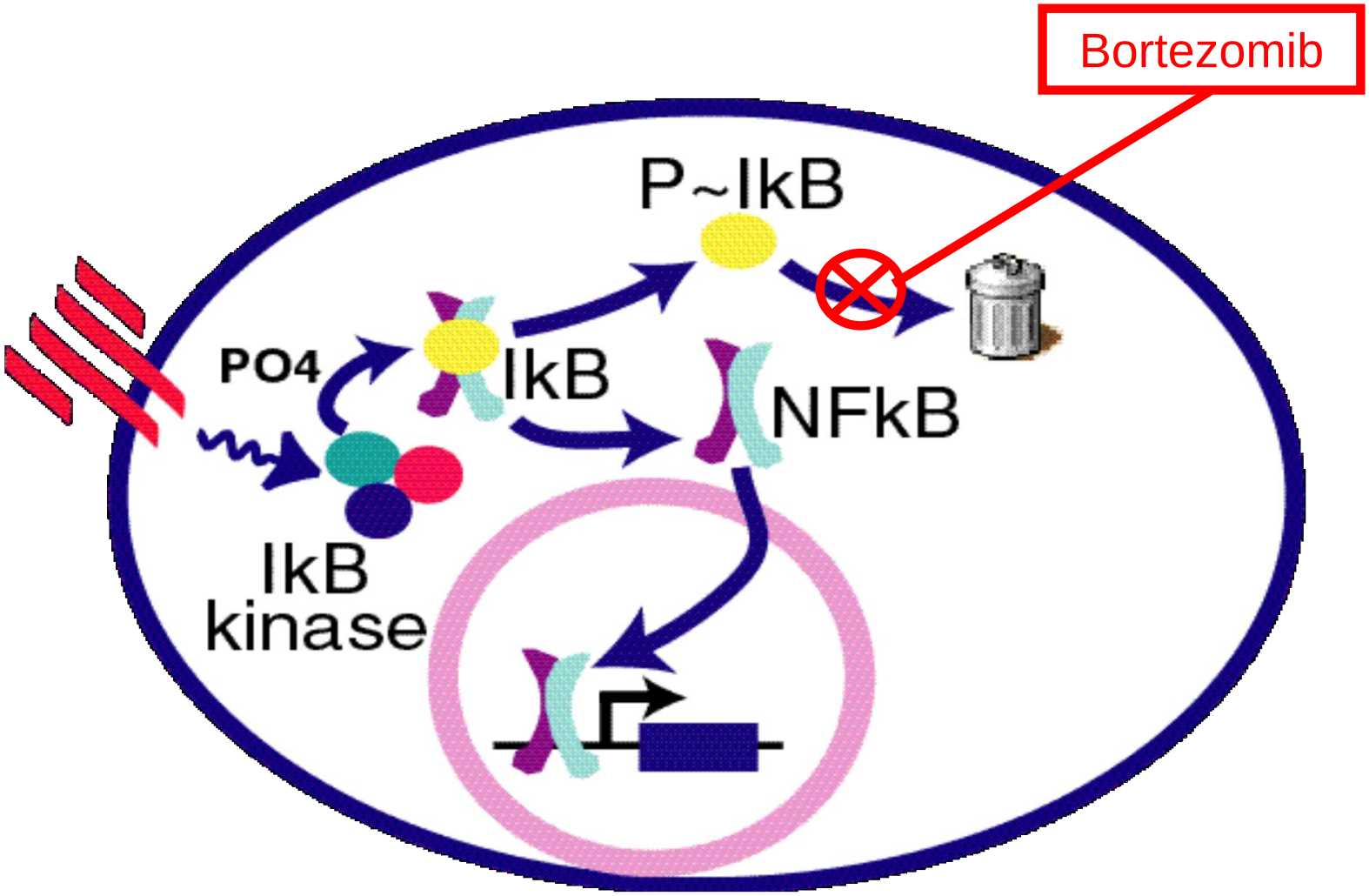
Activated B-cell ABC DLBCL
Targeting B-cell Receptor Signaling

Constitutive Expression of NFKB in ABC DLBCL

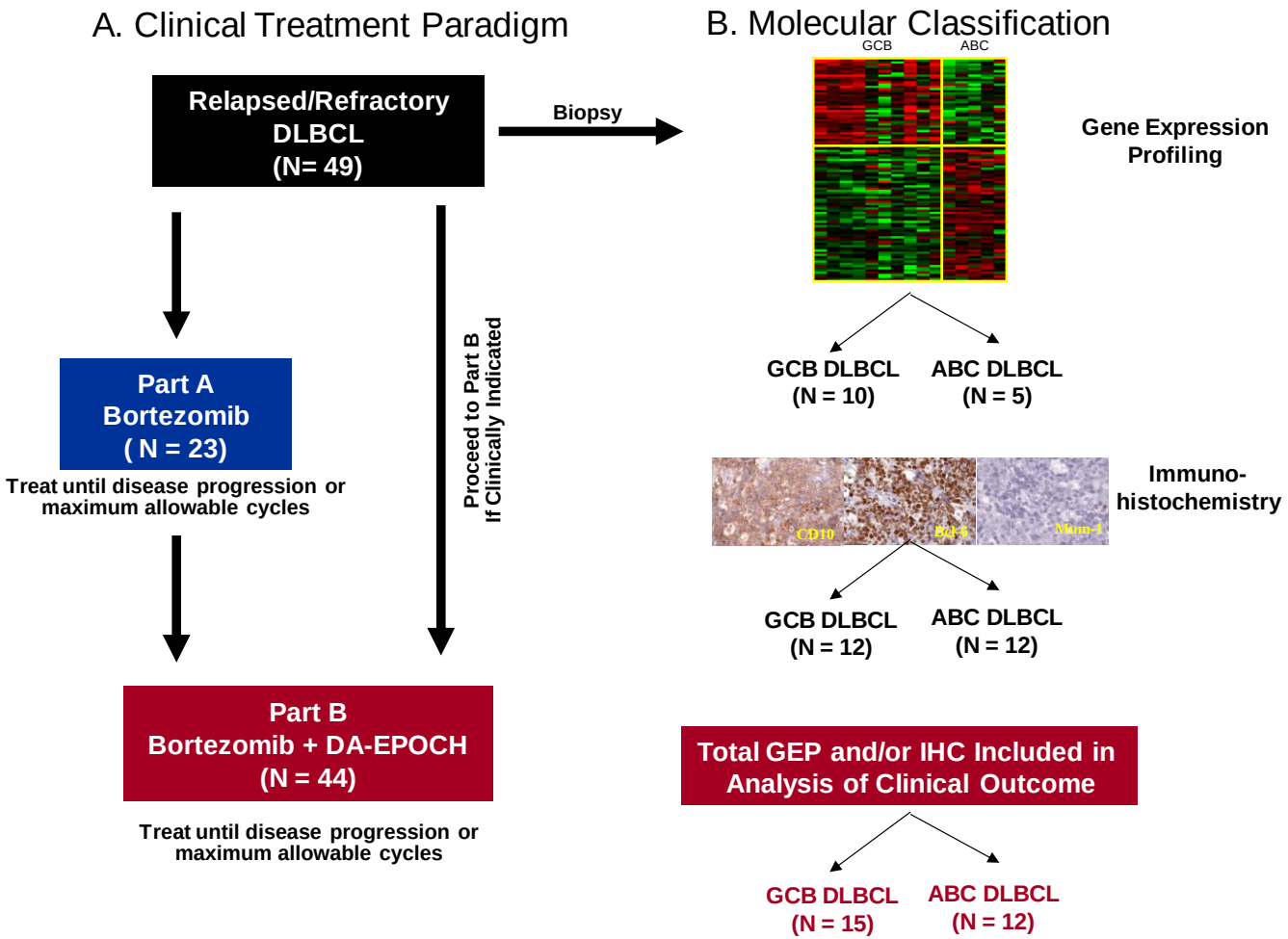


NF-kB target gene	p value
IRF-4	6.23 E-29
Cyclin D2	1.28 E-16
Pim-1	2.69 E-19
Lyn	5.34 E-19
BIC	6.49 E-18
CD44	2.35 E-13
FLICE	3.30 E-14
IM684838	8.74 E-14
IkB ε	7.64 E-09
EBI2	2.77 E-07
NCF2	6.67 E-07
DIFF48	2.86 E-06
CCR7	1.55 E-05
SNF2L2	1.16 E-05
NFkB1	6.68 E-05
IL-6	4.01 E-04

