Idelalisib In CLL

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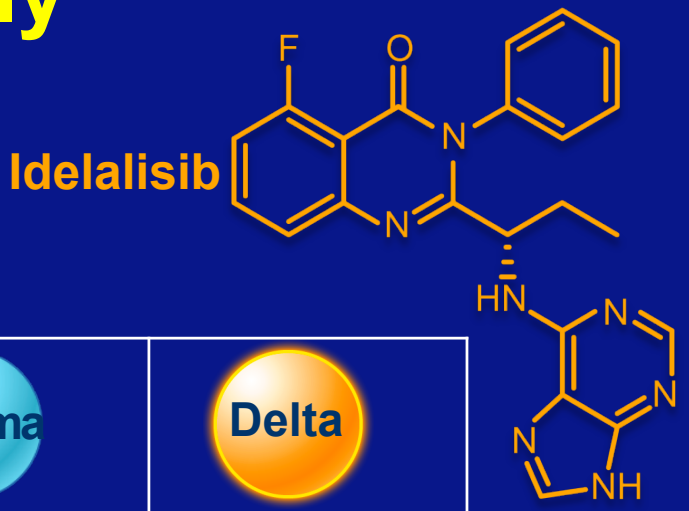
Idelalisib is an Orally Bioavailable Small Molecule that Inhibits PI3K Delta Potently and Selectively

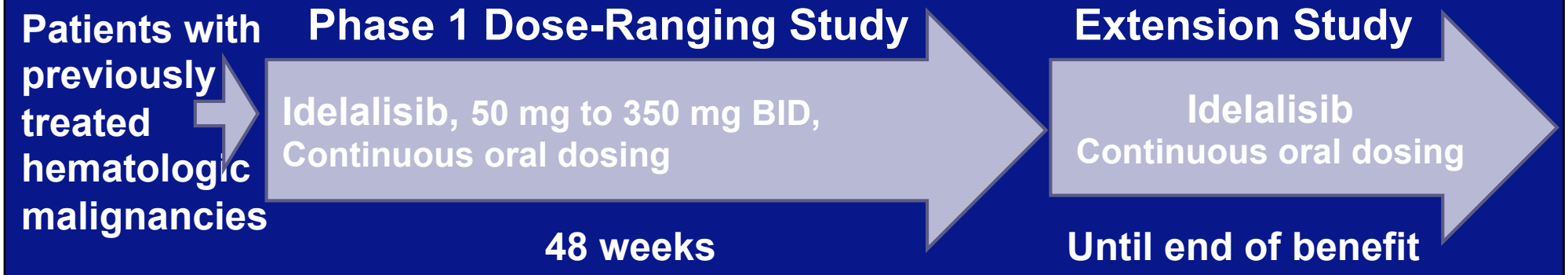


Class I PI3K Isoform	Alpha	Beta	Gamma	Delta
Cell-Based Activity	PDGF-induced pAKT	LPA-induced pAKT	fMLP-induced CD63+	FcεR1-induced CD63+
EC_{50} (nM)	>20,000	1,900	3,000	8

- Selectivity relative to Class I PI3K isoforms involved in insulin signaling and other physiological functions
- No off-target activity against Class II or III PI3K, mTOR, or DNA-PK
- No off-target activity seen in screen of >350 protein kinases (Ambit KINOMEscan™)

Lannutti, Blood, 2011

Idelalisib Phase 1 Study Design



Population reported:

- 54 patients with CLL
- Starting dose cohorts
  - 50mg BID, n=5
  - 100mg BID, n=11
  - 300mg QD, n=10
  - 150mg BID, n=11
  - 200mg BID, n=10
  - 350mg BID, n=7

Disease assessments:

- Weeks 0, 8, 16, 24
- Every 12 weeks thereafter

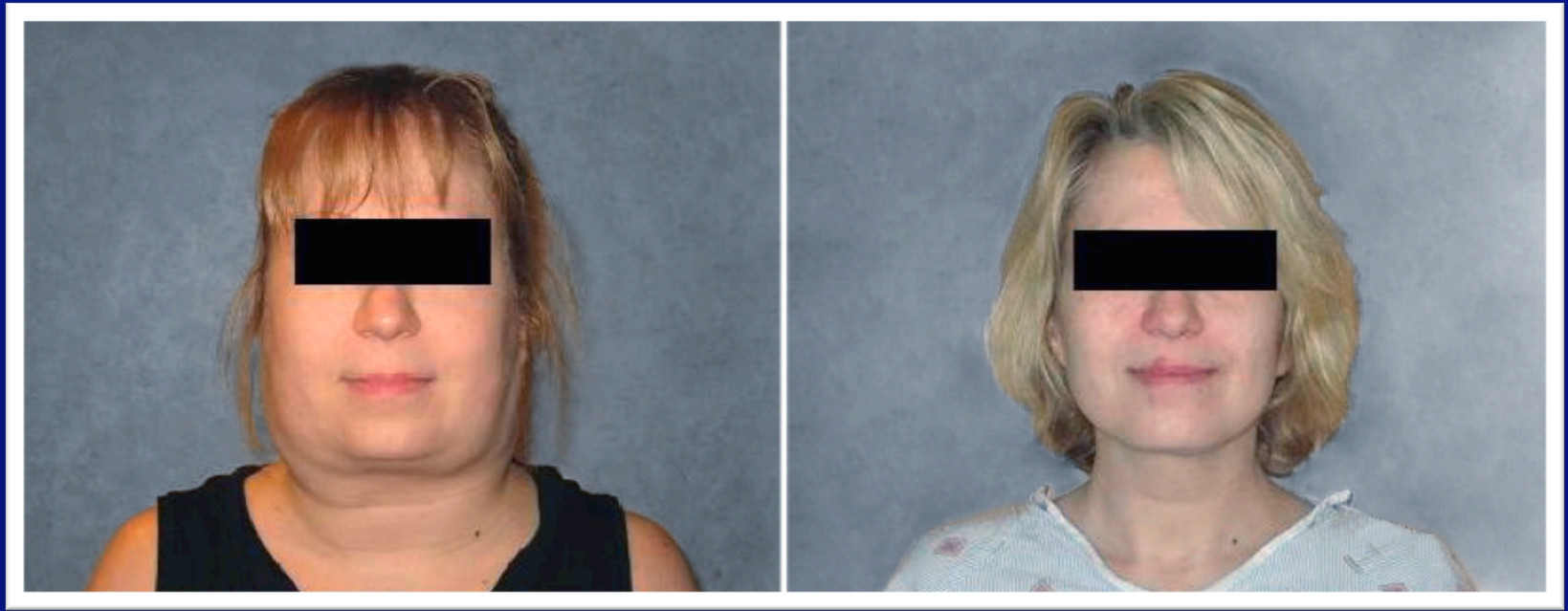
Endpoints:

- Dose selection
- Safety
- Pharmacodynamics
- Pharmacokinetics
- Efficacy

Brown et al. Blood. 2014 May 29; 123

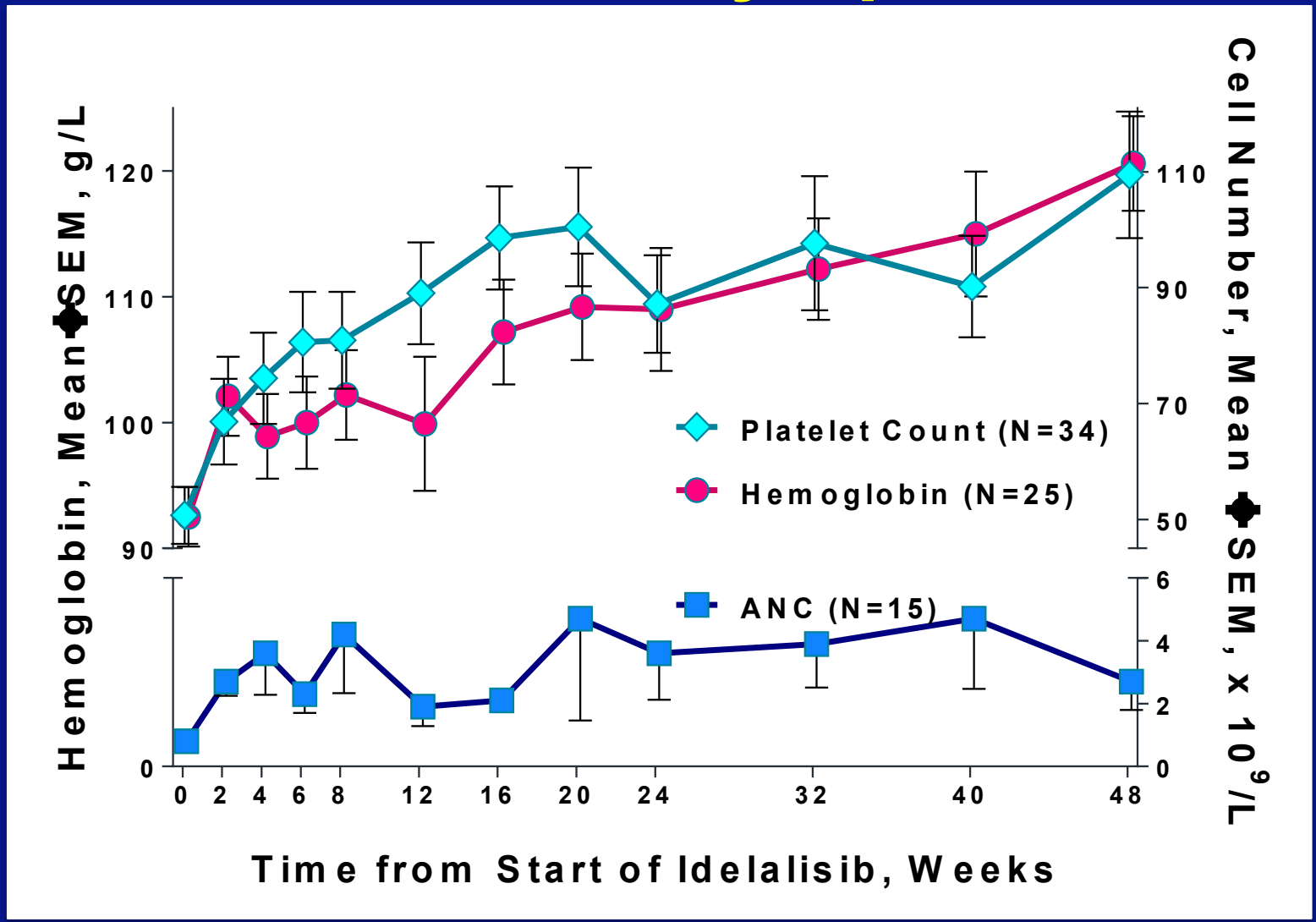
Marked Reductions in Peripheral Lymphadenopathy Were Observed

