Chłoniaki 2012

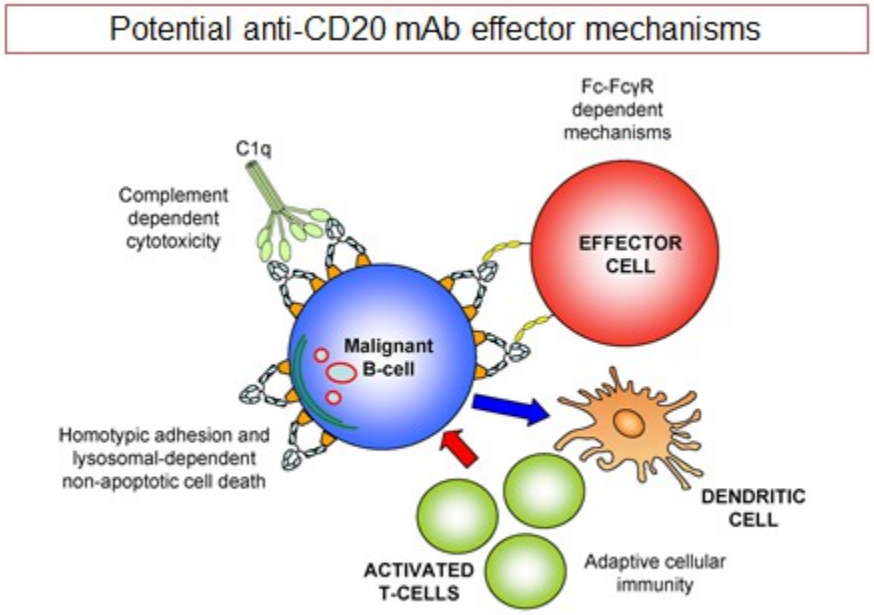
Onkologia spersonalizowana

Jan Walewski, Warszawa, 30.10.2012

Przeciwciało monoklonalne anty-CD20 było pierwszym w onkologii leczeniem selektywnym (1997 r.)

→ Nowa jakość w leczeniu:

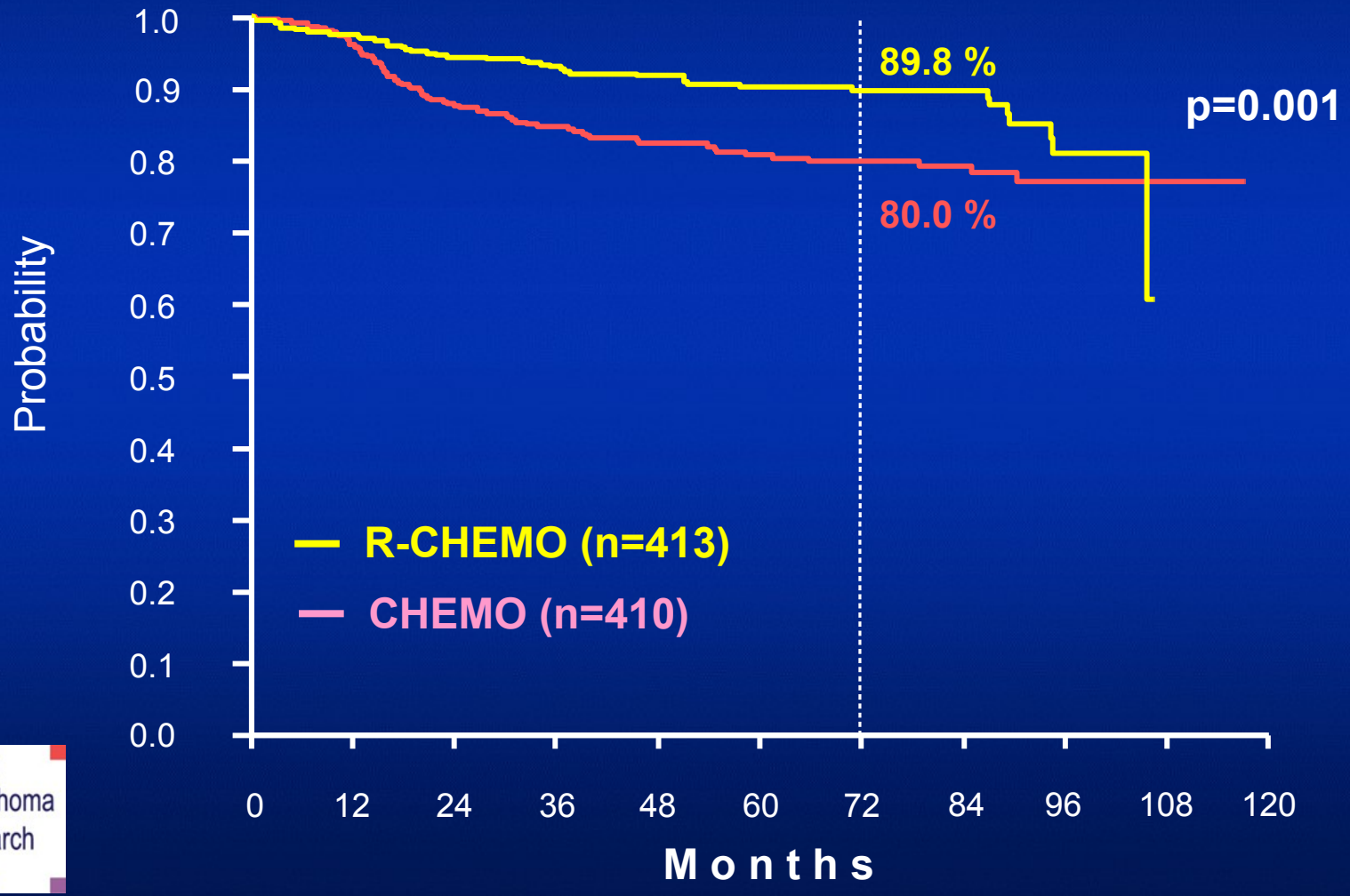
- wysoka skuteczność
- mała toksyczność



blood

Alduaij W, Illidge TM: *Blood* 2011; 117: 2993

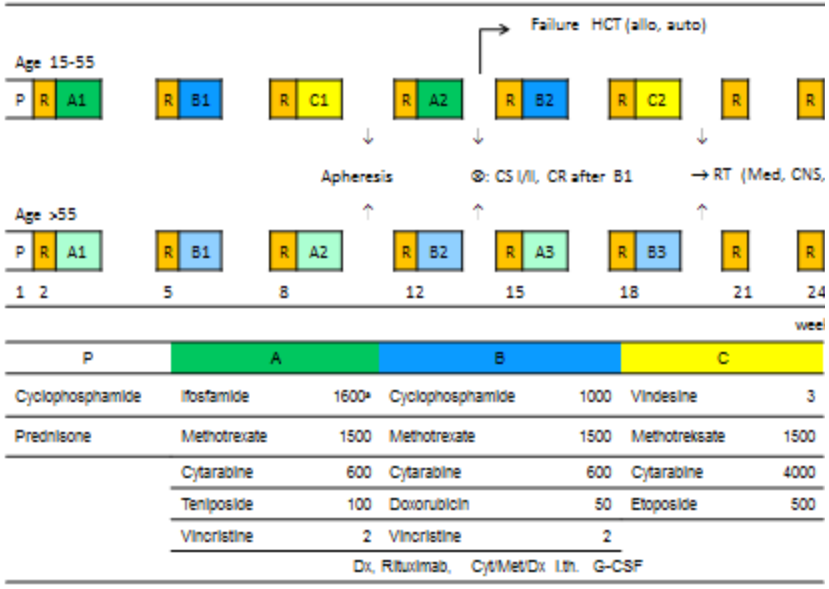
MInT Overall Survival



Polish Lymphoma Research Group

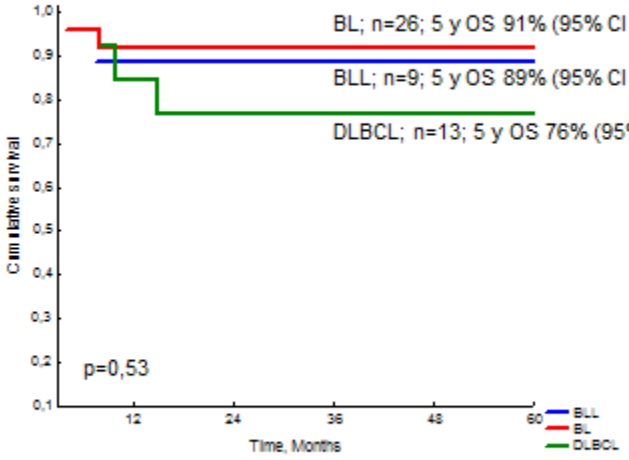
Połączenie przeciwciała anty-CD20 z intensywną sekwencyjną chemioterapią wypracowaną w pediatrii zrewolucjonizowało leczenie chłoniaka Burkitta, najbardziej złośliwego nowotworu limfoidalnego

GMALL B-ALL/NHL 2002 protocol



P	A		B		C	
Cyclophosphamide	Ifosfamide	1600*	Cyclophosphamide	1000	Vindesine	3
Prednisone	Methotrexate	1500	Methotrexate	1500	Methotreksate	1500
	Cytarabine	600	Cytarabine	600	Cytarabine	4000
	Teniposide	100	Doxorubicin	50	Etoposide	500
	Vincristine	2	Vincristine	2		
		Dx, Rituximab,		Cyt/Met/Dx i.th.	G-CSF	

Overall survival: BL vs BLL vs DLBCL



Median follow up for BL 23 (12 – 73) months
Median follow up for BLL 40 (23 - 84) months
Median follow up for DLBCL 38 (18 -72)months

European Working Group for Adult ALL (EWALL)

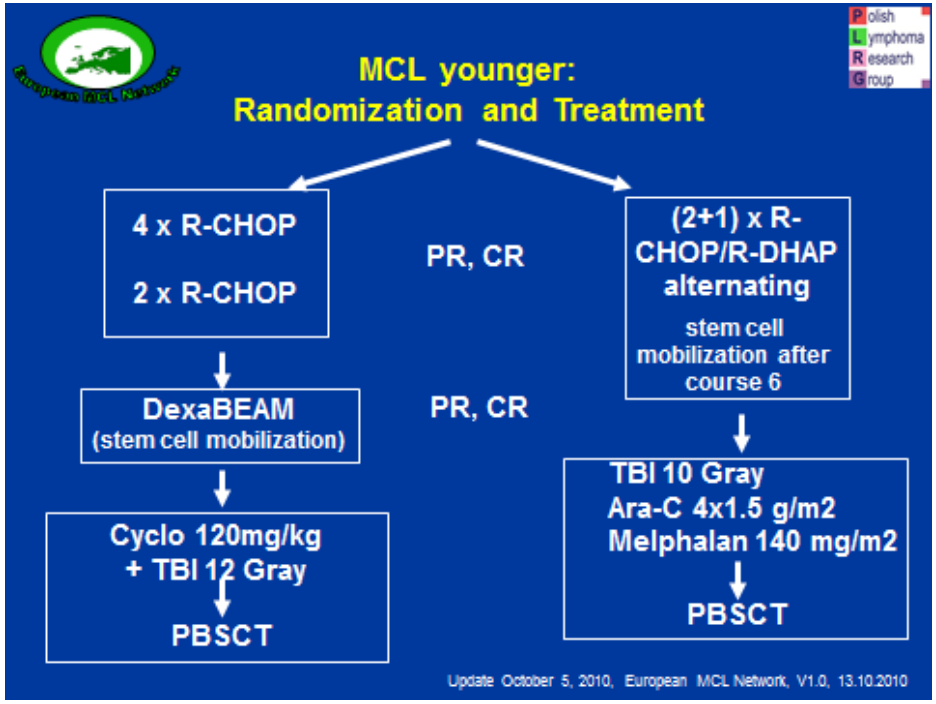
EWALL Results in Burkitt's Leukemia/Lymphoma

