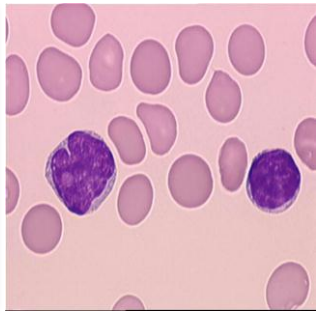
*Molecular targets in malignant lymphoma * ESMO 2012*

mTOR inhibitors and beyond: Targeting a critical pathway



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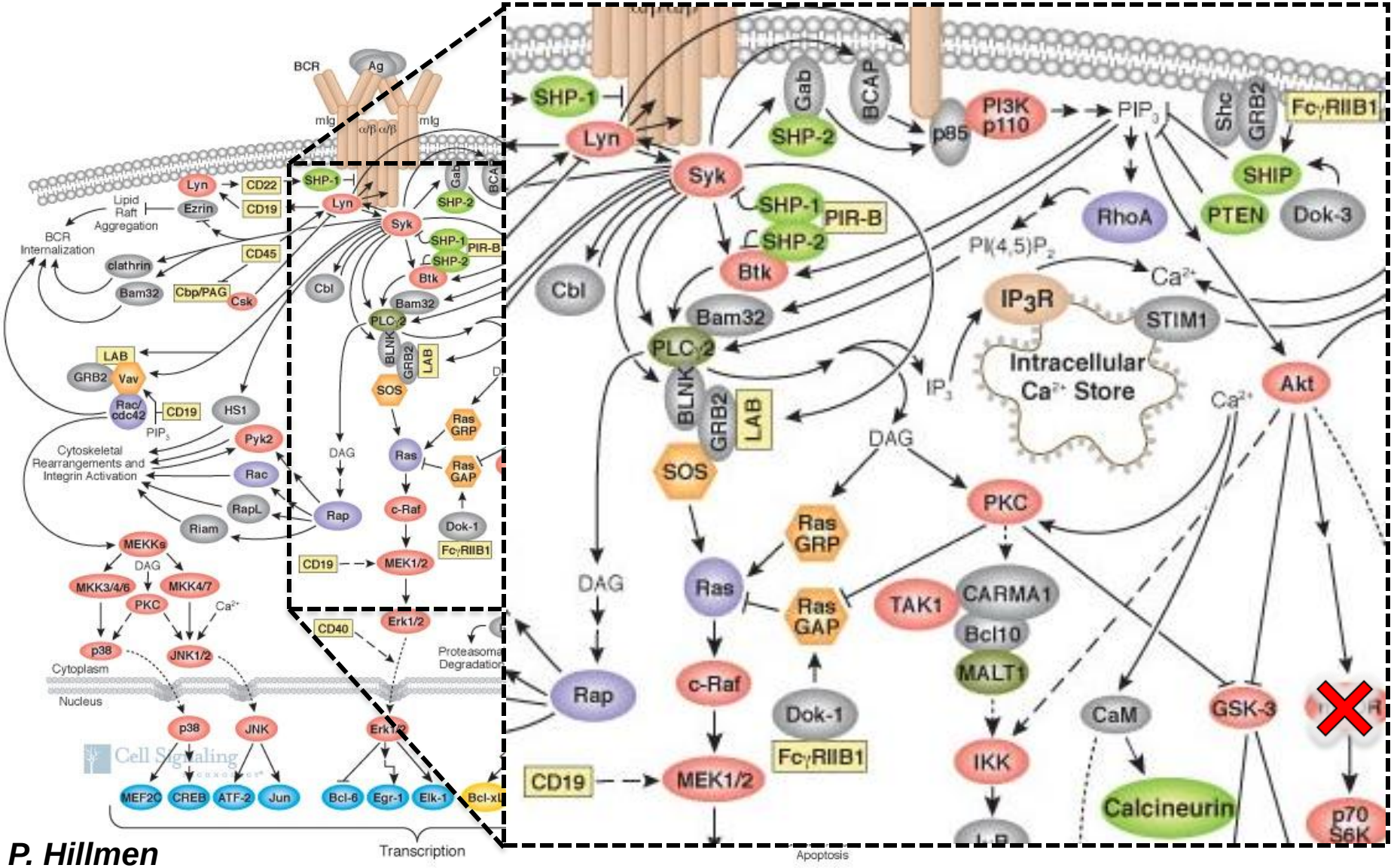
Disclosures

Research Support	**Celgene, Janssen, Mundipharma, Pfizer, Roche**
Employee	**-**
Major Stockholder	**-**
Speakers Bureau	**Celgene, Janssen, Pfizer, Roche**
Honoraria	**-**
Scientific Advisory Board	**Celgene, Janssen, Pfizer, Roche**

mTOR and beyond

Targeting a critical pathway

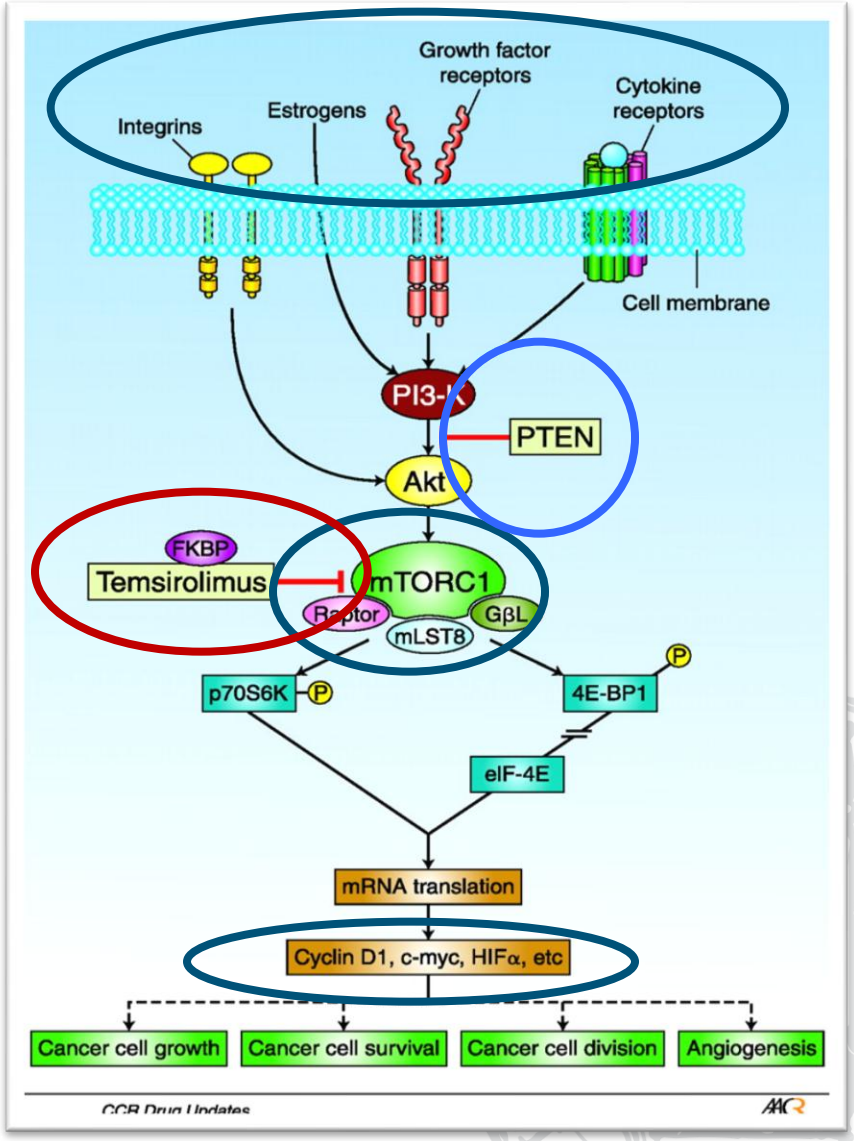


P. Hillmen

mTOR-signal pathway in lymphoma

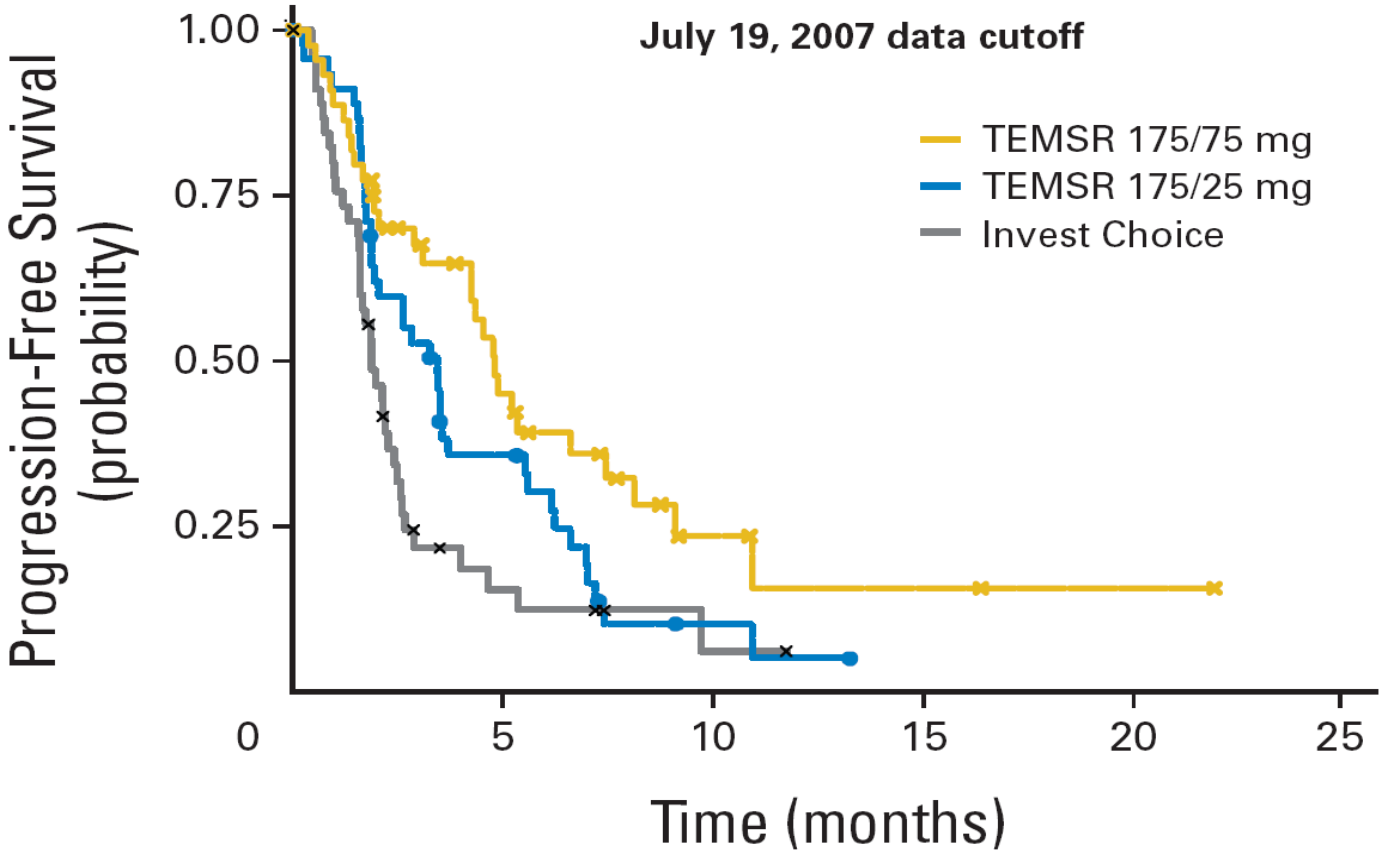
- Highly conserved Ser/Thr-kinase
  - mTORC1 + Raptor
    - Nutrition sensitive signal pathway
      - PI3K/Akt signal pathway
      - normal function
      - Cell growth
      - translation initiation
      - Cell motility
      - adaptation to cellular stress
      - neoangiogenesis
  - mTORC2 + Rictor

    Function:
    - reorganisation of cytoskeleton



Rini, Clin Cancer Res 2008

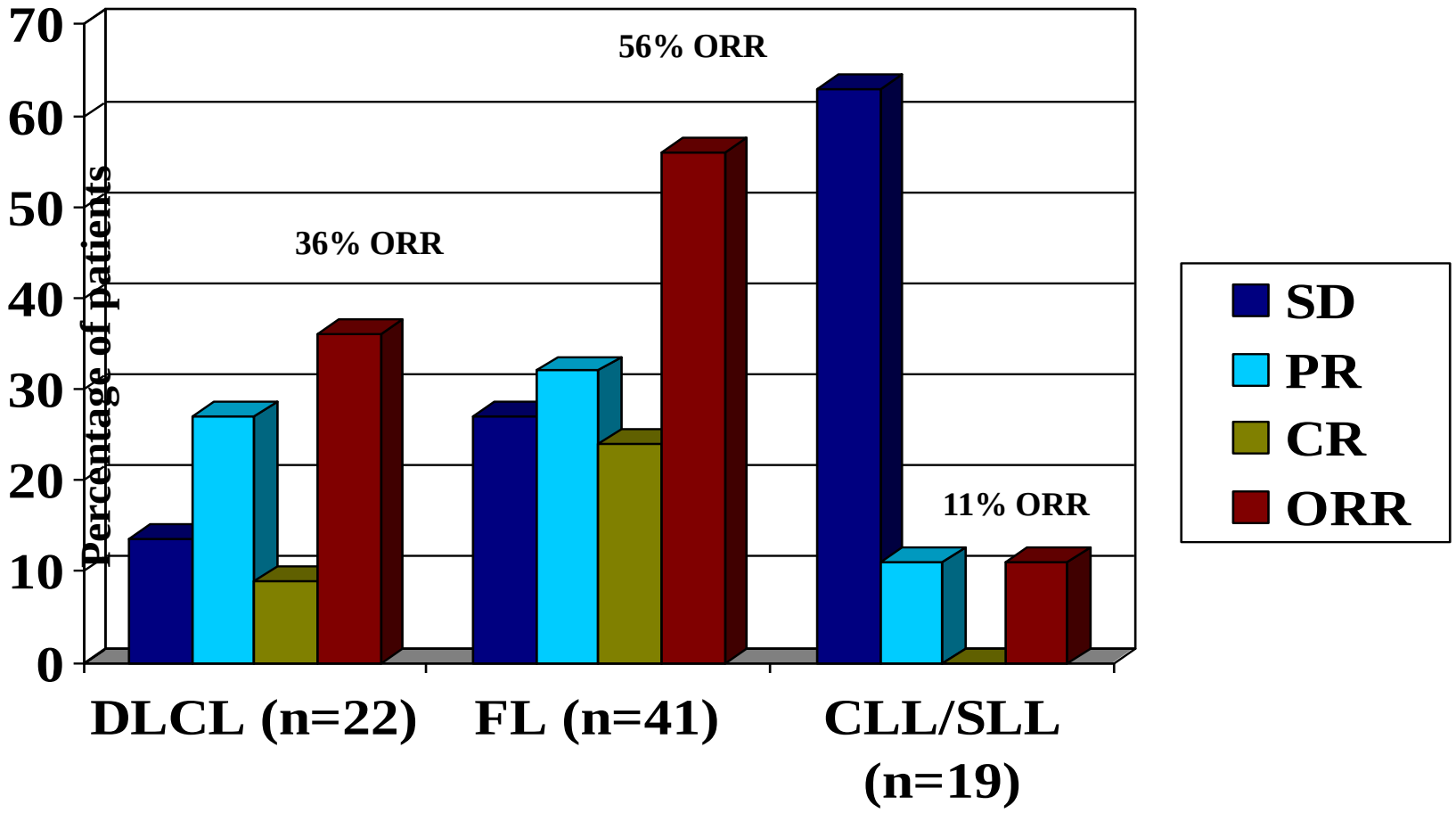
Progression-free survival (ITT) in MCL



No. of patients at risk						
TEMSR 175/75 mg	54	16	4	2	1	0
TEMSR 175/25 mg	54	14	2	0	0	0
Invest Choice	54	5	1	0	0	0

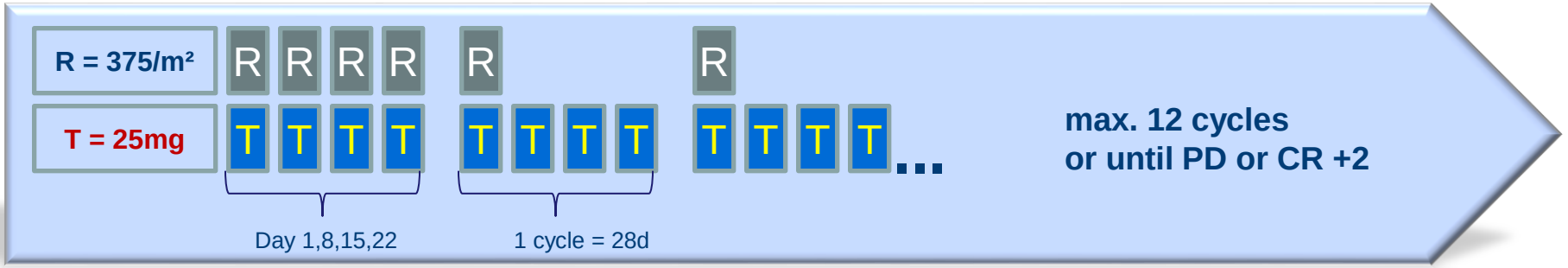
Hess, JCO 2009

Response by Histology



Smith, JCO 2010

Temsirolimus with Rituximab in MCL



	Rituximab-sensitive patients (n=48)	Rituximab–refractory patients (n=21)	Total (n=69)*
Complete response + partial response	30 (63%; 47–76)	11 (52%; 30–74)	41 (59%)
Complete response	8 (17%; 8–30)	5 (24%; 8–47)	13 (19%)
Partial response	22 (46%; 31–61)	6 (29%; 11–52)	28 (41%)

Data are number (%; 95% CI) or number (%). *95% CIs are not appropriate statistically for the whole group because patients in the two cohorts were analysed separately and with different designs.