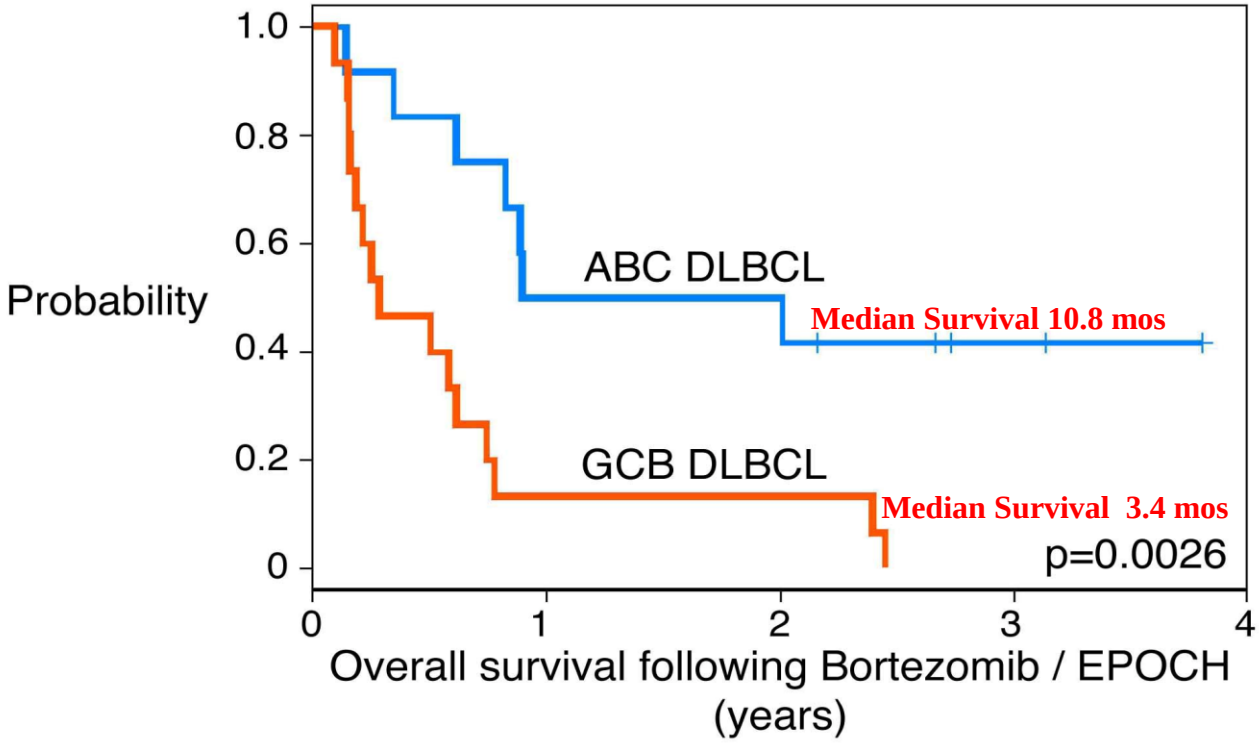
Blockade of the NF-kB Pathway in ABC DLBCL by the Proteasome Inhibitor Bortezomib



