The “New” Concept of Chemo-Free Treatment Regimens

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Dicloure$

- Celgene – Consulting, Research funding*
- Pharmacyclics - Consulting, Research funding
- Gilead - Consulting, Research funding
- Roche-Genentech - Consulting, Research funding
- Medimmune/AZ - Consulting, Research funding
- Seattle Genetics - Consulting, Research funding
- Abbvie – Consulting, Research funding
- Astellas - Consulting
- Teva – Research Funding
- Acerta – Research Funding

* All research funding to institution

History of Chemotherapy: Alkylating Agents

WWI/WWII – chemical warfare
- Skin ulcerations
- Blindness
- Lung Damage
- Nausea, vomiting
- Mutagenic
- Carcinogenic

- Accidental exposure led to low lymphs
- May have similar effect on cancer cells
- 1940's – first i.v. tx of lymphoma with mustard – impressive, brief responses

Alkylating Agents in Lymphoma/CLL

NHL
R-CHOP
R-CVP
B-R
ICE
BEAM

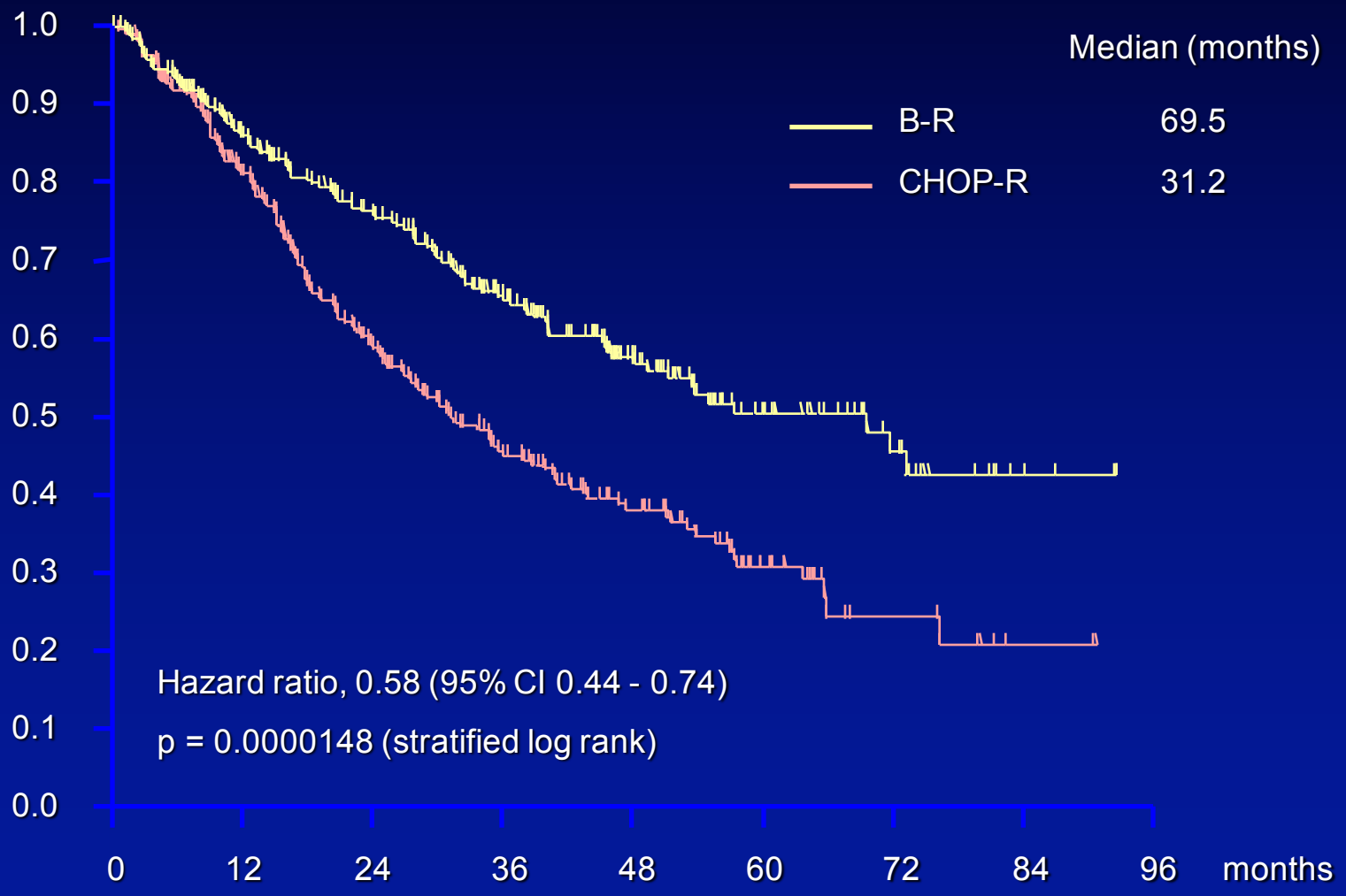
Hodgkin's
MOPP
ABVD
BEACOPP

CLL
FCR
BR

Various
Chlorambucil
Busulphan