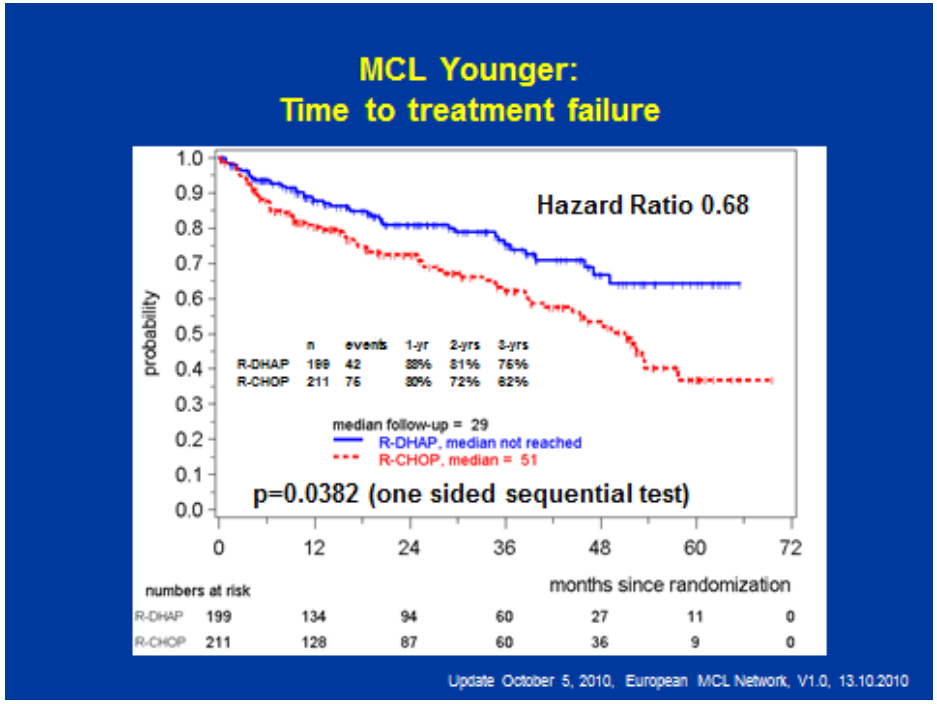
Group	N Pts	B-ALL/Burkitt	Age	CR	OS
GMALL	144	Burkitt	15-55	89%	90%
Hoelzer	65	B-ALL	15-55	91%	78%
Gökbuget					
NILG	105	50/54	47 (17-78)	79%	67%
Bassan					
PETHEMA	127	26/101	44 (15-83)	85%	75%
Ribera					
PLRG	34	3% B-ALL	37 (18-62)	94%	91%
Walewski					

Chłoniak z komórek płaszcza

nowy standard u młodszych chorych:

- Immunochemioterapia indukcyjna naprzemienna
- Autotransplantacja komórek krwiotwórczych w konsolidacji

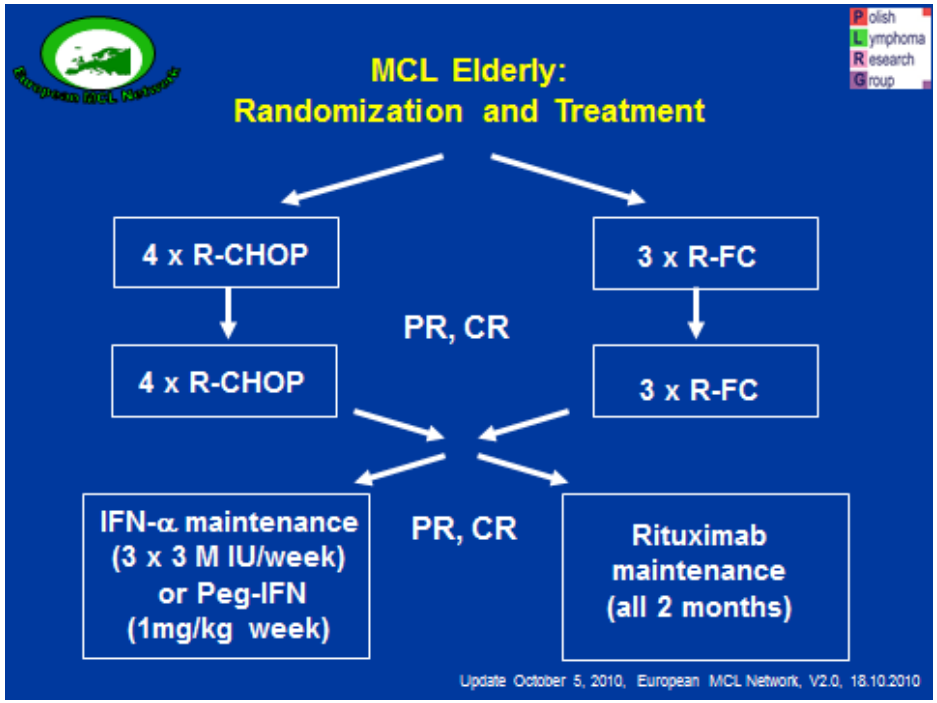


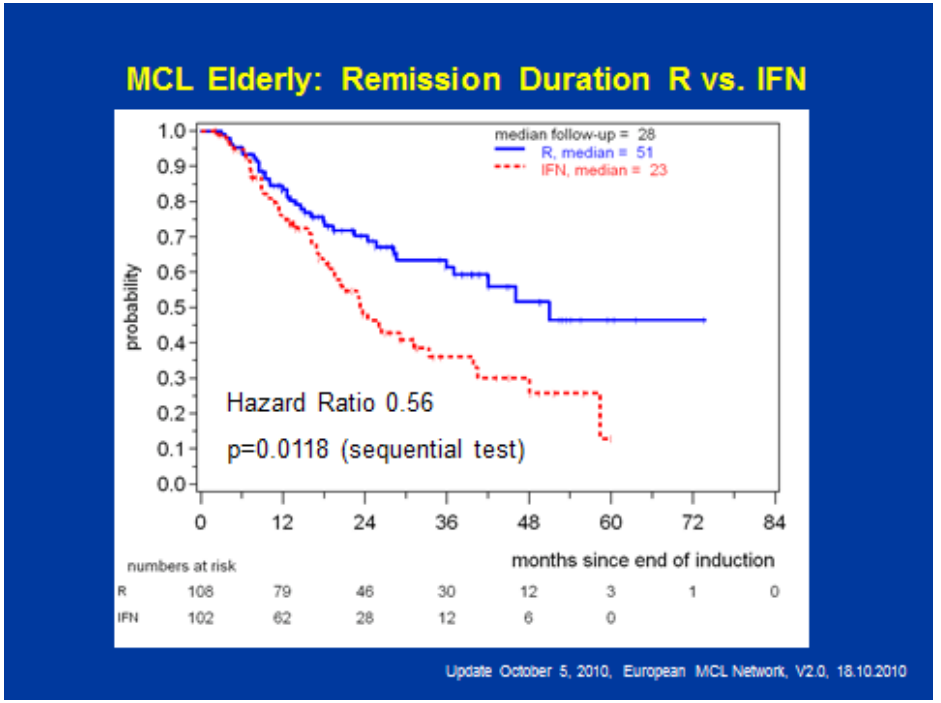


Chłoniak z komórek płaszcza

nowy standard u starszych chorych:

- Immunochemioterapia indukcyjna standardowa
- Leczenie podtrzymujące przeciwciałem anty-CD20

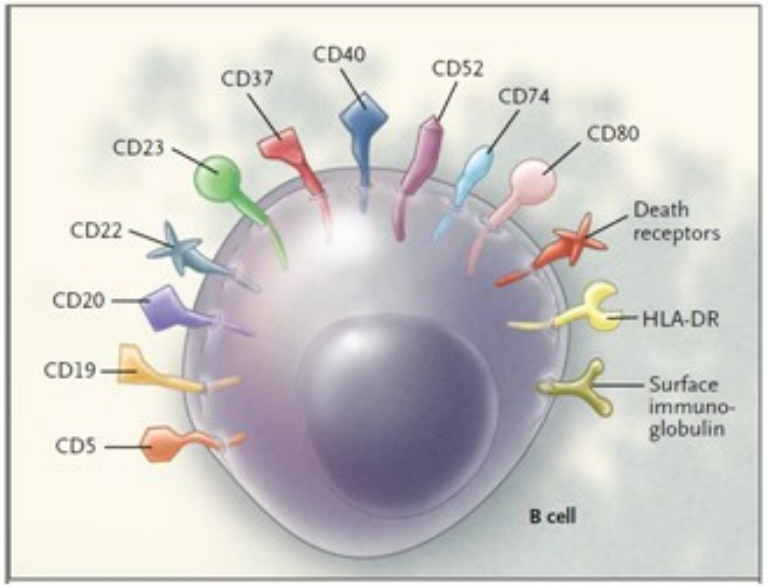




Nowe rodzaje przeciwciał:

- wolne
- sprzężone z radioizotopoem
- sprzężone z toksyną
- immunoregulacyjne (anty-CTLA4, anty-PD1)

Antygeny na powierzchni limocyta B



Cheson BD, Leonard JP; *N Eng J Med.* 2008; 359: 613-626

Brentuximab Vedotin Mechanism of Action

Brentuximab vedotin (SGN-35) ADC

monomethyl auristatin E (MMAE), potent antitubulin agent

protease-cleavable linker

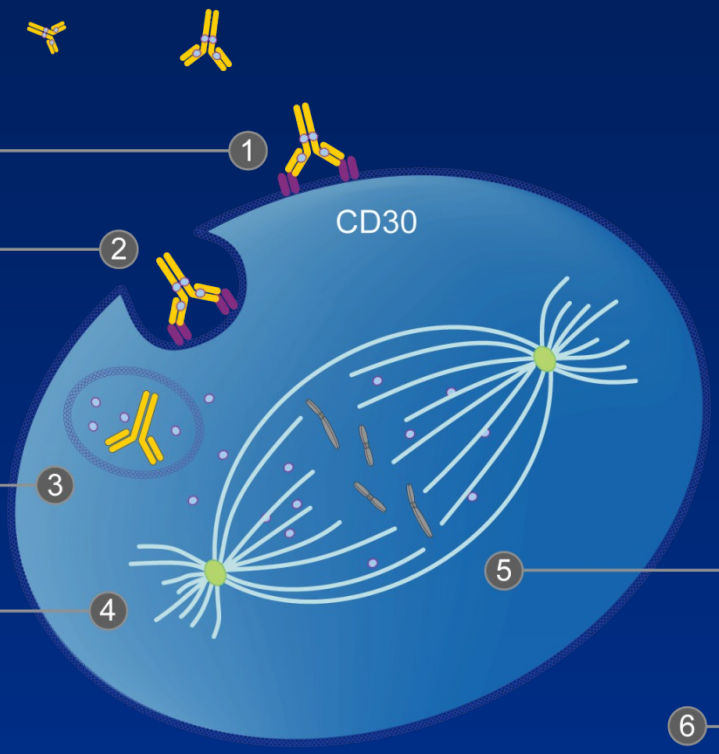
anti-CD30 monoclonal antibody

ADC binds to CD30

ADC-CD30 complex traffics to lysosome

MMAE is released

MMAE disrupts microtubule network



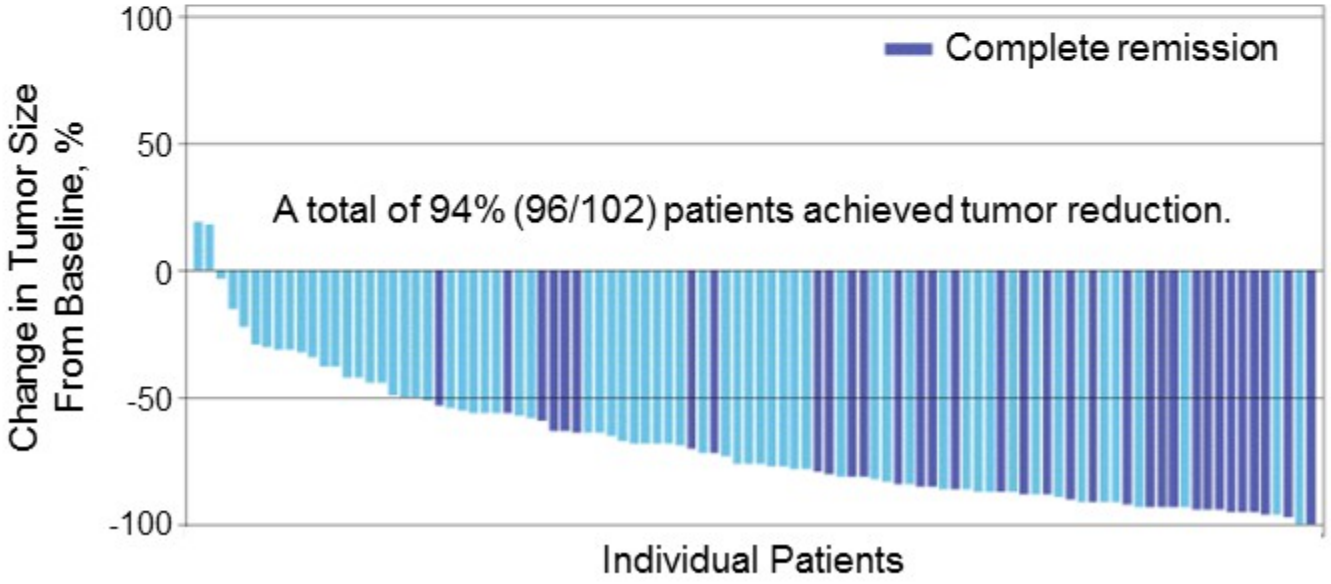
G2/M cell cycle arrest

Apoptosis

Targeting CD30
Brentuximab Vedotin (SGN-35)

Pivotal Phase 2 Study in Patients With Relapsed or Refractory HL

ORR, % (95% CI)	75 (65, 83)
Median duration of OR, mo (95% CI)	6.7 (3.6, 14.8)
Treatment cycles, median, No. (range)	9 (1-16)
Estimated 12-mo OS, %	89



N = 102

Chen RW, et al. J Clin Oncol. 2011;29. Abstract 8031.