Clinical Trial Paradigm

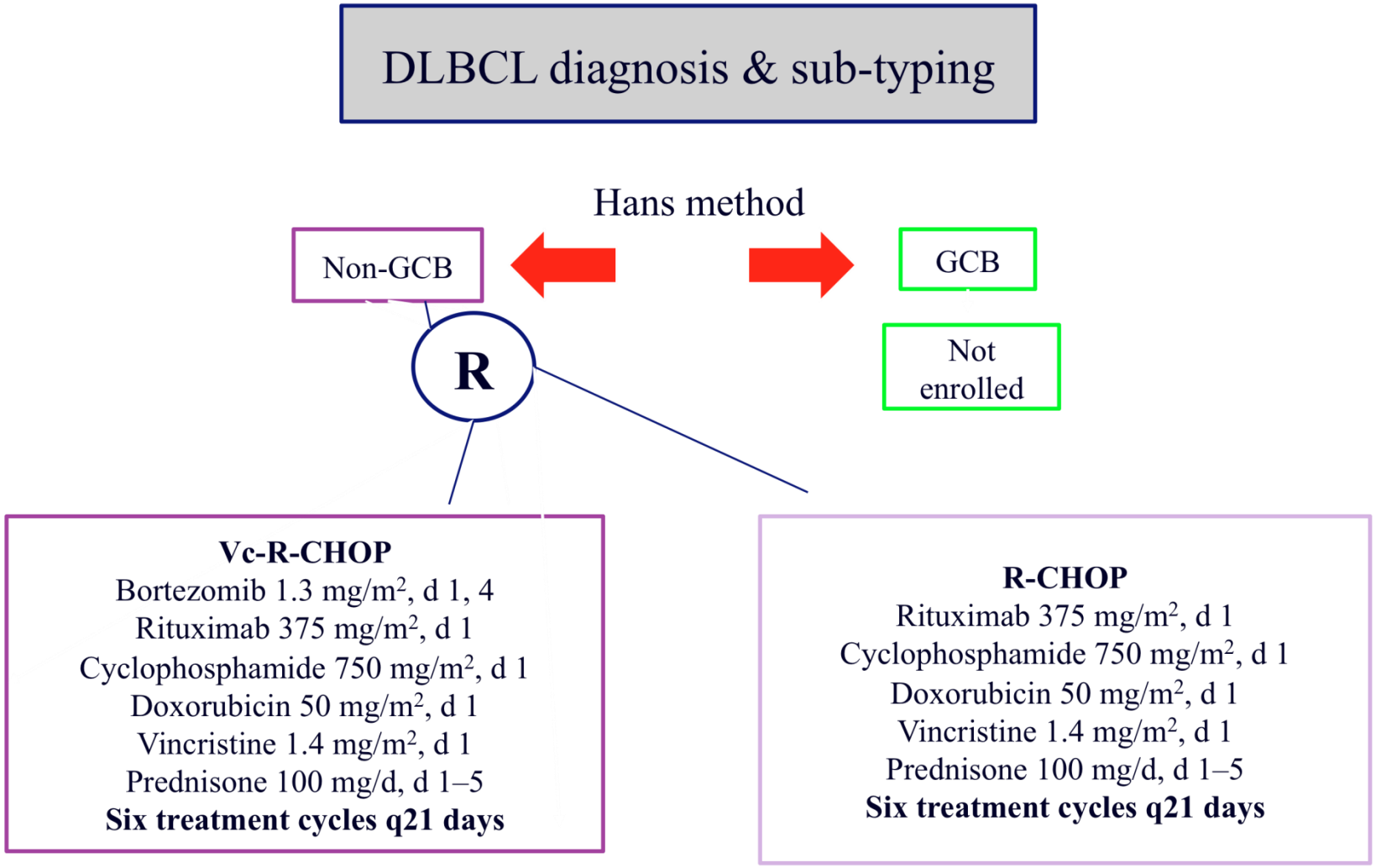


ABC Outcome is Superior to GCB DLBCL Following Bortezomib and DA-EPOCH

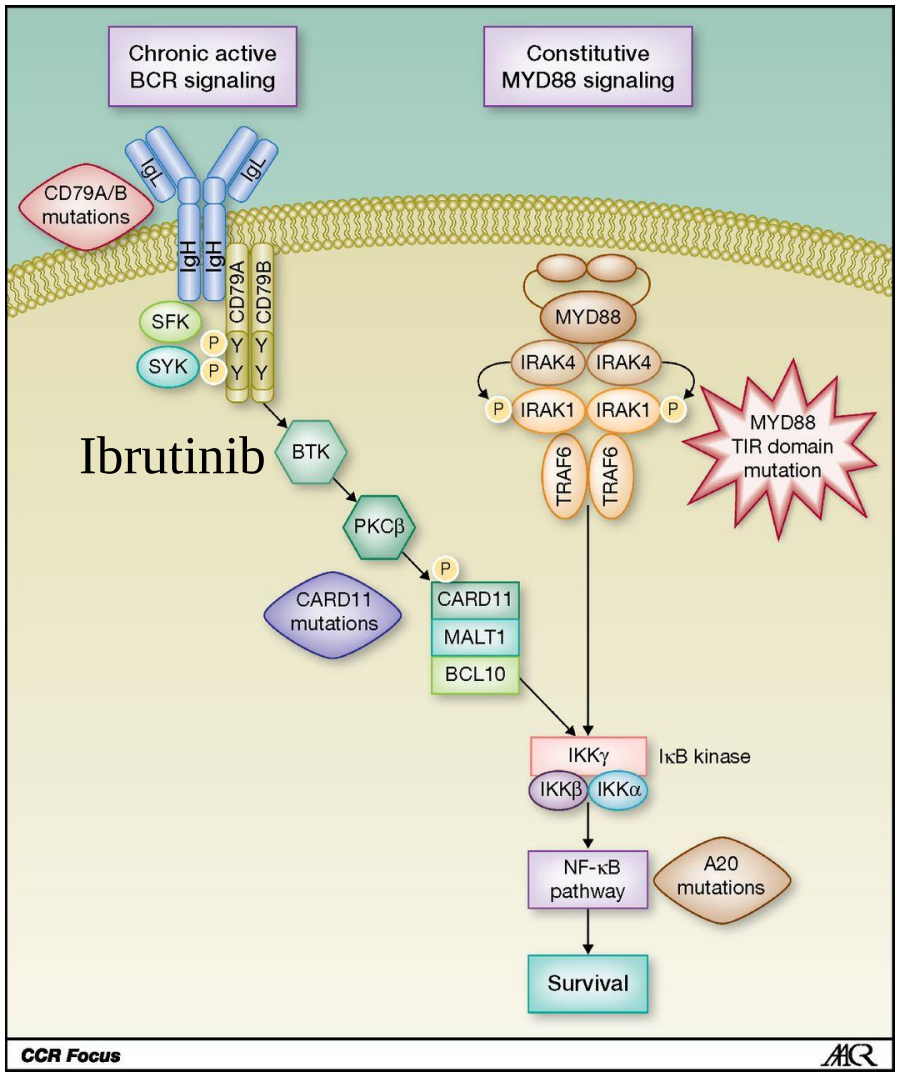


Subtype	Total	Complete response	Partial response	No response	p-value
ABC DLBCL	12	5 (41.7%)	5 (41.7%)	2 (17%)	0.0004
GCB DLBCL	15	1 (6.5%)	1 (6.5%)	13 (87%)	