Pretreatment | With IdelalisibTreatment



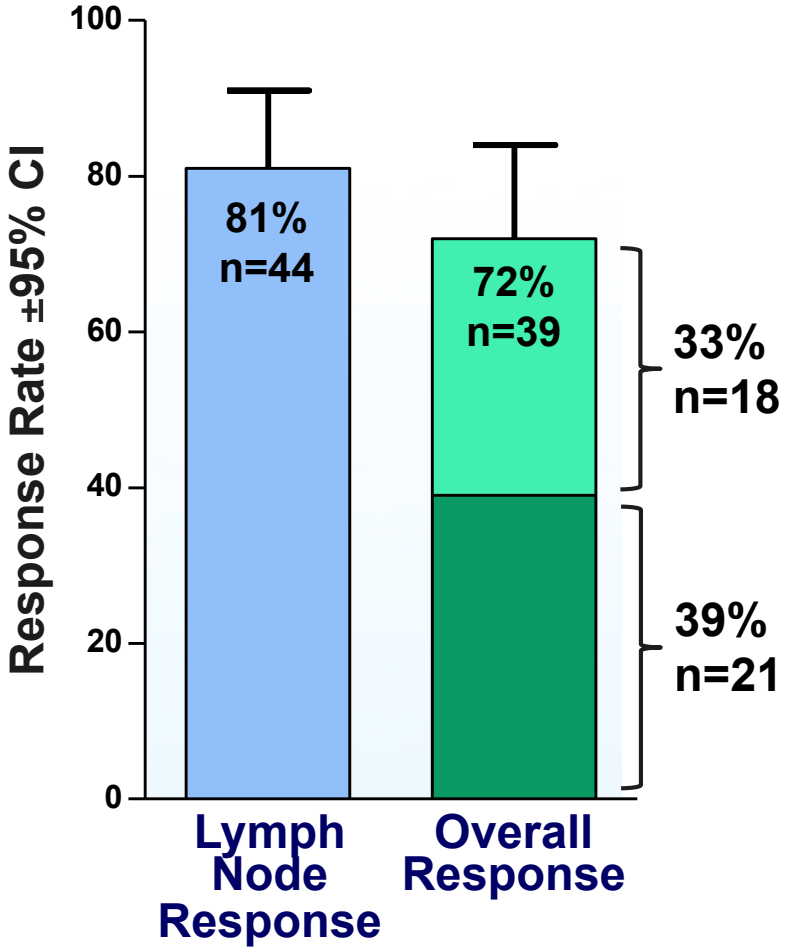
38-year-old patient with refractory CLL and 5 prior therapies

Idelalisib: Idelalisib Improvement of Baseline Cytopenias

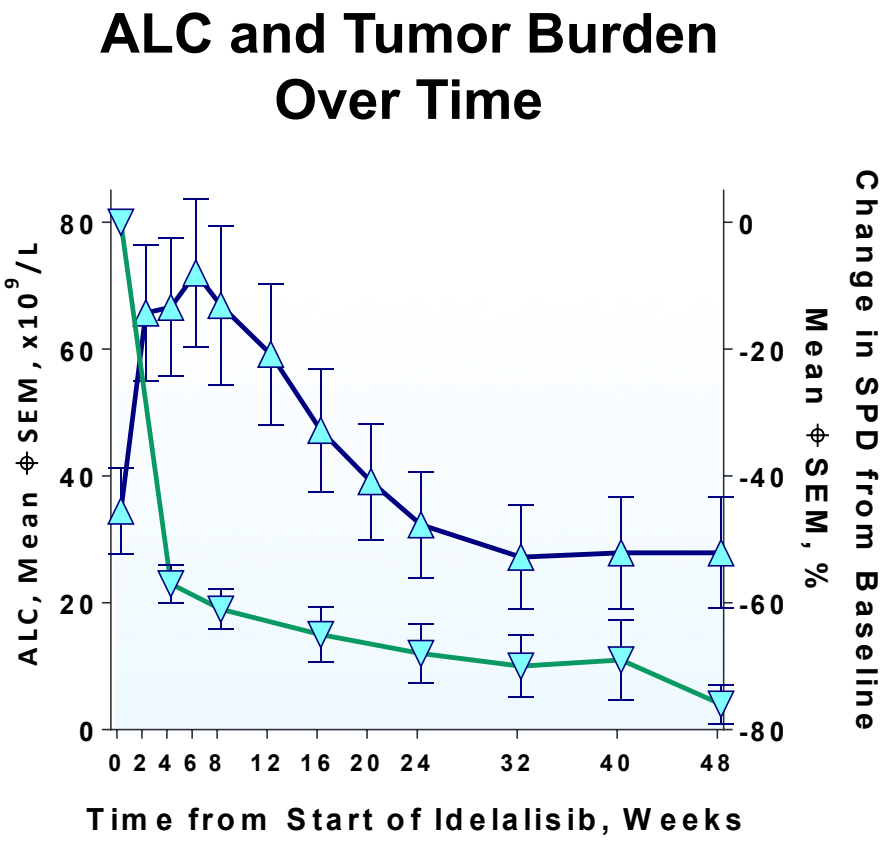


Brown et al. Blood. 2014 May 29; 123 (22): 3390-7

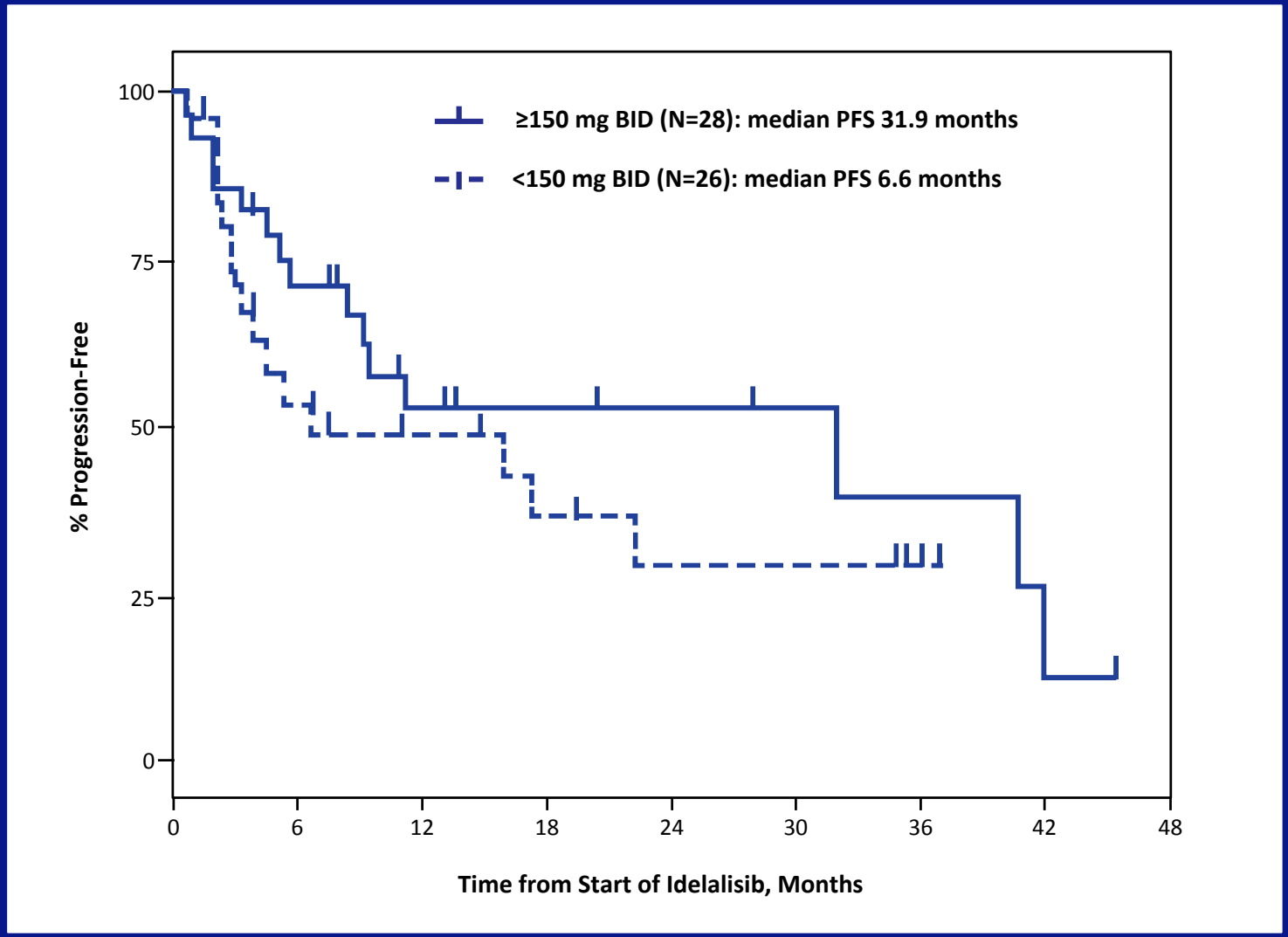
Idelalisib: Nodal and Overall Response Rate