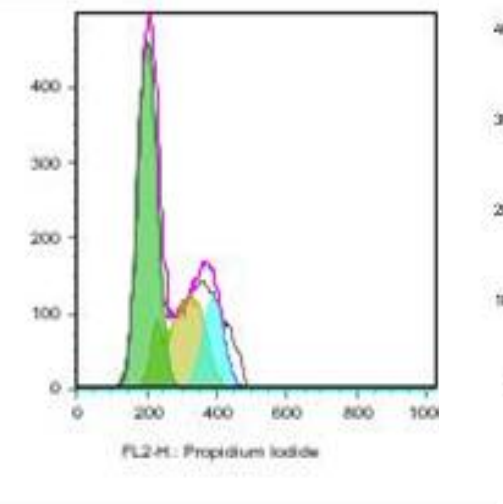
Table 2: **Response rates**

Ansell, Lancet Oncology, 2011

In vitro combination Temsirolimus – chemotherapy

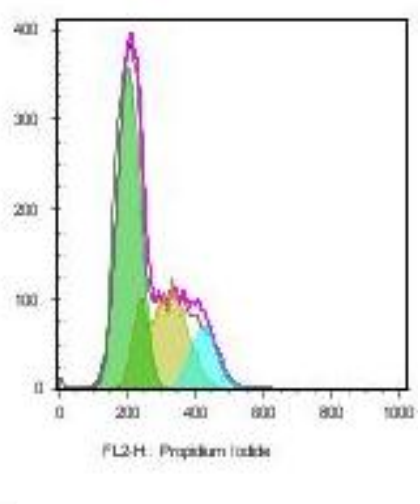
Cell cycle dysregulation

control



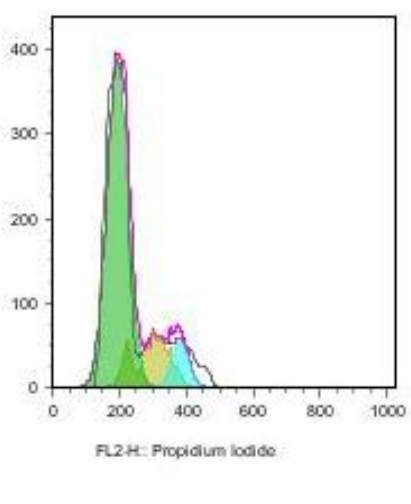
G1	G2/M
55,7%	14,4%

Cisplatinum



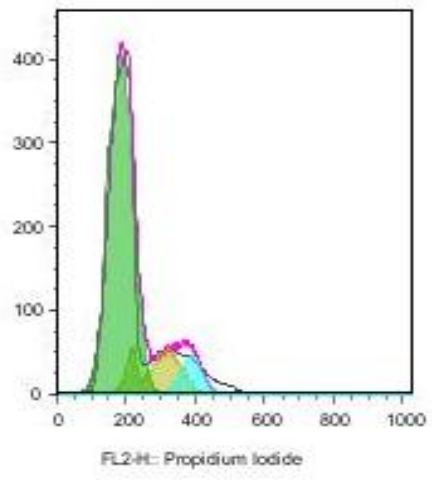
G1	G2/M
55,2%	13,2%

Temsirolimus



G1	G2/M
75,4%	5,8%

Temsirolimus + Cisplatinum



G1	G2/M
74,6%	6,6%

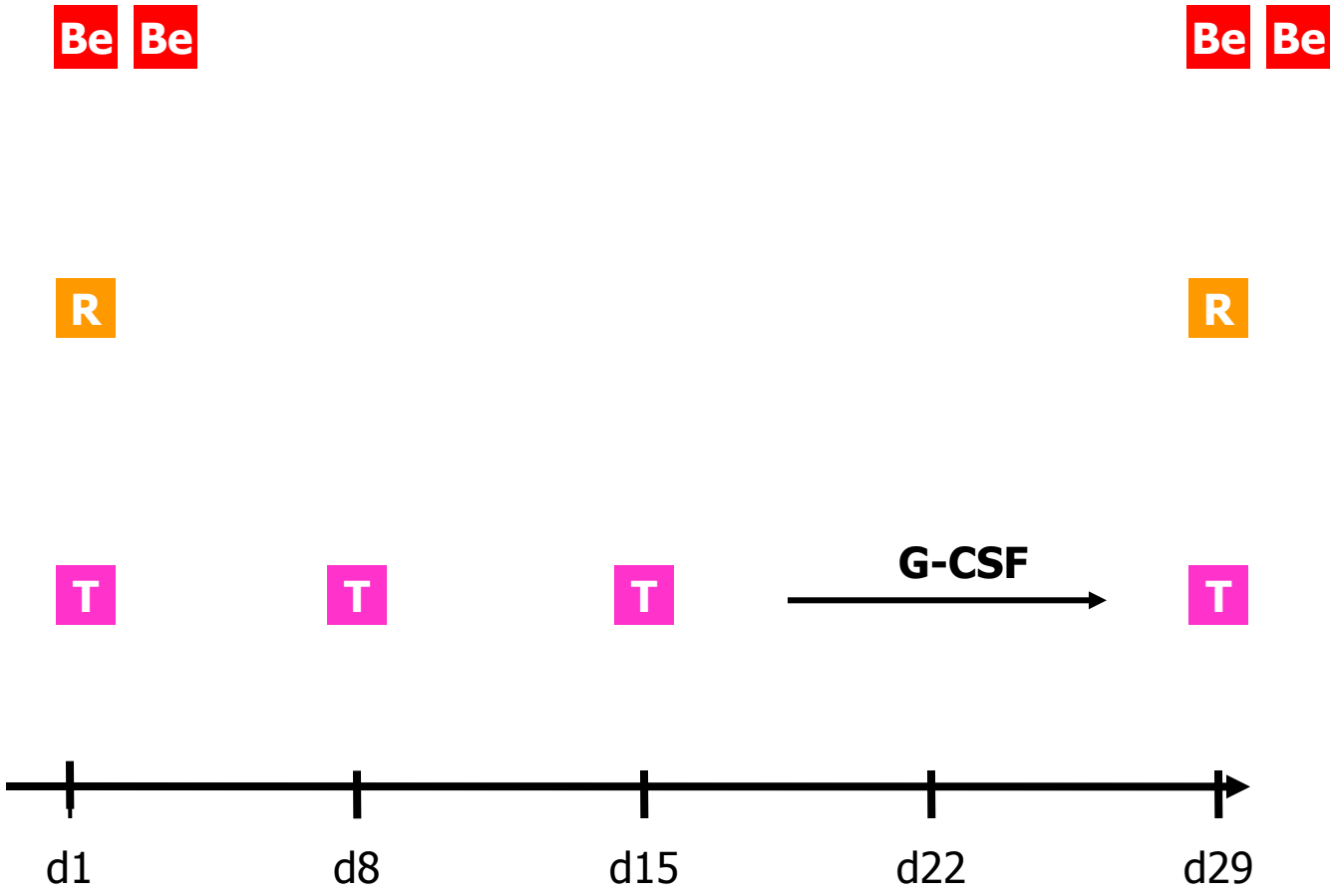
Zoellner, DGHO 2011

BeRT: Benda/Rituximab/Temsirolimus

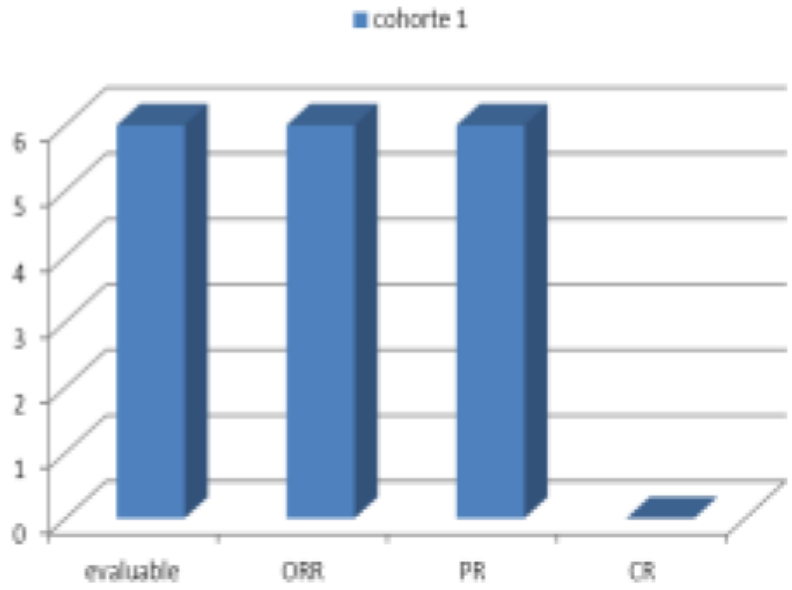
Bendamustin
90 mg/m²

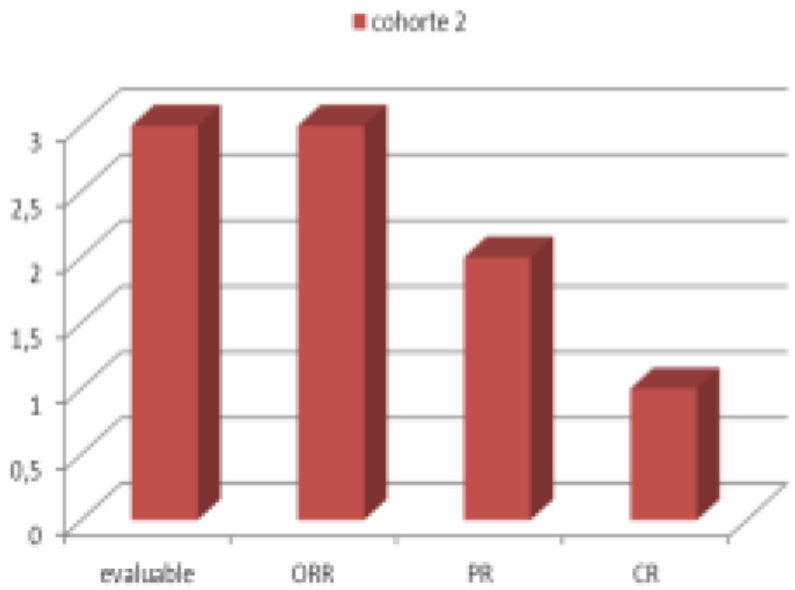
Rituximab
375 mg/m²

Temsirolimus
25/50/75 mg



BeRT: Benda/Rituximab/Temsirolimus
Response rate in MCL

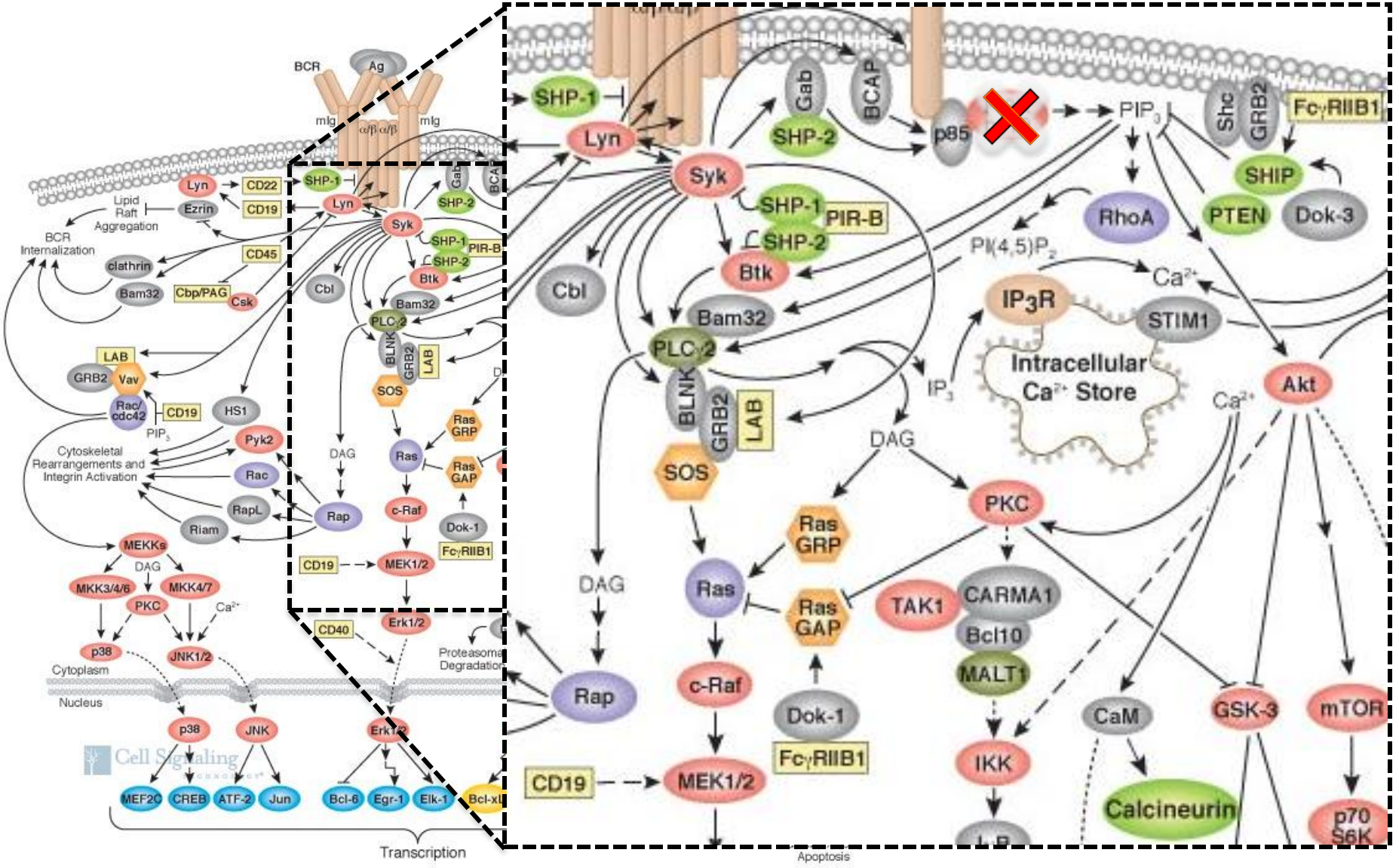




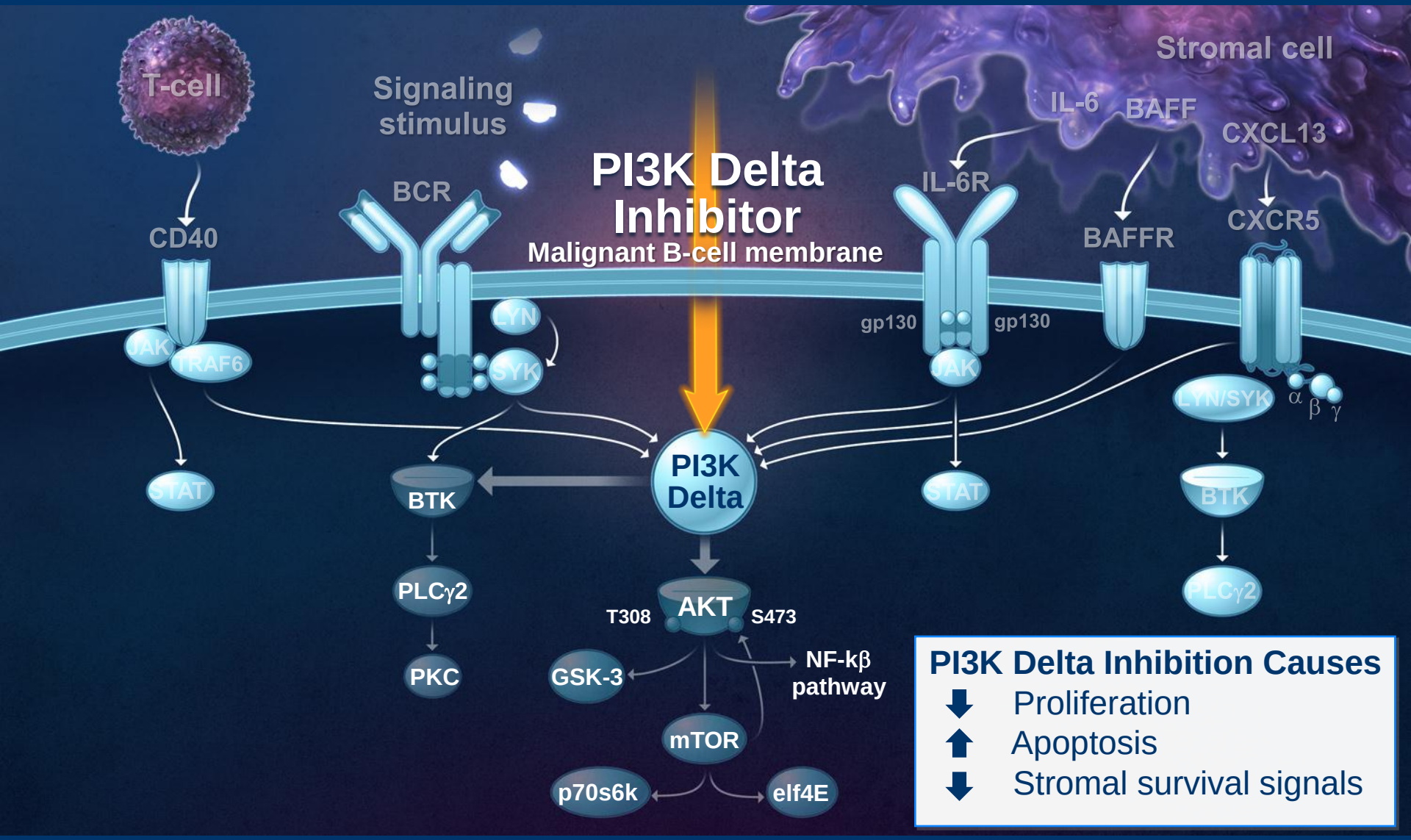
Hess, ASH 2011

mTOR and beyond

Targeting a critical pathway



PI3K Delta Inhibition Offers a Novel Targeted Therapeutic Approach in B-Cell Malignancies



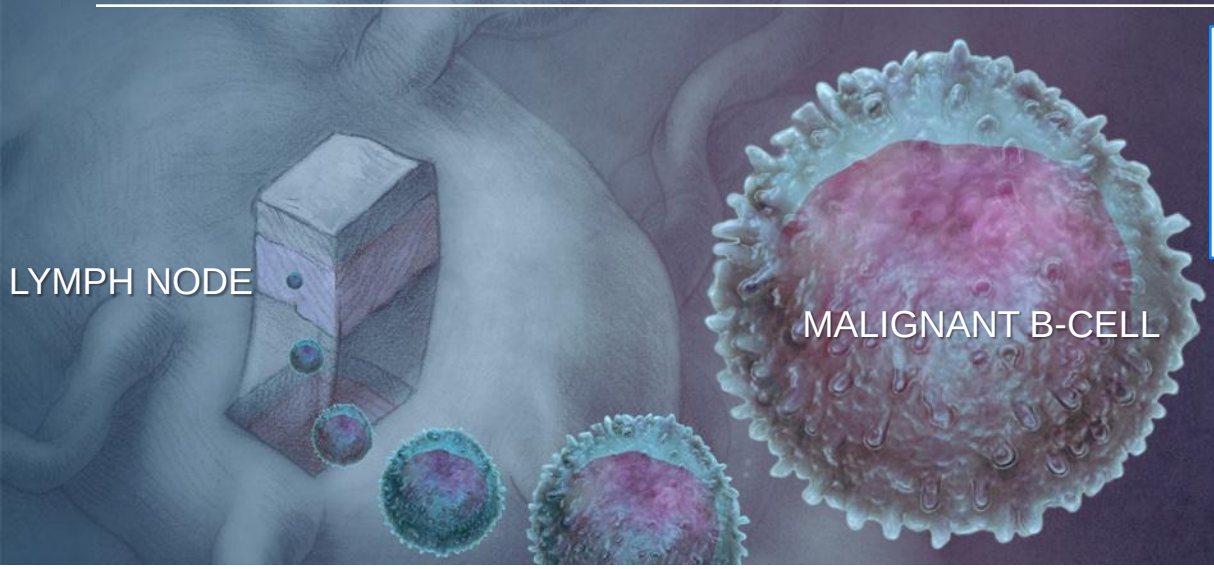
PI3K Delta Inhibition Causes

- ⬇ Proliferation
- ⬆ Apoptosis
- ⬇ Stromal survival signals

Lannutti, Blood, 2011