PYRAMID study design

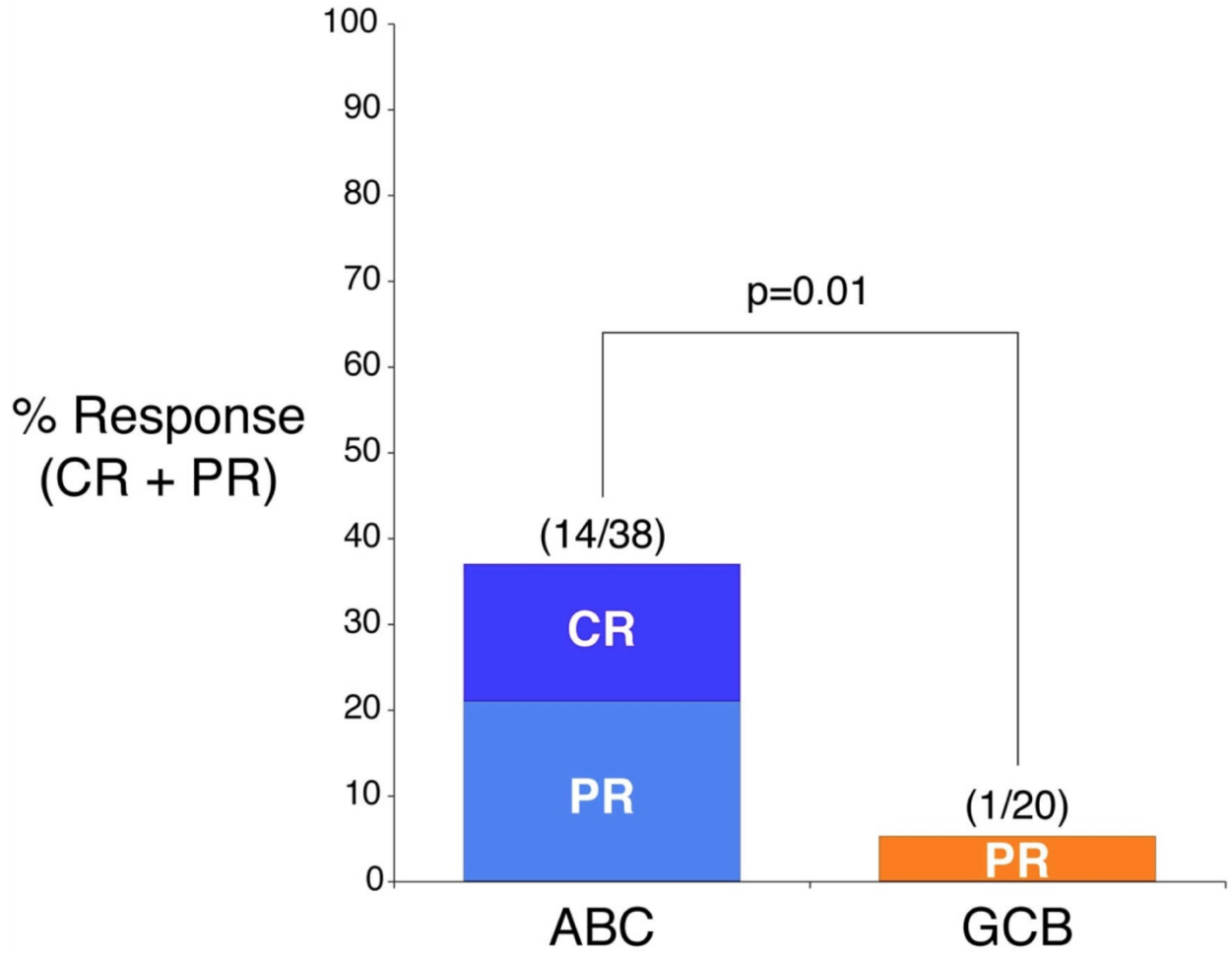


BCR and MYD88 Signalling Pathways

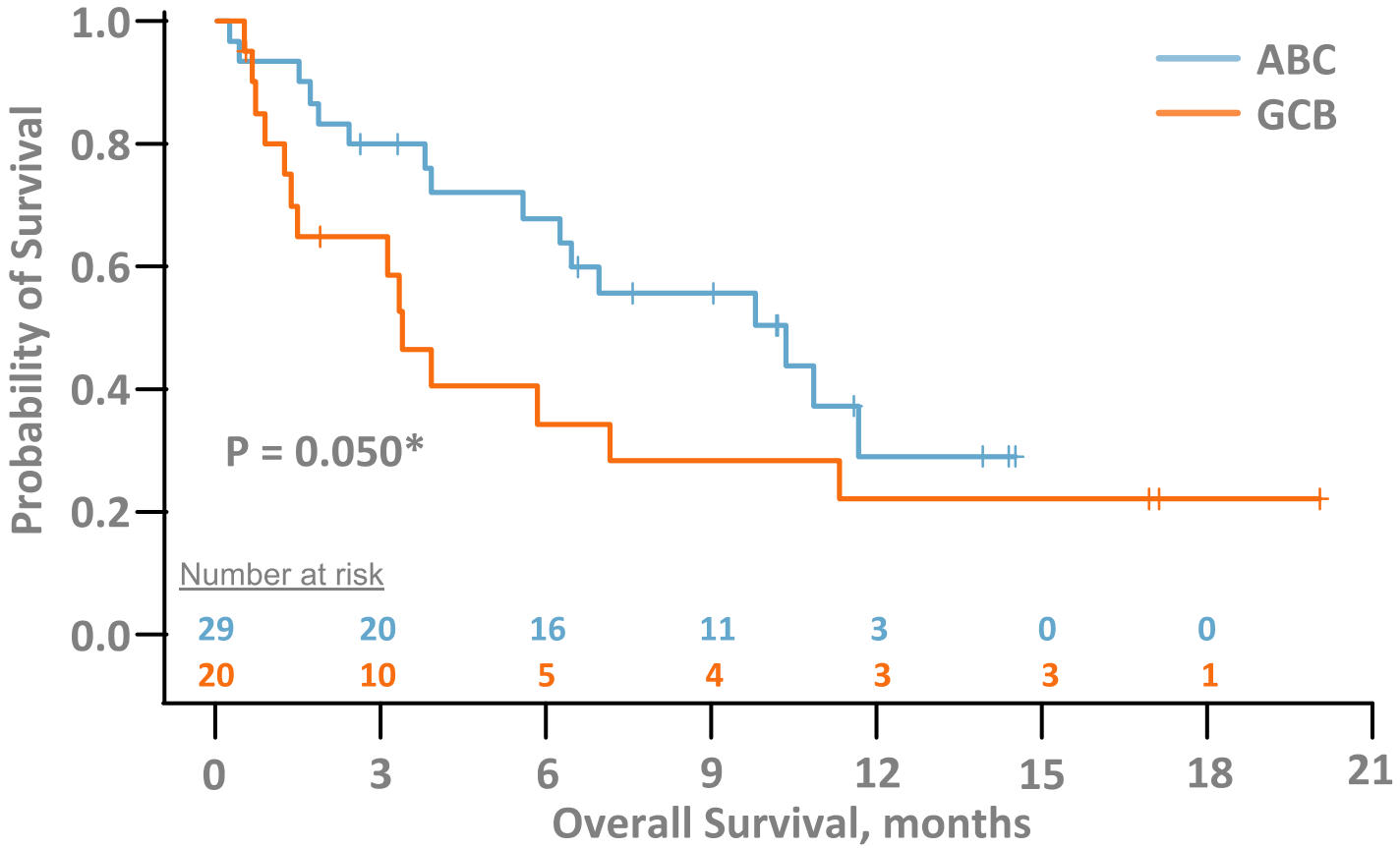


Kieron Dunleavy et al. Clin Cancer Res 2014;20:5182-5193

Ibrutinib is Preferentially Active in ABC DLBCL



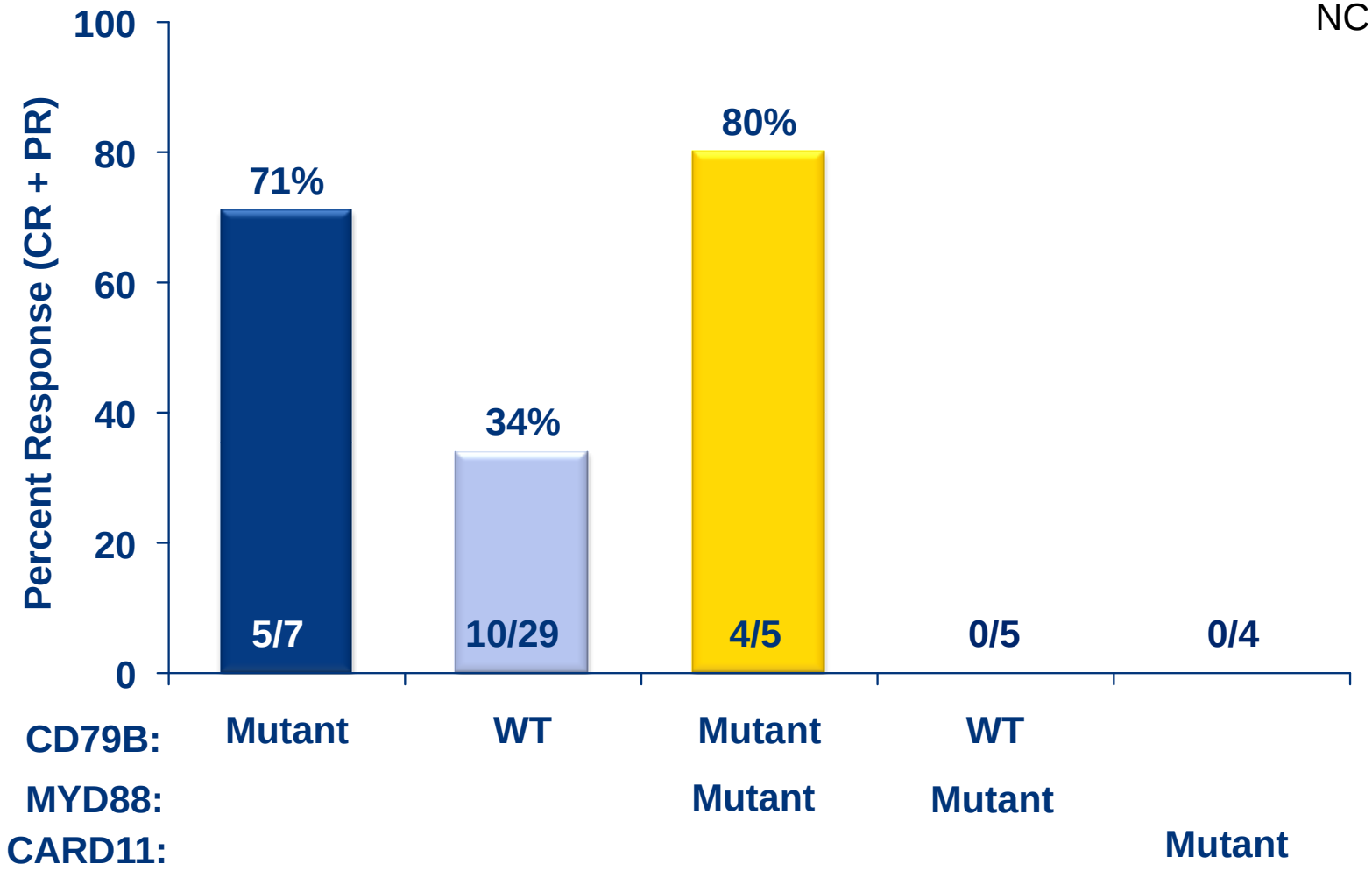
Overall Survival in ABC and GCB DLBCL



- Median ABC OS 9.76 (95% CI: 3.88, 11.63)
- Median GCB OS 3.35 (1.22, 7.13)

Response Rate in the Mutational Subsets ABC DLBCL

NCI data



Ibrutinib + RCHOP

Study Design

Part 1: DOSE ESCALATION (MCL, FL, DLBCL)

Ibrutinib 280 mg + R-CHOP	Ibrutinib 420 mg + R-CHOP	Ibrutinib 560 mg + R-CHOP

Part 2: DOSE EXPANSION at recommended Phase 2 dose (only DLBCL pts)

Ibrutinib 560 mg + R-CHOP

Younes A, et al: The Lancet Oncology 2014

Safety: Serious AEs (SAEs)[a]

Assigned ibrutinib dose	Ibrutinib + R-CHOP			
	Part 1			Part 2
	280 mg N = 7	420 mg N = 4	560 mg N = 6	560 mg N = 15
Pts with ≥ 1 SAE, n (%)	5 (71.4)	1 (25.0)	1 (16.7)	5 (33.3)
Febrile neutropenia, n (%)	2 (28.6)	0 (0.0)	0 (0.0)	2 (13.3)
Syncope, n (%)	0 (0.0)	1 (25.0)	1 (16.7)	0 (0.0)
Pyrexia, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	2 (13.3)
Chest pain, n (%)	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)
Peri-orbital cellulitis, n (%)	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)
Headache, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)
Hypertensive crisis, n (%)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)
Hypotension, n (%)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)
Acute coronary syndrome[b], n (%)	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhea, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)

[a]All SAEs reported.