Decrease by ≥50% of nodal SPD
PR with lymphocytosis (Cheson 2012)
PR by IWCLL criteria (Hallek 2008)



Idelalisib: Progression-Free Survival by Dose



Brown et al. Blood. 2014 May 29; 123 (22): 3390-7

Idelalisib: Adverse Events (≥ 15%) and Selected Lab Abnormalities (N = 54)

AE, n (%)	Any Grade, (%)	Grade ≥ 3, (%)
Fatigue	17 (32)	1 (2)
Diarrhea	16 (30)	3 (6)
Pyrexia	16 (30)	2 (4)
Cough	13 (24)	2 (4)
Back pain	12 (22)	0
Rash	12 (22)	0
URI	12 (22)	0
Pneumonia	11 (20)	10 (19)
Night sweats	10 (19)	0
Chills	9 (17)	0
Laboratory abnormality, n (%)		
AST, increased*	13 (24)	1 (2)
ALT, increased*	10 (19)	1 (2)
*15 subjects total with transaminase elevations		

Brown et al. Blood. 2014 May 29; 123 (22): 3390-7

Serious Adverse Events (SAEs), n≥2, and AEs Leading to Study Drug Discontinuation (N=54)

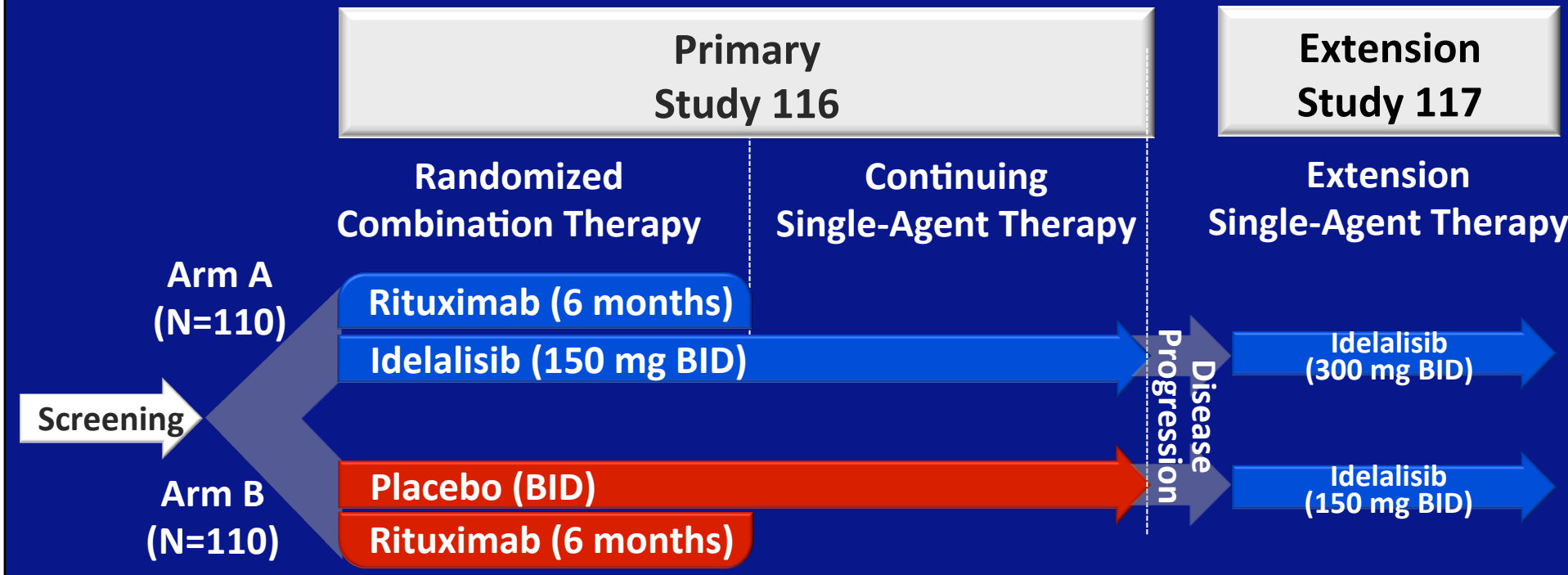
SAE	n	%
Pneumonia	10	19%
Febrile Neutropenia	5	9%
Cellulitis	3	6%
Colitis	3	6%
Diarrhea	2	4%
Bronchitis	2	4%
Infection	2	4%
Organizing pneumonia	2	4%
Pneumoc. jirov. pneumonia	2	4%
Pneumonia fungal	2	4%
Sepsis	2	4%
Pseudomonal bacteremia	2	4%