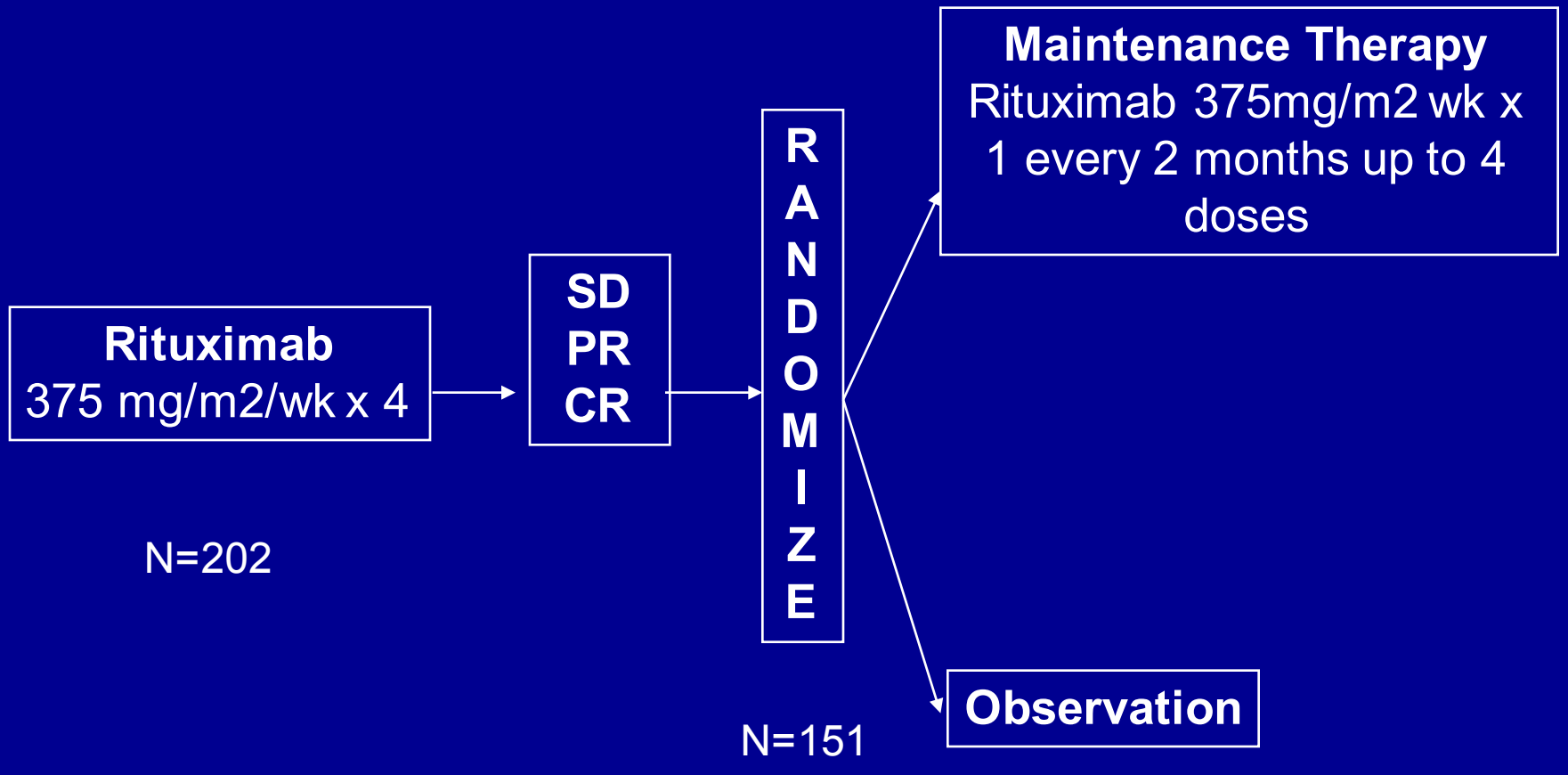
Progression free survival

45 months follow-up



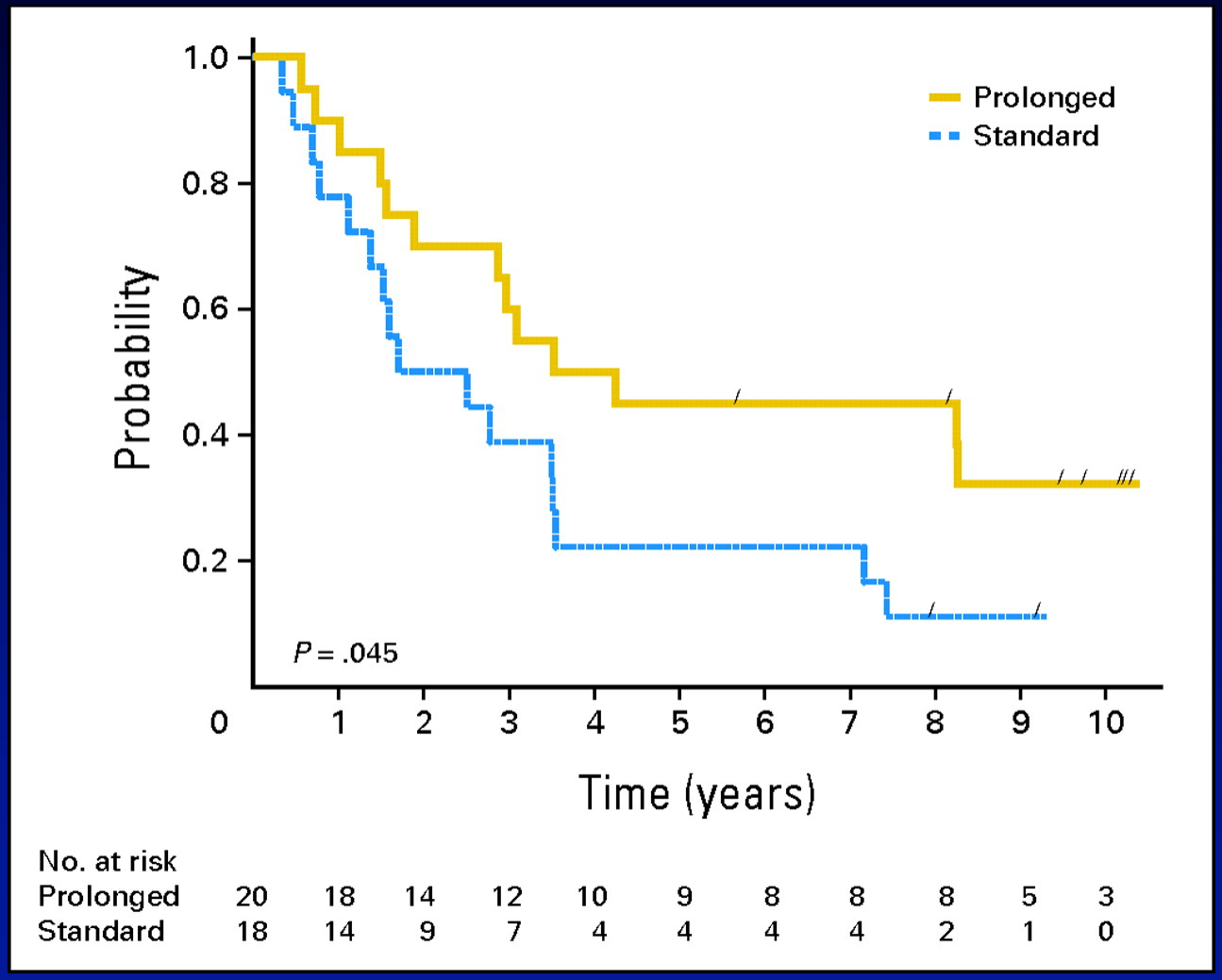
Lancet 381:1203, 2013

SAKK 35/98: Prolonging Remission with Rituximab Maintenance Therapy



Ghielmini et al, Blood 103:4416, 2004

EFS for previously untreated patients responding to induction treatment



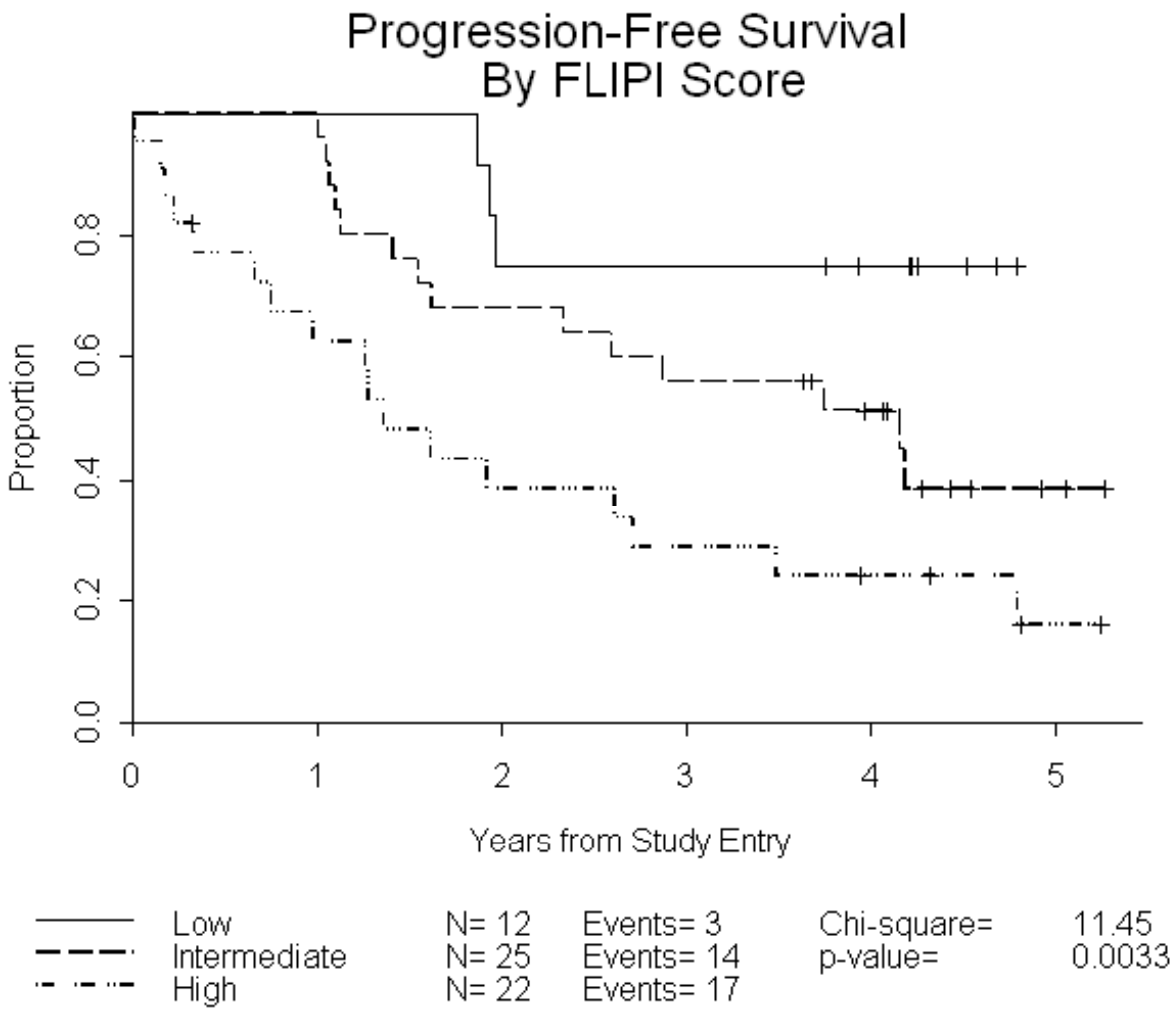
Martinelli G et al. JCO 2010;28:4480-4484

CALGB-50402: Galiximab+Rituximab in Previously Untreated FL

		ORR (p=0.059)	CR (p=0.03)
FLIPI Score	**0-1**	**11 (92%)**	**9 (75%)**
	2	**20 (80%)**	**12 (48%)**
	3-5	**12 (55%)**	**6 (27%)**

- ORR not associated with stage, gender, bulky disease, marrow involvement, or age > 60

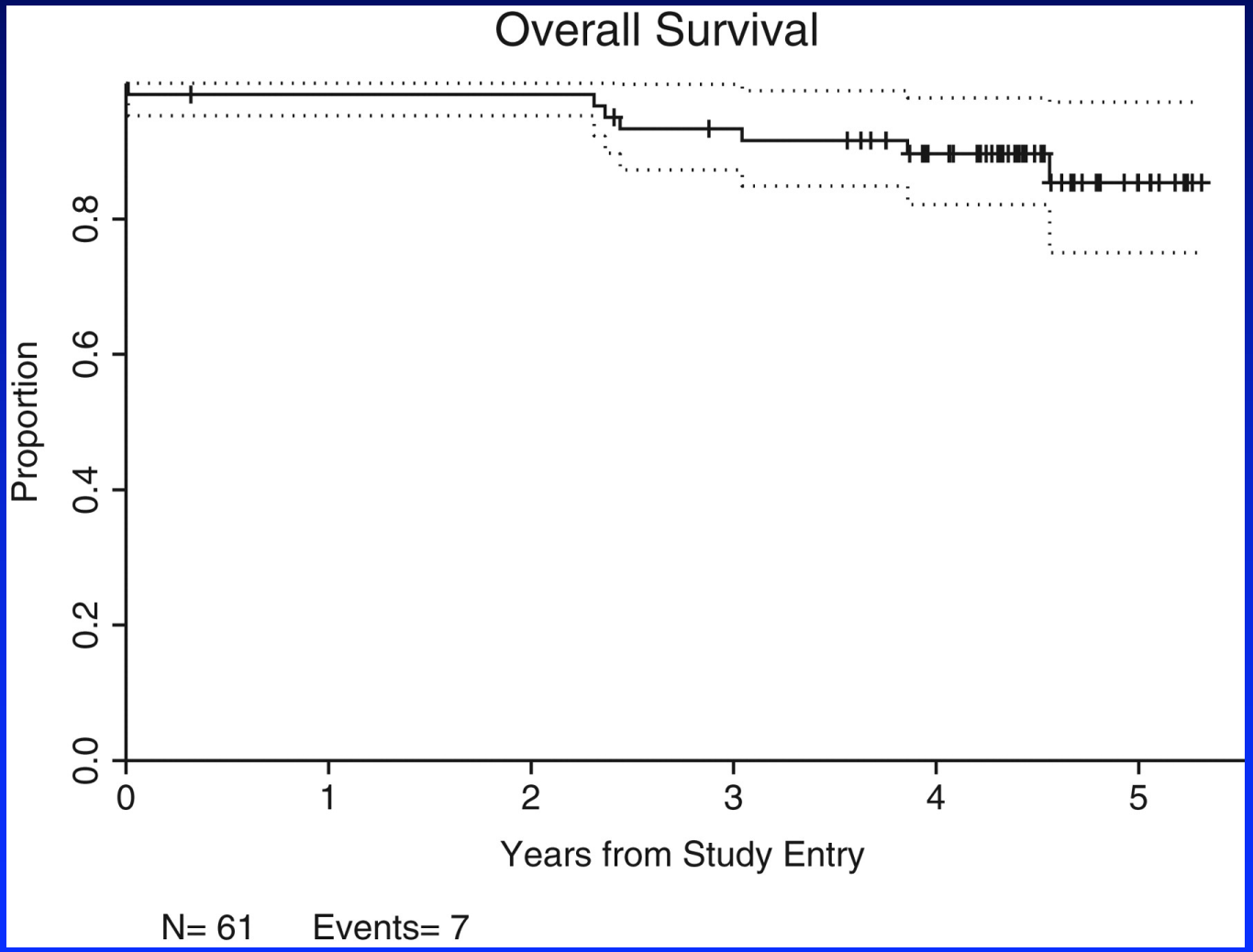
Czuczman et al, Ann Oncol, 23:2356, 2012



Czuczman et al, Ann Oncol, 23:2356, 2012

(Med f/u 4.3 y)

Overall survival of 61 assessable pts over a median follow-up time of 4.3 years

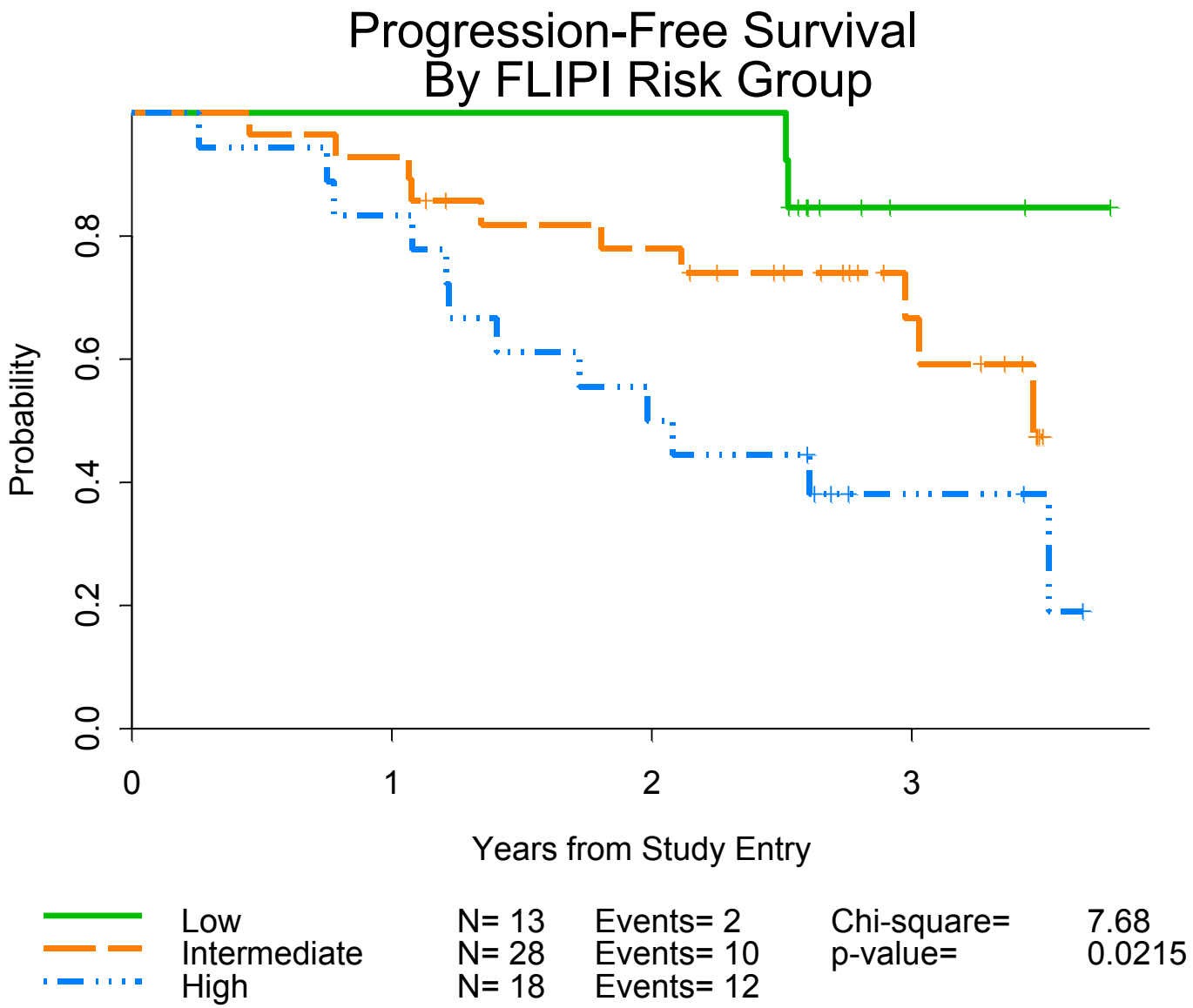


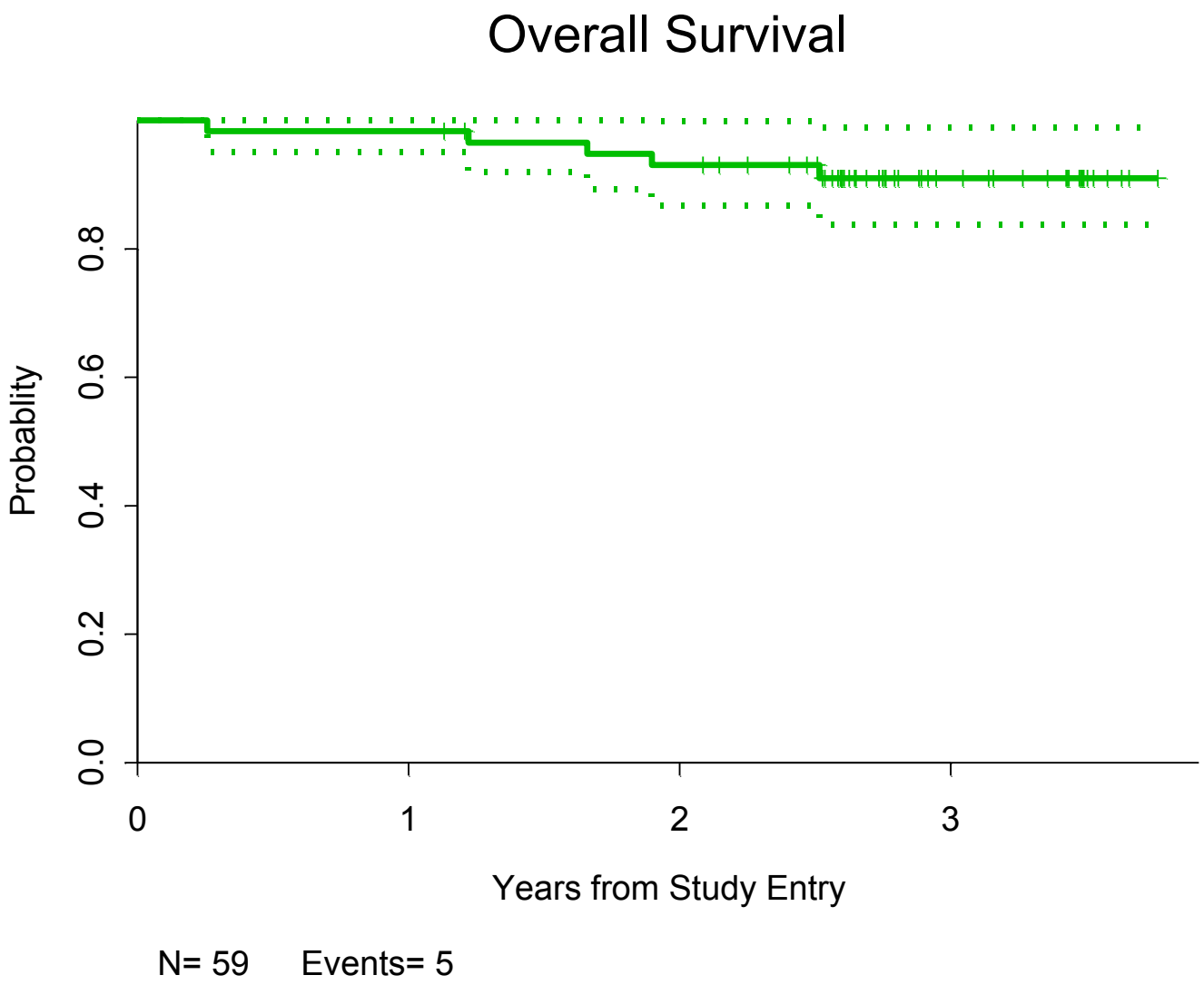
Czuczman M S et al. Ann Oncol 2012;23:2356-2362