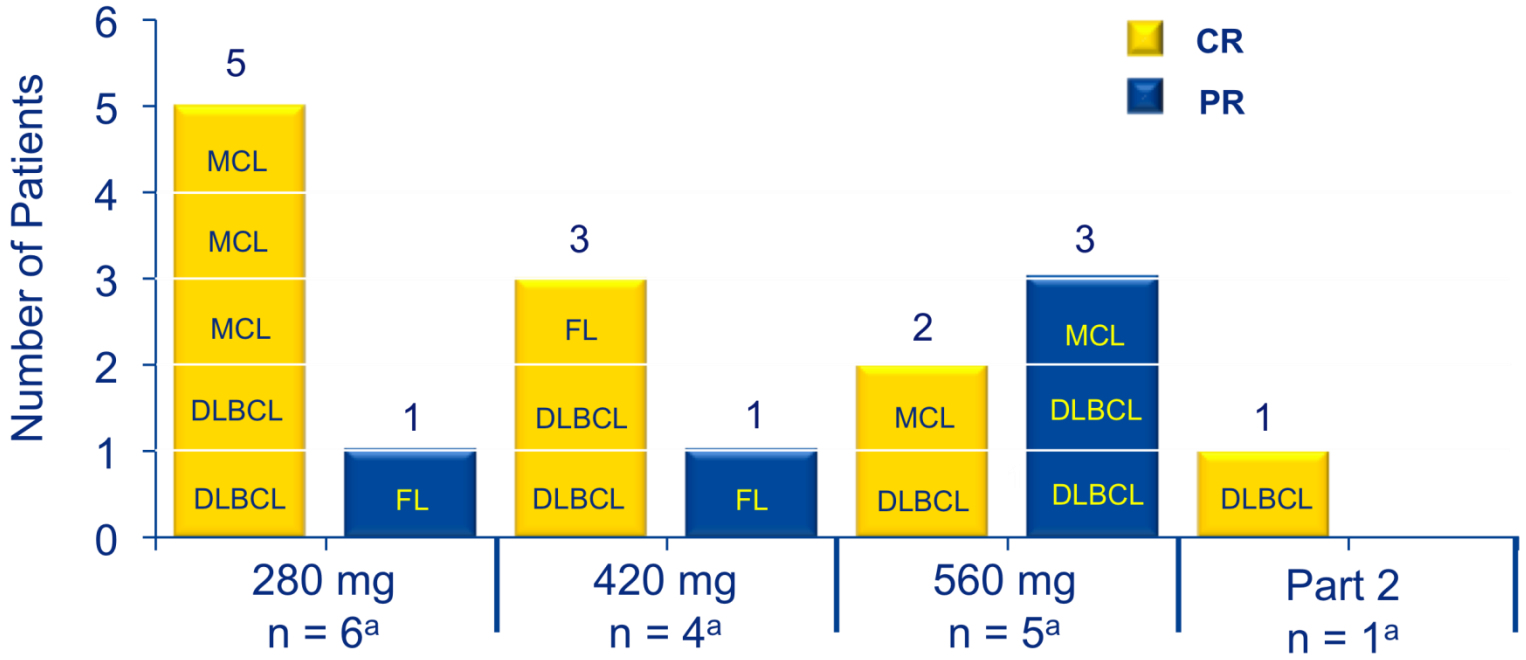
[b] SAE reported, but occurred >28 days after last dose of Ibrutinib. N, number of patients in the full analysis set.

Data cut-off 1-May-2013

PCI-32765DBL1002

Efficacy: ORR

- **ORR 100% (CR 69%, PR 31%)**



[a]Evaluable population - (based on 16 patients with post-treatment tumor assessment).
CR, complete response; PR, partial response.

Data cut-off 1-May-2013

PCI-32765DBL1002

A Study of the Bruton's Tyrosine Kinase Inhibitor, PCI-32765 (Ibrutinib), in Combination With Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone in Patients With Newly Diagnosed Non-Germinal Center B-Cell Subtype of Diffuse Large B-Cell Lymphoma

Verified March 2015 by Janssen Research & Development, LLC

Sponsor:

Janssen Research & Development, LLC

Collaborator:

Pharmacyclics

Information provided by (Responsible Party):

Janssen Research & Development, LLC

ClinicalTrials.gov Identifier:

NCT01855750

Purpose

The purpose of this study is to evaluate if ibrutinib administered in combination with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) improves the clinical outcome in newly diagnosed patients with non-germinal center B-cell subtype (GCB) of diffuse large B-cell lymphoma (DLBCL).

Condition	Intervention	Phase
Lymphoma	Drug: Ibrutinib Drug: Placebo Drug: Rituximab Drug: Cyclophosphamide Drug: Doxorubicin Drug: Vincristine Drug: Prednisone (or equivalent)	Phase 3

A Study of the Bruton's Tyrosine Kinase Inhibitor, PCI-32765 (Ibrutinib), in Combination With Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone in Patients With Newly Diagnosed Non-Germinal Center B-Cell Subtype of Diffuse Large B-Cell Lymphoma