PI3K promotes survival and cell growth

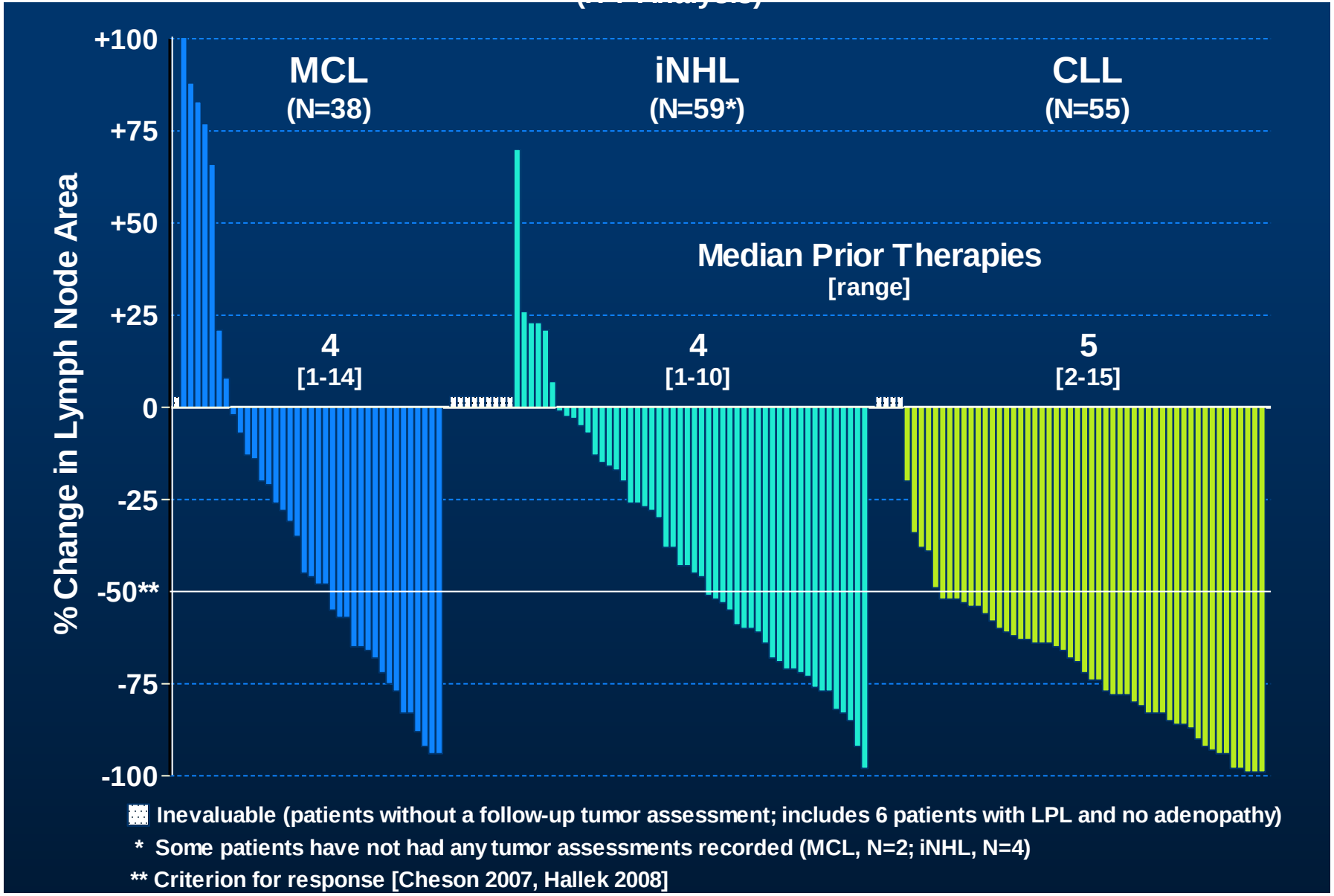
Class I PI3K Isoform	Cellular Expression	Primary Physiological Role
Alpha (α)	Broad	Insulin signaling and angiogenesis
Beta (β)	Broad	Platelet function
Gamma (γ)	Leukocytes	Neutrophil and T-cell function
Delta (δ)	Leukocytes	B-cell signaling, development and survival



PI3K Delta Pathway Drives B-Cell Malignancies

Okkenhaug Nat Rev Immunol 2003

GS-1101 in relapsed MCL, iNHL, and CLL

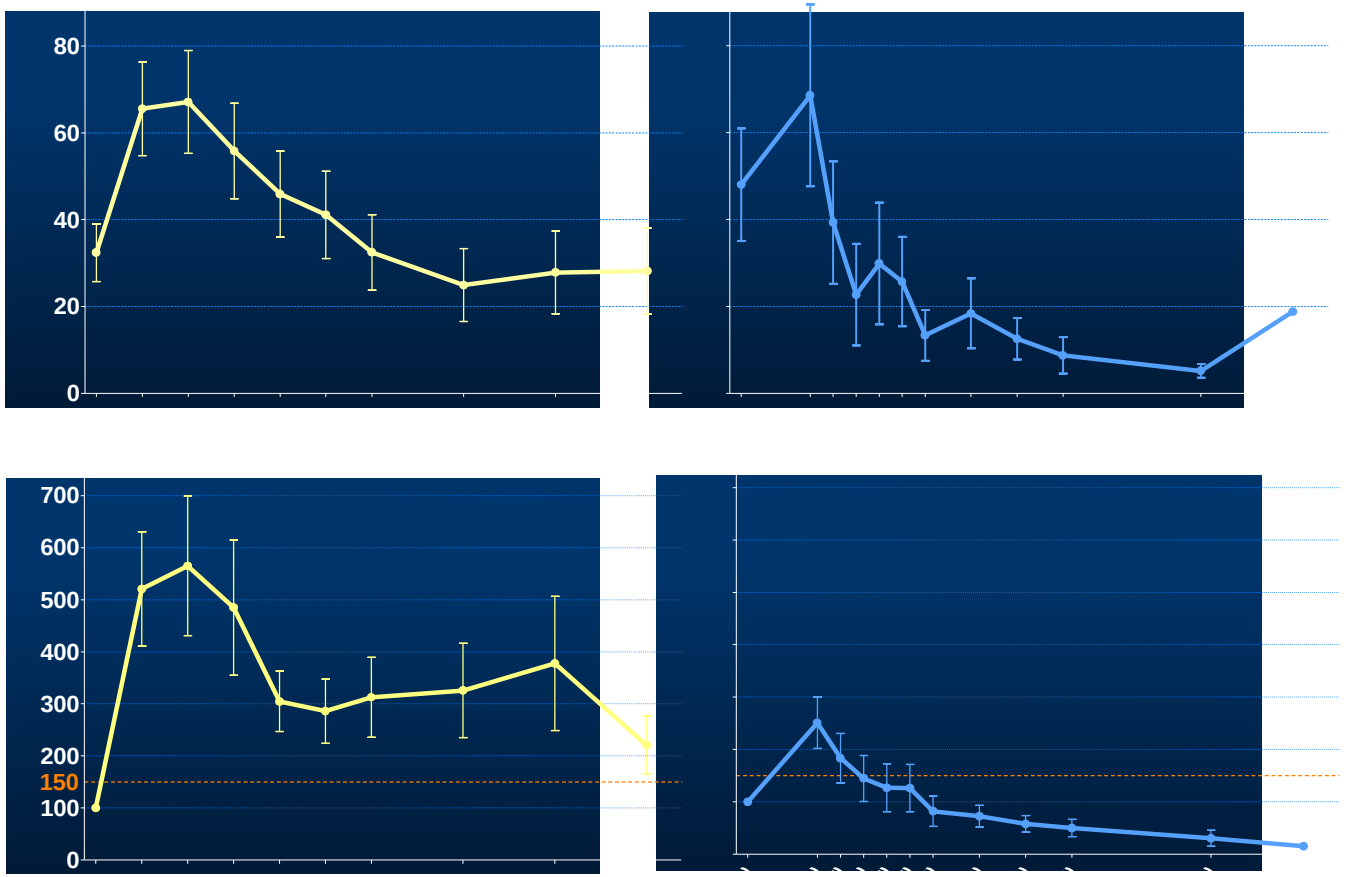


Mono- and combination therapy in CLL

GS-1101: Leukocyte values

GS-1101 Mono

GS-1101 + O



Cycle (N)

Furman, ASCO 2012

GS-1101 in r/r CLL
Toxicity

Grade ≥3 Adverse Events % (n)	Mono GS-1101	Combo GS-1101+O	All
	(N=55)	(N=21)	(N=76)
Anemia	7% (4)	5% (1)	7% (5)
Neutropenia	18% (10)	19% (4)	18% (14)
Febrile neutropenia	7% (4)	5% (1)	7% (5)
Neutropenic sepsis	–	5% (1)	1% (1)
Thrombocytopenia	5% (3)	5% (1)	5% (4)
ALT/AST elevated	5% (3)	14% (3)	8% (6)
ARDS	–	5% (1)	1% (1)
Colitis	–	5% (1)	1% (1)
Diarrhea	–	5% (1)	1% (1)
Endocrine disorder/hyperglycemia	–	10% (2)	3% (2)
Pneumonia/Pneumonitis	24% (13)	10% (2)	20% (15)
Rash/Infusion reaction	2% (1)	5% (1)	3% (2)