CALGB-50701

- Epratuzumab + rituximab
- 59 evaluable pts
- Fifty-five of the 59 eligible pts completed all therapy
- ORR 86.5%
  - 25 CRs (42.4%)
  - 27 PRs (45.8%)
  - 6 had stable disease (10.2%)
- Median time to CR was 9.2 months
- 21 pts progressed (4 after CR, 13 after PR; 4 after stable disease)

Grant et al, Cancer, 119:3797, 2013


Progression-Free Survival
By FLIPI Risk Group
Probability
0.0
0.2
0.4
0.6
0.8
0
1
2
3
Years from Study Entry
Low
Intermediate
High
N= 13
N= 28
N= 18
Events= 2
Events= 10
Events= 12
Chi-square= 7.68
p-value= 0.0215

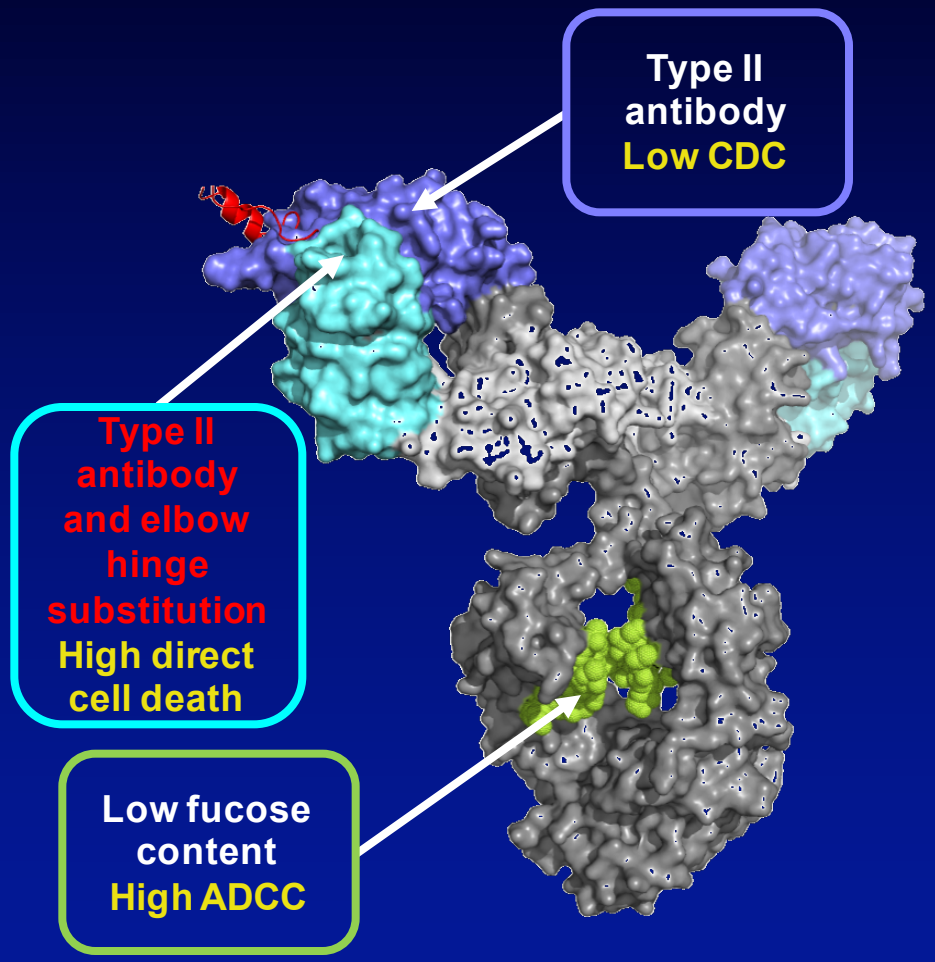

Overall Survival
Probablity
0.0
0.2
0.4
0.6
0.8
0
1
2
3
Years from Study Entry
N= 59
Events= 5

New Targeted Agents

Agent	Target
Obinutuzumab/Ublituximab	CD20
Polatuzumab vedotin	CD79b
Ibrutinib	Btk
Acalabrutinib (ACP-196)	Btk
Entospletinib (GS-9973)	Syk
Idelalisib	PI3-K
TGR-1202	PI3-K
Duvelisib (IPI-145)	PI3-K
Venetoclax (ABT-199)	Bcl-2
Selinexor	XP01 (Nuclear transport)
Lenalidomide	Multiple
Nivolumab	PD-1
Pembrolizumab	PD-1
Pidilizumab	PD-1

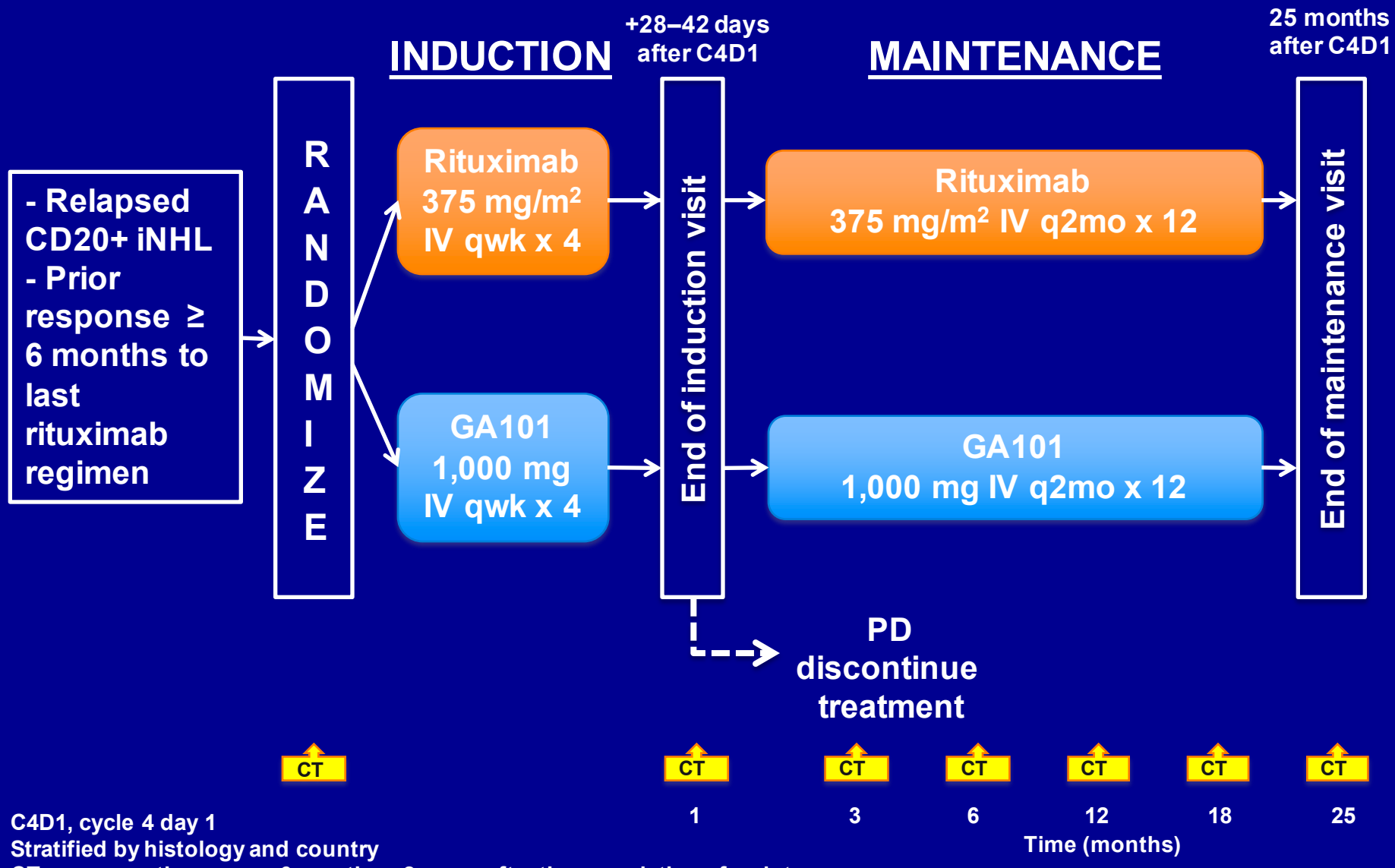
Obinutuzumab

- Obinutuzumab: humanized, glycoengineered, anti-CD20, type II monoclonal antibody[1]
  - Recognizes different epitope on CD20 than rituximab and therefore engages different signals on the target cell (type II)[2]
  - Optimized for direct cell death activity[3]
  - Glycoengineering improves affinity for FcγRIIIa receptors[3]
- Obinutuzumab has demonstrated superior preclinical activity to type I antibodies in vitro and in vivo[1]



1. Mössner E, et al. Blood. 2010;115:4393-4402. 2. Niederfellner G, et al. Blood. 2011;118:358-367.
3. Alduaij W, et al. Blood. 2010;117:4519-4529.

GAUSS: Open label Phase II randomized study



C4D1, cycle 4 day 1
Stratified by histology and country
CT scans continue every 6 months x 2 years after the completion of maintenance
Response assessment based upon Cheson BD, et al. *JCO.* 1999;17:1244

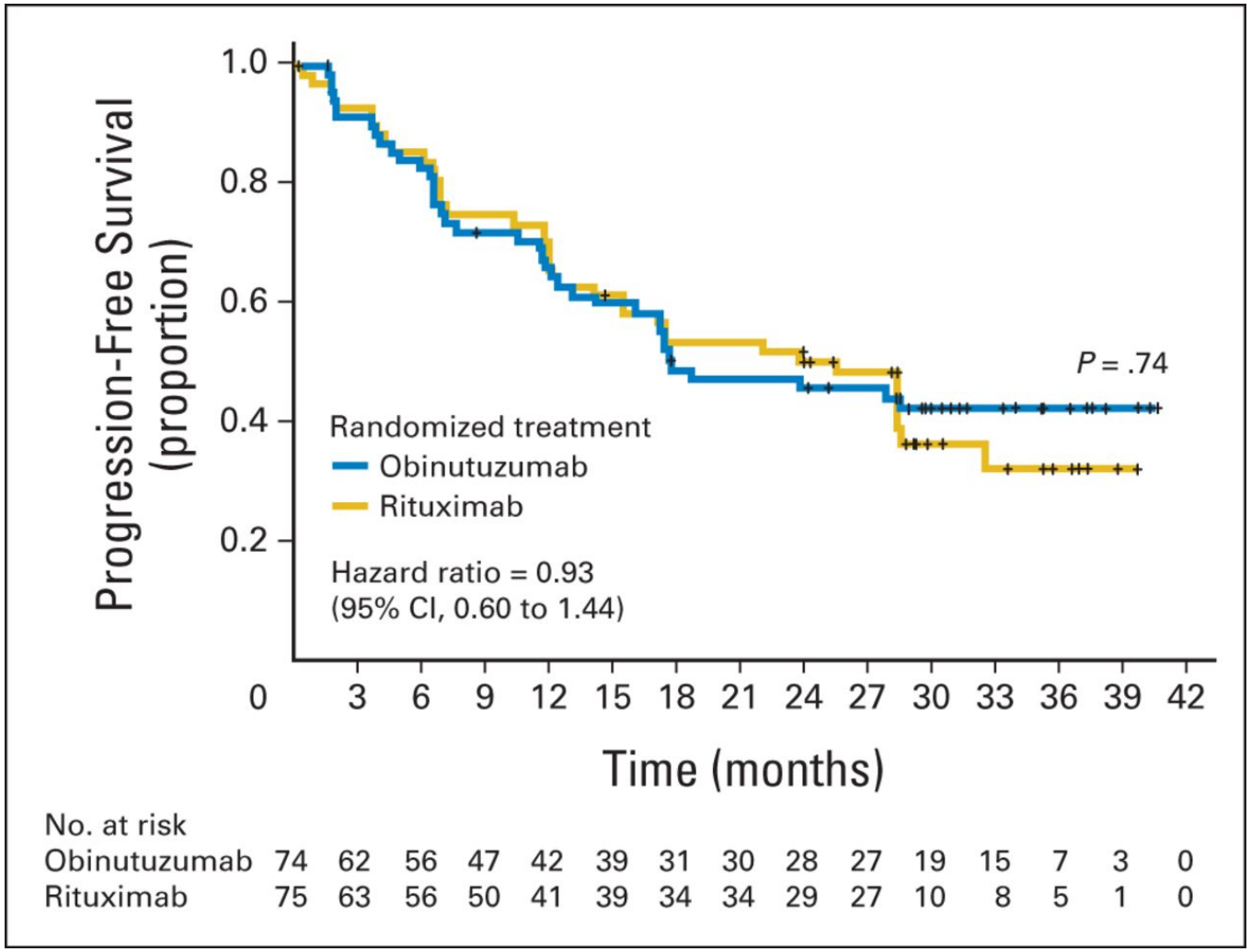
Sehn LH, et al, J Clin Oncol 33:3467, 2015

Best overall response by IRF in FL patients

Response, n (%)	Rituximab (n = 75)	GA101 (n = 74)
Overall response rate (ORR)	35 (46.7)	45 (60.8)
CR/CRu	15 (20.0)	20 (27.0)
PR	20 (26.7)	25 (33.8)
Difference in ORR, % [95% CI]	14.1 [–2.5; 30.8]	
p-value (one-sided, chi-squared test)	0.04	

IRF, independent review facility

Progression-free survival of patients with follicular lymphoma treated with obinutuzumab versus rituximab monotherapy.