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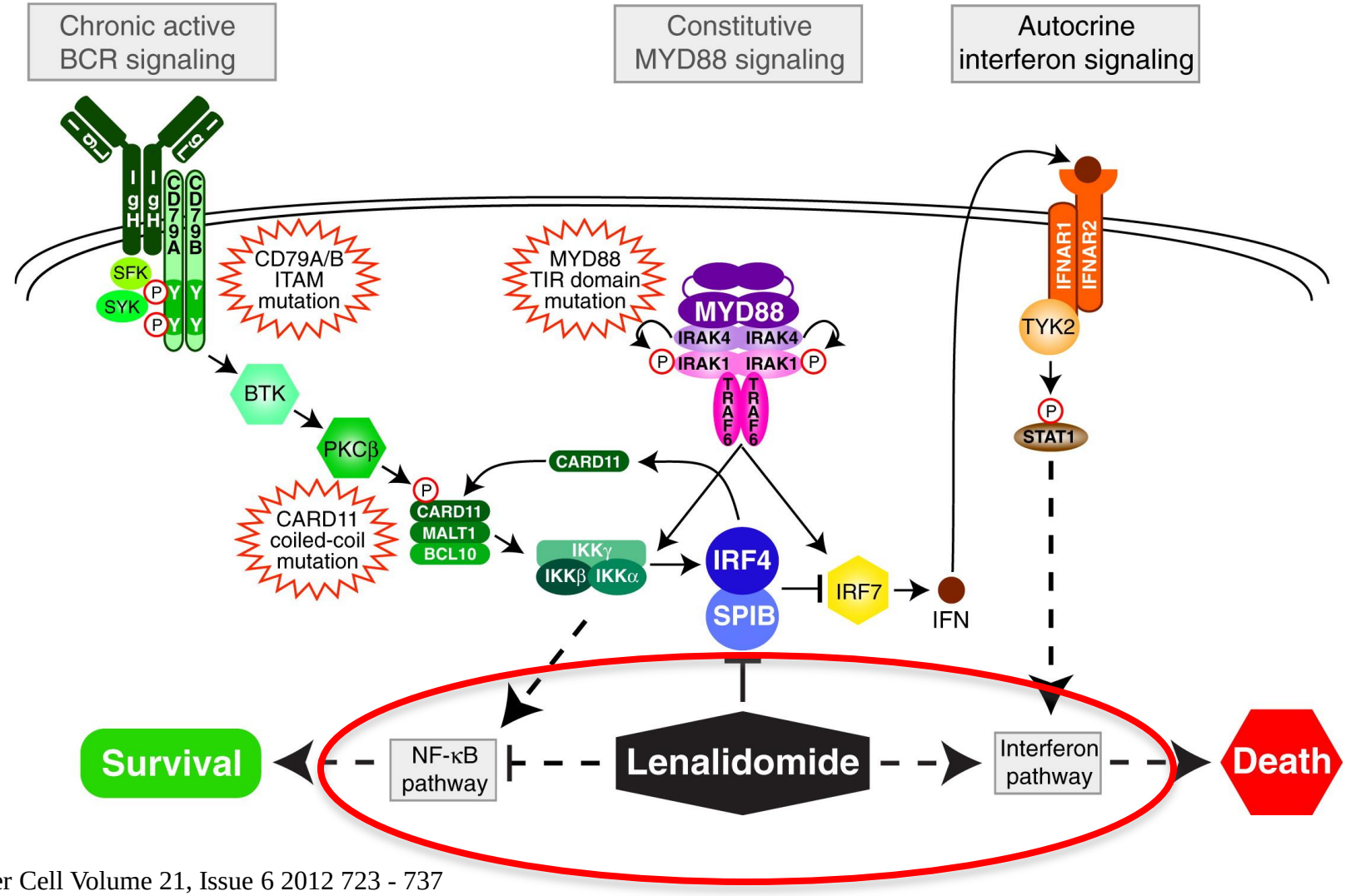
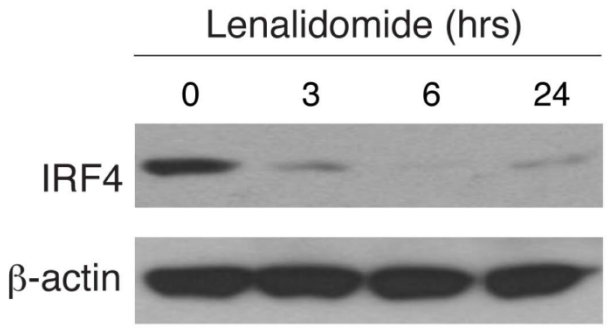
Targeting BCR and MYD88 Signaling in DLBCL