Furman, ASCO 2012

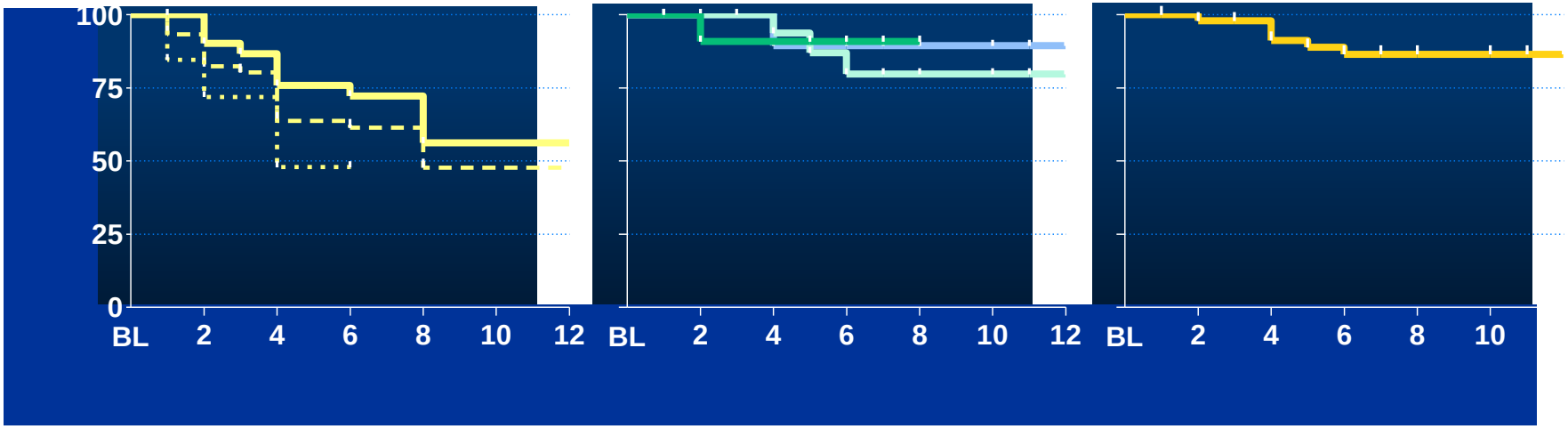
Mono- and combination therapy in NHL

GS-1101: Progression-free survival

GS-1101 Mono

GS-1101 + R (N=19)
GS-1101 + B (N=20)
GS-1101 + R + B (N=13)

GS-1101 Combination
(N=52)



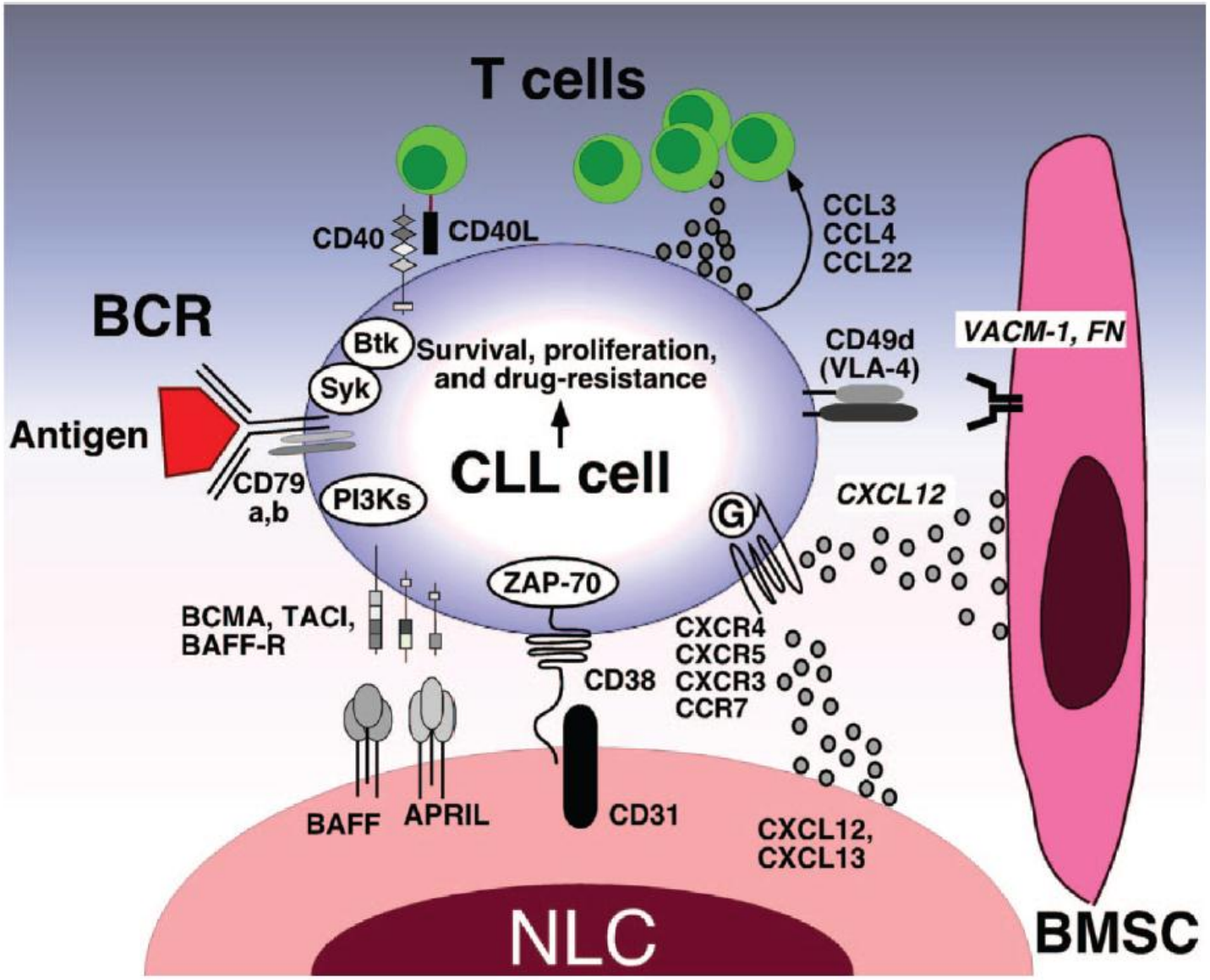
GS-1101 single agent:

- **≥100 mg BID (n=34)**
- **All (N=60)**
- **<100 mg BID (n=26)**

Leonard, ICML 2011

Mono- and combination therapy

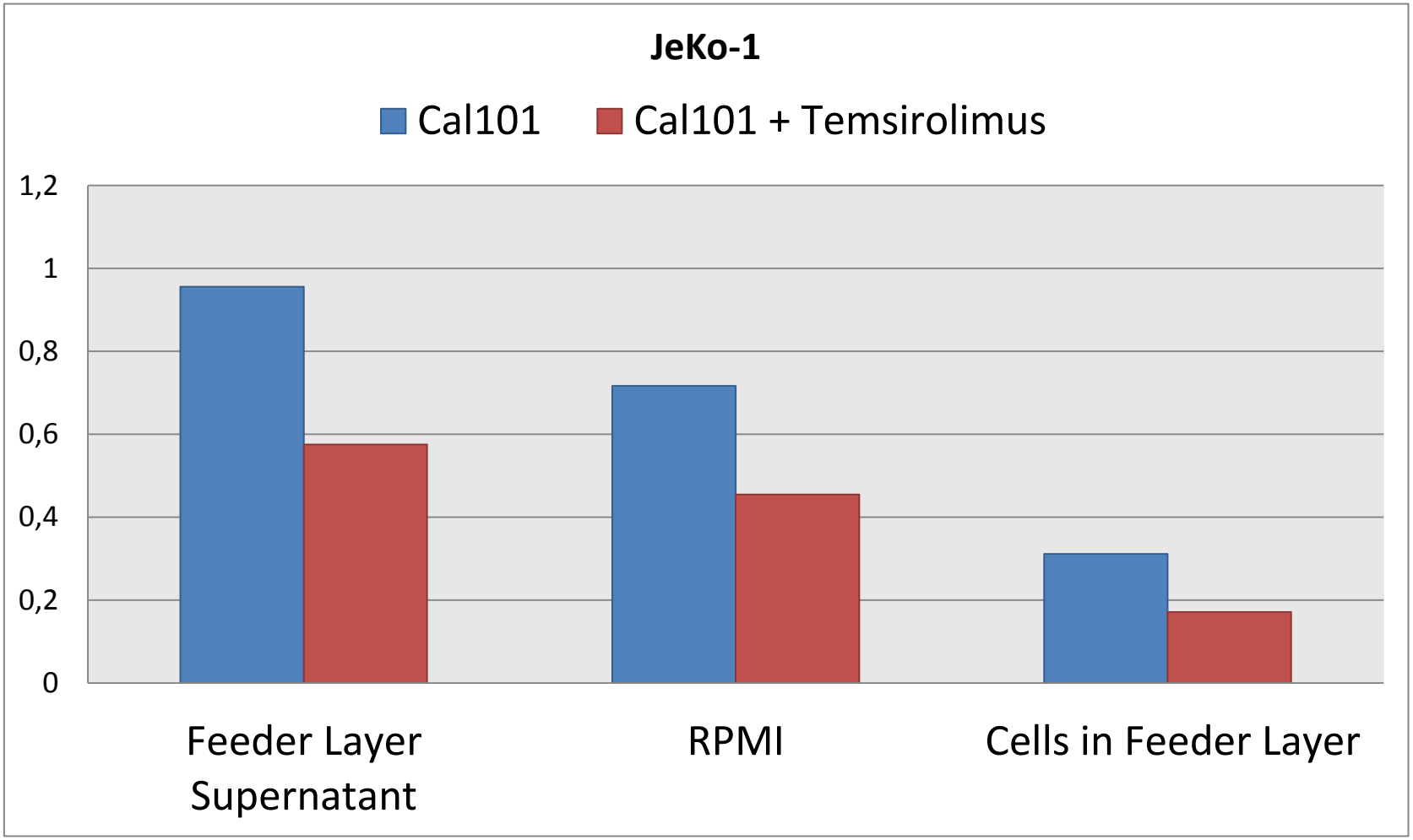
CLL and microenvironment



Burger, ASH Educational 2012

Mono- and combination therapy in DLCL

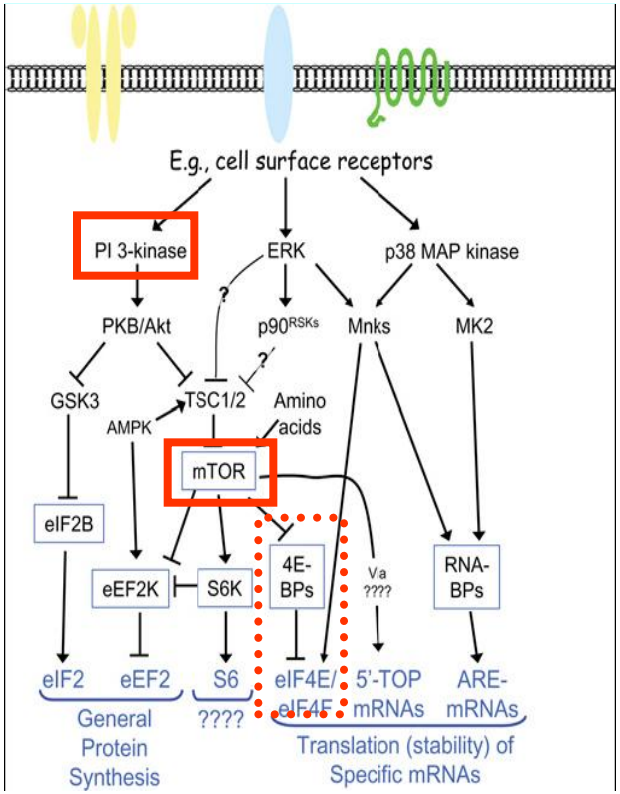
PI3K Inhibitor and microenvironment

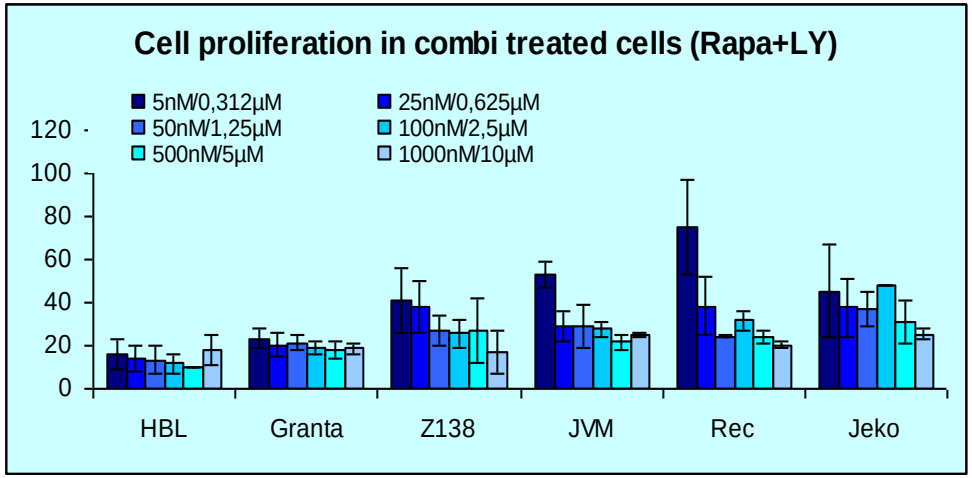


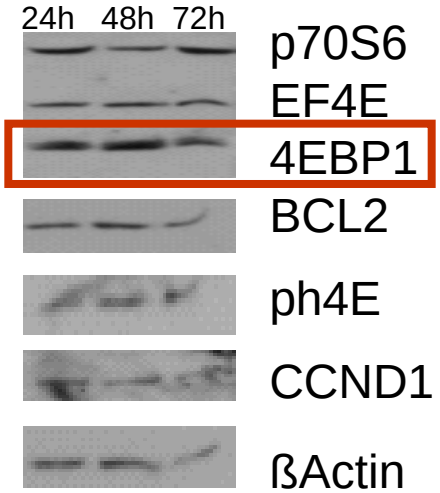
Zoellner, unpublished data

Synergismus of PI3K and mTOR inhibitors

Dephosphorylation of 4EBP1



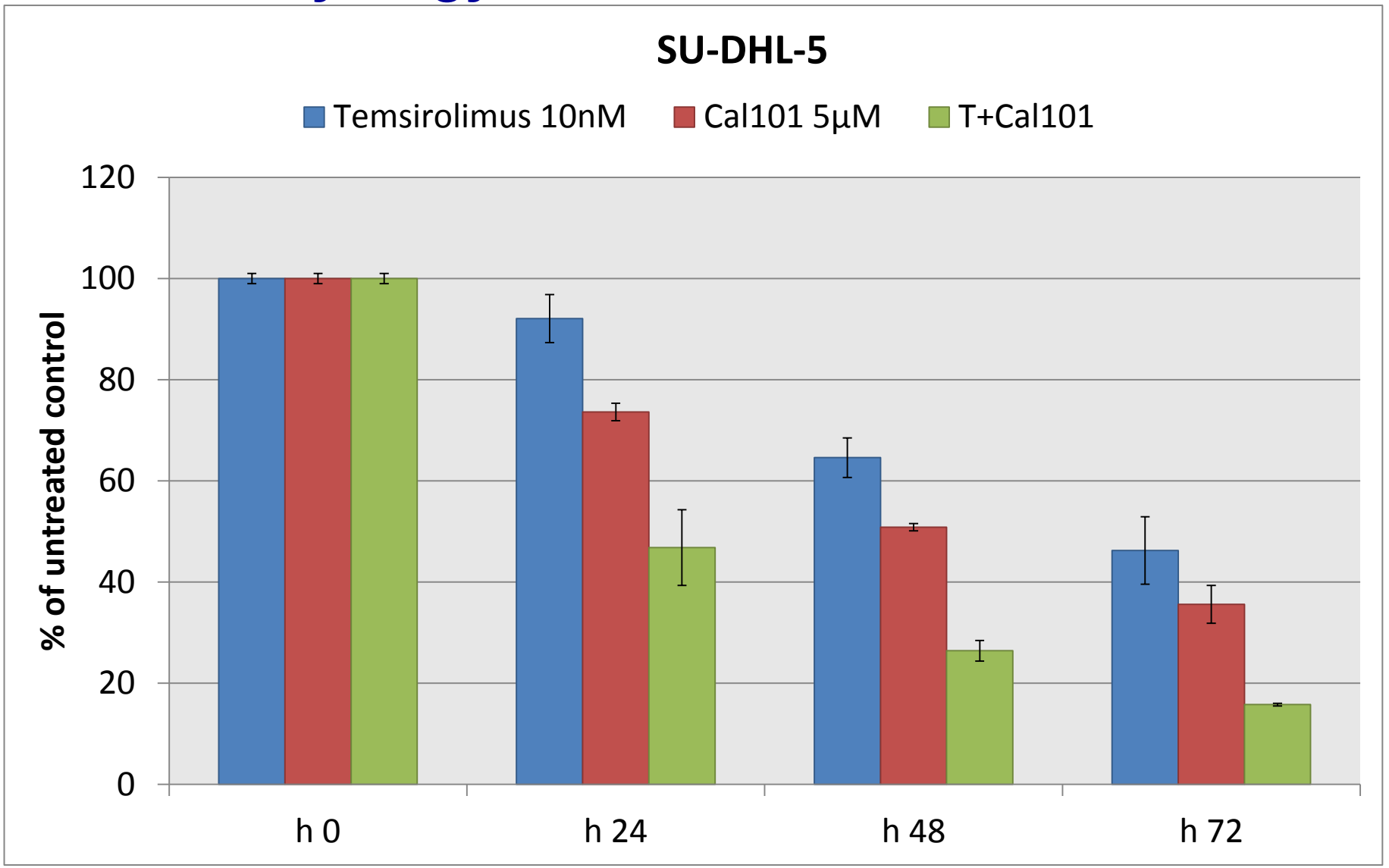




Hutter, ASH 2008;
Hutter, Leukemia 2012

B-cell receptor in GCB DLCL

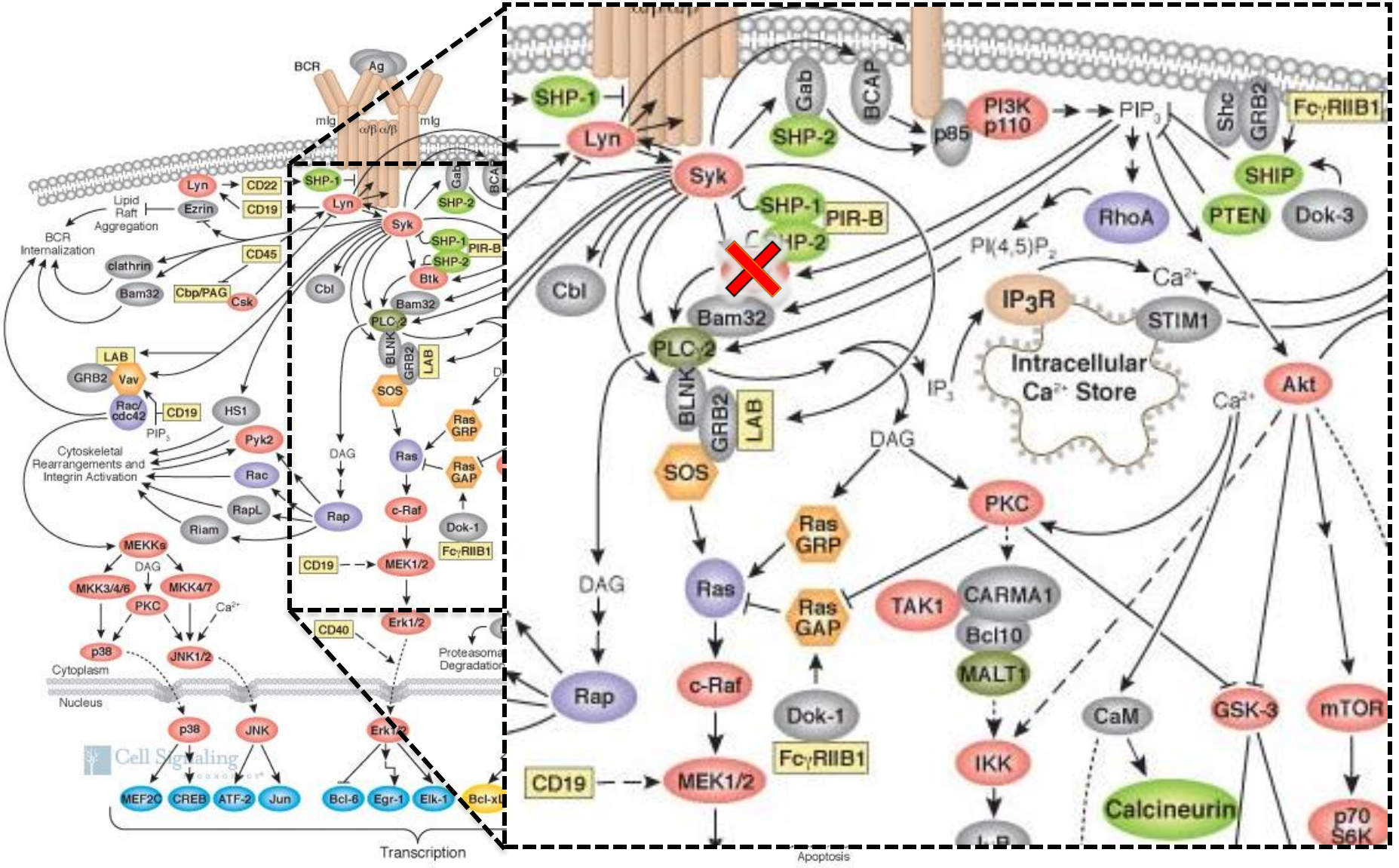
Synergy of mTOR and GS 1101



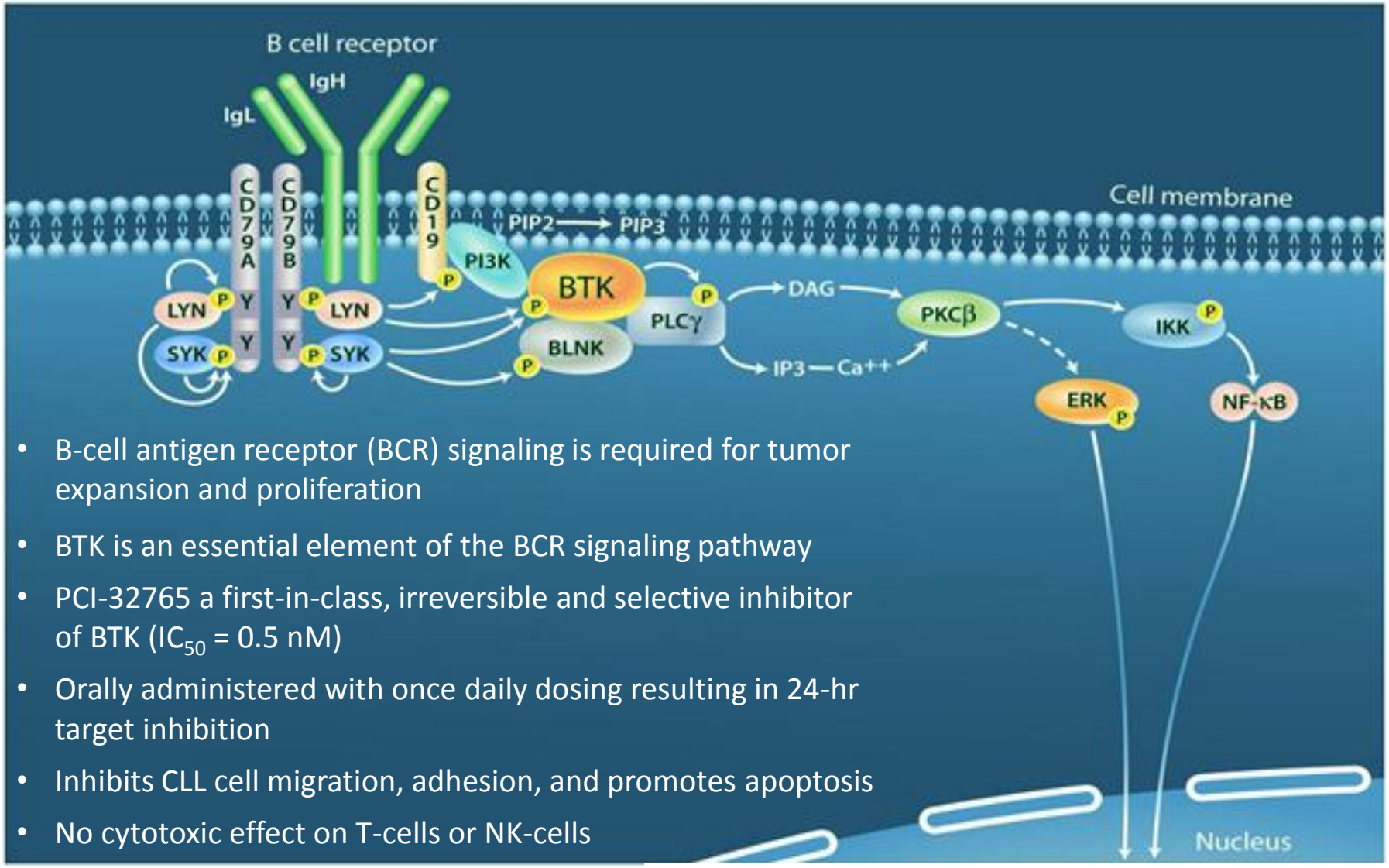
Zoellner, ASH 2012

mTOR and beyond

Targeting a critical pathway



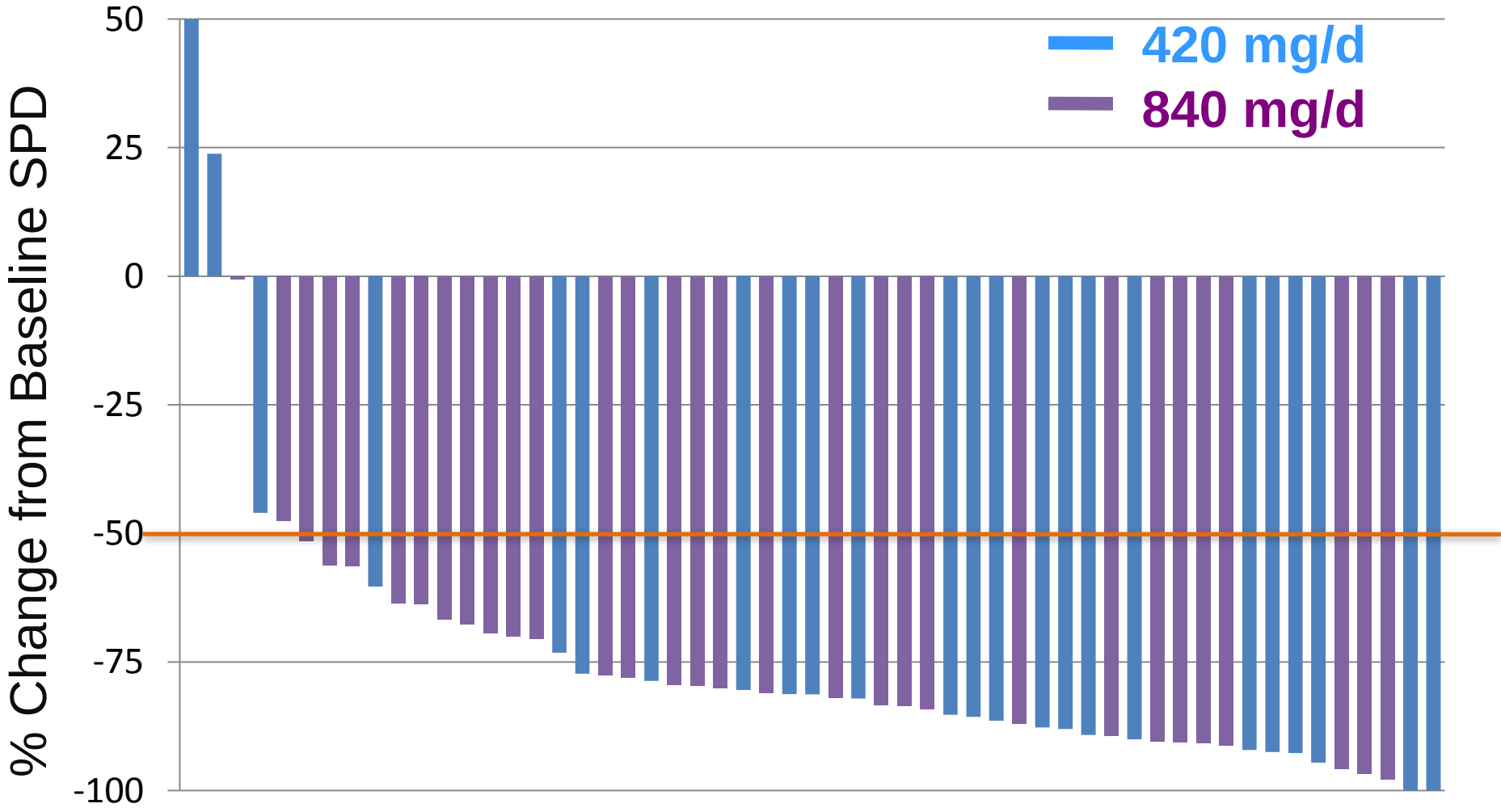
Bruton's Tyrosine Kinase (BTK)



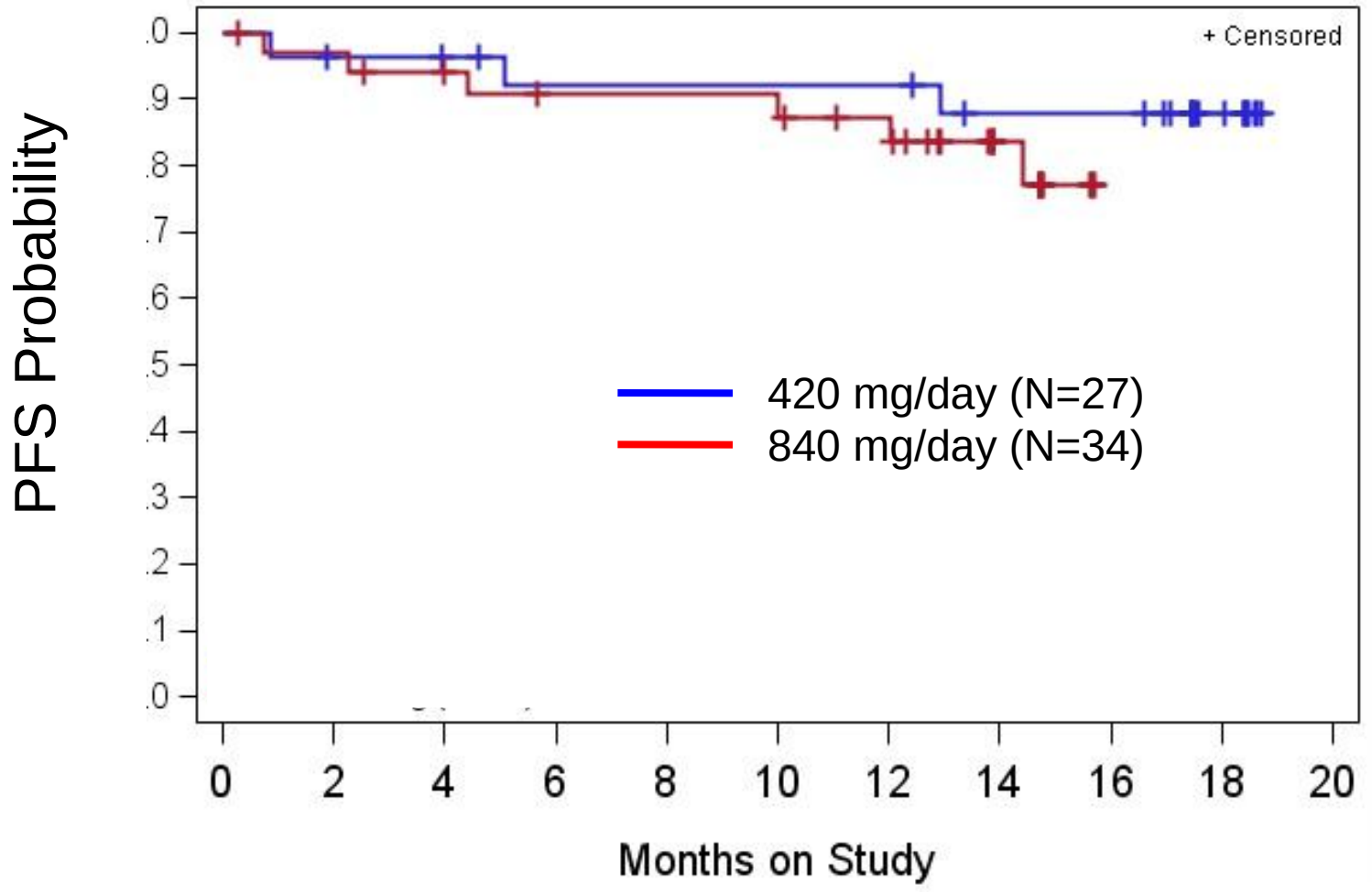
- B-cell antigen receptor (BCR) signaling is required for tumor expansion and proliferation
- BTK is an essential element of the BCR signaling pathway
- PCI-32765 a first-in-class, irreversible and selective inhibitor of BTK (IC_{50} = 0.5 nM)
- Orally administered with once daily dosing resulting in 24-hr target inhibition
- Inhibits CLL cell migration, adhesion, and promotes apoptosis
- No cytotoxic effect on T-cells or NK-cells