Laurie H. Sehn et al. JCO 2015;33:3467-3474

Amping up monoclonal antibodies: Antibody-drug conjugates (ADC)

Sievers Annu Rev Med. 2013;64:15-29

ROMULUS:Investigator-Assessed Best Responses in Treated Patients [a]

	DLBCL		FL	
	R+CD22 ADC (N=42)	R+CD79b ADC (N=39)	R+CD22 ADC (N=21)	R+CD79b ADC (N=20)
Objective response, n (%)	**24 (57%)**	**22 (56%)**	**13 (62%)**	**14 (70%)**
Complete Response	10 (24%)	6 (15%)	2 (10%)	8 (40%)
95% CI	[12%-39%]	[6%-31%]	[11%-30%]	[19%-64%]
Partial Response	14 (33%)	16 (41%)	11 (52%)	6 (30%)
95% CI	[20%-50%]	[26%-58%]	[30%-74%]	[12%-54%]
Stable disease, n (%)	3 (7%)	4 (10%)	6 (29%)	6 (30%)
Progressive disease, n (%)	7 (21%)	11 (30%)	1 (5%)	0
Unable to evaluate, n (%)	8 (19%)	2 (5%)	1 (5%)	0
Median Duration of Response, mo. (95% CI)	6.0 (2.9-12.2)	NR (2.6-NR)	5.8 (2.6-10.1)	NR (5.7-NR)

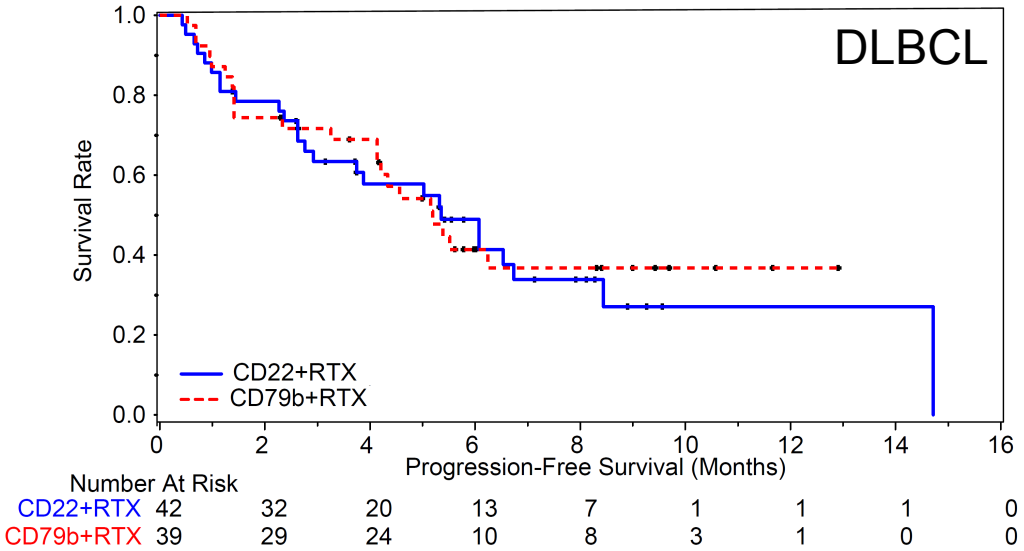
[a] Patients who received ≥ 1 dose of study treatment; patients unable to evaluate did not have a post-baseline tumor assessment

NR = Not reached

Data Cut-Off: 21FEB2014

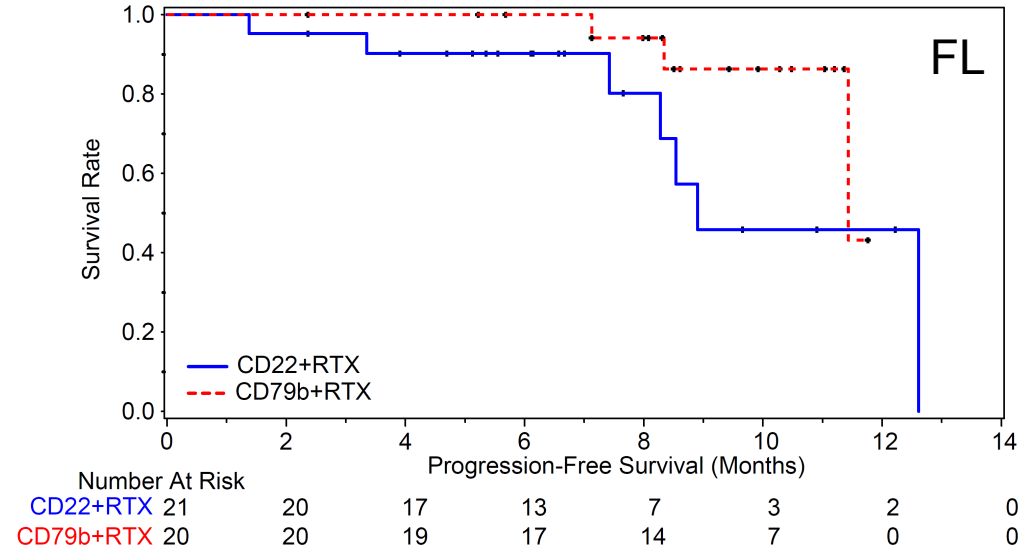
Morschhauser JCO 32:5a abstr 8519, 2014

Progression Free Survival



Median PFS, mo. (95% CI)	
R+CD22 ADC (N=42)	R+CD79b ADC (N=39)
5.4 mo. (2.8-8.4)	5.2 mo. (4.1-NR)

NR = Not reached

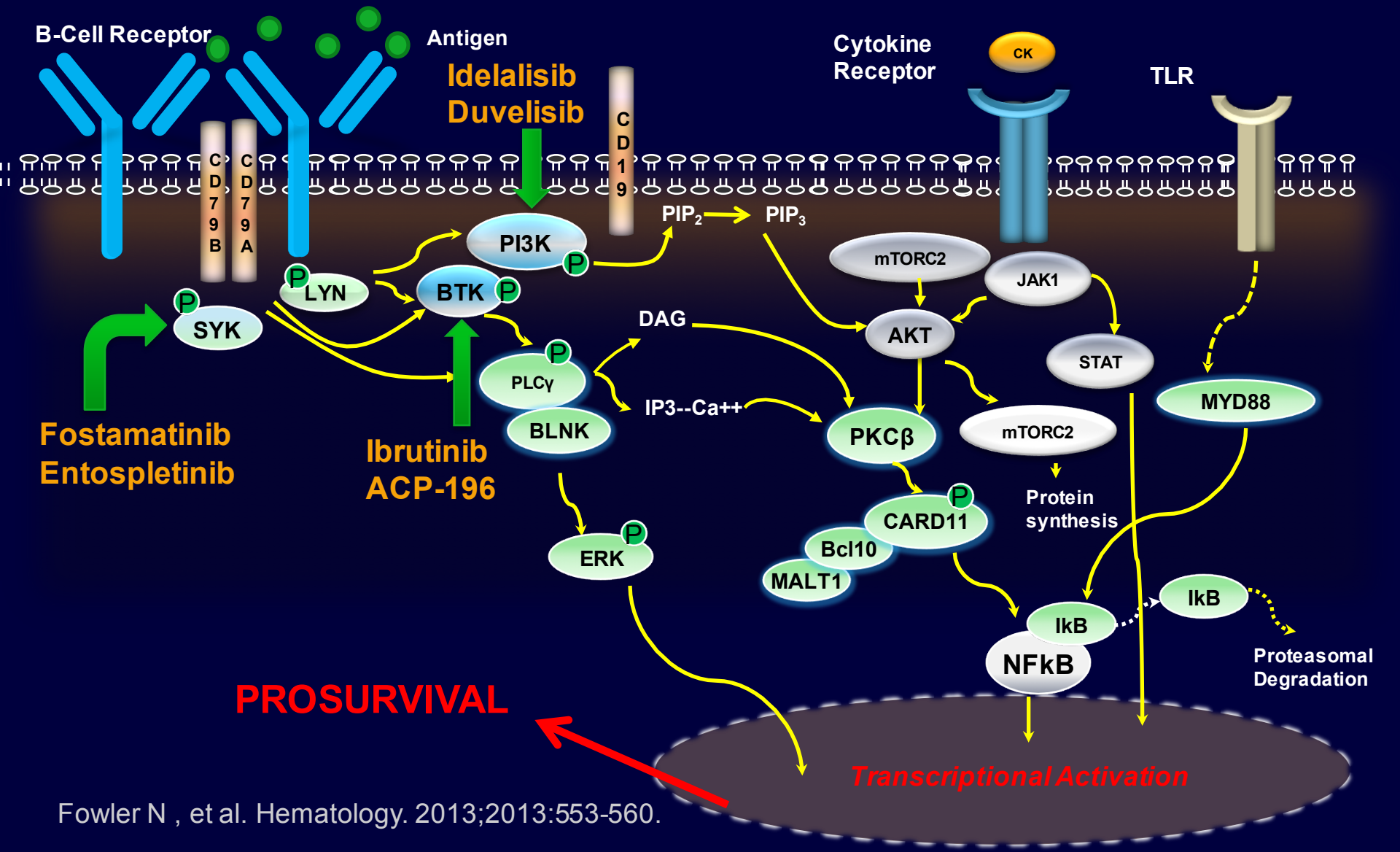


Median PFS not reported due to insufficient duration of follow-up

Data Cut-Off: 21FEB2014

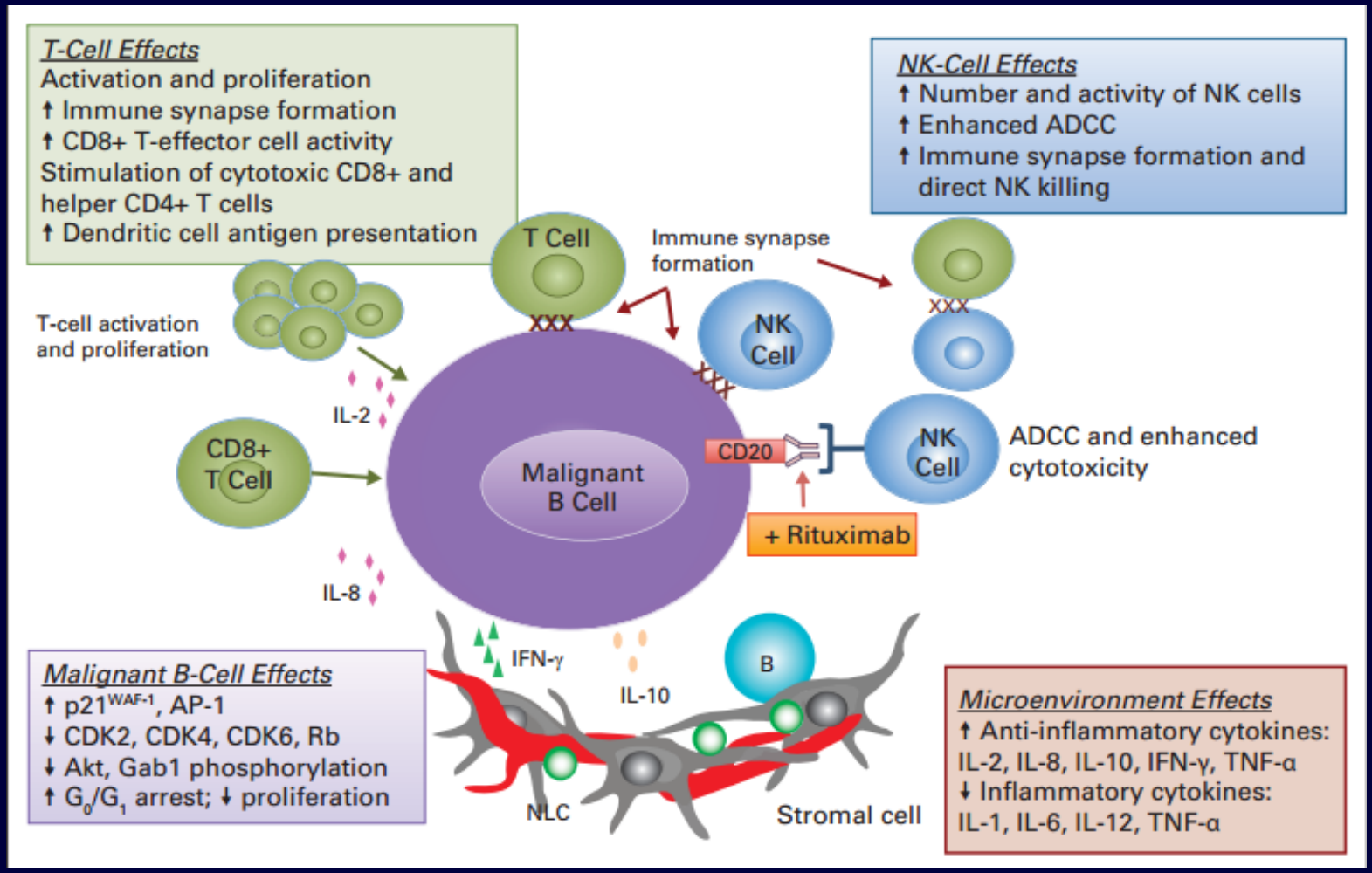
Morschhauser JCO 32:5a abstr 8519, 2014

Targets of B-Cell Receptor Signaling



Fowler N , et al. Hematology. 2013;2013:553-560.