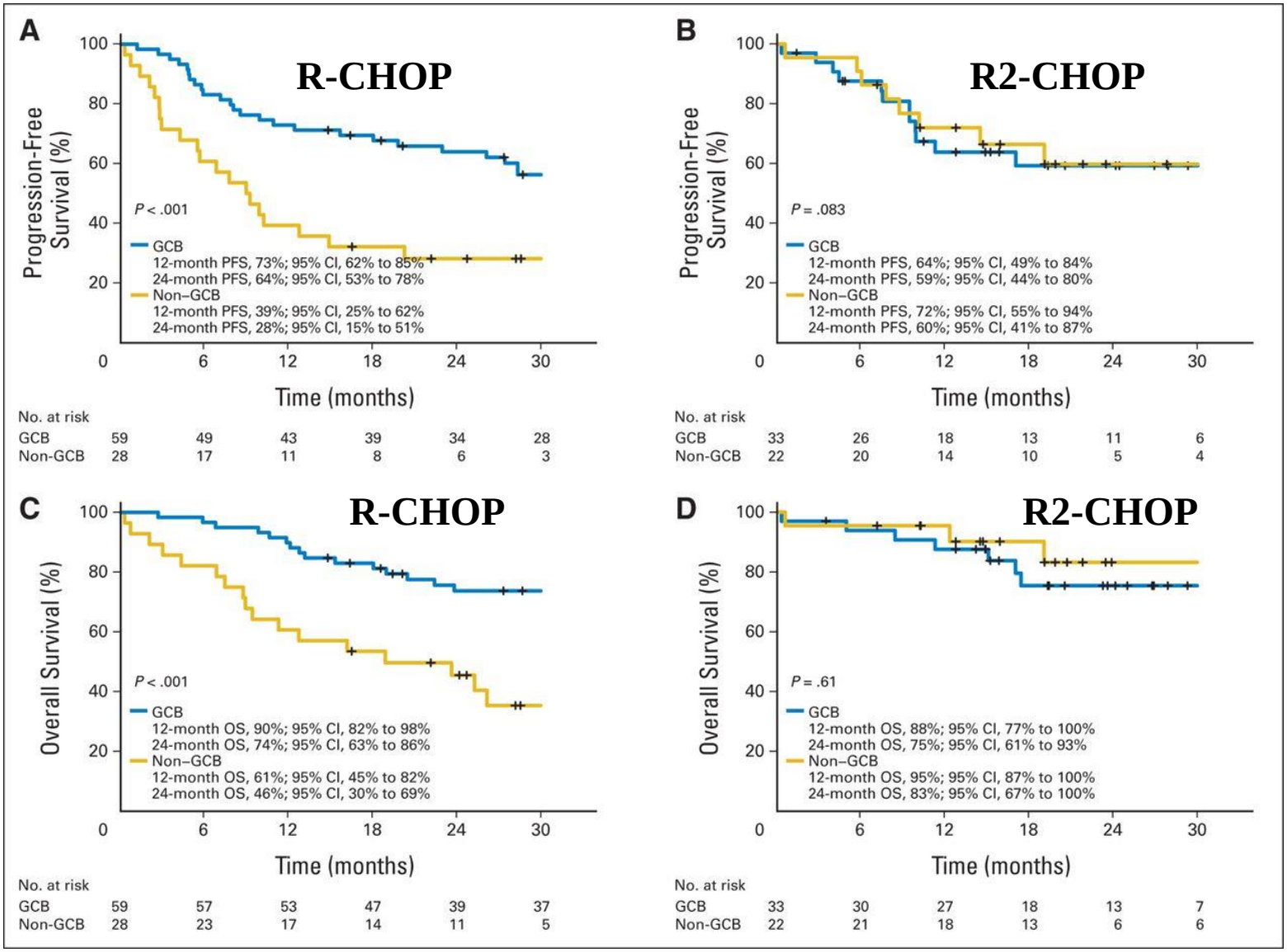


Cancer Cell Volume 21, Issue 6 2012 723 - 737

Lenalidomide Kills ABC DLBCL Cells by Antagonizing IRF4

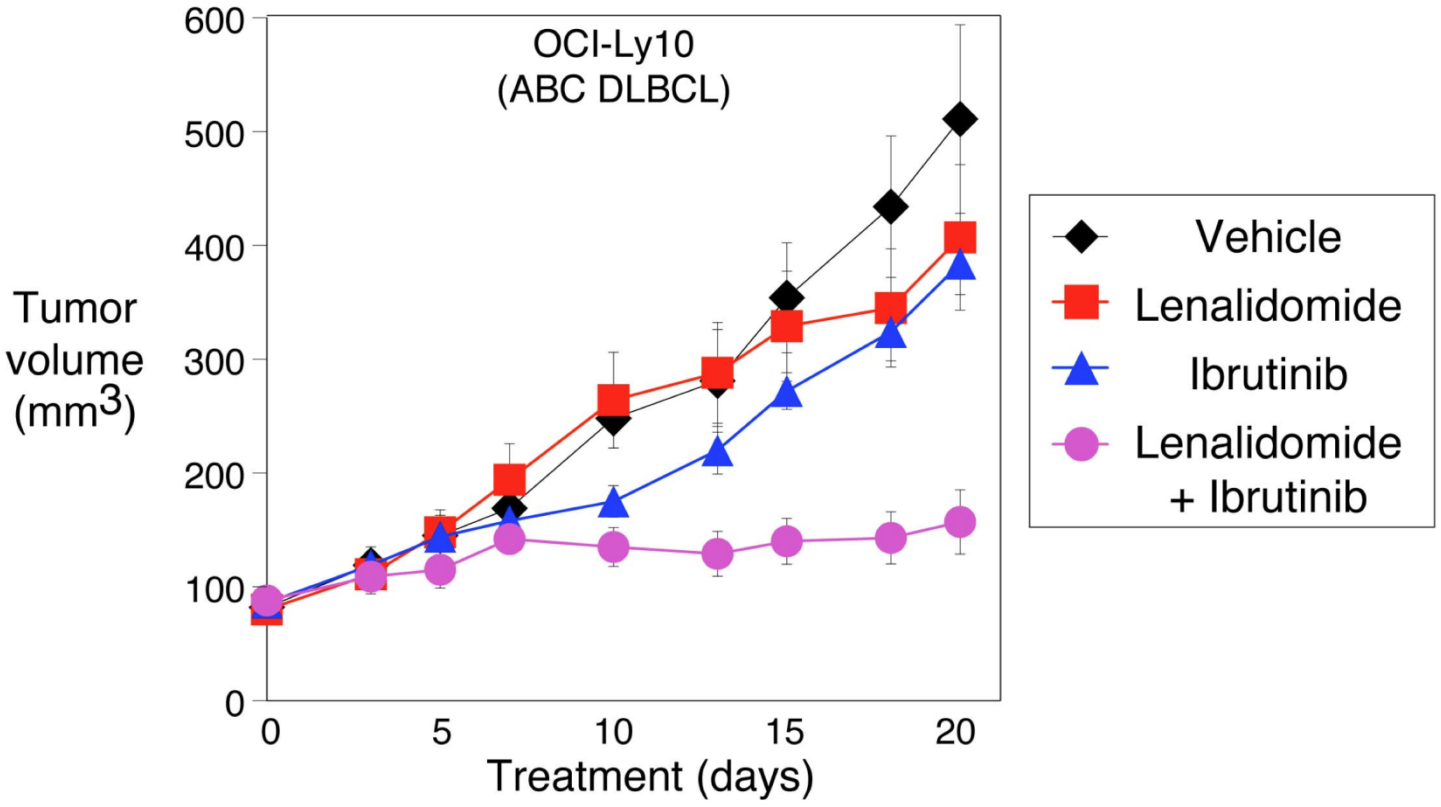


R2CHOP in Untreated DLBCL compared to R-CHOP



Grzegorz S. Nowakowski et al. JCO 2015;33:251-257

Lenalidomide Synergizes With Ibrutinib in a Xenograft Model of ABC DLBCL



Phase 2 Clinical Trial of Ibrutinib plus Lenalidomide With Dose-adjusted EPOCH-R Chemotherapy

Ibrutinib and Lenalidomide With Dose Adjusted EPOCH-R in Subjects With Relapsed/Refractory Diffuse Large B-cell Lymphoma

This study is currently recruiting participants. (see Contacts and Locations)

Verified August 2014 by Pharmacyclics

Sponsor:
Pharmacyclics

Collaborator:
Celgene Corporation

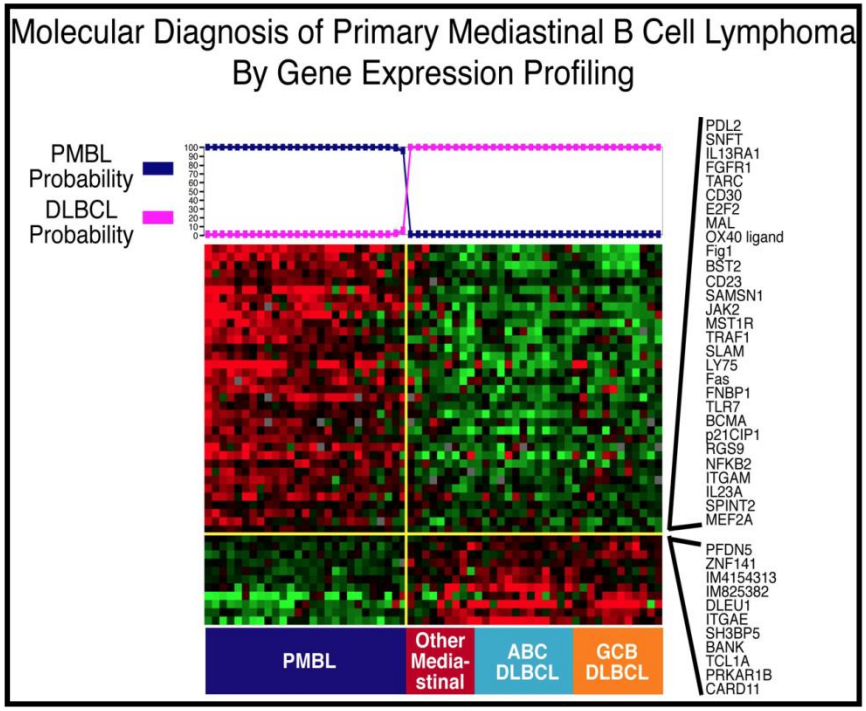
Information provided by (Responsible Party):
Pharmacyclics

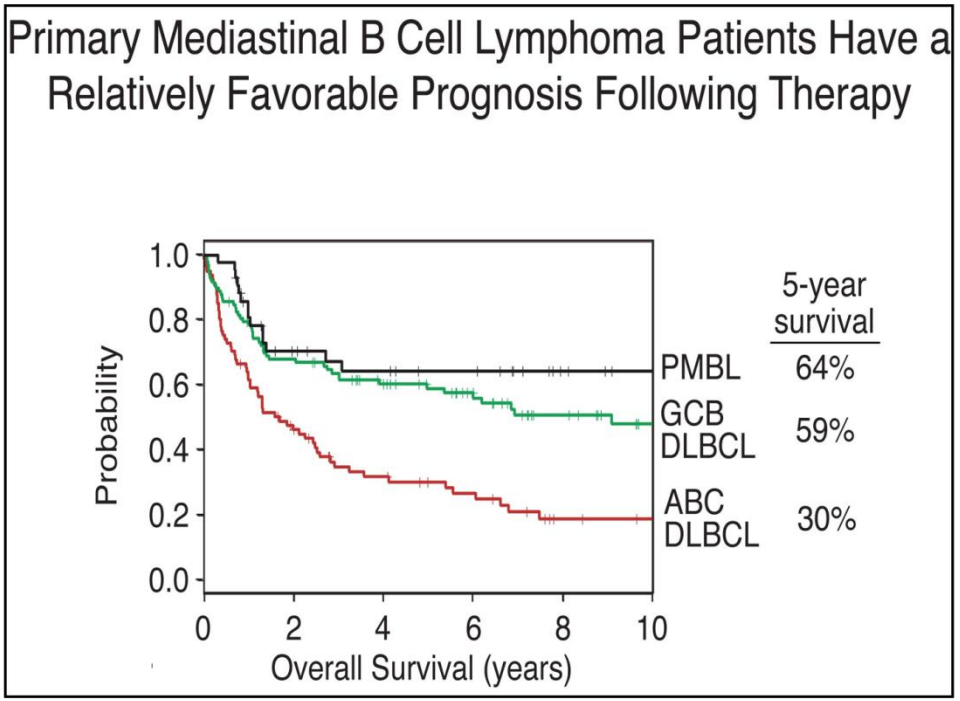
ClinicalTrials.gov Identifier:
NCT02142049

First received: May 12, 2014
Last updated: August 18, 2014
Last verified: August 2014
History of Changes