Honigbergl; PNAS 2010; Herman, Blood 2011

Ibrutinib: Nodal response in r/r CLL (n=55)



Ibritumomab in r/r CLL:
Progression-free Survival

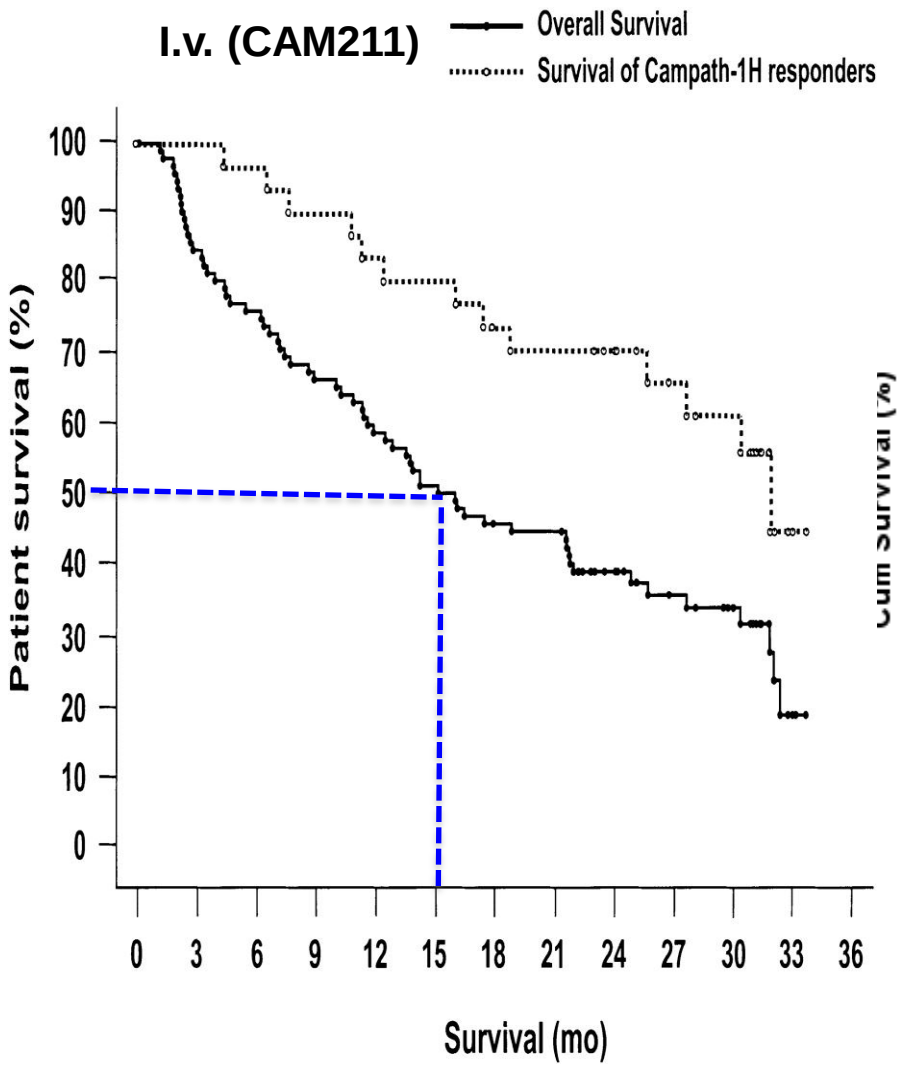


O'Brien, EHA 2012

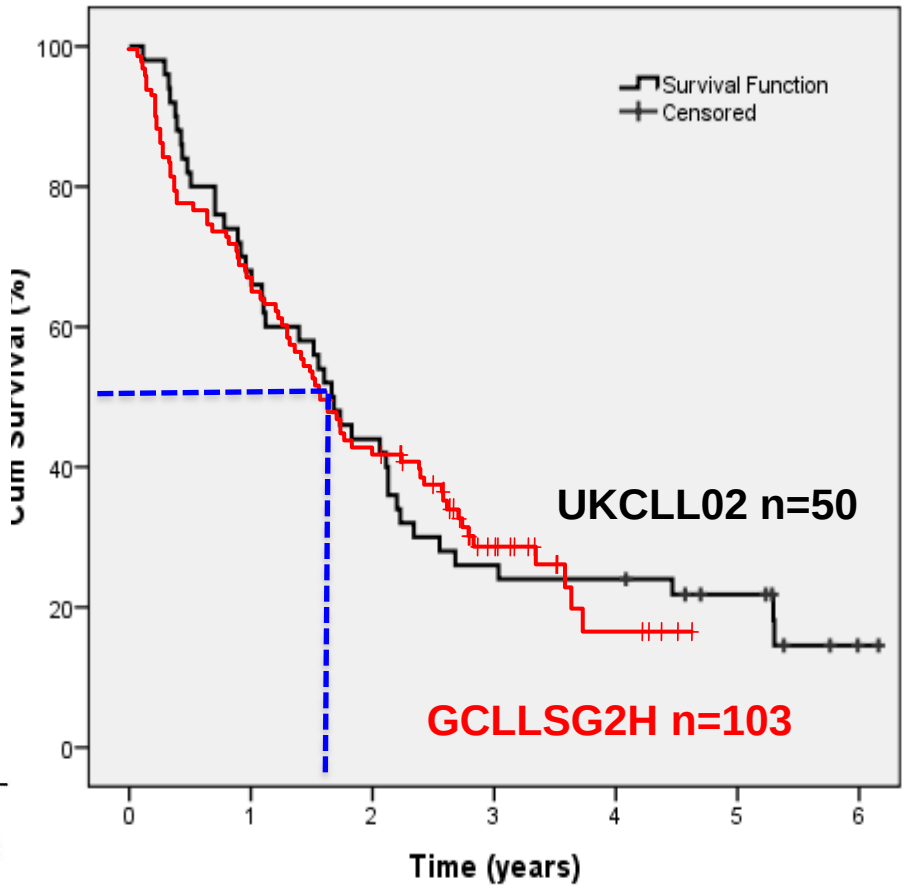
alemtuzumab – flud refr CLL

Overall Survival

I.v. (CAM211)

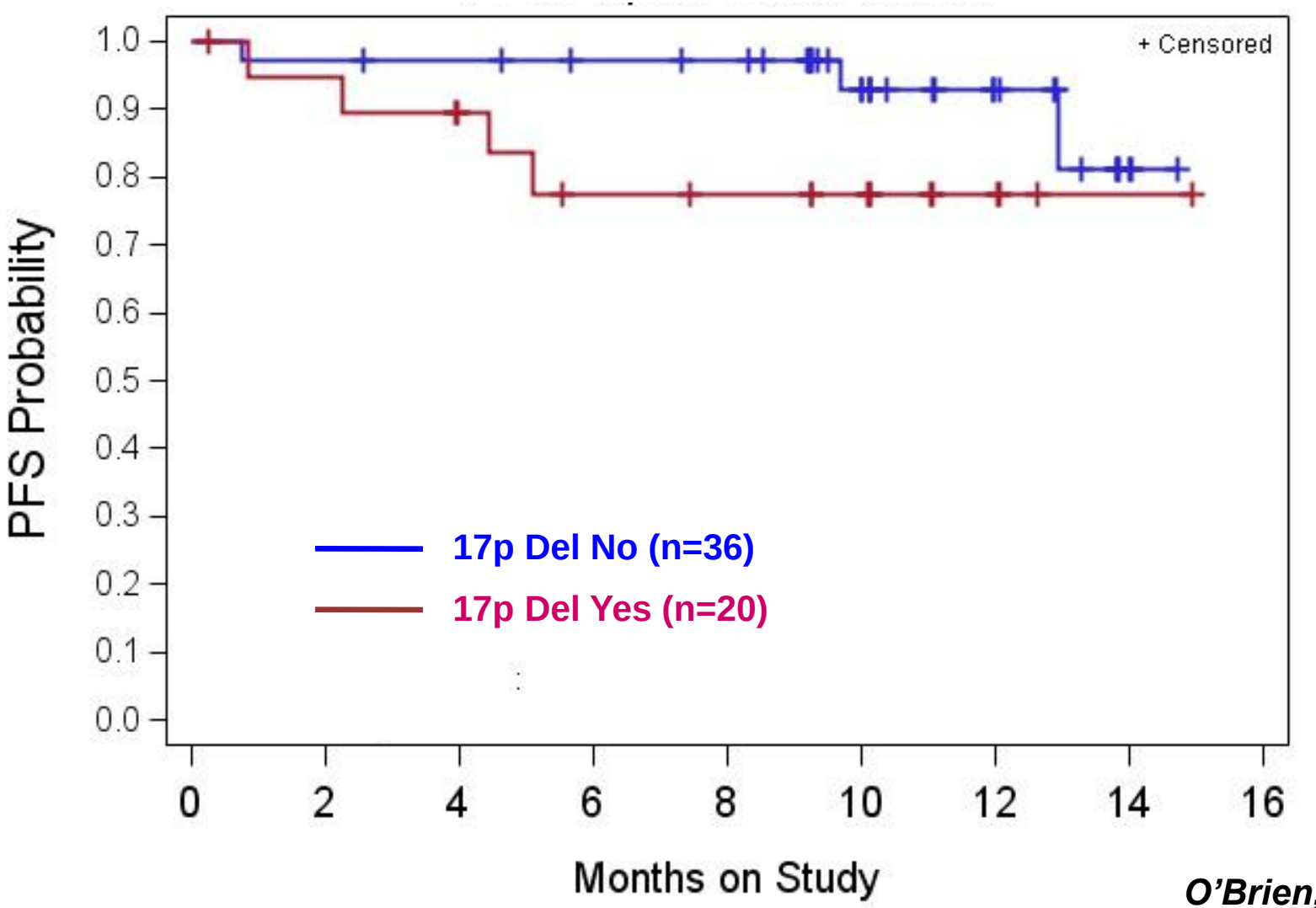


s.c. (UKCLL02 & CLL2H)