Brentuximab Vedotin in Patients with Relapsed or Refractory Systemic Anaplastic Large Cell Lymphoma: A Phase 2 Study Update

Clinical response	**(n = 58)**
Objective response rate	86%
Complete remission rate	59%
Median duration of response	
Objective response	13.2 mo
Response in patients with CR	Not reached

Advani RH et al. *Proc ASH* 2011;Abstract 443.

Przeciwciało monoklonalne anty-CS1 w szpiczaku plazmocytowym

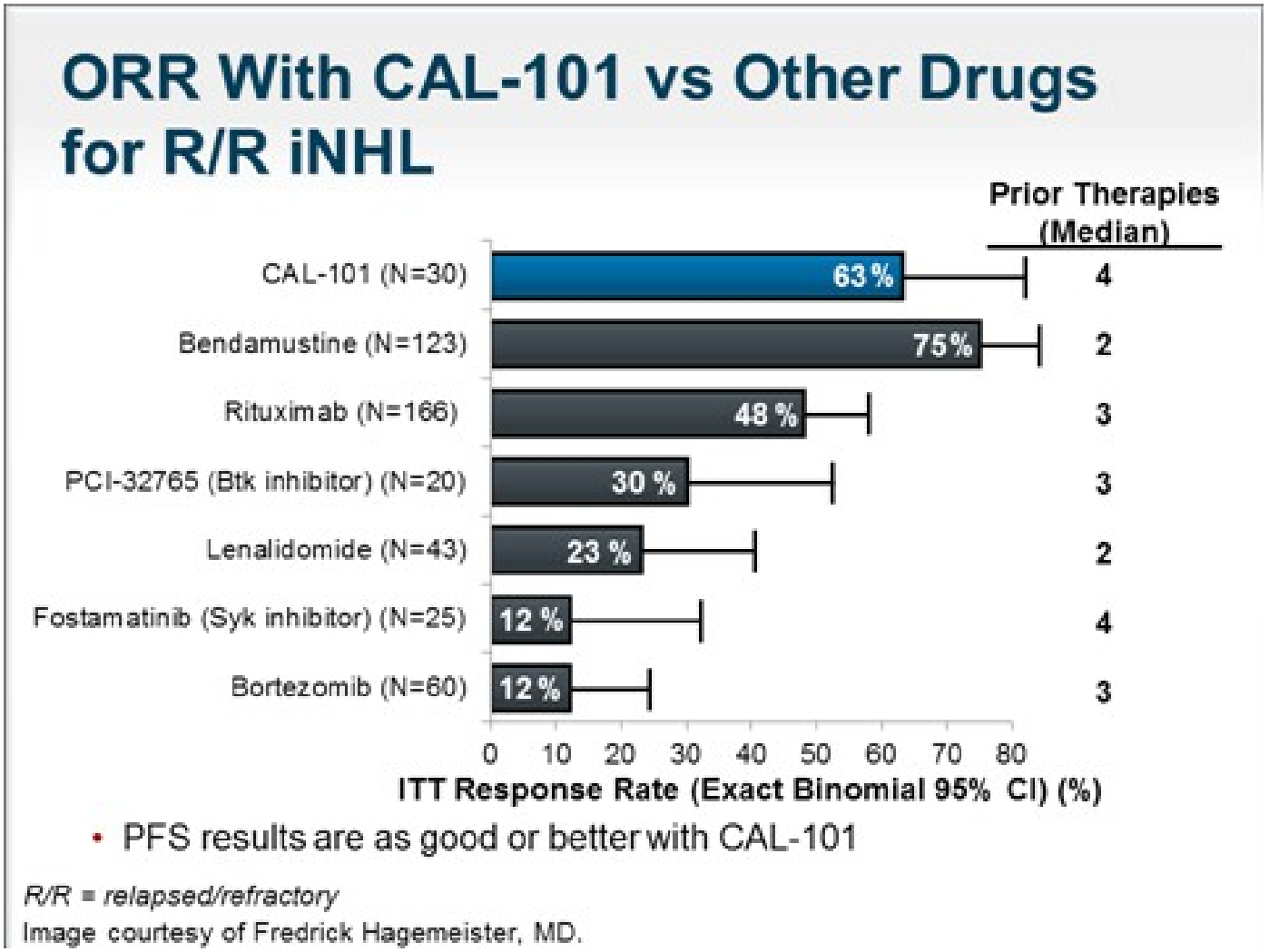
Elotuzumab Phase II Study

- **Elotuzumab: investigational humanized monoclonal antibody directed against CS1, which is highly expressed on myeloma cells in > 95% MM patients**
- **Current study randomized relapsed/refractory MM patients to different schedules of elotuzumab plus lenalidomide and dexamethasone**
  - **High ORR in both groups**
  - **Median time to response: 1.0 mos (range: 0.7-4.3)**
  - **Median PFS not reached after median follow-up of 14 mos**
  - **Similar safety profiles between groups**

Response	Elotuzumab 10 mg/kg (n = 36)	Elotuzumab 20 mg/kg (n = 37)	Total (N = 73)
ORR (≥ PR), n (%)	33 (92)	27 (73)	60 (82)
▪ Pts with 1 previous therapy	16 (100)	14 (82)	30 (91)
▪ Pts with ≥ 2 previous therapies	17 (85)	13 (65)	30 (75)

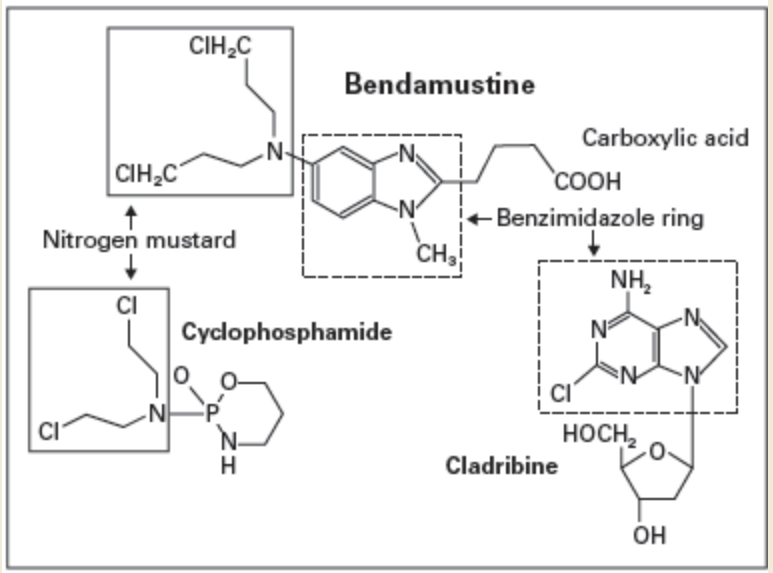
Lonial S, et al. ASH 2011. Abstract 303.

Nowe leki „inteligentne” w leczeniu chłoniaków



Bendamustyna

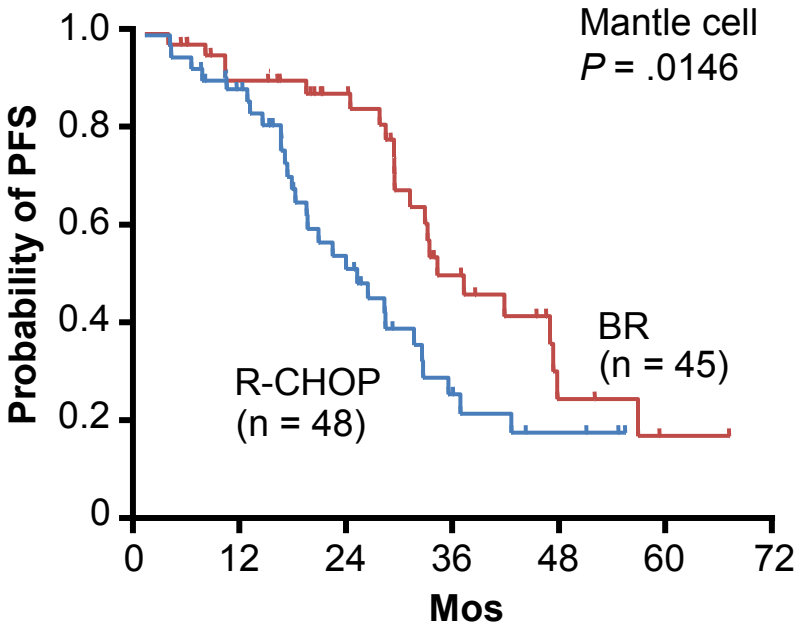
- Unikalny mechanizm działania alkilującego
- Wysoka aktywność przeciwchłoniakowa i przeciwbiałaczkowa
- Długotrwałe odpowiedzi
- Niska toksyczność
- Wysoki wskaźnik terapeutyczny
- Mniej podatny na mechanizmy oporności od innych leków alkilujących