Lenalidomide: Mechanisms of Action

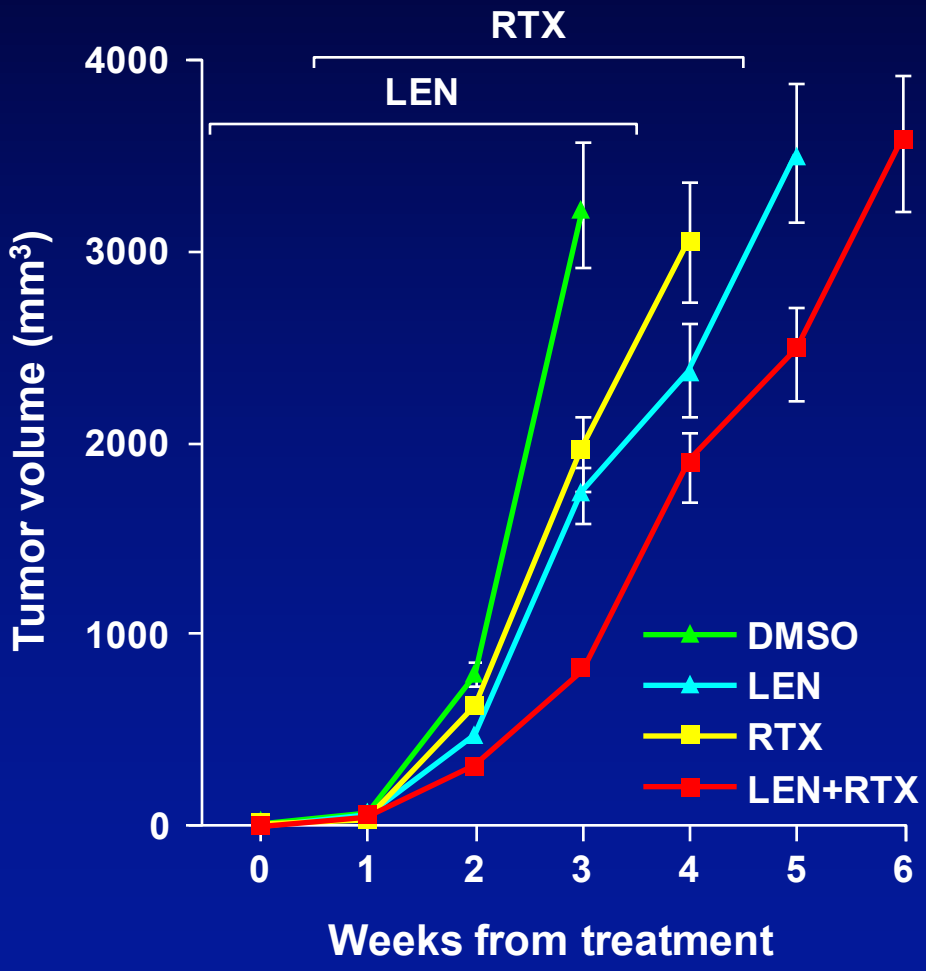


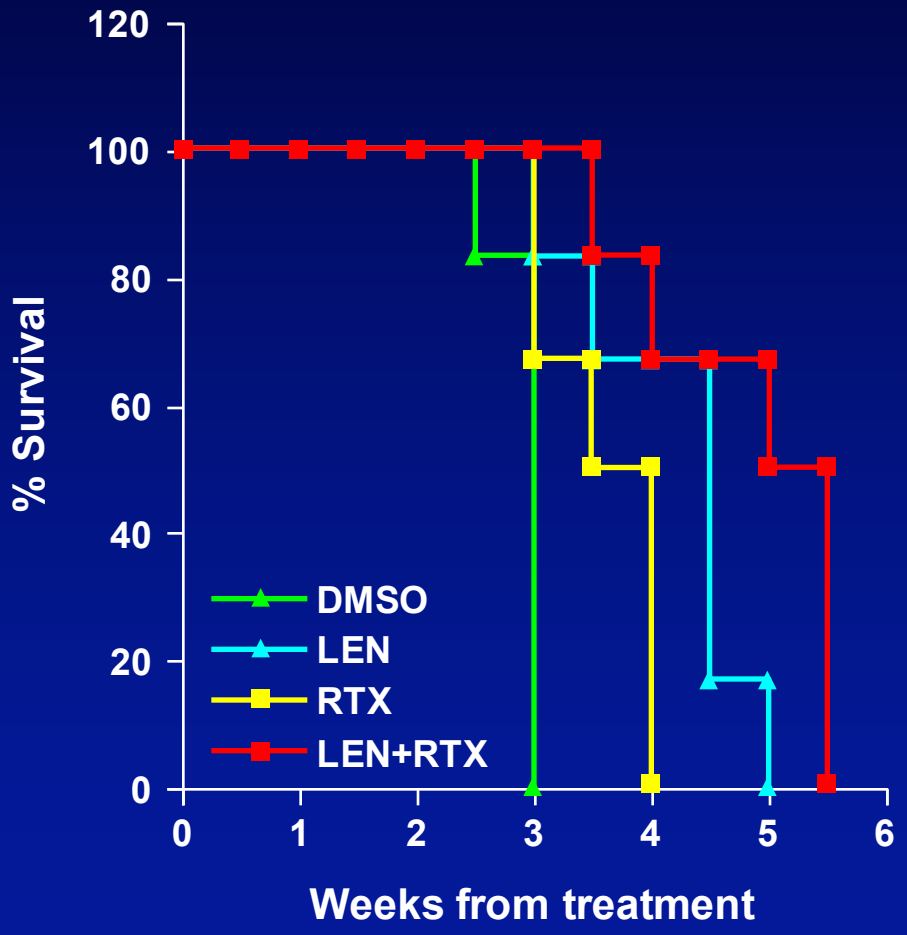
Gribben JG, et al. J Clin Oncol. 2015;33:2803-2811.

Lenalidomide in CLL and B-NHL

Histology	ORR (%)	CR/CRu (%)
CLL	32-45	7-9
Follicular/Indolent	23-51	7-13
DLBCL	28	12

Lenalidomide+Rituximab MCL Cells in SCID Mice





Zhang L, et al. Am J Hematol. 2009;84:553-9.

CALGB 50401: Response and event-free survival

	L (N=45)	L + R (N=44)
Overall (ORR)	51.1% 95% CI (35.8-66.3)	72.7% 95% CI (52.2-85.0)
Complete (CR)	13.3%	36.4%
Partial (PR)	37.8%	36.4%
Median EFS	1.2 yrs	2.0 yrs
2 year EFS	27%	44%

Median F/U 1.7 years (0.1 – 4.1)

Unadjusted EFS HR of L vs L+R is 2.1 (p=0.010)

Adjusted (for FLIPI) EFS HR of L vs L+R is 1.9 (p=0.061)

Leonard et al, JCO 33:3635, 2015

CALGB50803:Best Response

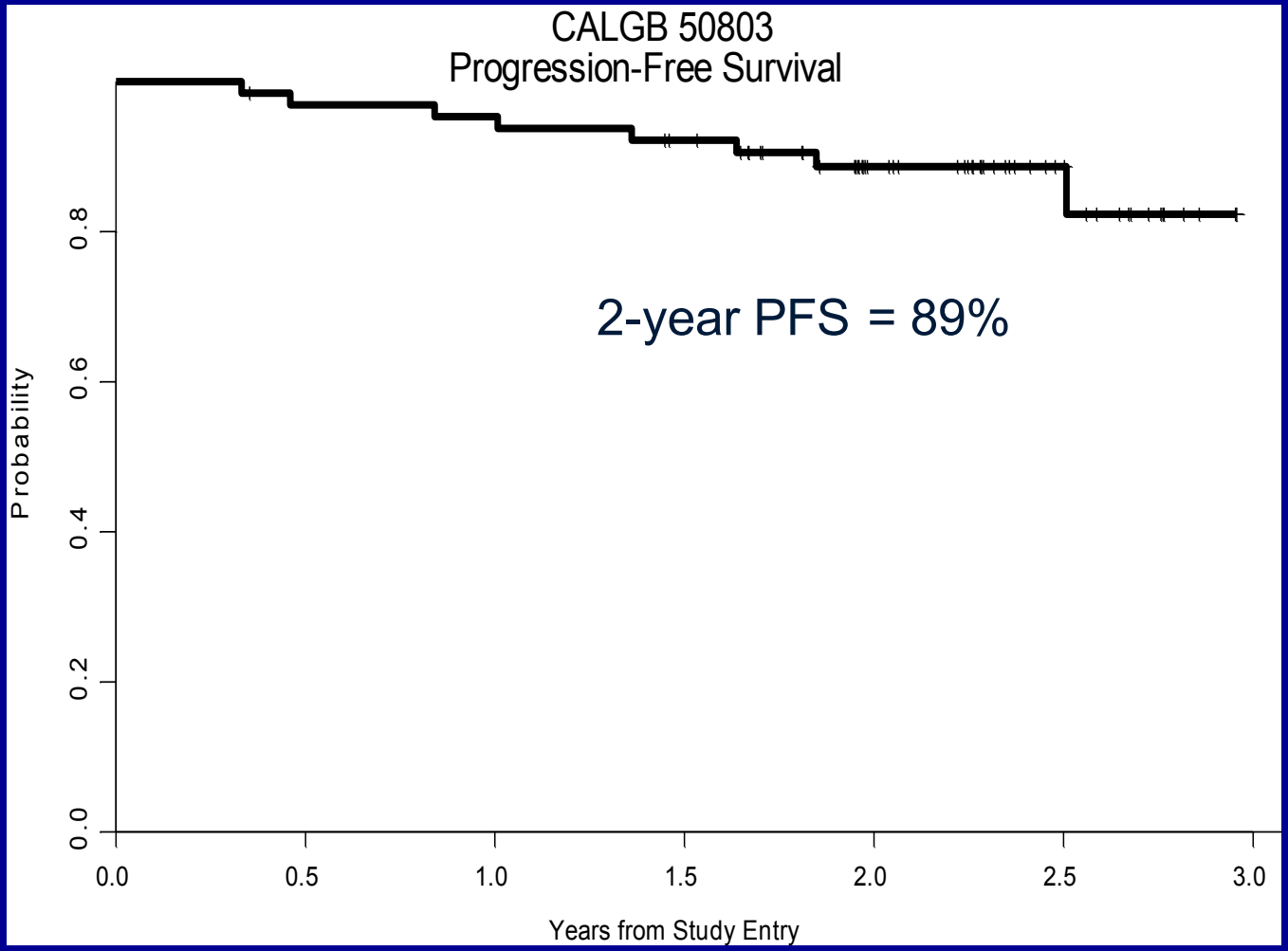
	Overall N =55	FLIPI 0-1 N = 16	FLIPI 2 N = 35	FLIPI 3 N = 2	FLIPI unk N=2
ORR	**53 (96%)**	16 (100%)	33 (94%)	2 (100%)	2 (100%)
CR	**39 (71%)**	12 (75%)	24 (69%)	2 (100%)	1 (50%)
PR	**14 (25%)**	4 (25%)	9 (26%)	-	1 (50%)
SD	**2 (4%)**	0 (0%)	2 (6%)	-	-

4 additional patients in PET- CR but not confirmed by BMBx. There was no significant association between CR rate and FLIPI score, presence of bulky disease, or grade.

Martin et al, Proc ASCO 2014, abstr 8521

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

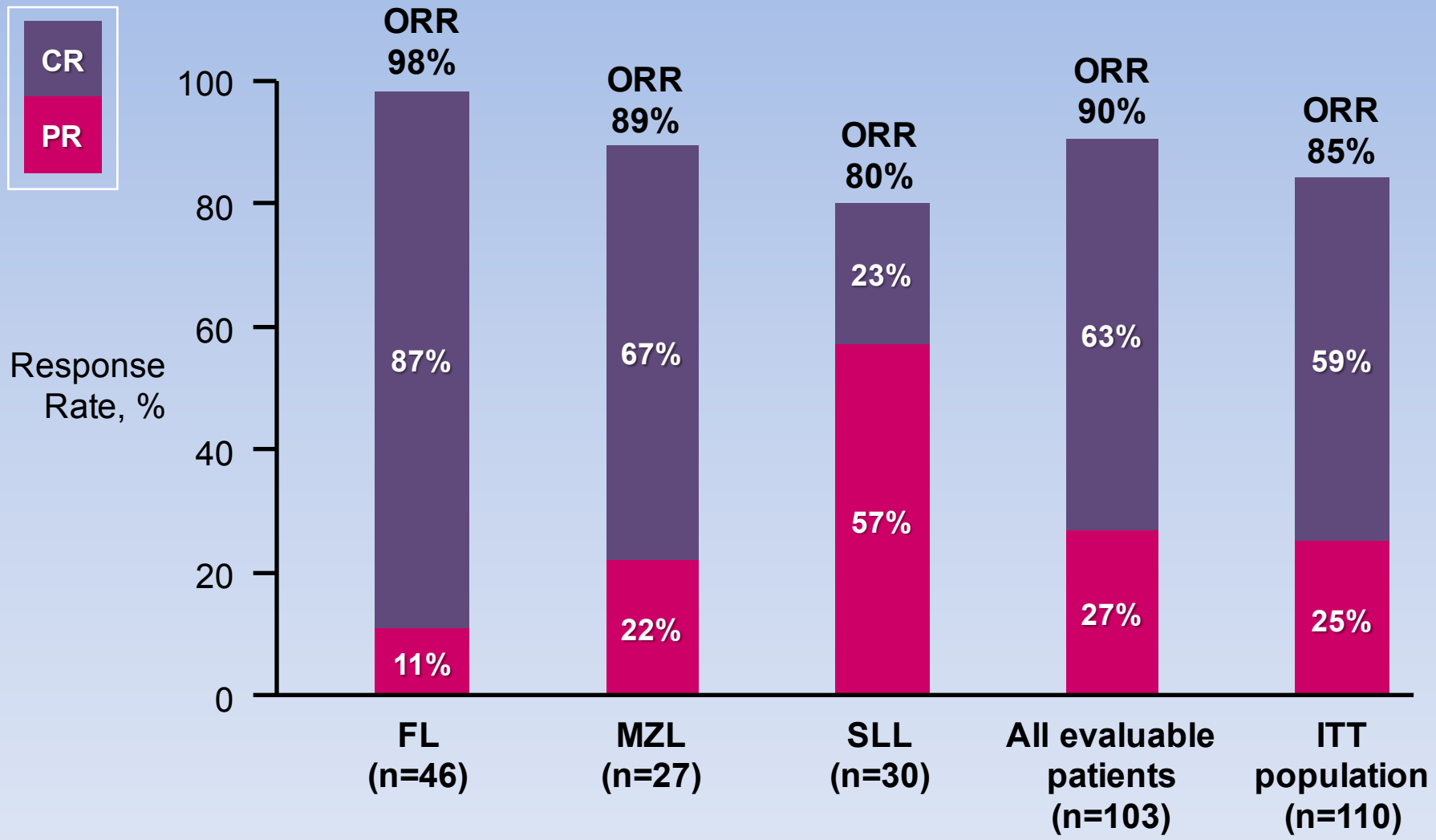
Progression-free survival



ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Lenalidomide + Rituximab (R2) in Untreated Indolent Lymphoma

Response Rates



Fowler NH, et al. *Lancet Oncol.* 2014,15:1311-1318.