AE (Any Grade) Leading to Drug Discontinuation	n
Pneumonia pneumocoocal	1
Pneumonia fungal	1
Lung infection pseudomonal	1
Transaminase elevation	1
Febrile neutropenia[1]	1
Pneumonia[1]	1
Renal failure[1]	1
Respiratory failure[1]	1
MDS[2]	1
Cholecystitis[2]	1

[1] Same subject, [2] Extension study

Brown et al. Blood. 2014 May 29; 123 (22): 3390-7

Study 116: Randomized, Double-Blind, Placebo-Controlled



Rituximab administration

- 375 mg/m^2, then 500 mg/m^2 Q2W x 4, then 500 mg/m^2 Q4W x 3

Clinical Endpoints

- Primary: PFS as assessed by IRC
- Events: Disease progression or death
- Secondary: ORR, LNR, OS

Planned interim analyses at 50% and 75% of events

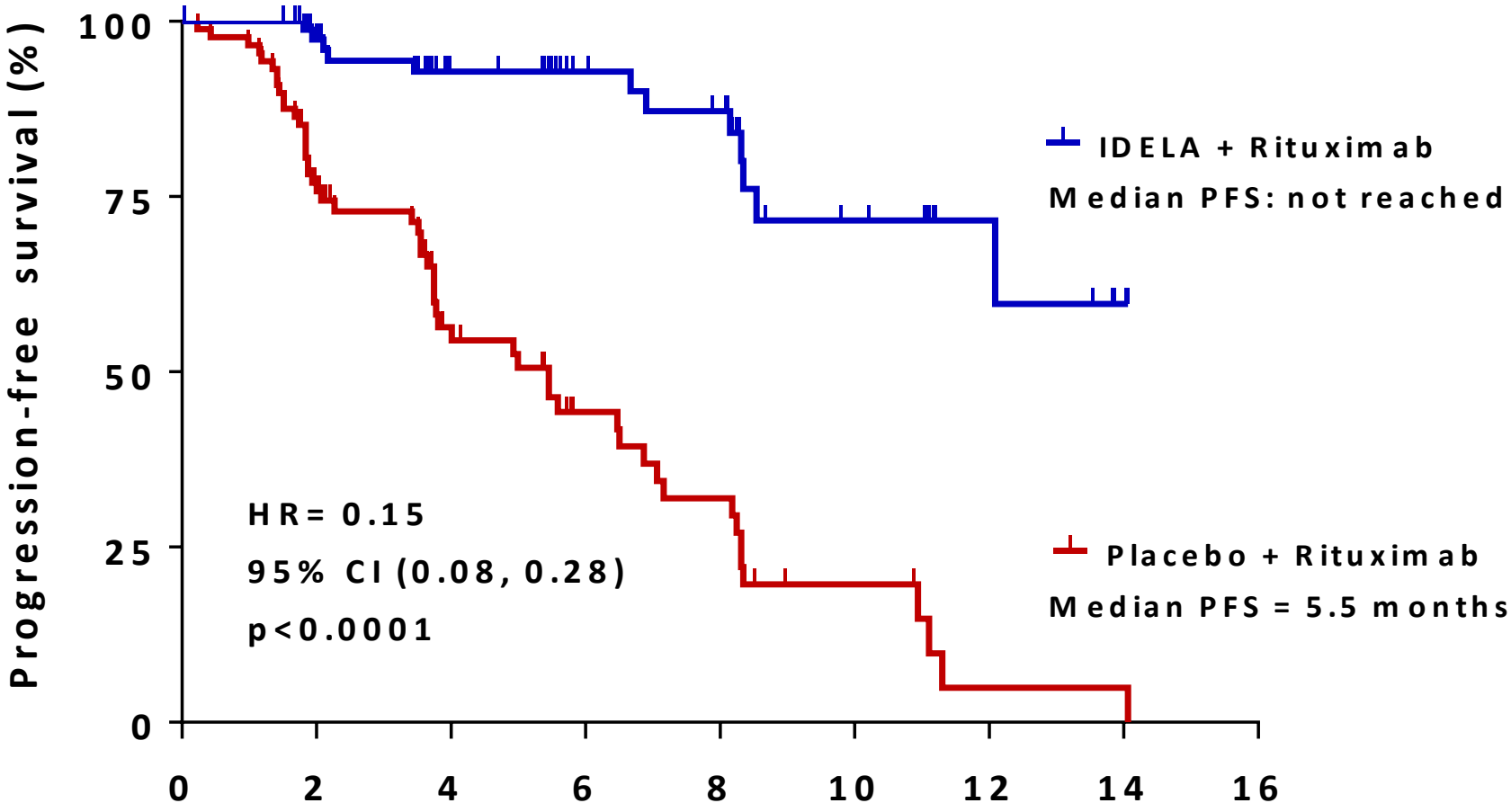
Furman et al N Engl J Med 2014, Mar 13, 370 (11): 997-1007

Study 116: Key Eligibility

Criteria	Requirement
Relapsed CLL	• CLL progression <24 months since last therapy • Treatment warranted according to IWCLL criteria
Lymphadenopathy	• Presence of ≥1 measurable nodal lesion
Prior therapies	• ≥ 1 anti-CD20 antibody containing therapy or ≥ 2 prior cytotoxic therapies
Appropriate for non-cytotoxic therapy	• CIRS score >6 or creatinine clearance <60 ml/min (≥30 mL/min) or Grade 3/4 neutropenia or thrombocytopenia due to prior myelotoxicity
Bone marrow function	• Any grade anemia, neutropenia or thrombocytopenia allowed
Karnofsky score	• ≥40