Cheson BD, Rummel MJ: *JCO* 2009; 27: 1492

Bendamustine/Rituximab vs R-CHOP for Indolent and MCL: PFS

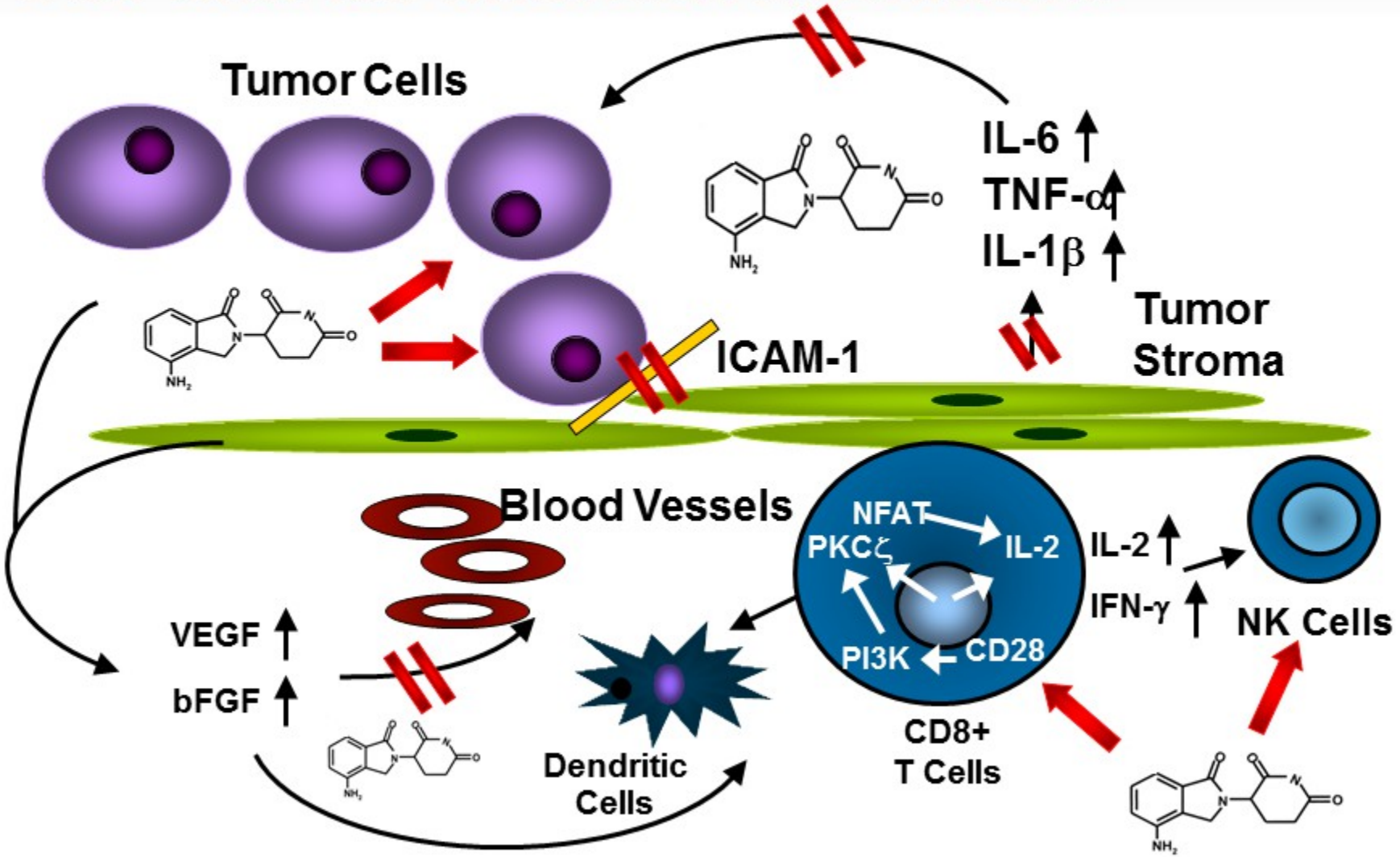
Dg	Median PFS, m	
	BR	R-CHOP
FL	Not reached	46
MCL	33	23
Indolent/WM	NR	~ 36



→ Conclusion: BR improves PFS and CR rates vs R-CHOP, has a better toxicity profile, and can be considered as a first-line treatment option for indolent and MCL

Rummel MJ, et al. ASH 2009. Abstract 405.

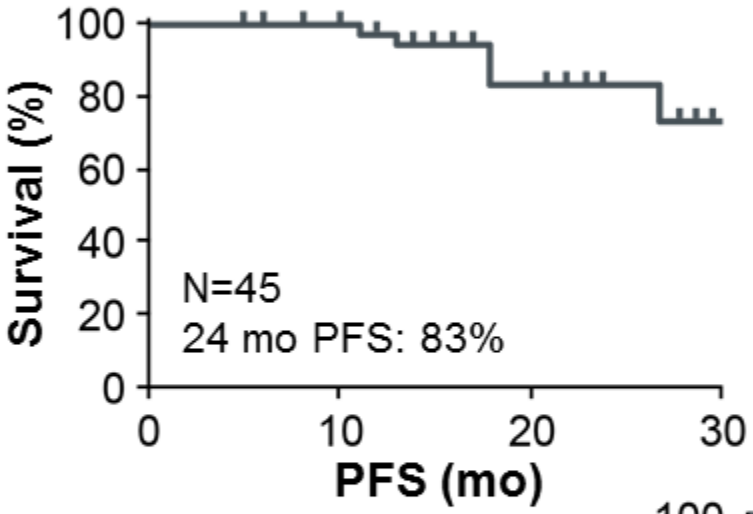
Lenalidomide: Targeting the Tumor Cell and Its Microenvironment



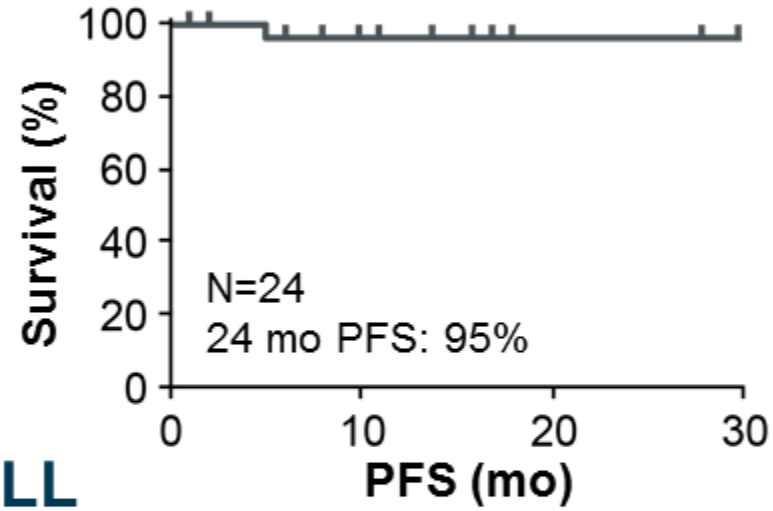
Chng WJ, et al. *Cancer Control*. 2005;12:91-104.
Drach J, et al. *Expert Rev Anticancer Ther.* 2005;5:477-485.

Lenalidomide + Rituximab for Untreated iNHL (cont)