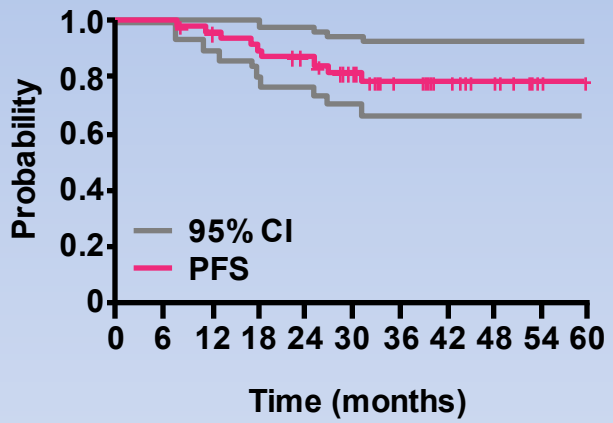
Lenalidomide + Rituximab (R2) in Untreated Indolent Lymphoma

Efficacy

Median PFS for the entire cohort was 53.8 months (95% CI, 50.6–NA)

FL Median PFS: **not reached**

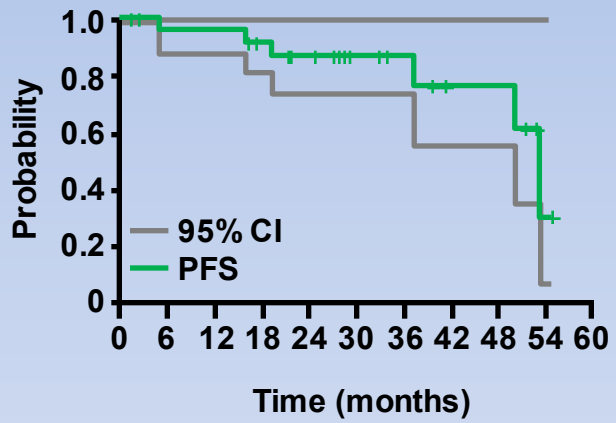
(median follow-up 40.6 months)



Patients at Risk

46 46 43 40 36 29 20 14 10 2 0

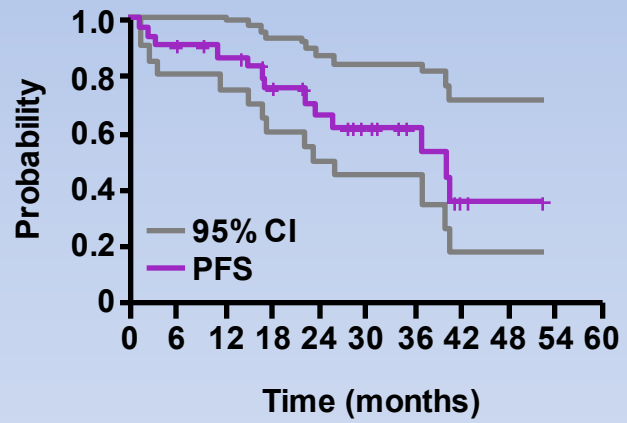
MZL Median PFS: **53.8 months**



Patients at Risk

27 23 23 19 16 10 8 5 5 1 0

SLL Median PFS: **40.4 months**



Patients at Risk

30 26 24 19 15 11 7 2 1 0 0

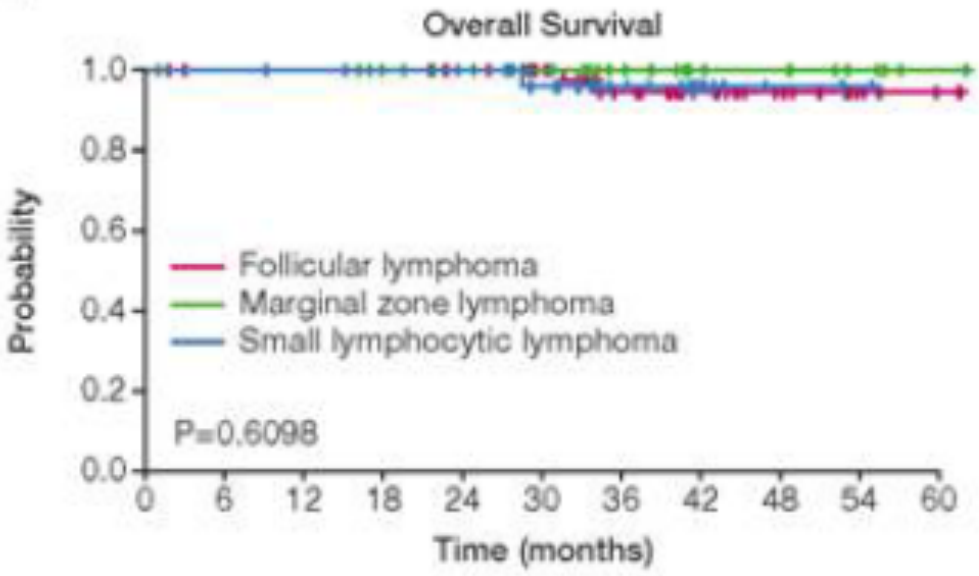
- As part of an exploratory analysis, pre- and post-treatment PET scans were obtained and available for 45 patients
- 44 (98%) were PET-positive prior to therapy
- **After treatment, 42 (93%) patients were PET-negative**

NA, not available.

Fowler NH, et al. *Lancet Oncol.* 2014,15:1311-1318.

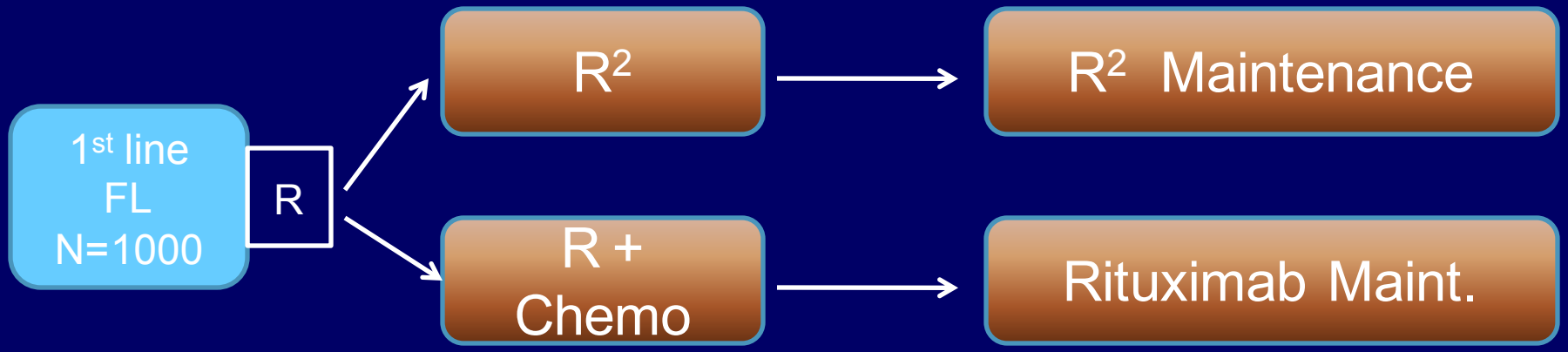
R^2 in Untreated Indolent Lymphoma: Overall Survival

Estimated 3-year OS was 96.1%
(95% CI 91·9–100%)



Fowler et al. Lancet Oncol [accepted]; ASH 2012, Abstract 901.

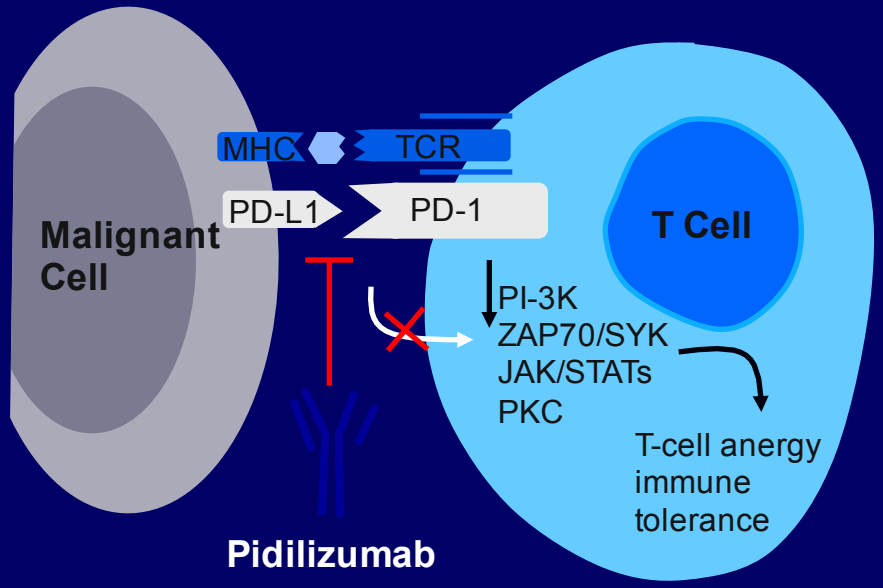
RELEVANCE Study Design
(Rituximab and LEnalidomide versus Any ChEmotherapy)



- R+Chemo:
  - Investigator's choice of R-CHOP, R-CVP, BR
- Lenalidomide 20mg for 6 cycles, then 10mg if CR
- LYSA (PI: Morschhauser) + North America (PI: Fowler)

Pidilizumab: Activity in Relapsed/ Refractory NHL

Pidilizumab: Anti–PD-1 Antibody[1]



Phase II Study	Regimen	ORR, %
Armand et al[2]	Pidilizumab	DLBCL: 51
Westin et al[3]	Pidilizumab + rituximab	FL: 66

- Pidilizumab blocks interaction between PD-1 and its ligands
  - Attenuates apoptotic processes in lymphocytes (eg, effector/memory T cells)
  - Enhances NK cell antitumor activity

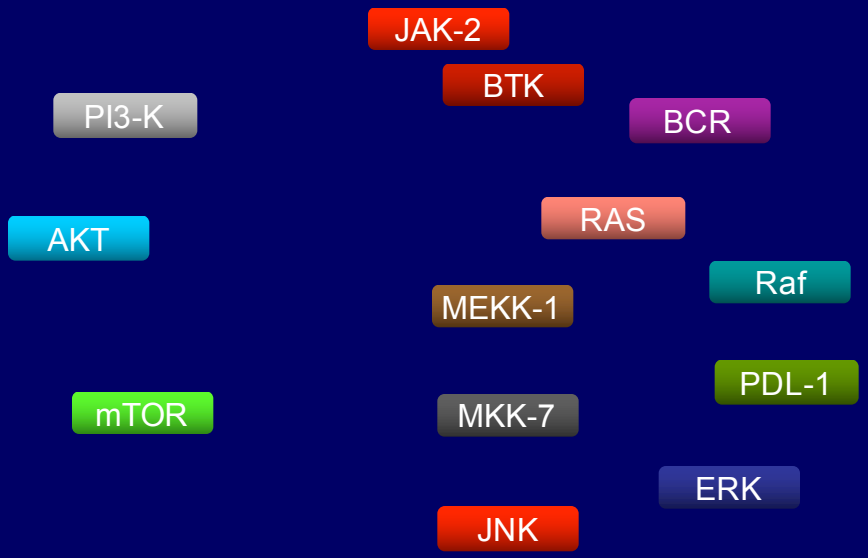
1. Suresh et al. J Hematol Oncol. 2014;7:58. 2. Armand P, et al. J Clin Oncol. 2013;31:4199-4206.
3. Westin JR, et al. Lancet Oncol. 2014;15:69-77.

Nivolumab in R/R NHL: Efficacy

Types	n	ORR, n (%)	CR, n (%)	PR, n (%)	SD, n (%)
B cell lymphoma	29	8 (28)	2 (7)	6 (21)	14 (48)
DLBCL	11	4 (36)	1 (9)	3 (27)	3 (27)
FL	10	4 (40)	1 (10)	3 (30)	6 (60)
T cell lymphoma	23	4 (17)	0	4 (17)	10 (43)
Mycosis fungoides	13	2 (15)	0	2 (15)	9 (69)
PTCL	5	2 (40)	0	2 (40)	0
Multiple myeloma	27	0	0	0	18 (67)
Primary mediastinal B-cell lymphoma	2	0	0	0	2 (100)

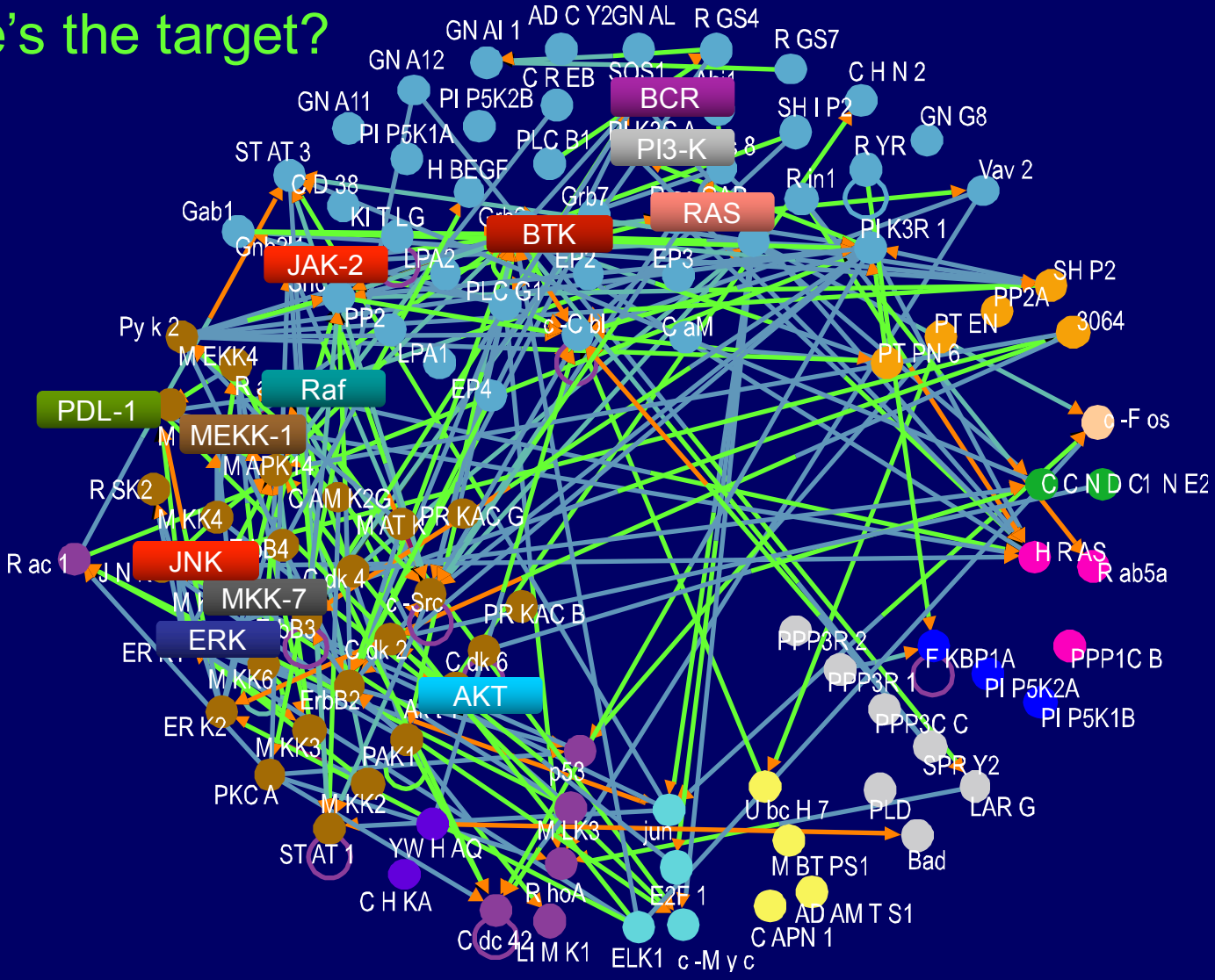
Lesokhin et al. ASH 2014. Abstract 291.