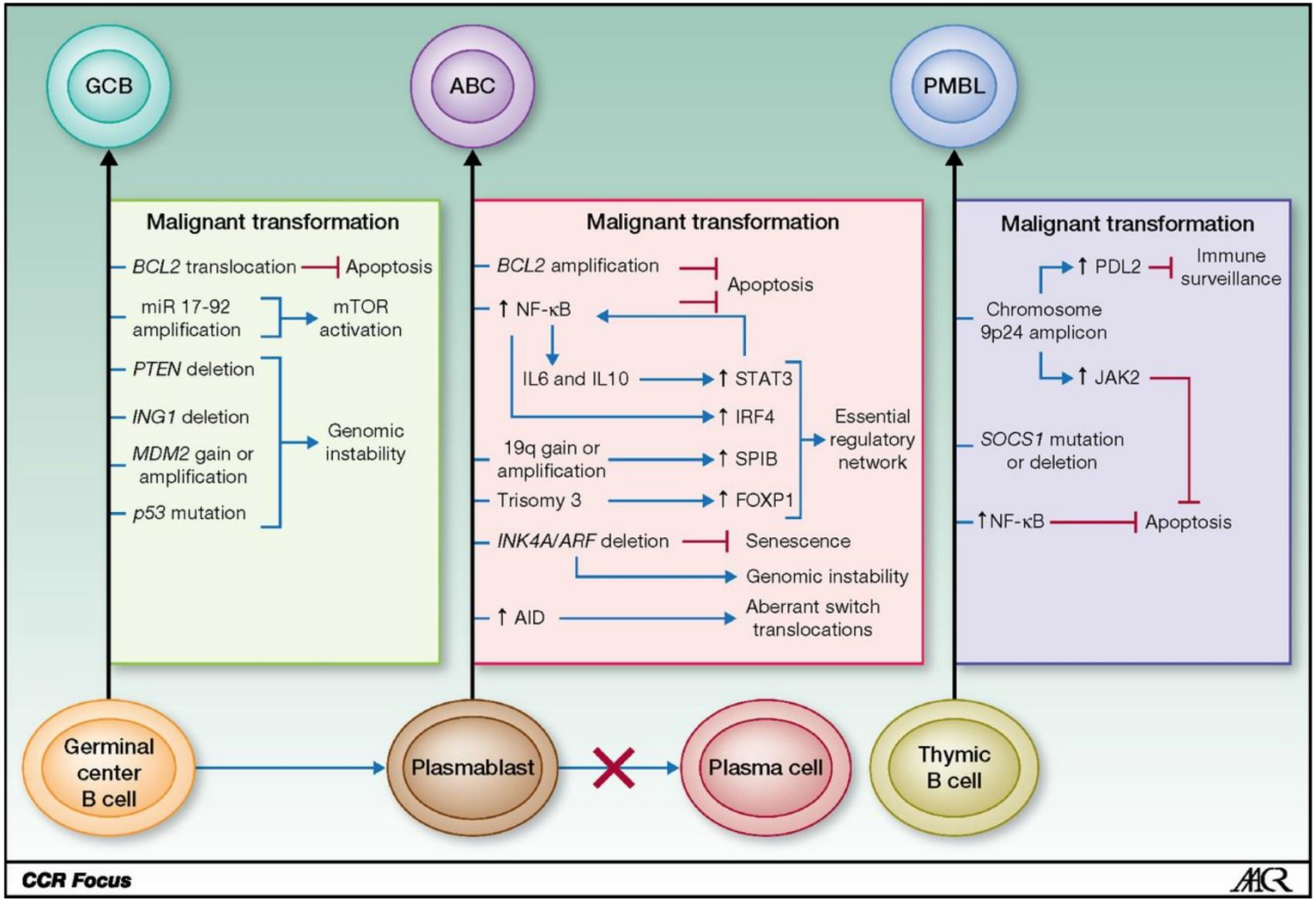
Primary Mediastinal B-cell Lymphomas

Distinct Subtype of diffuse large B-cell lymphoma (DLBCL)





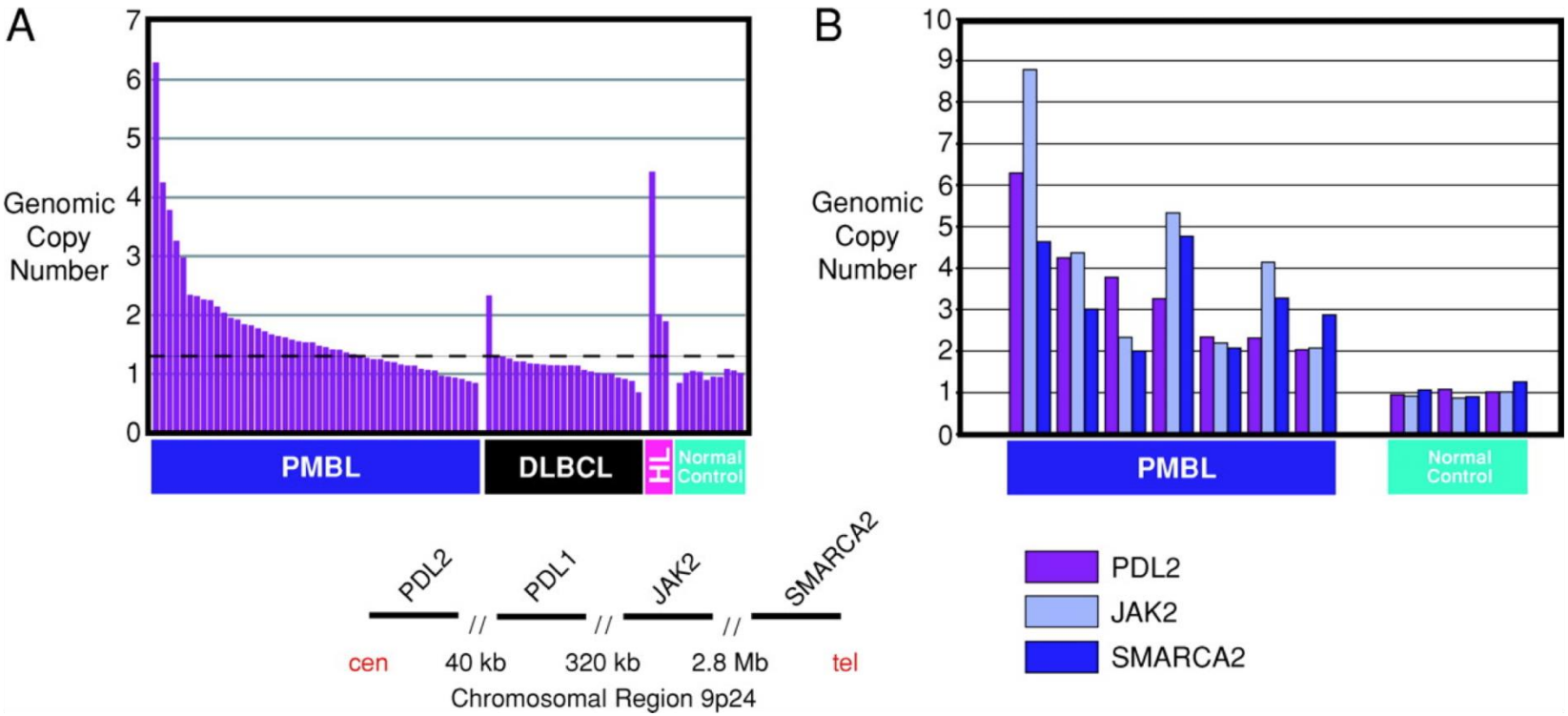
Targeting Primary Mediastinal B-cell Lymphoma



Nivolumab
Pembrolizumab

Kieron Dunleavy et al. Clin Cancer Res 2014;20:5182-5193

Primary Mediastinal B-cell Lymphomas



Rosenwald et al. JEM vol. 198 no. 6 851-862

Immunochemotherapy + X

- Targeting GCB DLBCL
  - Lenalidomide (?) + R-CHOP
  - Everolimus + R-CHOP
  - Venetoclax + R-CHOP
- Targeting ABC DLBCL
  - Bortezomib + R-CHOP
  - Ibrutinib + R-CHOP
  - Lenalidomide + R-CHOP
  - Ibrutinib + Lenalidomide + DA-EPOCH-R

Immunochemotherapy + X

- Targeting PMBL/Mediastinal Gray Zone
  - Brentuximab vedotin + R-CHOP
  - Nivolumab + DA-EPOCH-R or R-CHOP