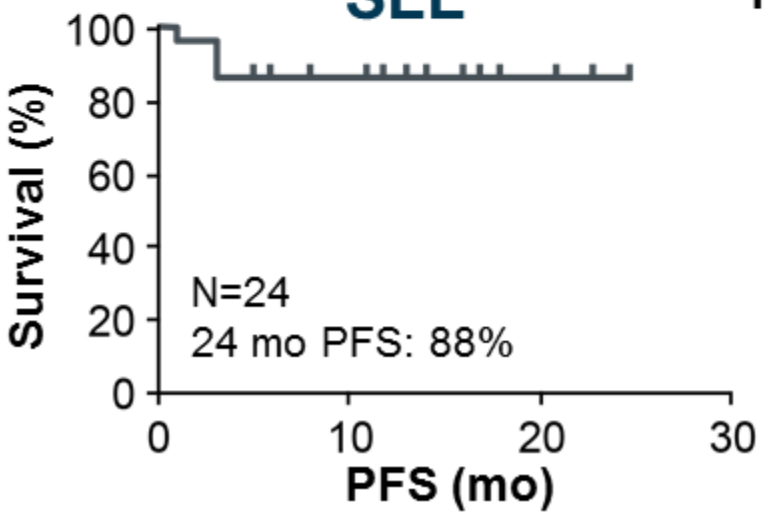
Follicular Lymphoma



Marginal Zone

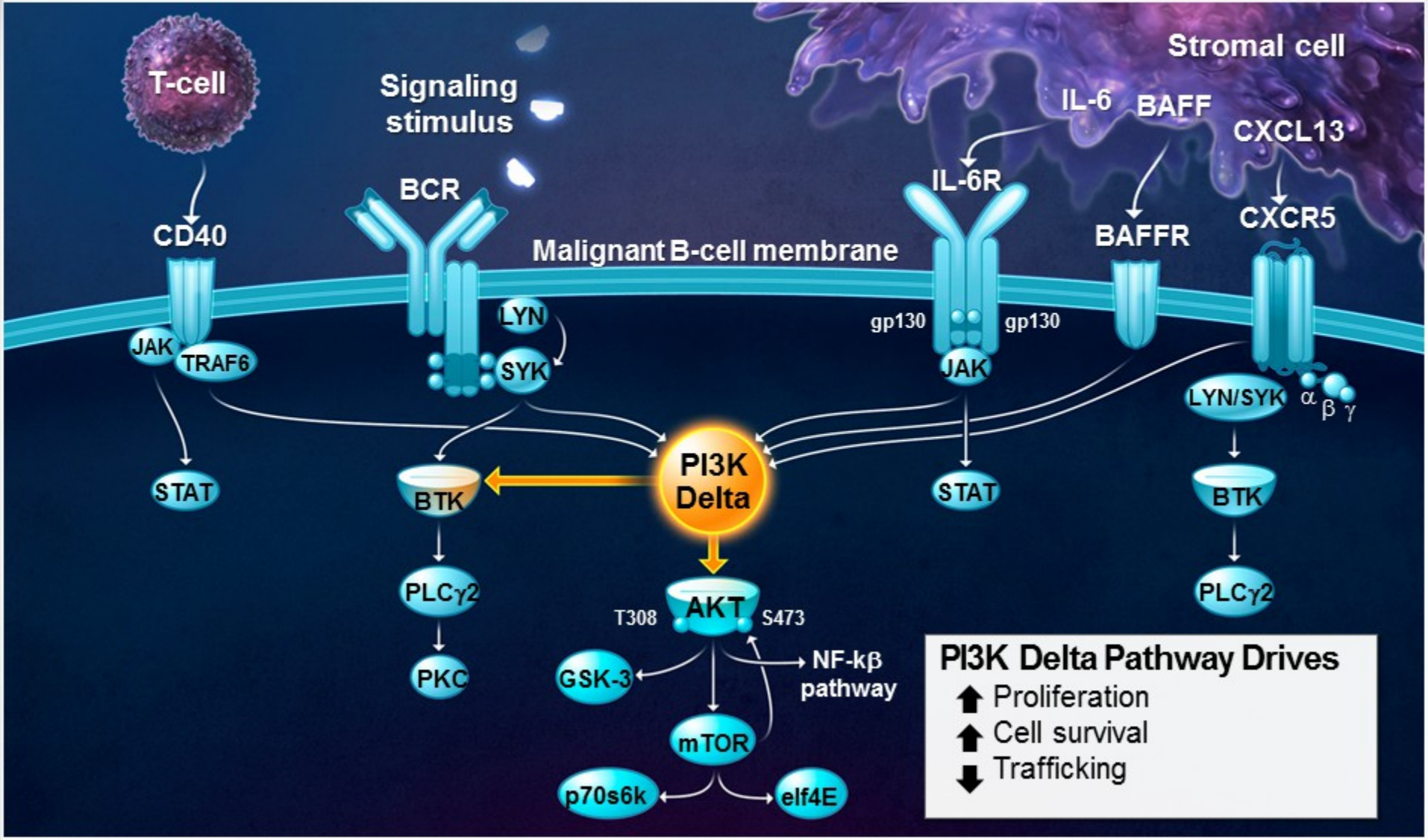


SLL



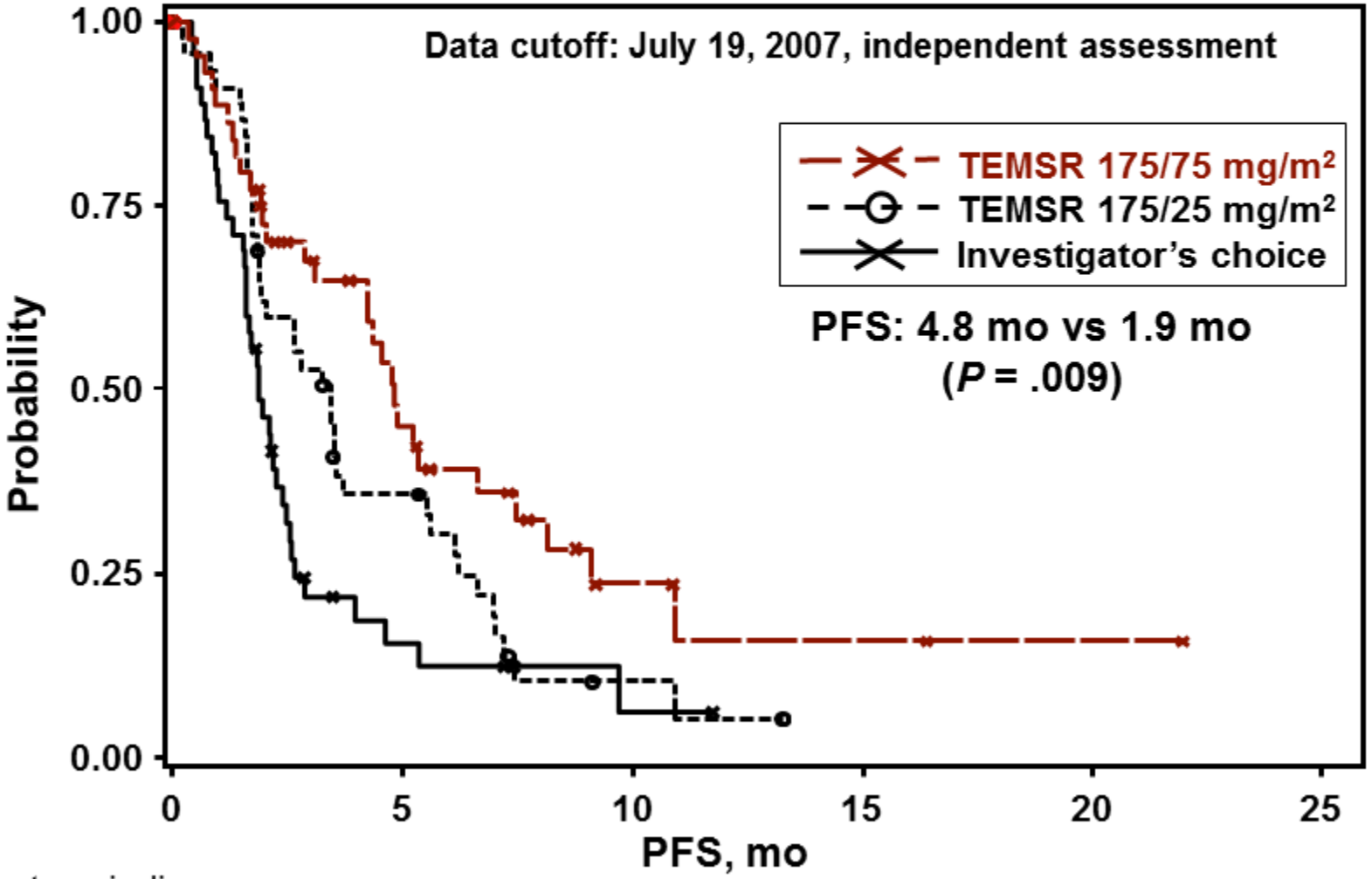
Fowler N, et al. International Conference on Malignant Lymphoma. Abstract 137. 2011.

In B-cell Malignancies, PI3K Delta Is at the Crossroads of Critical Signaling Pathways



Lannutti BJ, et al. *Blood.* 2011;117:2591-2594 .

Phase 3 Trial in Relapsed/Refractory MCL: Temsirolimus vs Investigator's Choice

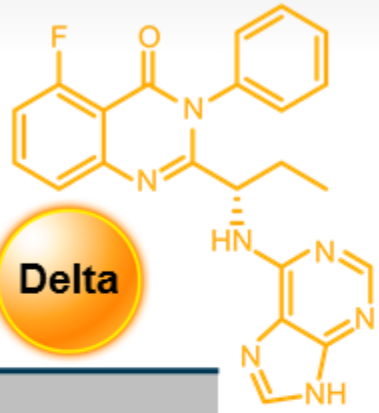


TEMSR = temsirolimus.

Hess G, et al. *J Clin Oncol*. 2009;27:3822-3829. Republished with permission.

CAL-101 Is an Oral Bioavailable Small Molecule That Inhibits PI3K Delta Potently and Selectively

CAL-101

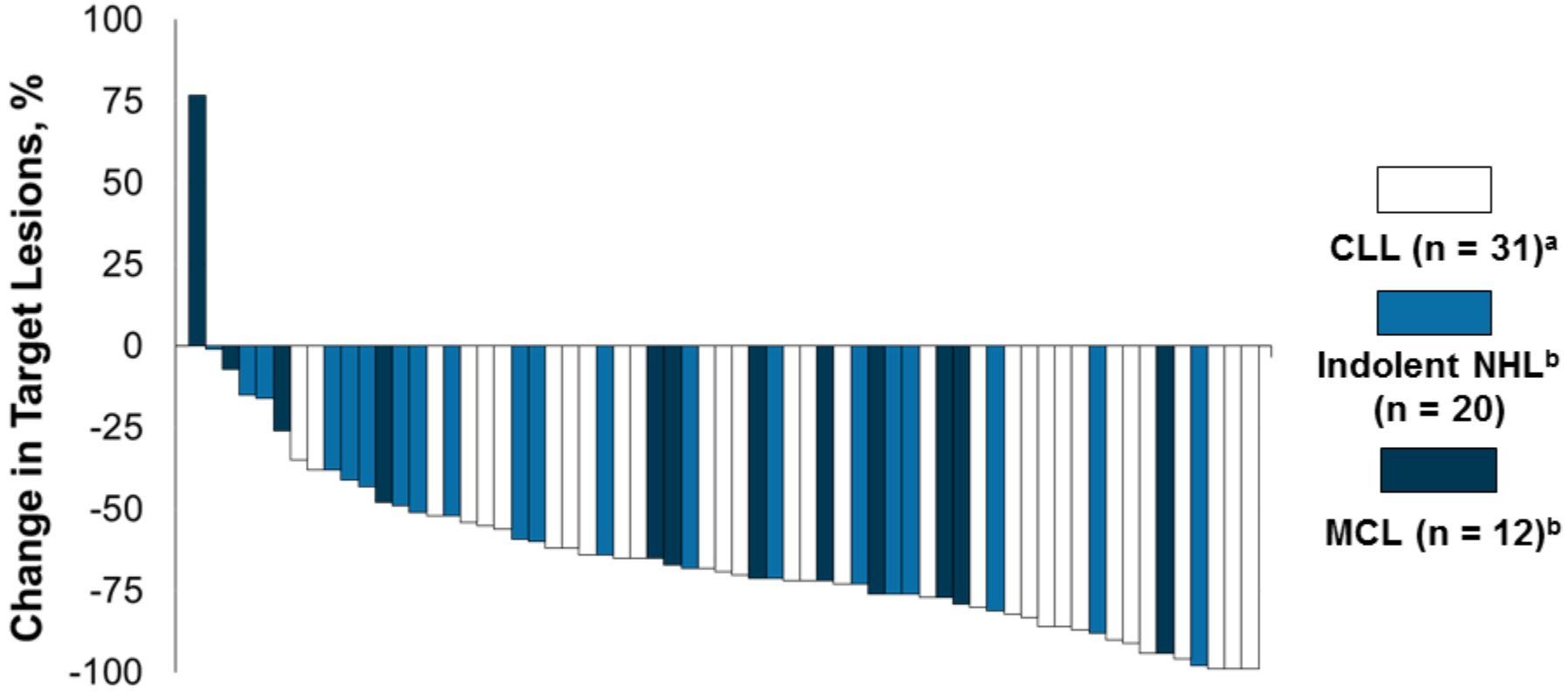


Class I PI3K Isoform	Alpha	Beta	Gamma	Delta
Cell type	Mouse embryonic fibroblasts	Mouse embryonic fibroblasts	Human basophils	Human basophils
Cell-based activity	PDGF-induced pAKT	LPA-induced pAKT	fMLP-induced CD63+	**FcεR1-induced CD63+**
EC_{50} (nM)	> 20,000	1900	3000	**8**

CAL-101 is potent against PI3K delta: EC_{50} = 8 nM in serum-free assay and 62 nM (27 ng/mL) in whole blood. It is selectivity relative to class I PI3K isoforms involved in insulin signaling and other physiological functions. No off-target activity has been seen against class II or III PI3K, mTOR, or DNA-PK; no off-target activity was seen in screen of more than 350 protein kinases (Ambit KINOMEscan).

Lannutti BJ, et al. *Blood.* 2011;117:491-594.

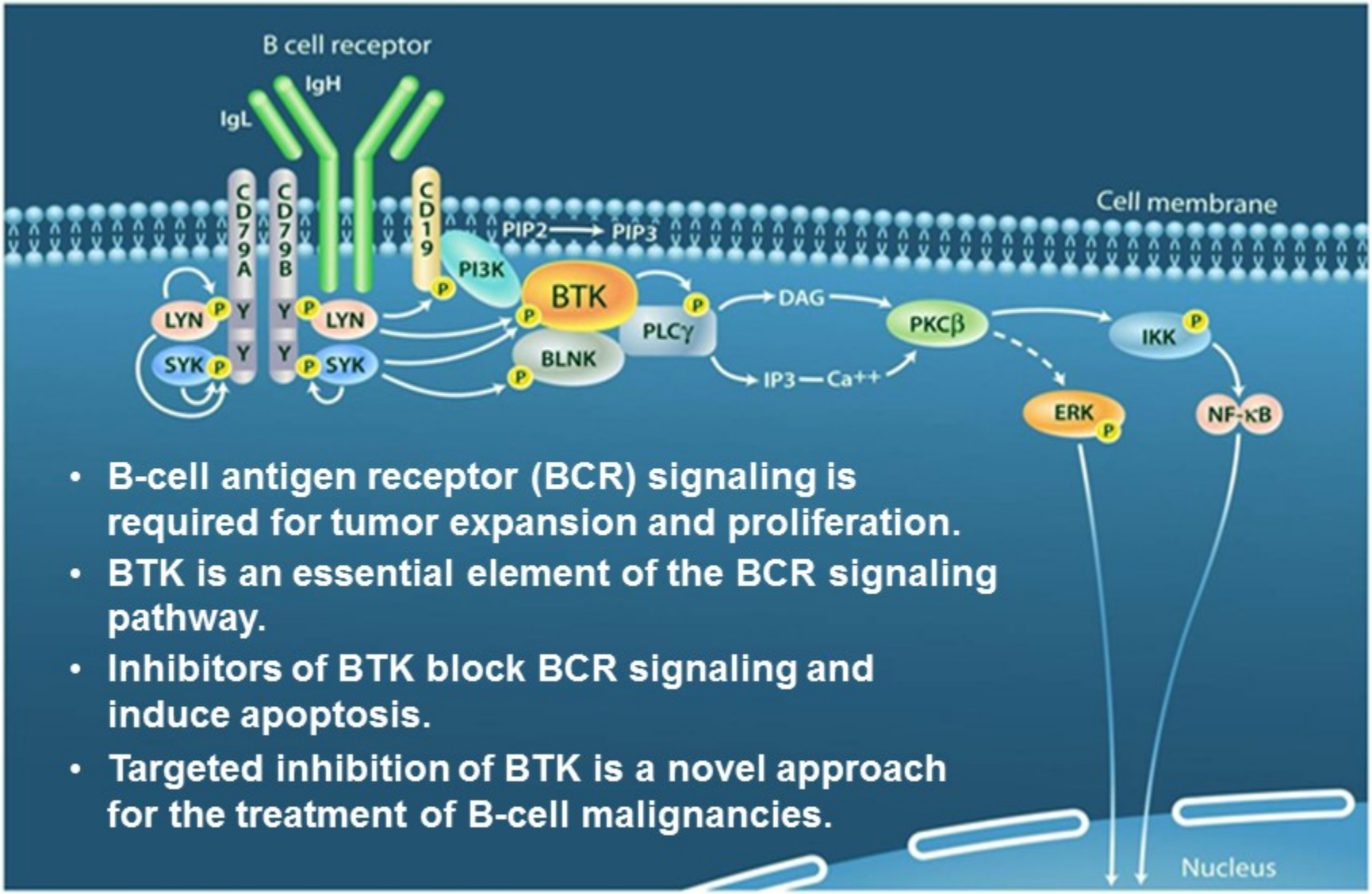
CAL101: Best Tumor Response in CLL, Indolent NHL, and MCL (N = 63)



Anti-tumor response (> 50% reduction) was observed at every dose level evaluated, with no obvious dose response.

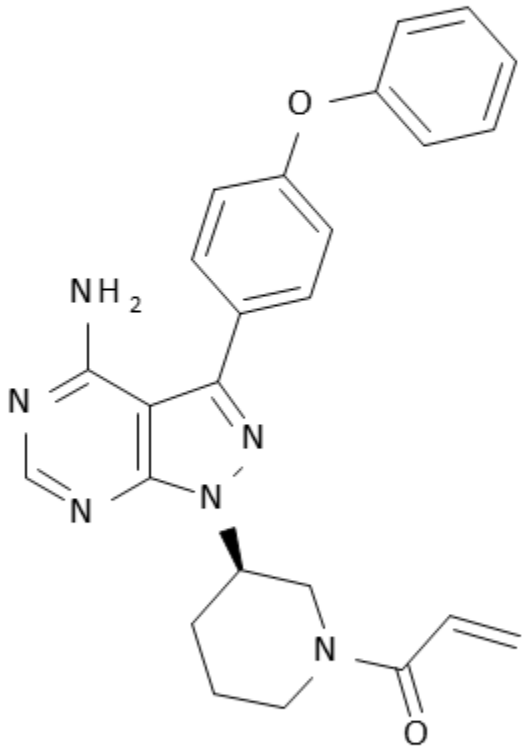
a. Furman RR, et al. *J Clin Oncol*. 2010;28. Abstract 3032.
b. Kahl BS, et al. *Blood*. 2010;116. Abstract 1777.