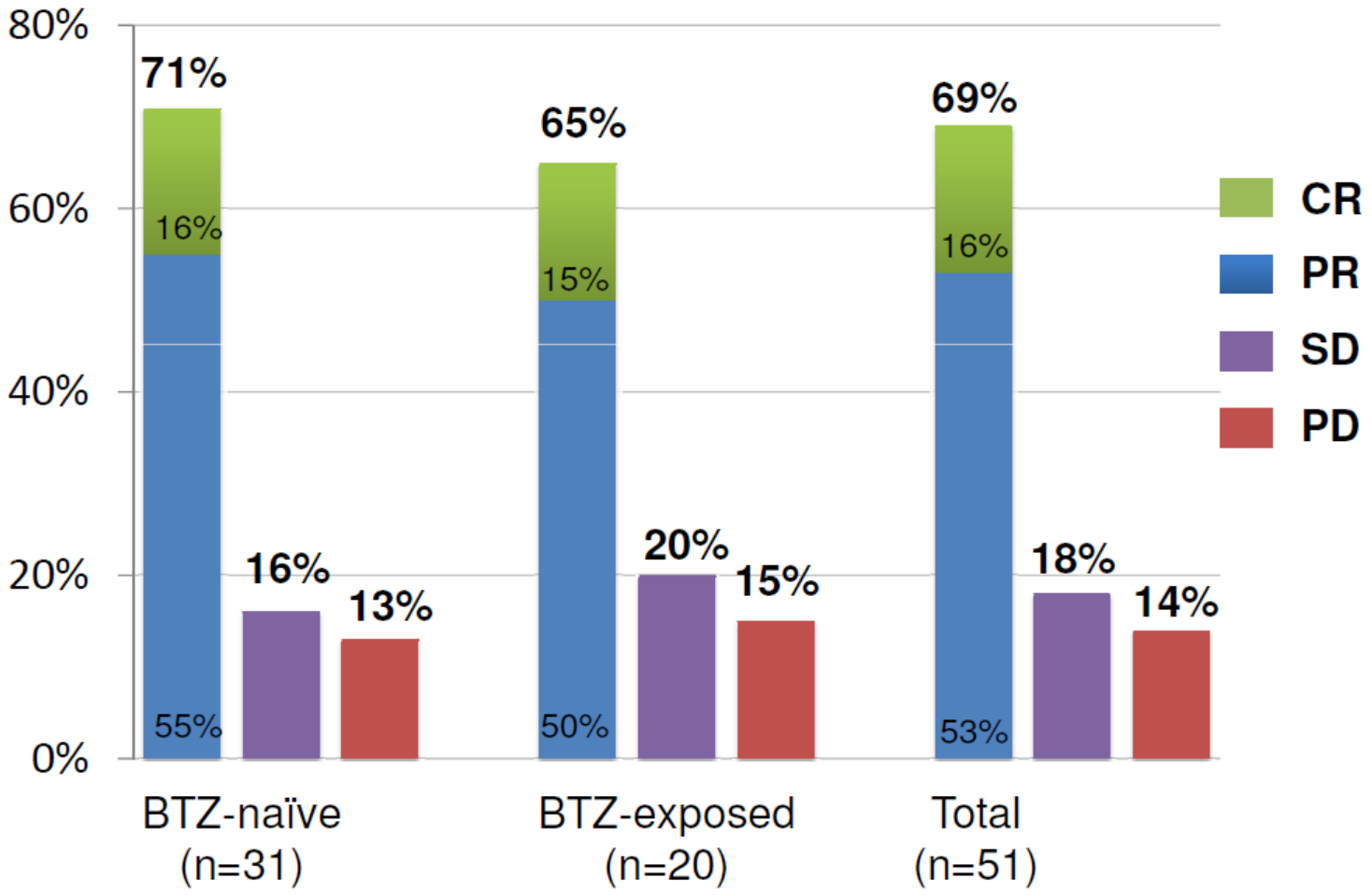
Ibrutinib monotherapy

Progression-free Survival in 17p del CLL



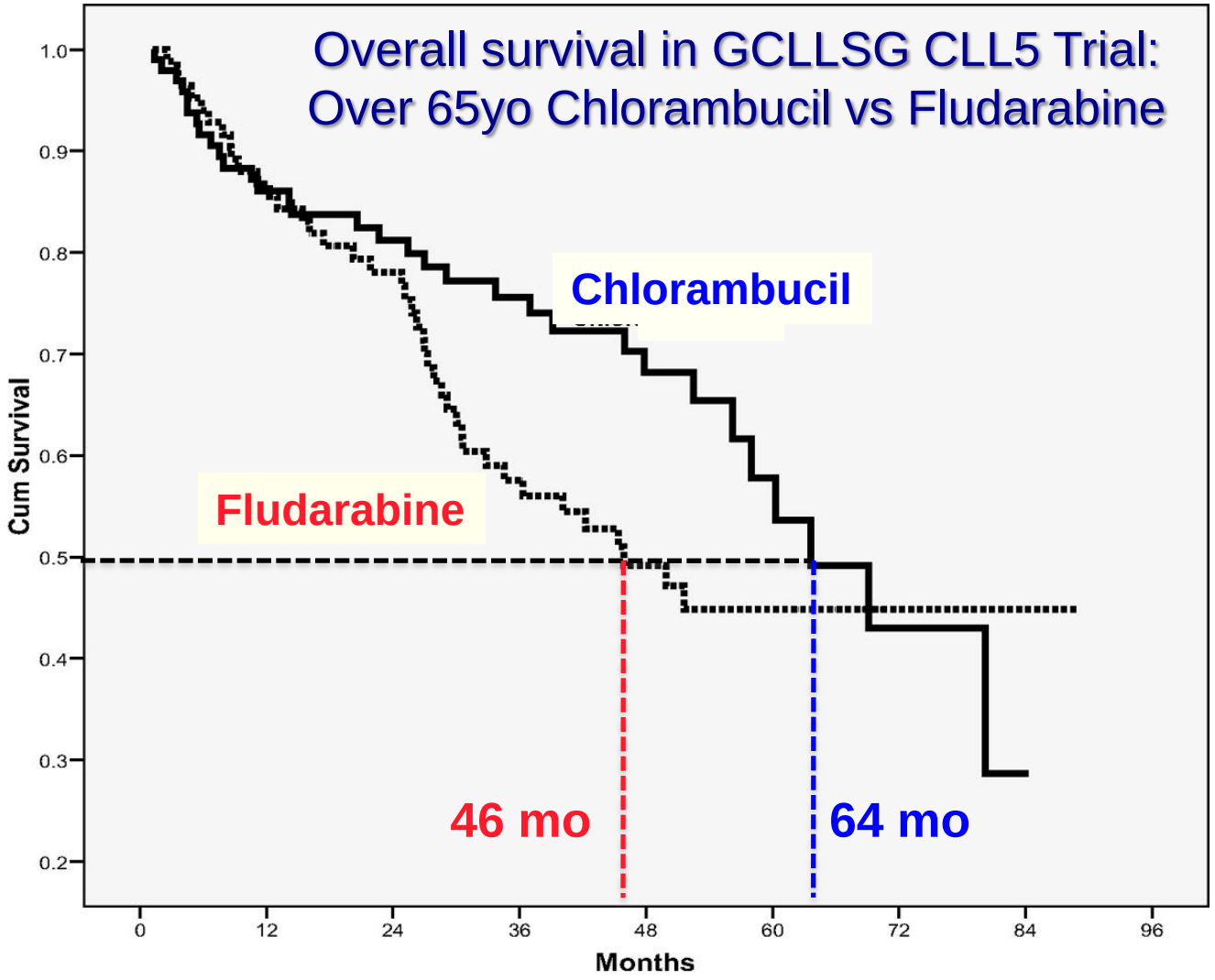
O'Brien, ASH 2011

BTK inhibitor
Response rates in MCL



Wang, ASH 2011

First line therapy in CLL

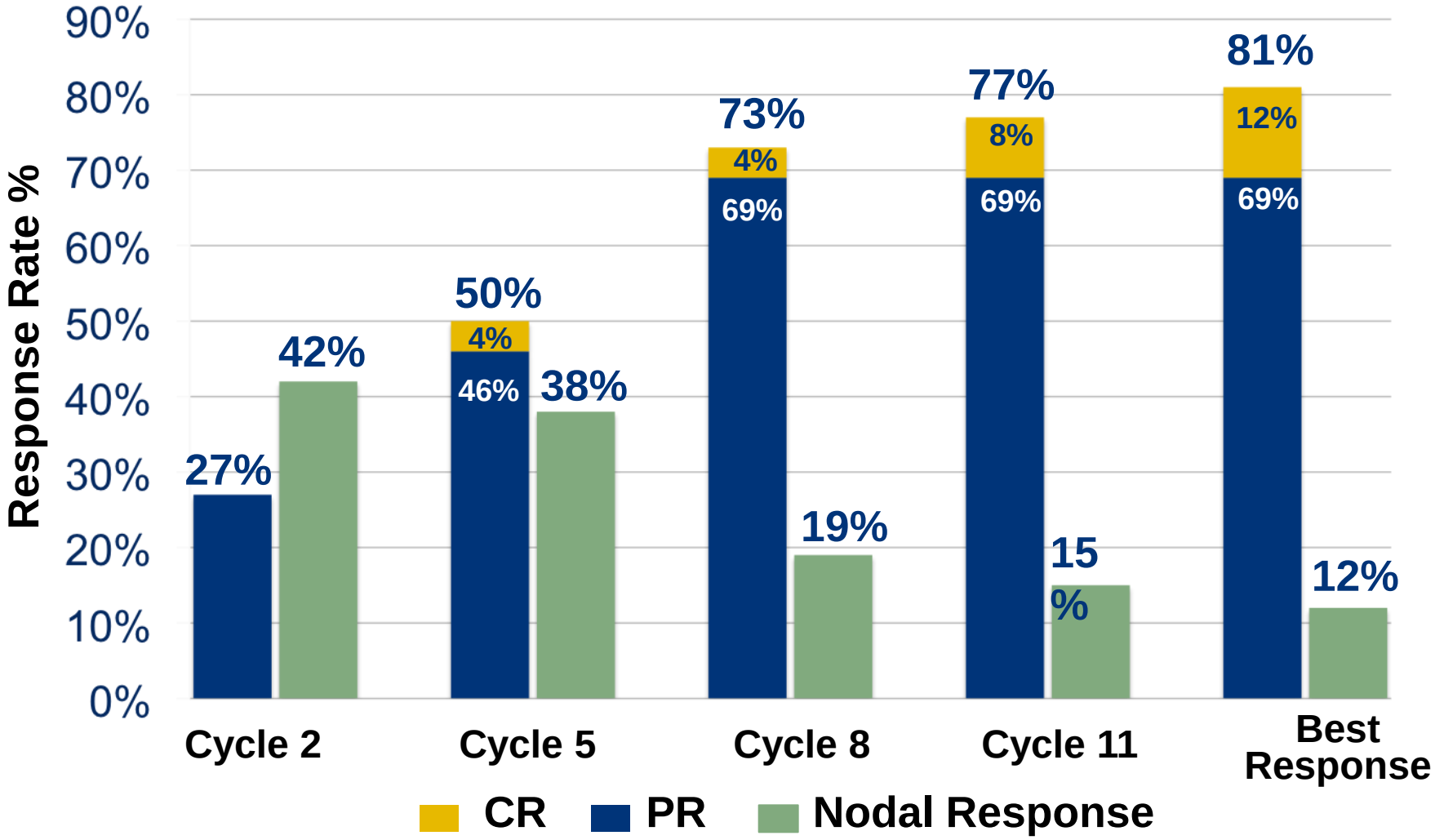


Patients at risk

Chlorambucil	98	75	63	47	33	14	7	1
Fludarabine	87	71	59	39	26	16	6	1

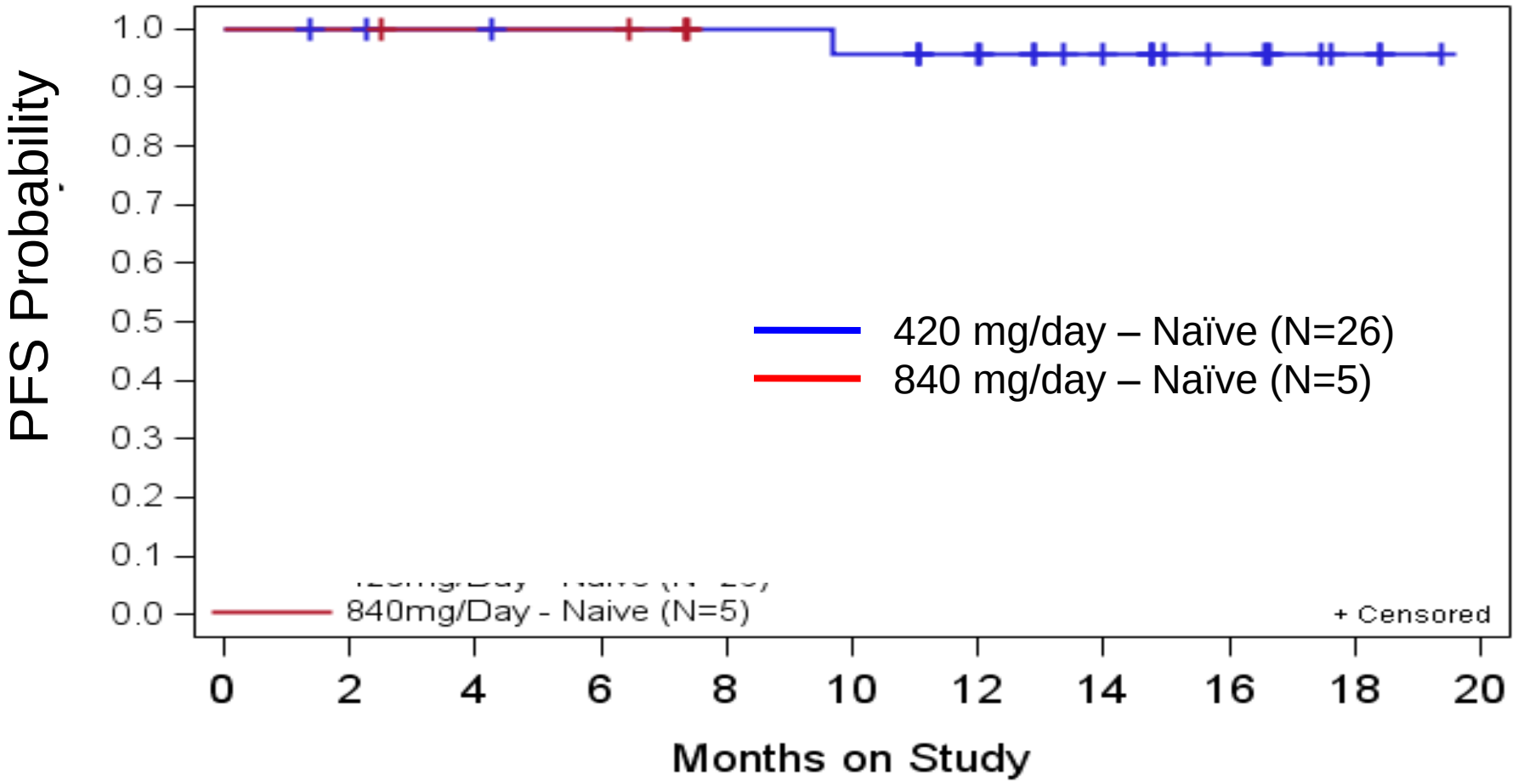
Eichhorst Blood 2009

Firstline ≥ 65 yrs
Ibrutinib: Response in CLL



O'Brien, EHA 2012

Firstline ≥ 65 yrs
Ibrutinib: Progression-free survival in CLL



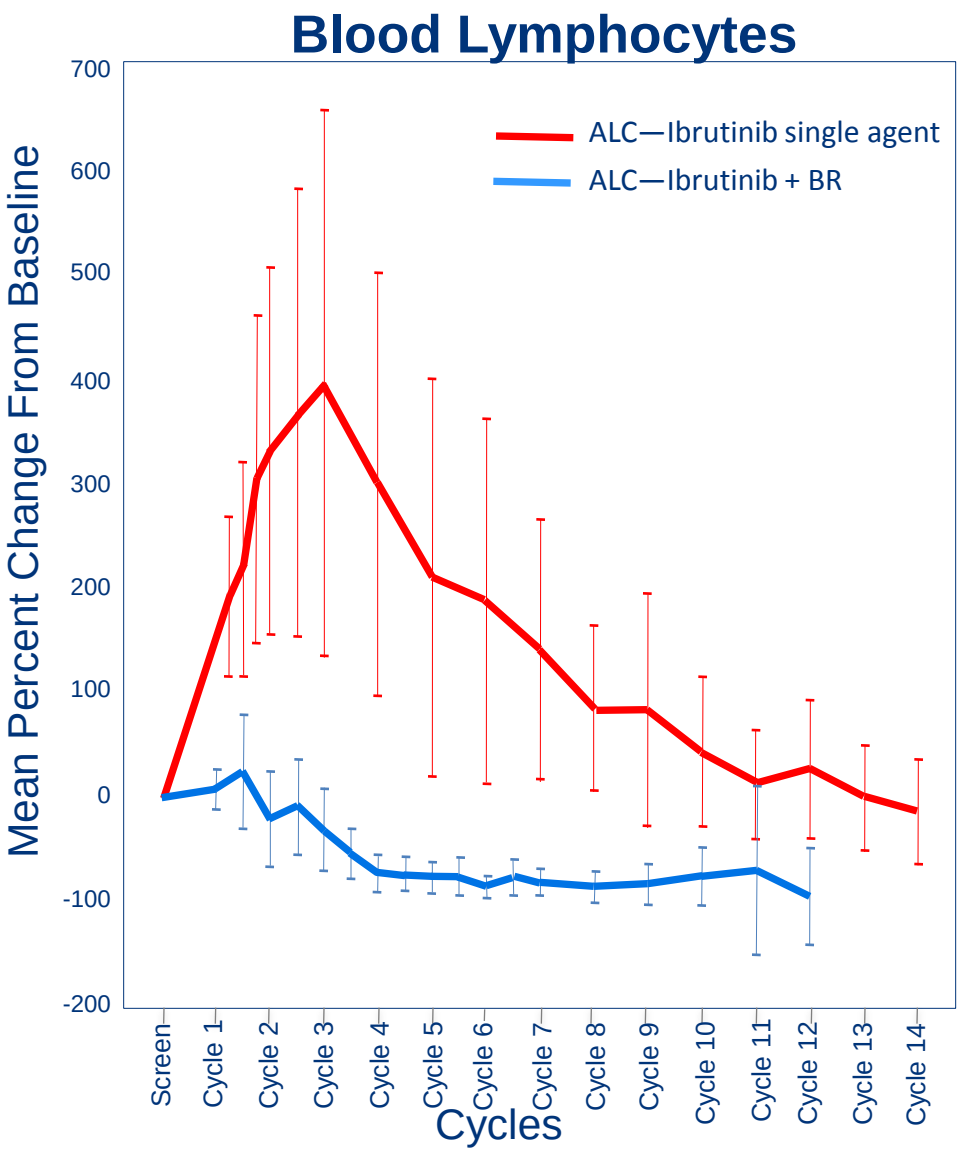
O'Brien, EHA 2012

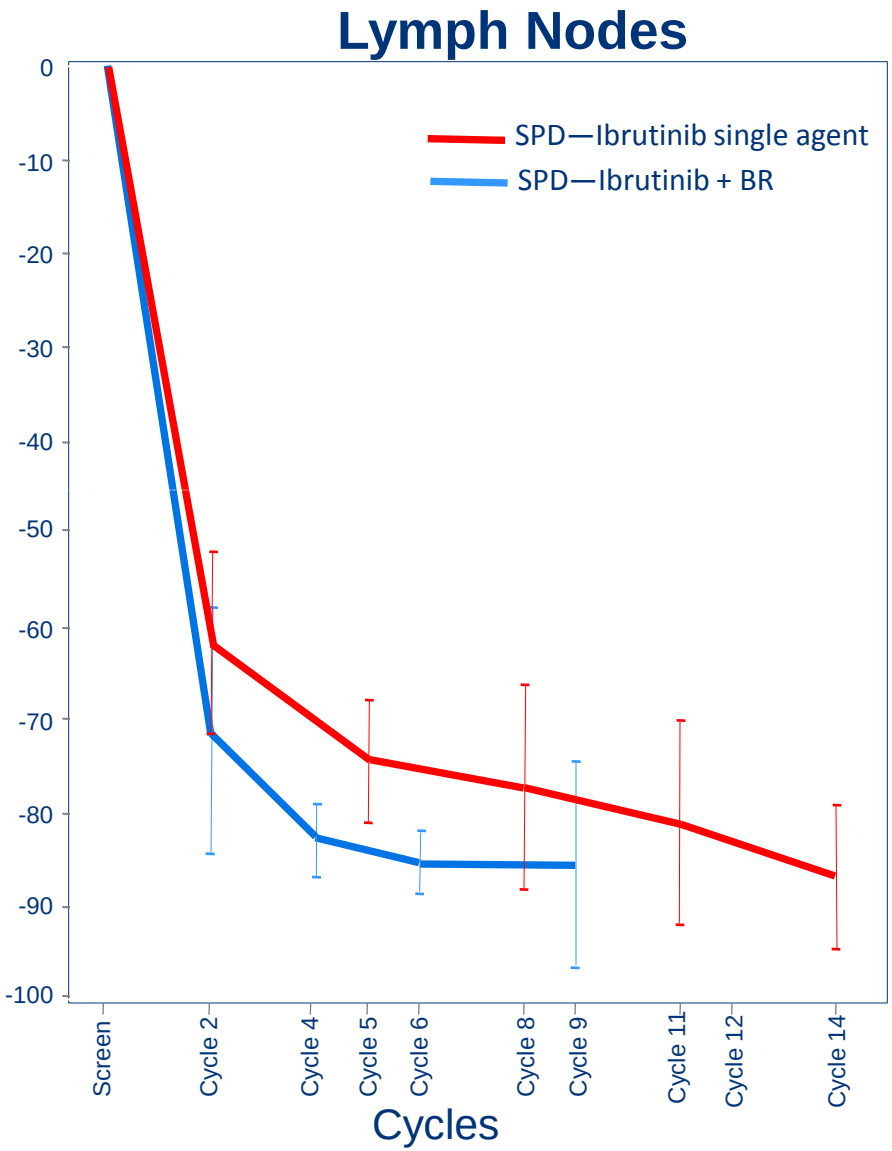
Firstline ≥ 65 yrs
Ibrutinib: Toxicity in CLL