Which Target?



The Target Interactome

Where's the target?



Courtesy of I. Serebriiskii and E. Golemis, Fox Chase Cancer Center

Ongoing “Non-chemo” Trials in FL

Drugs	Sponsor
Obinutuzumab+Atezolizumab	Genentech
Obinutuzumab+Polatuzumab	Genentech
Obinutuzumab+Atezolizumab+lenalidomide	Genentech
Obinutuzumab+Polatuzumab+lenalidomide	Genentech
Obinutuzumab+Polatuzumab+venetoclax	Genentech
Obinutuzumab-idasanutlin	Genentech
GO29687 (Thiomab)+rituximab	Genentech
Acalabrutinib (ACP-196)+pembrolizumab	Acerta
Acalabrutinib+ACP-319	Acerta
Acalabrutinib+rituximab	Acerta
Ono/GS-4059+idelalisib	Gilead
Ibrutinib+Venetoclax	Georgetown
Ublituximab+ibrutinib	TG Therapeutics
Ublituximab+TG1202	TG Therapeutics
Ublituxumab+TGR-1202+ibrutinib	TG Therapeutics

Combinations/Permutations of Available New Agents

Assumption: 8 drugs + rituximab

	Doublets	Treblets
Combinations	36	84
Permutations	72	504


PERICOLO:
COMBINAZIONIS
AVANTI!!

SYK and PI3Kδ Pathway Inhibition Results in Increased Rates of Pneumonitis: Implications for Developing Future Small-Molecule Combinations

P.M. Barr,[1] G. Saylors,[2] S. Spurgeon,[3] B. Cheson,[4] D. Greenwald,[5] S. O'Brien,[6] A. Liem,[7] R. McIntyre,[8] A. Joshi,[9], E. Abella-Dominicis,[9] M. Hawkins,[9] A. Reddy,[9] J. Di Paolo,[10] H. Lee,[9] J. He,[9] J. Hu,[9] L. Dreiling,[9] J W Friedberg[1]

[1]James P. Wilmot Cancer Center, University of Rochester Medical Center, Rochester, New York, USA; [2]Charleston Hematology Oncology Associates, Charleston, South Carolina, USA; [3]Oregon Health & Science University, Portland, Oregon, USA; [4]MedStar Georgetown University Hospital, Washington, DC, USA; [5]Cancer Center of Santa Barbara, California, USA; [6]University of California, Irvine; [7]Pacific Shores Medical Group, Long Beach, California; [8]Ventura County Hematology-Oncology Specialists, Ventura, California; [9]Gilead Sciences, Inc., Foster City, California; [10]Gilead Sciences, Inc., Branford, Connecticut, USA

ICML 2015, Lugano, Switzerland

Histology

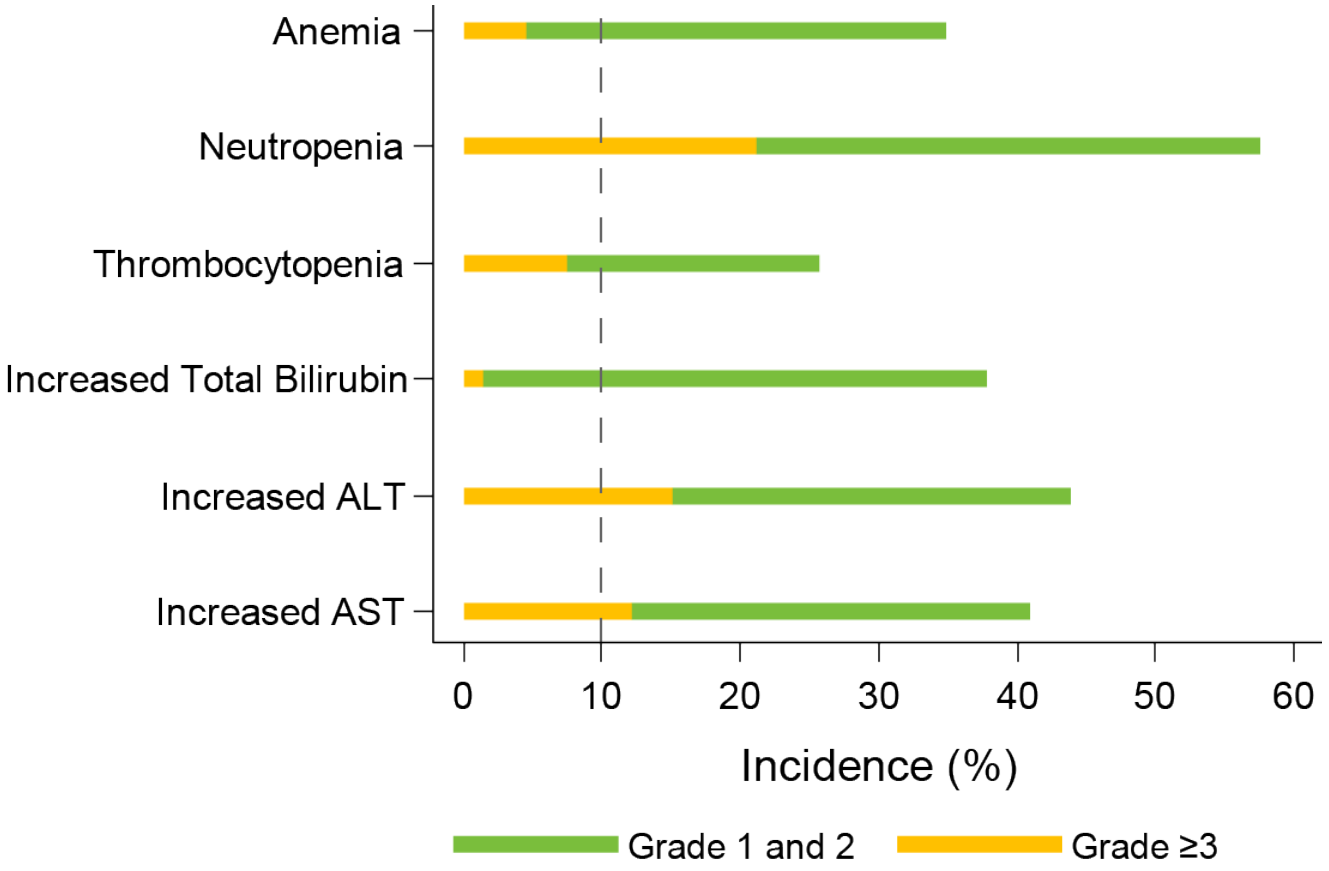
Histology, n (%)	Entospletinib + Idelalisib N=66
CLL	35 (53)
Follicular lymphoma	14 (21)
Diffuse large B-cell lymphoma	6 (9)
Mantle-cell lymphoma	3 (5)
Small lymphocytic lymphoma	3 (5)
Marginal-zone lymphoma	3 (5)
Lymphoplasmacytic lymphoma	2 (3)

Best Overall Response
IRC Assessed

Best Overall Response, n (%)	CLL n=35	FL n=14	Other NHL n=17
Complete response	0	0	0
Partial response	21 (60)	5 (36)	4 (24)
Stable disease	7 (20)	6 (43)	9 (53)
Progressive disease	1 (3)	2 (14)	3 (18)
Assessment not done	6 (17)	1 (7)	1 (6)

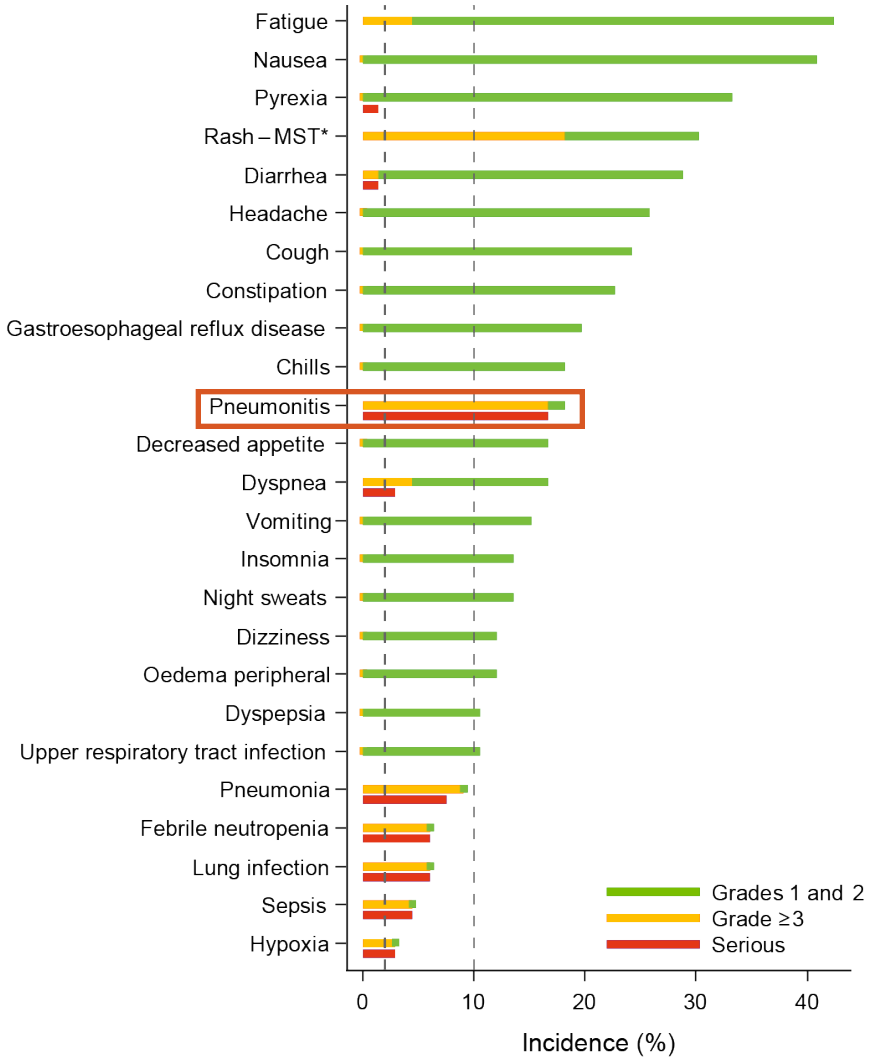
Median exposure to combination therapy: 10 wk
CLL: 12 wk; FL: 9 wk; other NHL: 7 wk

Treatment-Emergent Lab Abnormalities (N=66)



- AST/ALT elevations were generally reversible and allowed for continued treatment

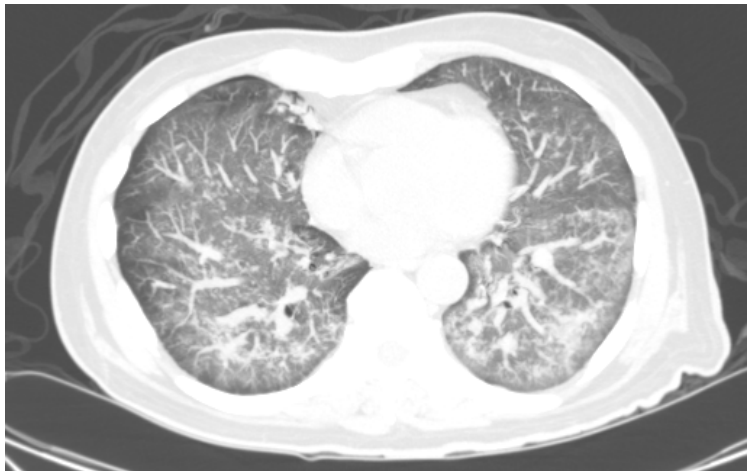
Treatment-Emergent Adverse Events (N=66)

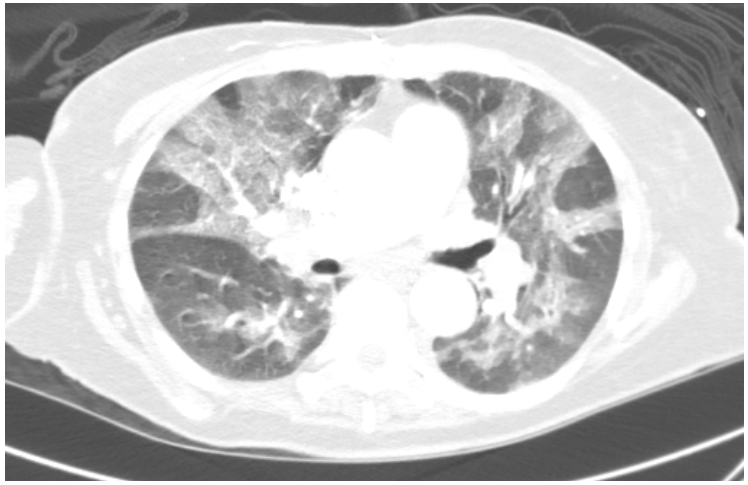


*Rash defined per Medical Search Term (MST), including dermatitis exfoliative, drug eruption, rash, rash erythematous, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic, rash morbilliform, and exfoliative rash.