Bruton's Tyrosine Kinase (BTK): Critical for Lymphoma Cell Survival and Proliferation



- B-cell antigen receptor (BCR) signaling is required for tumor expansion and proliferation.
- BTK is an essential element of the BCR signaling pathway.
- Inhibitors of BTK block BCR signaling and induce apoptosis.
- Targeted inhibition of BTK is a novel approach for the treatment of B-cell malignancies.

Ibrutinib: Novel Small Molecule Inhibitor of BTK

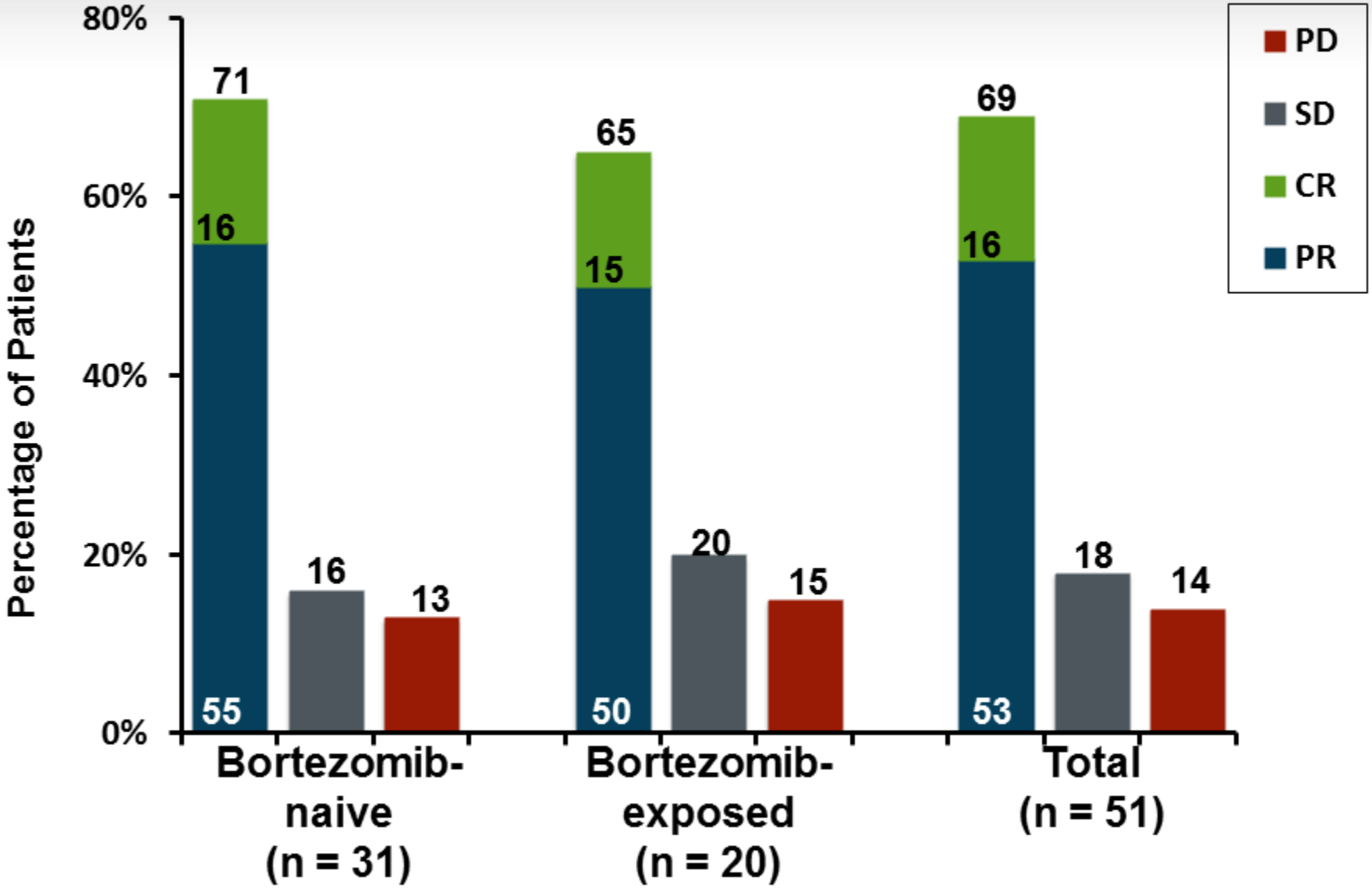


PCI-32765

- Forms a specific and irreversible bond with cysteine-481 in BTK
- Potent BTK inhibition at IC_{50} = 0.5 nM
- Orally bioavailable with daily dosing resulting in 24-h target inhibition
- Inhibits BCR signaling and has activity in spontaneous canine B-cell lymphoma
- In CLL cells, promotes apoptosis, inhibits ERK1/AKT phosphorylation, NF-κB DNA binding, CpG-mediated proliferation
- Inhibits CLL cell migration and adhesion

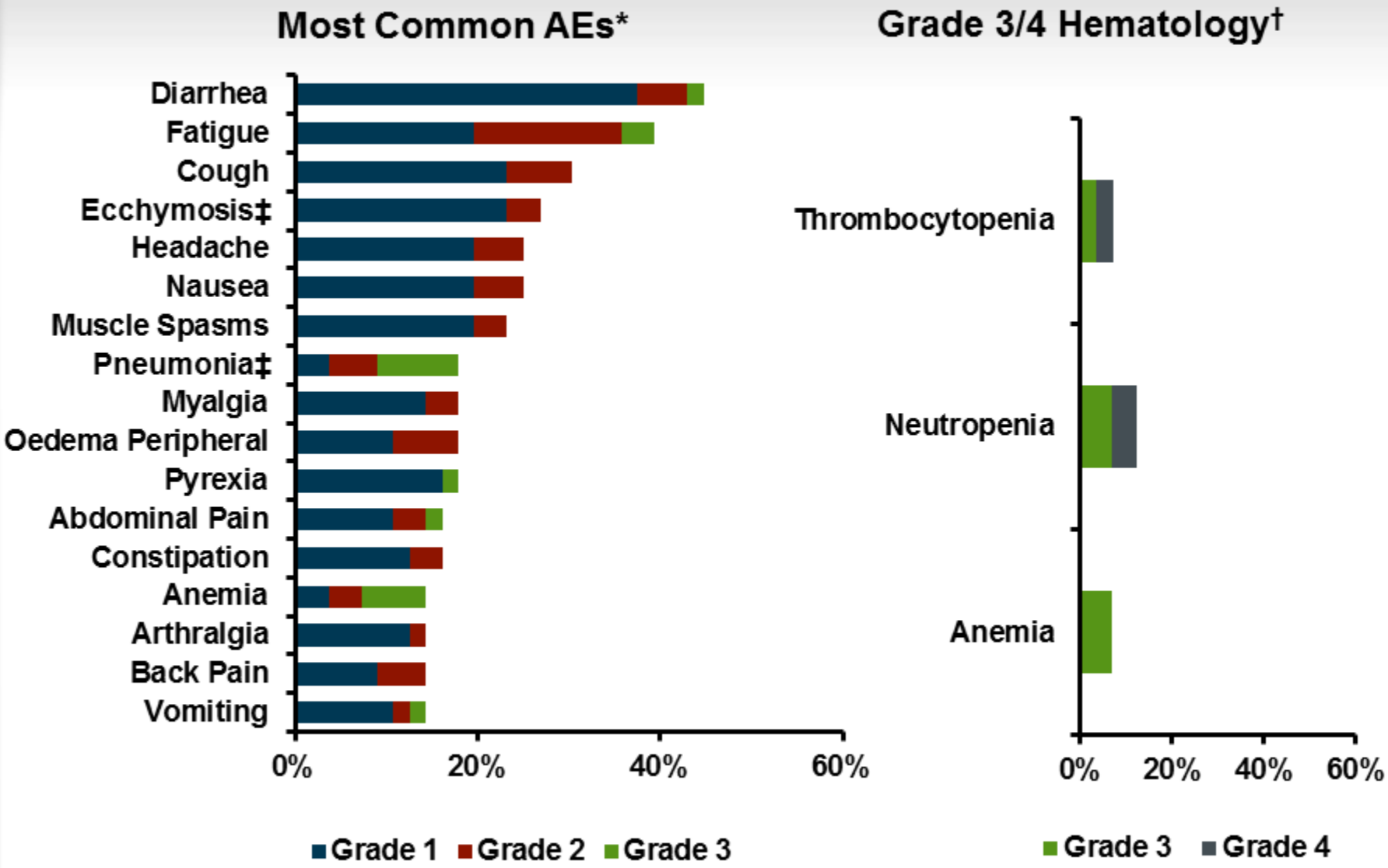
Honigberg LA, et al. *Proc Natl Acad Sci U S A*. 2010;107:13075; Herman SEM, et al. *Blood*. 2011;117:6287-6296.

Best Response to Ibrutinib*



Wang, et al. *Blood*. 2011;118. Abstract 442. Data updated by Pharmacyclics study investigators as of October 25, 2011.

AEs With Ibrutinib

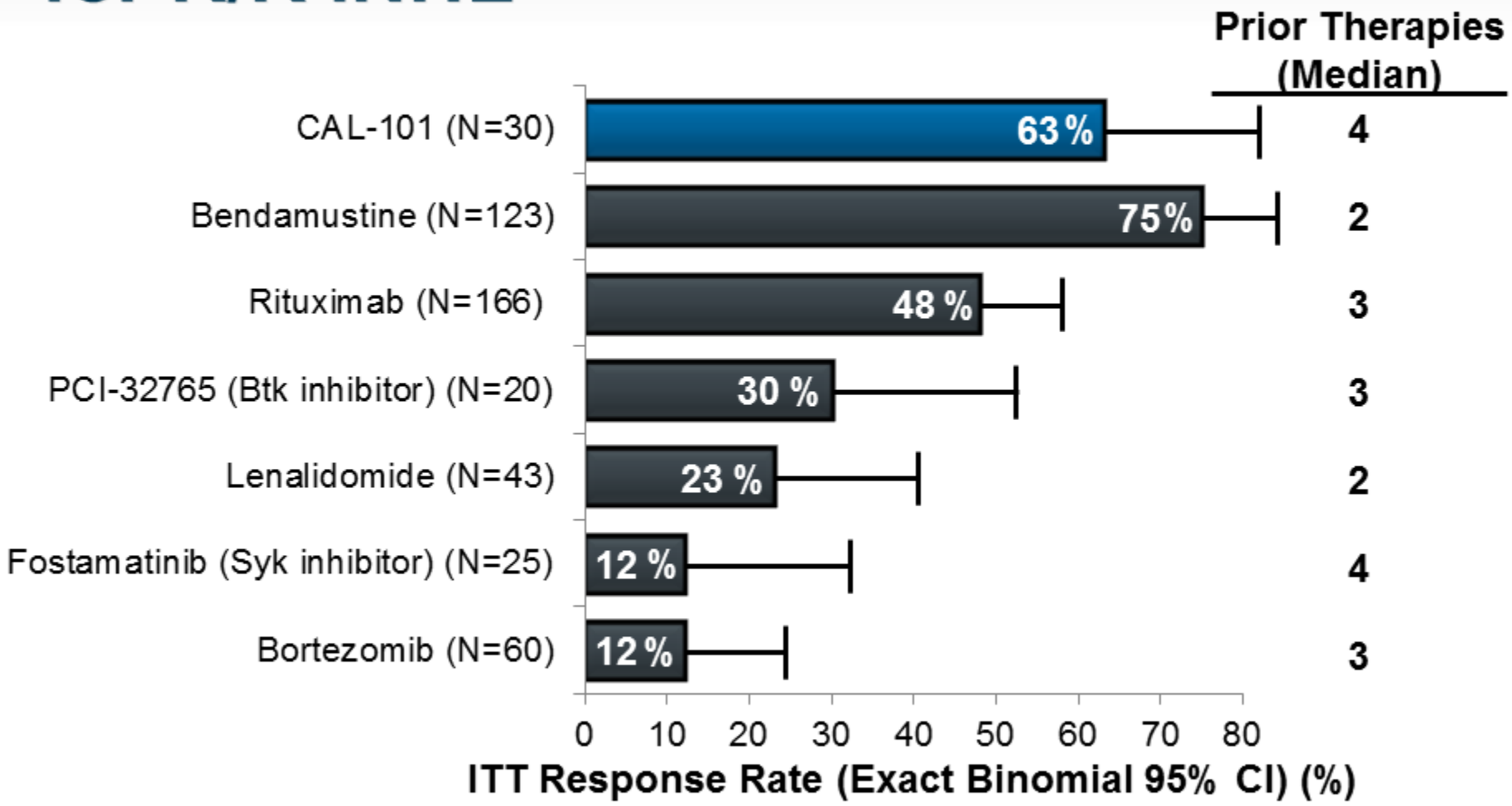


* AEs >14%.