	Total (N=31)	
	Grade 3	**Grade 4**
Grade 3/4 hematology toxicity, # (%)	**2 (6)**	**2 (6)**
Neutropenia	0	0
Anemia	1 (3)	1 (3)
Thrombocytopenia	1 (3)	1 (3)
Grade 3/4 non-hematology toxicity regardless of relatedness	**6 (19)**	0
Diarrhea	4 (13)	0
Hyponatremia	2 (6)	0
Enterocolitis hemorrhagic	1 (3)	0
Grade 3/4 infections	**3 (10)**	**0**

O'Brien, EHA 2012

Lymphocytosis after ibrutinib in CLL

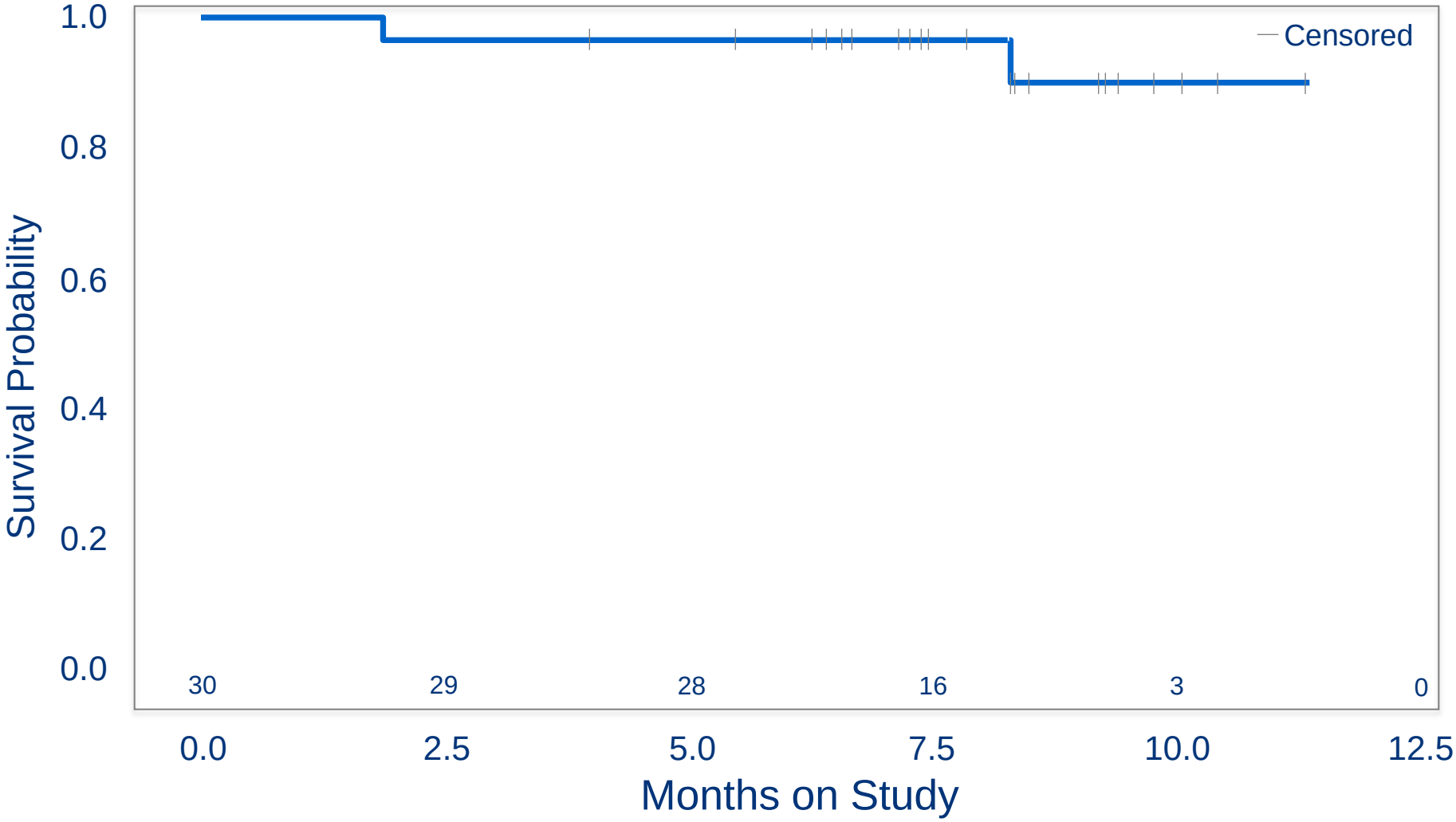




ASCO 2012

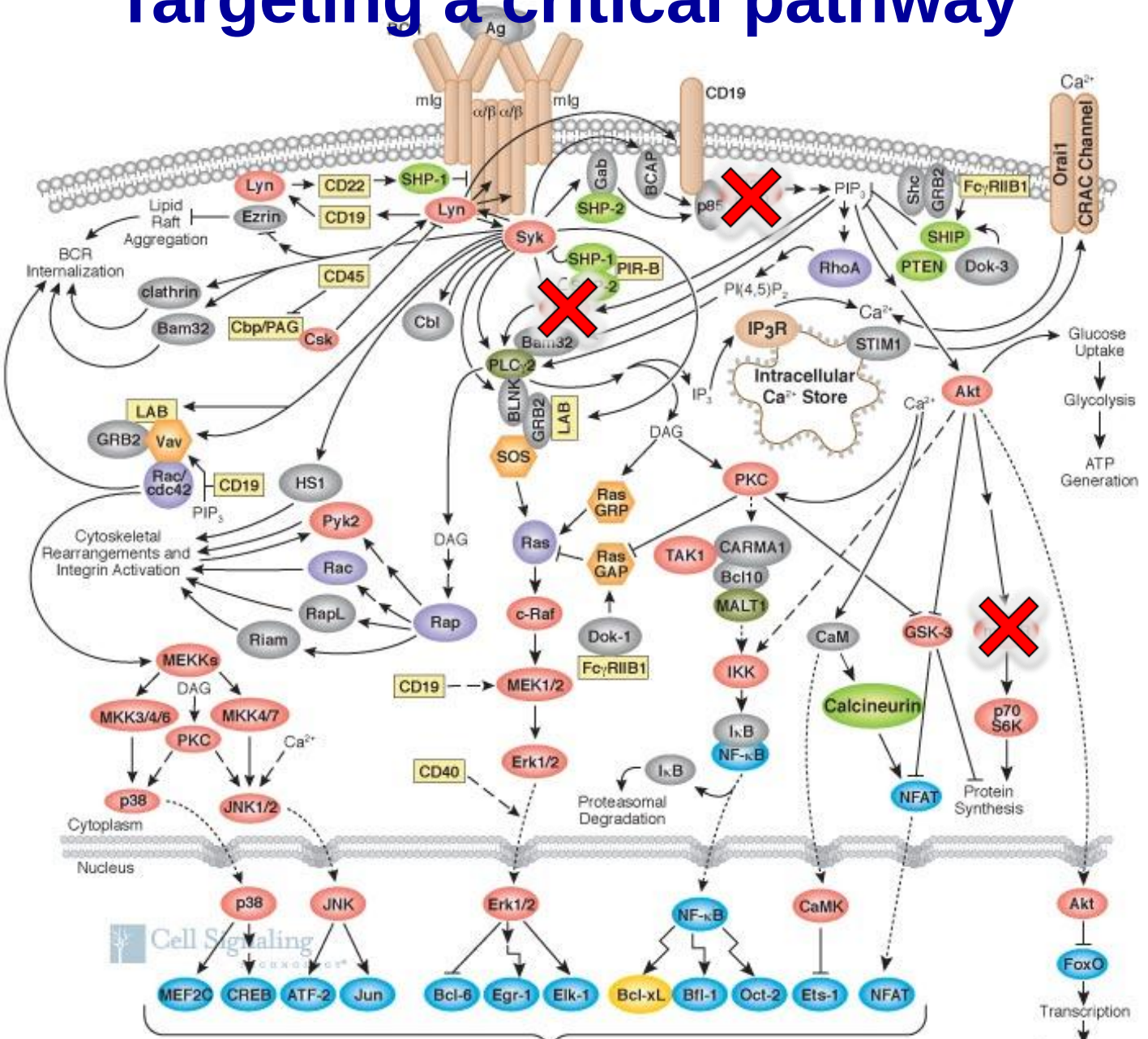
Ibrutinib + BR in CLL

Progression-free Survival



mTOR and beyond

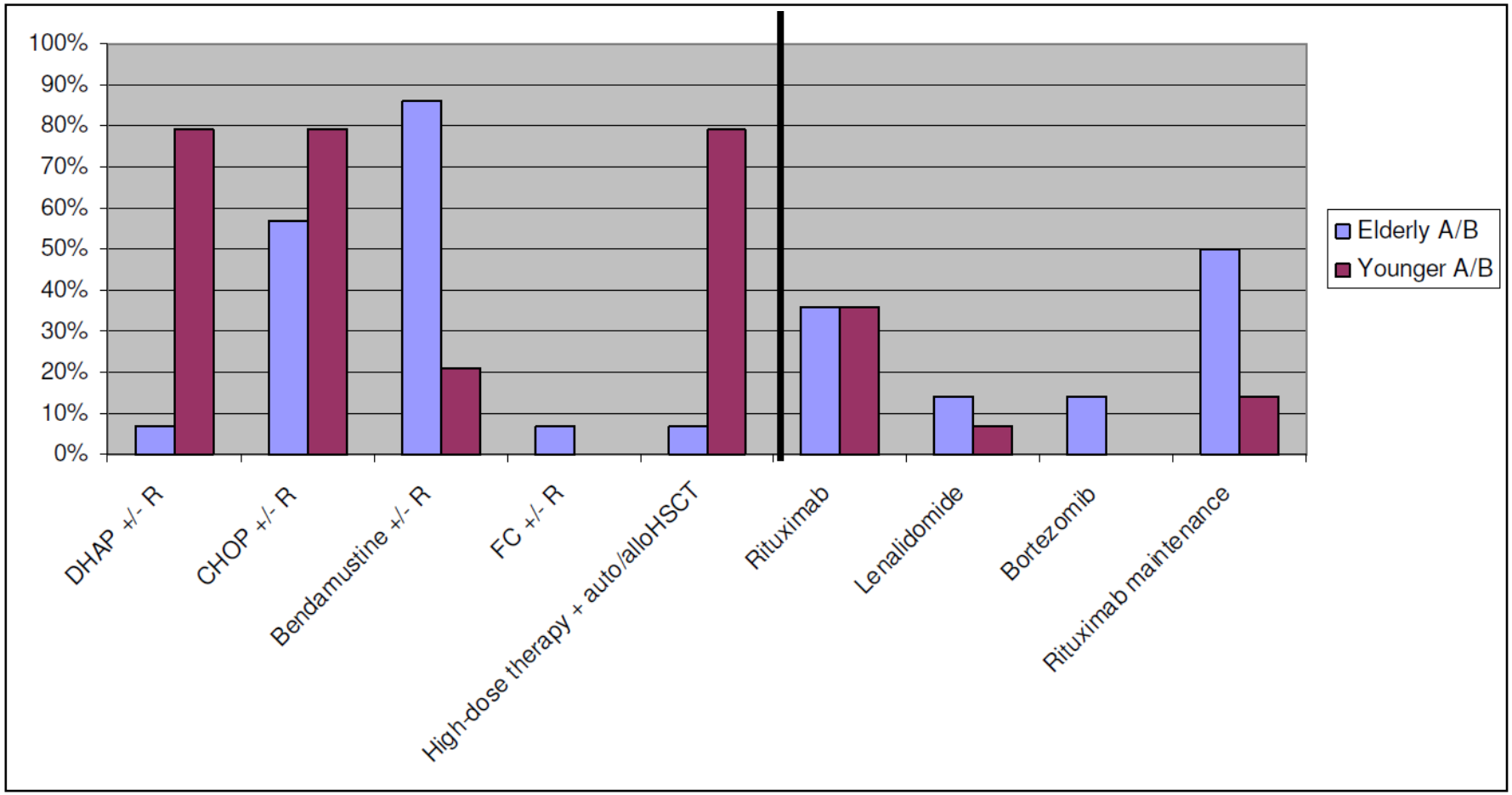
Targeting a critical pathway



P. Hillmen

Mantle cell lymphoma

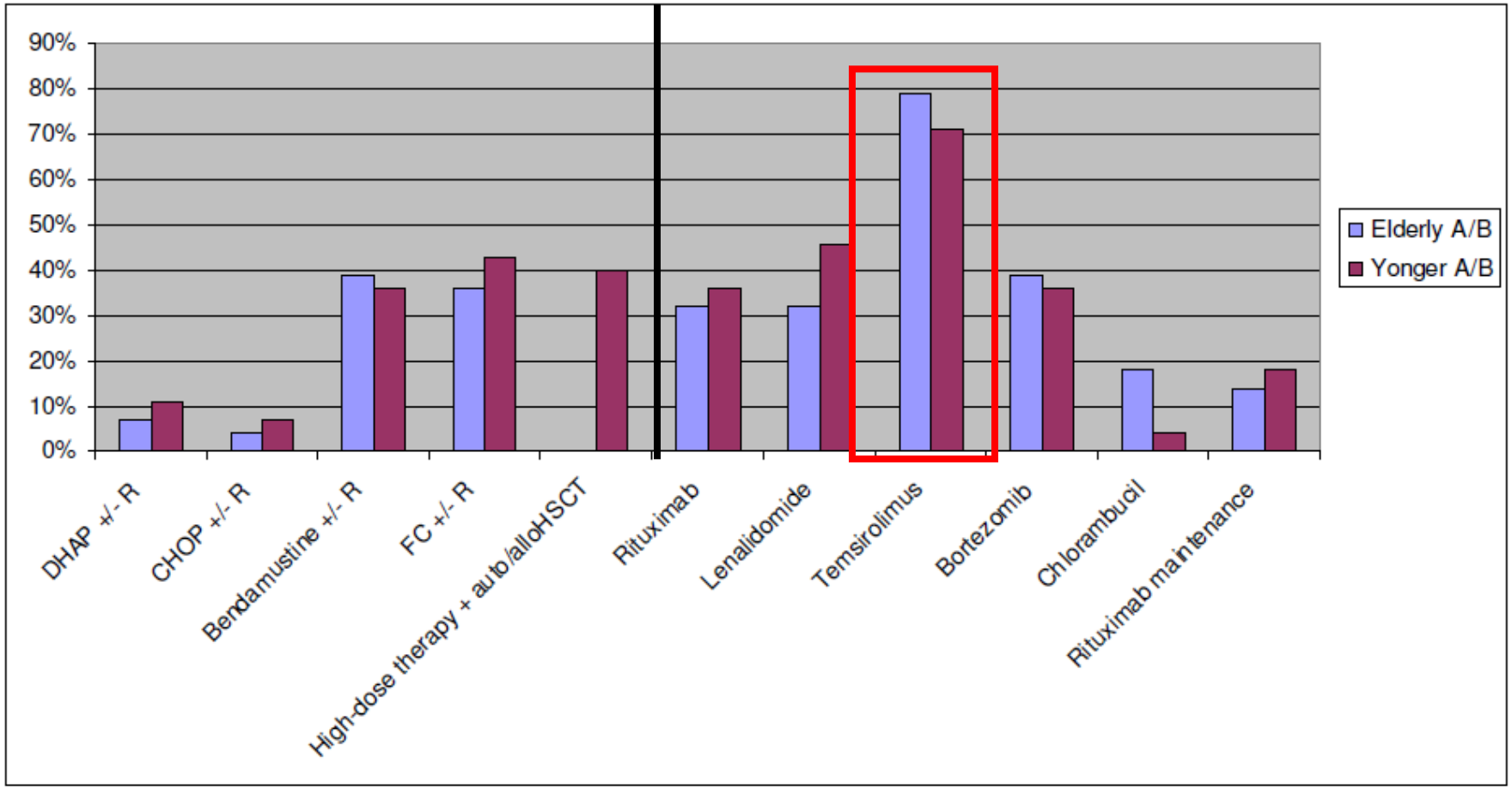
First line therapy



Witzens-Harig, Ann Hematol 2012

Mantle cell lymphoma

>2 line therapy



Witzens-Harig, Ann Hematol 2012

Acknowledgements