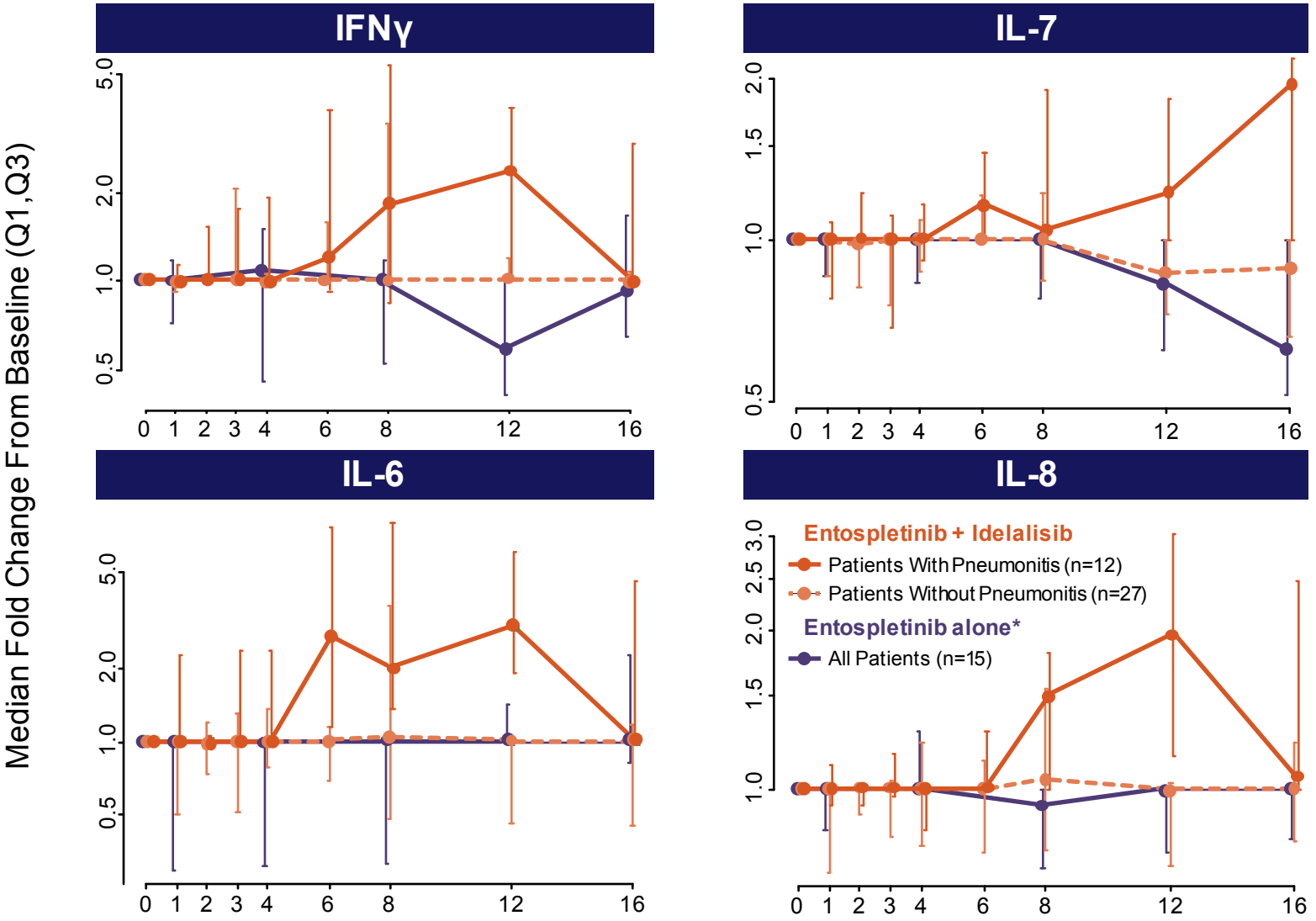
Clinical Characteristics of Pneumonitis

- 12 of 66 patients (18%)
- Median onset (range): 86 d (51–149)
- Prodrome included cough, fever, and hypoxia
  - 5 patients required ventilatory support
  - 2 deaths
- Chest CT infiltrates characterized as ground-glass opacities
- Infectious etiology not identified
- Responded to steroid treatment
- No significant difference in entospletinib or idelalisib exposure between patients experiencing pneumonitis and others





Pneumonitis Was Associated With Increasing Serum Cytokines Changes in IFNγ, IL-6, IL-7, and IL-8 Over Time



*Gilead Data on File

Unexpected and serious toxicity observed with combined idelalisib, lenalidomide and rituximab in rel/ref lymphomas: ALLIANCE A051201 and A051202

Objectives and Brief Eligibility Criteria

Primary Objective

To determine MTD, safety and tolerability of lenalidomide, idelalisib and rituximab in patients with recurrent MCL (A051201) and FL (A051202)

Eligibility Criteria

A051201	A051202
Previously treated MCL No prior idela or lenalidomide No prior alloSCT Measurable disease >1cm ANC ≥1000mm^3, plts ≥ 75K CrCL ≥60mL/min Total bili ≤2 x ULN	Previously treated FL gr 1-3a CD20+ Measurable disease >1cm ANC ≥1000mm^3, plts ≥ 75K CrCL ≥60mL/min AST/ALT ≤ 2 x ULN Total bili ≤2 x ULN

Patient Characteristics

Gender	
Female	**4**
Male	**7**
Med age (yr)	**58.5 y (range, 47-77)**
Histology	
MCL	**3**
FL	**8**
Prior treatment	
SCT	**1 (13%)**
Radiation	**1 (13%)**
Rituximab	**11 (100%)**
Med prior regimens	**2 (range, 1-7)**

Toxicity/AE's

	A051201 (n=3)*		A051202 (n=8)*	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
Hematologic Adverse Events				
Anemia	2 (67%)	0	6 (75%)	0
Lymphocyte count decr	2 (67%)	0	7 (88%)	6 (75%)
Neutrophil count decr	2 (67%)	1 (33%)	3 (38%)	0
Platelet count decr	3 (100%)	0	4 (50%)	1 (13%)
White blood cell decr	2 (67%)	0	3 (38%)	0
Non- Hematologic Adverse Events				
Constipation	0	0	4 (50%)	1 (13%)
Diarrhea	0	0	3 (38%)	0
Mucositis oral	2 (67%)	0	1 (13%)	0
Fatigue	2 (67%)	0	7 (88%)	1 (13%)
Fever	1 (33%)	0	4 (50%)	1 (13%)
Lung infection	0	0	2 (25%)	2 (25%)
Alanine Aminotransferase incr	2 (67%)	2 (67%)	5 (63%)	0
Alkaline phosphatase incr	0	0	2 (25%)	0
Aspartate aminotransferase incr	2 (67%)	1 (33%)	2 (25%)	0
Hyperglycemia	0	0	3 (38%)	1 (13%)
Hyperuricemia	0	0	2 (25%)	0
Hypoalbuminemia	1 (33%)	0	3 (38%)	0
Hypocalcemia	2 (67%)	0	3 (38%)	1 (13%)
Hyponatremia	0	0	2 (25%)	0
Hypophosphatemia	0	0	3 (38%)	1 (13%)
Rash maculo-papular	2 (67%)	2 (67%)	5 (63%)	4 (50%)

DLT Evaluation

A051201 (MCL)					
Dose Level	Dose			No. pts	DLT
	Len	Idela	Ritux		
0	15 mg	150 mg	375 mg/m^2	1	1 Grade 4 elevated ALT
A051202 (FL)					
Dose Level	Dose			No. pts	DLT
	Len	Idela	Ritux		
0	15 mg	150 mg	375 mg/m^2	5	1 Septic Shock 1 Grade 3 hypotension and rash
-1	10 mg	150 mg	375 mg/m^2	2	1 Grade 3 lung infection

After DLTs were noted, protocols were amended to remove rituximab and 3 additional patients were enrolled

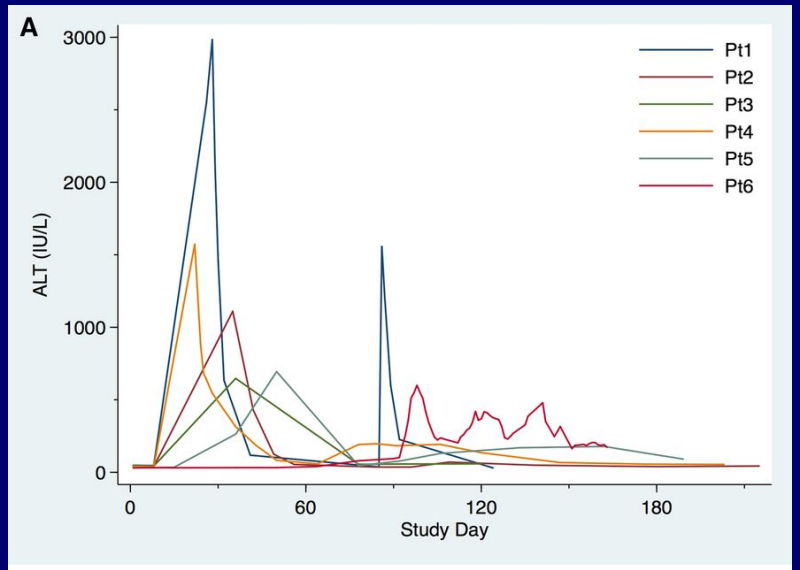
Conclusions

- While doublet therapy with lenalidomide/rituximab and idelalisib/rituximab have been safely utilized, we observed 4 DLTs among the first 8 patients
- All DLTs were concerning for high-level immune activation (fevers, rash, hypotension and/or pneumonitis)
- Both studies were amended to remove rituximab and an additional 3 patients were enrolled
  - 2 pts developed rash leading to drug discontinuation
  - 1 pt developed liver function abnormalities and 1 had pulmonary infiltrates
  - No patients remain on treatment
- Both studies have been permanently closed to further accrual

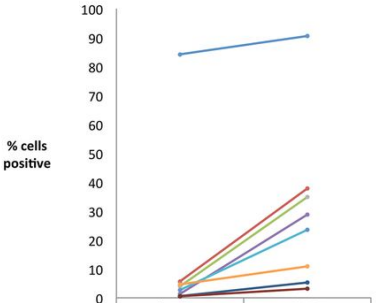
There is greater than additive and unexpected toxicity with combined idelalisib, lenalidomide and rituximab that has not been previously described and has not been observed with doublets.

The ALLIANCE experience illustrates that future combinations of targeted and otherwise well-tolerated agents must be performed with careful attention to development of new toxicities. Aggressive monitoring and regular conference calls provide one effective way to monitor for risks.

Biochemical and immunologic changes in patients treated with rituximab, lenalidomide, and idelalisib over time

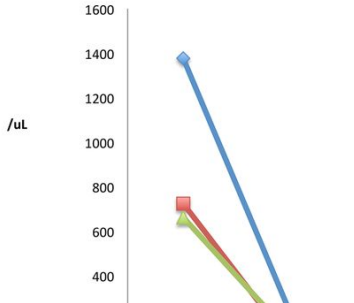


B T-cell activation markers pre- and post-treatment



	baseline	D116
CD4+OX40+	84.2	90.6
CD8+CD69+	5.7	37.8
CD8+OX40+	3.9	34.8
CD8+ICOS+	1.3	28.8
CD8+41BB+	2.7	23.5
CD4+CD69+	4.6	10.8
CD4+ICOS+	0.6	5.3
CD4+41BB+	0.5	3.2

C Lymphocyte subsets pre- and post-treatment



	baseline	D116
CD3+ T-cells	1376	194
CD4+ T-cells	722	76
CD8+ T-cells	661	117
CD56+ NK cells	36	11
Foxp3+ Tregs	15	21

Chan Yoon Cheah et al. Blood 2015;125:3357-3359

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Gilead Cancer Drug Reviewed After Deaths in Combo Trials

by Doni Bloomfield
DoniBloomfield

March 11, 2016 – 6:39 PM CET *Updated on* March 11, 2016 – 11:50 PM CET

- FDA, European drug regulators are reviewing Gilead treatments
- Deaths, side effects reported after drug used in combination

U.S. and European regulators are reviewing Gilead Sciences Inc.'s cancer drug Zydelig after some patients died or suffered other side effects while taking it with other drugs in

Gilead Sciences Halts Drug Studies Over Side Effects, Death

By THE ASSOCIATED PRESS •
FOSTER CITY, Calif. — Mar 15, 2016, 5:37 PM ET

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3
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Biologic drugmaker Gilead Sciences Inc. has halted several patient studies of its cancer drug, Zydelig, because of increased risk of death and serious side effects.

The company told The Associated Press the "adverse events" were spotted during an ongoing review of late-stage testing in patients with chronic lymphocytic leukemia, a blood cancer, and patients with relapsed non-Hodgkin's lymphoma, a cancer of the infection-fighting lymphatic system.

Nathan Kaiser, a spokesman for the Foster City, California, company, wouldn't disclose details, including how many patients died or suffered serious side effects.

"We are conducting a comprehensive review of all ongoing studies and are consulting with regulatory authorities," Kaiser wrote in an email Tuesday.

Conclusions

- Moving away from non-specific chemotherapy
- Novel new agents available that target
  - Cell surface (antibodies)
  - Intracellular pathways (kinases/proapoptotics)
  - Microenvironment (Imids, PD-1/PDL-1)
- Develop rational combinations
- Combinations may have unexpected toxicities
- Important to accrue patients to clinical trials
- Goal is to achieve individualized therapy
- Increase the potential for cure