Furman et al N Engl J Med 2014, Mar 13, 370 (11): 997-1007

Primary Endpoint: Progression-Free Survival

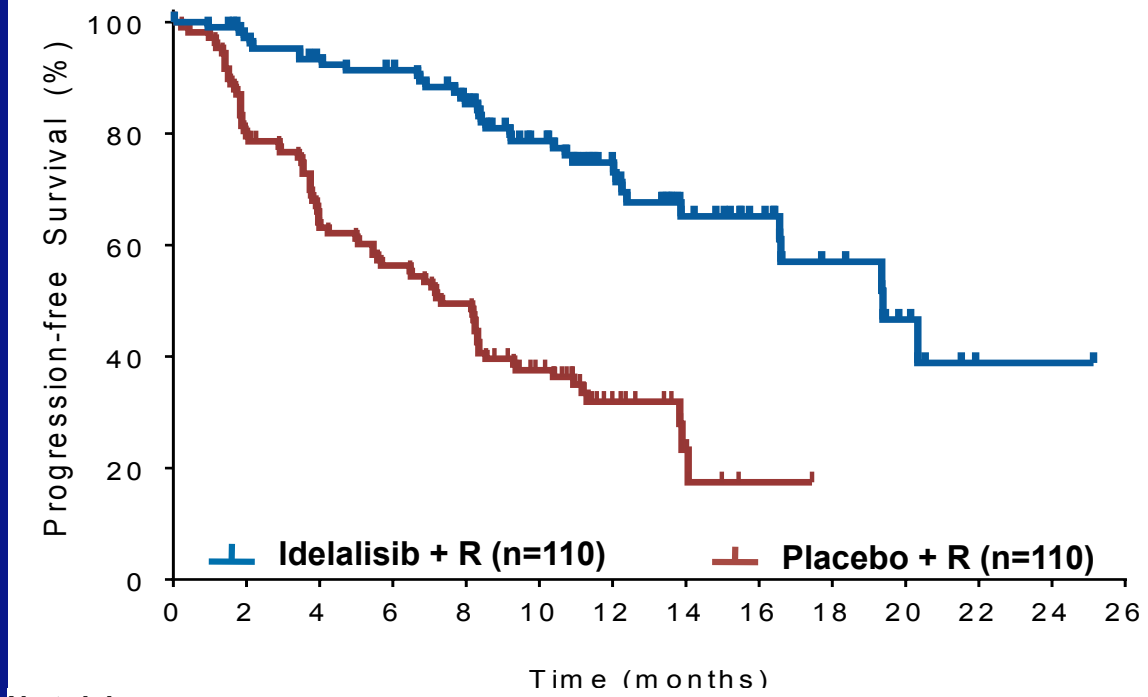


Subjects at risk, n

IDELA + R:	110	69	44	34	30	14	6	2	0
Placebo + R:	110	62	30	18	13	6	1	1	0

PFS, Including Extension Study*
Idelalisib + R vs Placebo + R

All Patients



N at risk

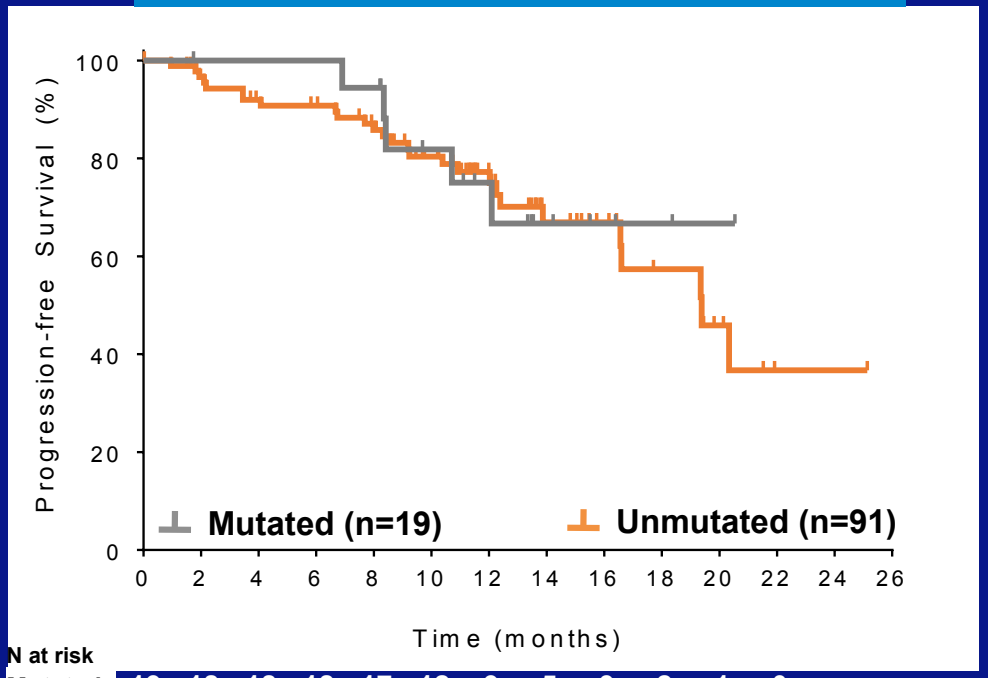
IDELA + R	110	102	95	92	83	64	43	26	19	12	7	1	1	0
PBO + R	110	86	66	58	51	33	15	5	1	0	-	-	-	-

	Median PFS (95% CI)	HR (95% CI)	p-value
IDELA + R	19.4 mo (16.6, –)	0.25 (0.16, 0.39)	<0.0001
PBO + R	7.3 mo (5.5, 8.5)		

*Placebo + R includes those patients who received open-label idelalisib after unblinding without prior progression (n=42).