† Based on clinical review of adverse event and laboratory data.

‡ Ecchymosis and pneumonia are combination of several preferred terms.

ORR With CAL-101 vs Other Drugs for R/R iNHL

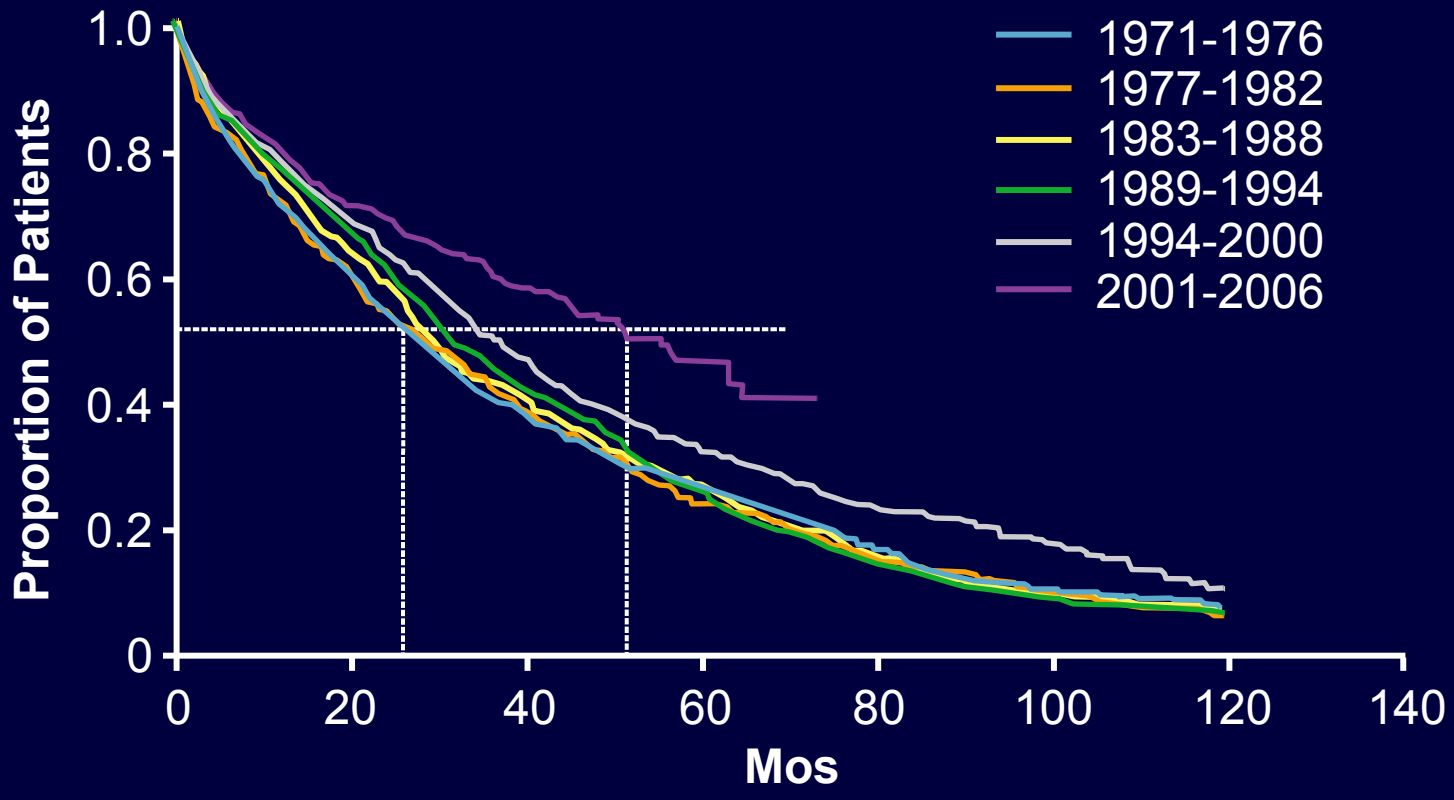


- PFS results are as good or better with CAL-101

R/R = relapsed/refractory

Image courtesy of Fredrick Hagemeister, MD.

New Treatment Options Have Improved OS in MM



Kumar SK, et al. Blood. 2008;111:2516-2520.

Plasma cell myeloma: Risk Categories

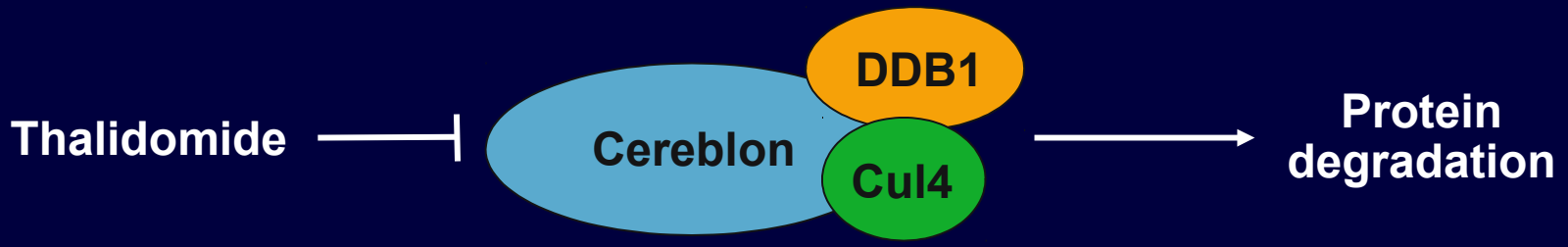
Risk Factors	Standard Risk (Expected OS: 6-7 Yrs)	High Risk (Expected OS: 2-3 Yrs)
FISH	• t(11;14) • t(6;14)	Del(17p) t(4;14)* t(14;16)
Cytogenetics	Hyperdiploidy	Hypodiploidy Del(13)
β2-microglobulin*	Low (< 3.5 mg/L)	High (≥ 5.5 mg/L)
PCLI	< 3%	High (≥ 3%)
Isotype	--	IgA
Gene expression profile	Good risk	High risk

*Patients with t(4;14), β2-microglobulin < 4 mg/L, and Hb ≥ 10 g/dL may have intermediate-risk disease.

Dispenzieri A, et al. Mayo Clin Proc. 2007;82:323-341. Fonseca R, et al. Leukemia. 2009;23:2210-2221. Munshi N, et al. Blood. 2011;117:4696-4700

Cereblon Protein Expression: Background

- Cereblon protein recently identified as primary target mediating thalidomide-related teratogenicity
  - Forms E3 ubiquitin ligase complex
  - Cereblon function in complex inhibited by thalidomide

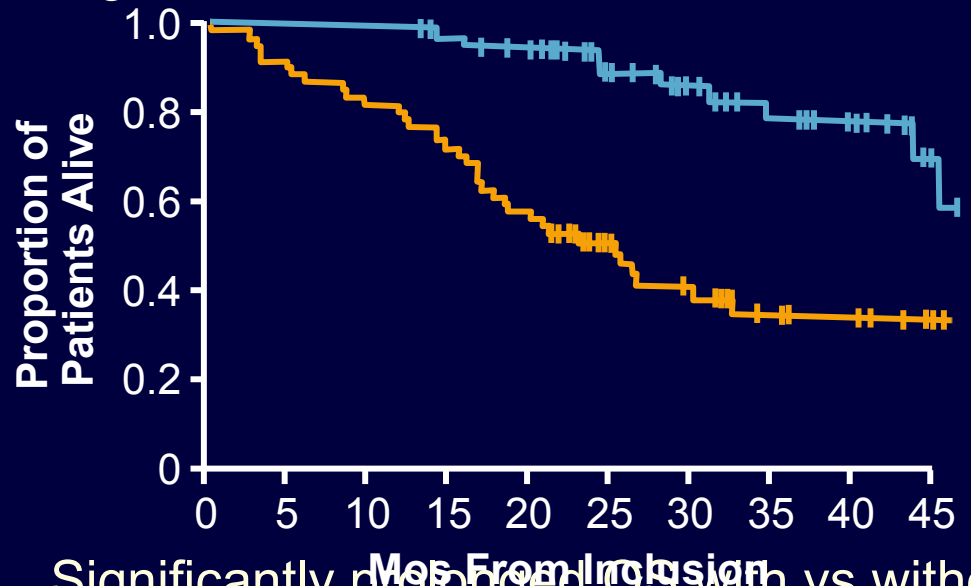


- Low levels of cereblon expression observed in lenalidomide-resistant cell lines

Ito T, et al. Science. 2010;327:1345-1350.

Smoldering myeloma (QuiRedex): TTP to Symptomatic MM and OS

- Significant increase in TTP with vs without treatment



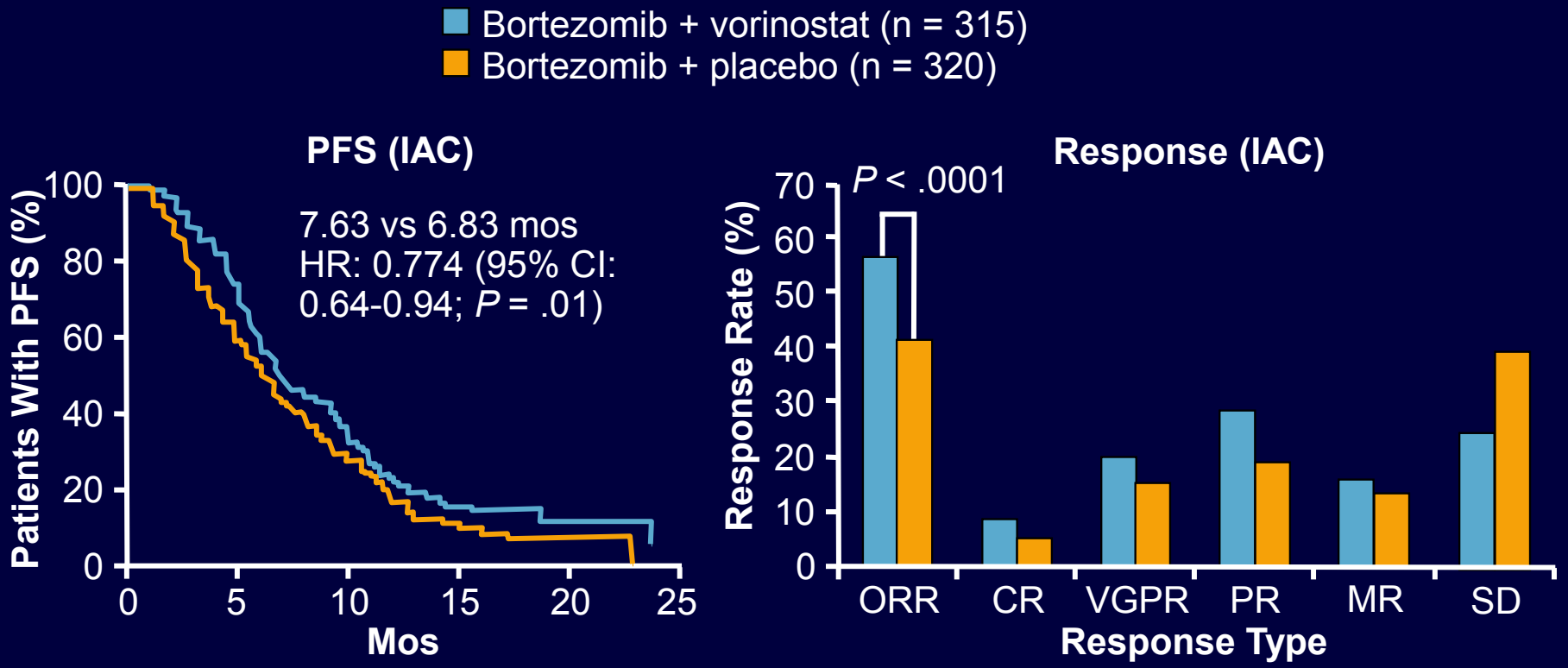
Median TTP
Lenalidomide + dexamethasone: NR
No treatment: 23 mos
HR: 6.0 (95% CI: 2.9-12.6; *P* < .0001)
Median follow-up: 32 mos (range: 12-49)

- Significantly prolonged OS with vs without treatment
  - Median 3-yr OS (from study inclusion): 93% vs 76%; *P* = .04
  - Median 5-yr OS (from diagnosis): 94% vs 79%; *P* = .03

Mateos MV, et al. ASH 2011. Abstract 991.