PFS Subgroup Analysis*
Idelalisib + R (n=110)

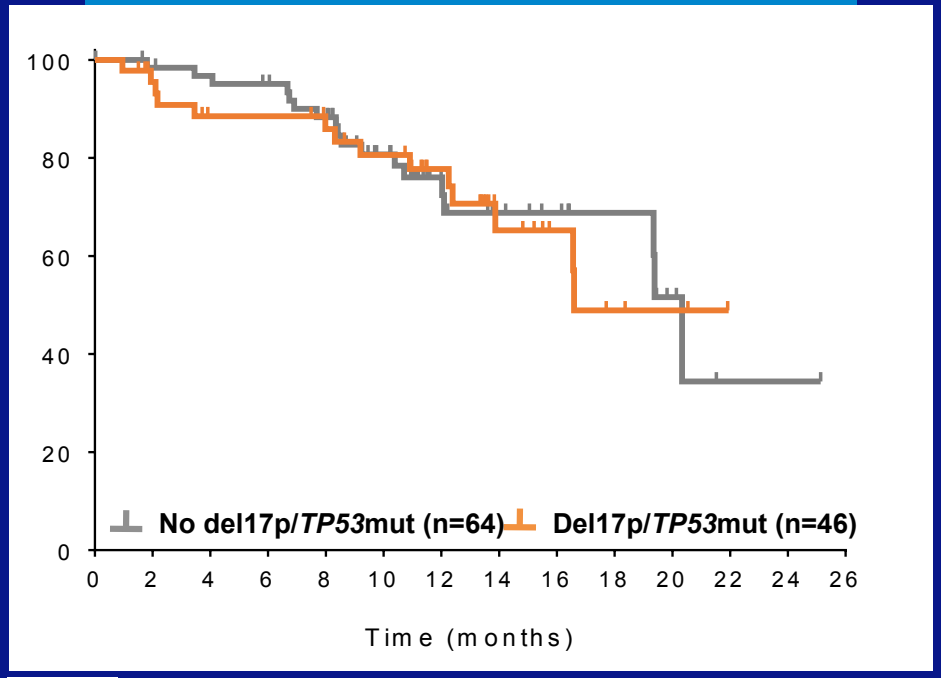
IGHV: Unmutated vs Mutated



N at risk													
Mutated	19	18	18	18	17	12	9	5	3	2	1	0	
Unmut	91	84	77	75	68	54	34	21	16	10	6	1	1	0

	Median PFS (95% CI)	p-value
Mut	NR (10.7, –)	0.75
Unmut	19.4 mo (16.6, –)	

Del17p/TP53mut: Present vs Not Present



No del	64	61	59	59	52	37	21	14	11	8	4	1	1	1
Del	46	41	36	36	33	30	22	12	8	4	3	0		

	Median PFS (95% CI)	p-value
No del	20.3 mo (19.4, –)	0.94
Del	16.6 mo (13.9, –)	

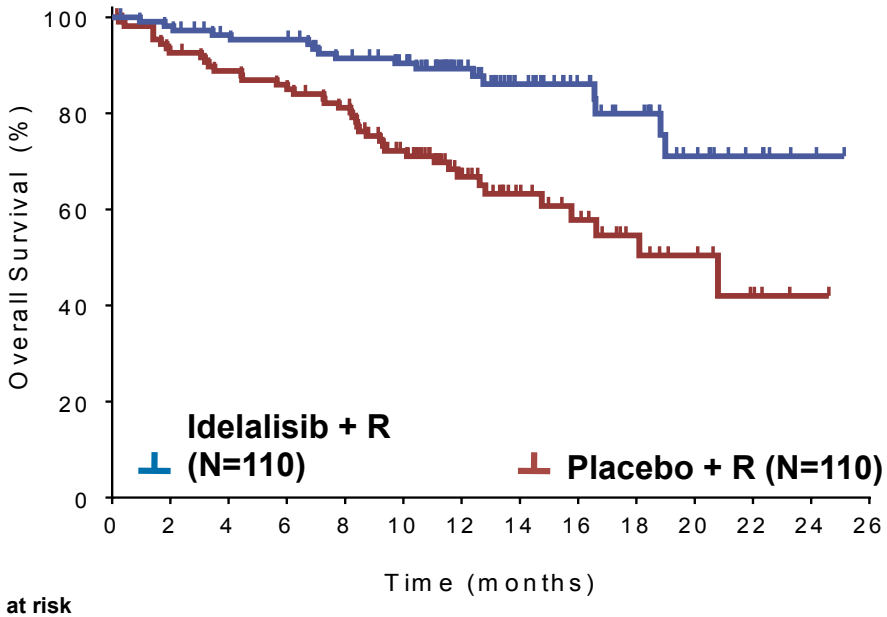
*Including extension study

Sharman et al ASH 2014

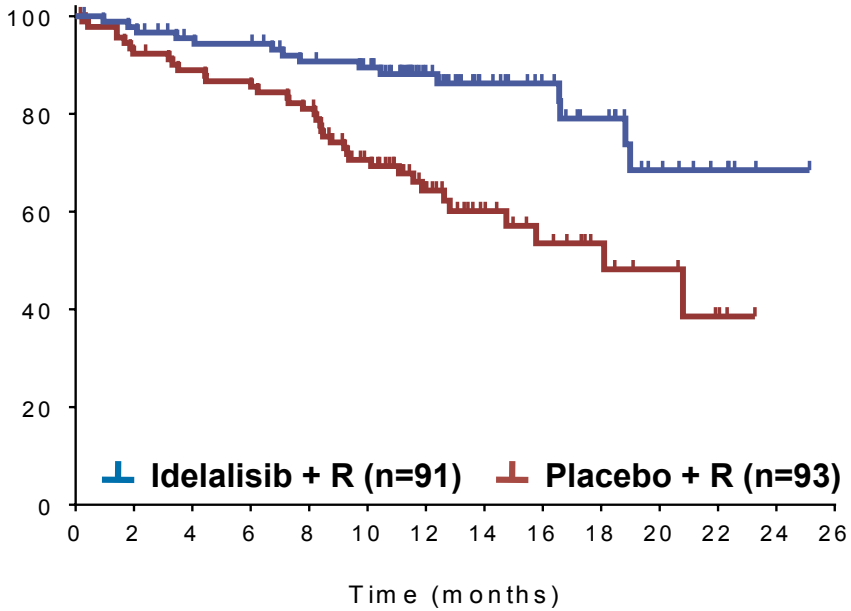
Overall Survival, Including Extension Study*