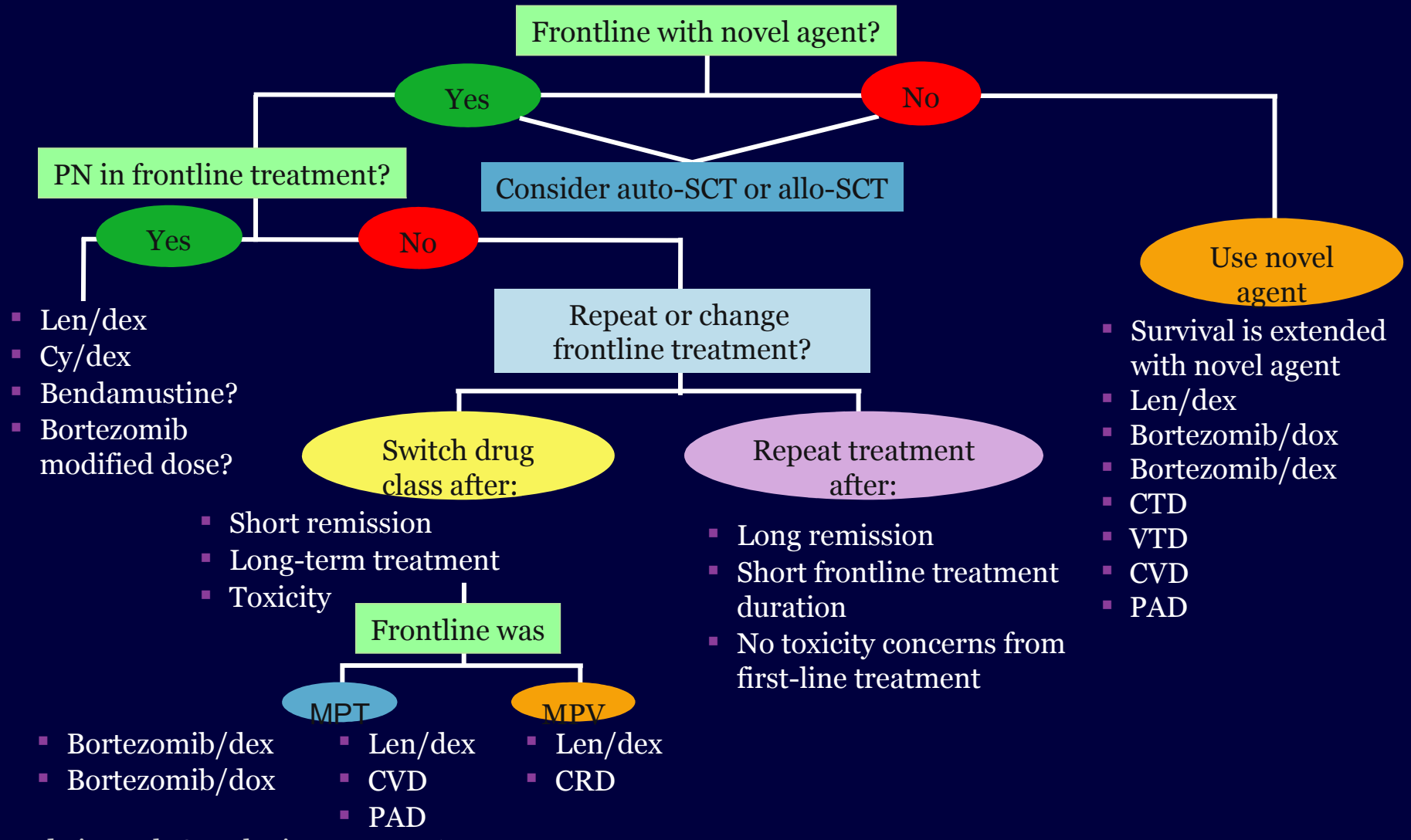
VANTAGE 088: PFS, OS, and Response

- PFS significantly prolonged with addition of vorinostat to bortezomib
  - No difference in median OS (data not yet mature)



Dimopoulos MA, et al. ASH 2011. Abstract 811.

Treatment at Relapse



Ludwig et al. Oncologist 2010;15:6-25

Polish Lymphoma Research Group

Investigator Initiated Trials – completed

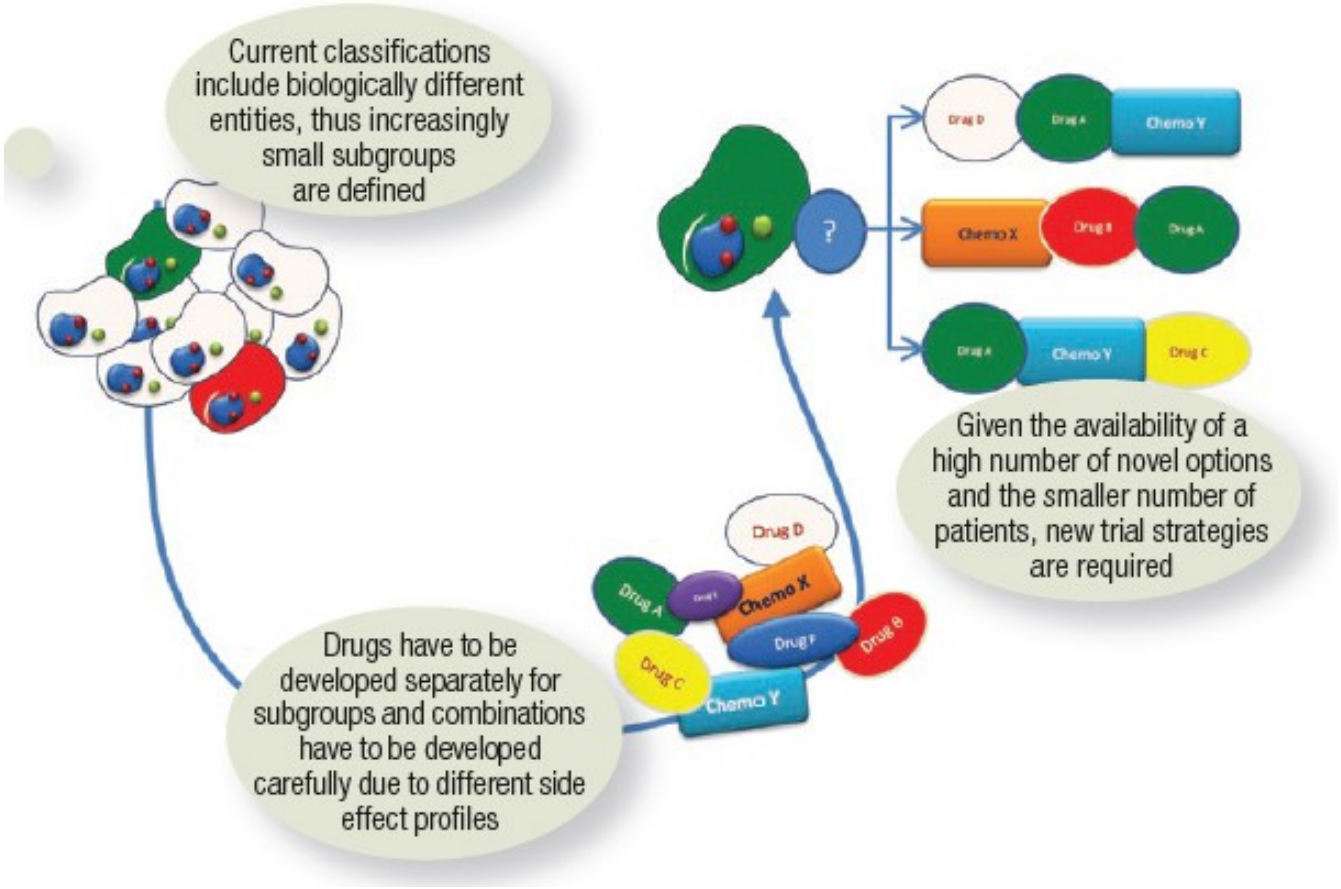
PLRG-1	Kalinka-Warzocha E et al. for the Polish Lymphoma Research Group: Randomized comparison of cladribine alone or in combination with cyclophosphamide, and cyclophosphamide , vincristine and prednisone in previously untreated low-grade B-cell non-Hodgkin lymphoma patients. ***Cancer*** 2008; 113: 367-75.
Watch & Wait	Ardeshna K et al.: An Intergroup Randomised Trial of Rituximab Versus a Watch and Wait Strategy In Patients with Stage II, III, IV, Asymptomatic, Non-Bulky Follicular Lymphoma (Grades 1, 2 and 3a). A Preliminary Analysis. ***Blood*** (ASH Annual Meeting Abstracts) 2010 116: Abstract 6
MInT	Pfreundschuh M et al.: 111 Randomised Intergroup Trial of First line Treatment for young Low-Risk Patients (<61 years) with Diffuse Large B-Cell Non-Hodgkin's Lymphoma (DLBCL) with a CHOP-like Regimen with or without the Anti-CD20 Antibody Rituximab – 6-Year Follow-up of the Mint Study of the Mabthera International Trial (MInT) Group. ***Blood*** (ASH Annual Meeting Abstracts) 2010 116: Abstract 111
PLRG-MCL	W Jurczak et al.: Radioimmunotherapy (RIT) as an alternative consolidation of MCL patients not eligible for transplant protocols – final analysis of multicenter Polish Lymphoma Research Group (PLRG) trial with 90Y-Zevalin (90Y-ibritumomab tiuxetan). ***Ann Oncol*** 2008; 19 (S4): Abstract 303

Polish Lymphoma Research Group

Investigator Initiated Trials – ongoing

PLRG-4/ ML 19931	First-line R-CVP vs R-CHOP induction immunochemotherapy for indolent lymphoma and R maintenance. A multicentre, phase III randomized study by the PLRG (accrual closed June 2011)
HOVON 68 CLL	A randomized phase III study in previously untreated patients with biological high-risk CLL: Fludarabine + cyclophosphamide (FC) versus FC + low-dose alemtuzumab (closed to accrual Nov. 2010)
ACT1	Sufficient and Timely Autologous Stem Cell Harvest After Chemoimmunotherapy with Alemtuzumab In Combination with Bi-Weekly CHOP as First Line Treatment In Systemic Peripheral T-Cell Lymphomas (PTCL): a Feasibility Analysis From the First Randomized Trial In Systemic PTCL (ACT trial). ***Blood*** (ASH Annual Meeting Abstracts) 2010 116: Abstract 2395
PET-HL	Interim-PET observational sudy
PLRG-8/ OMB114361	Badanie fazy II dotyczące zastosowania ofatumumabu w skojarzeniu z programem chemioterapii IVAC (O-IVAC) w leczeniu chorych na chłoniaki rozlane z dużych komórek B w fazie oporności lub nawrotu po uprzednim leczeniu zawierającym RCHOP niekwalifikujących się do autotransplantacji komórek krwiotwórczych

The development of novel agents can be limited, as the more specific the target is, the smaller the group of patients that can benefit from it



Hess G: New drugs and novel treatment strategies. In: Ghielmini M, Montoto S (Eds.) Lymphomas. Essentials for clinicians. pp. 85-88