Idelalisib + R vs Placebo + R → Idelalisib

All Patients



IGHV Unmutated



N at risk

IDELA + R	110	107	101	100	93	85	60	41	30	23	13	7	3	0
PBO + R	110	99	93	90	84	66	42	27	20	13	8	4	1	0

IDELA + R	91	88	82	81	75	70	48	33	25	19	10	6	2	0
PBO + R	93	83	79	77	72	55	35	22	15	10	6	3	0	

	Median OS (95% CI)	HR (95% CI)	p-value
IDELA + R	NR	0.34 (0.19, 0.6)	0.0001
PBO + R	20.8 mo (14.8, –)		

Median OS (95% CI)	HR (95% CI)	p-value
NR (19.0, –)	0.35 (0.19, 0.6)	0.0003
18.1 mo (14.8, –)		

*As randomized, including cross-over

Sharman et al ASH 2014

Adverse Events ≥10% In Either Study Arm

AE, n (%)	IDELA + R (N=110)		Placebo + R (N=107)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Patients with any AE	100 (91)	62 (56)	101 (94)	51 (48)
Pyrexia	32 (29)	3 (3)	17 (16)	1 (1)
Fatigue	26 (24)	3 (3)	29 (27)	2 (2)
Nausea	26 (24)	0	23 (22)	0
Chills	24 (22)	2 (2)	17 (16)	0
Diarrhea	21 (19)	4 (4)	15 (14)	0
Infusion-related reaction	17 (16)	0	30 (28)	4 (4)
Cough	16 (15)	0	27 (25)	2 (2)
Decreased appetite	13 (12)	0	9 (8)	1 (1)
Constipation	13 (12)	0	12 (11)	0
Vomiting	13 (12)	0	8 (8)	0
Dyspnea	12 (11)	2 (2)	20 (19)	3 (3)
Rash	11 (10)	2 (2)	6 (6)	0
Night sweats	11 (10)	0	8 (8)	0

Furman et al N Engl J Med 2014, Mar 13, 370 (11): 997-1007

Idelalisib Plus Bendamustine and Rituximab (BR) Is Superior to BR Alone in Patients With Relapsed/Refractory Chronic Lymphocytic Leukemia: Results of a Phase 3 Randomized Double-Blind Placebo-Controlled Study

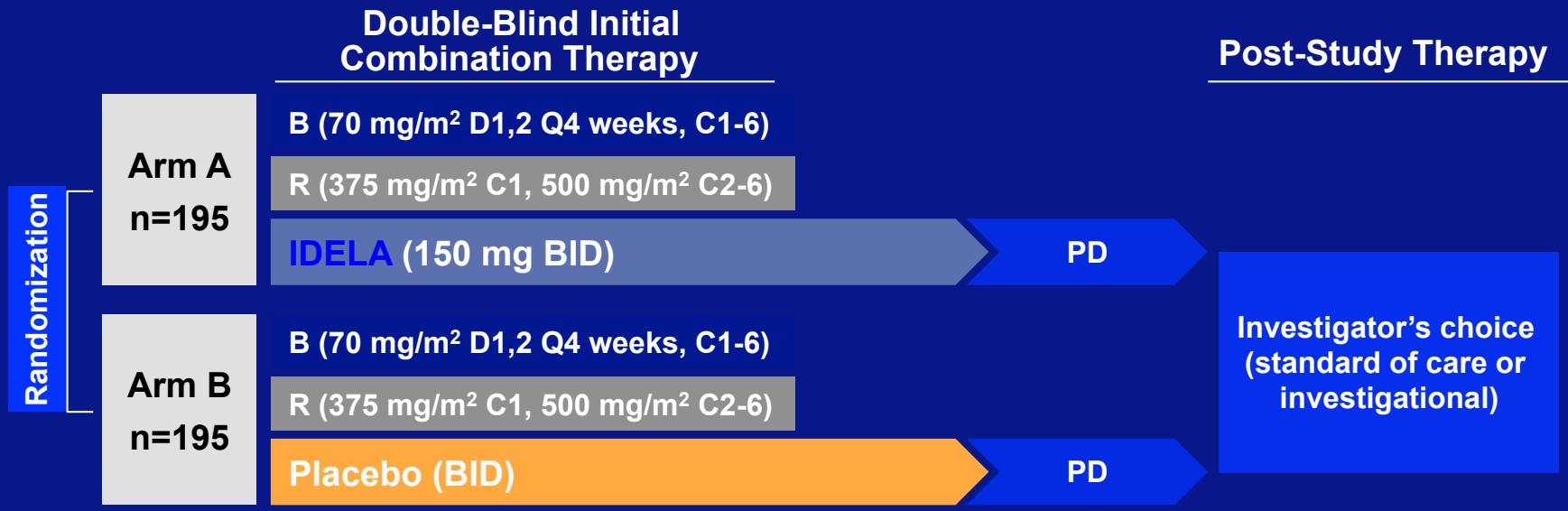
Andrew D. Zelenetz[1], Tadeusz Robak[2], Bertrand Coiffier[3], Julio Delgado[4],
Paula Marlton[5], Adeboye H. Adewoye[6], Yeonhee Kim[6], Lyndah K. Dreiling[6],
Peter Hillmen[7]

[1]Lymphoma Service/Department of Medicine, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY; [2]Medical University of Lodz and Copernicus Memorial Hospital, Lodz, Poland;
[3]Hospices Civils de Lyon, Pierre-Benite, France; [4]Department of Hematology, Hospital Clínic de Barcelona, Barcelona, Spain; [5]Clinical Hematology, Princess Alexandra Hospital, Brisbane, Australia; [6]Gilead Sciences, Inc., Foster City, CA; [7]Department of Hematology/Oncology, St. James's University Hospital, Leeds, UK

ASH 2015, Orlando, FL

Lancet Oncol 2017 Mar;18(3):297-311

Study 115 Design



Enrollment period June 2012 – August 2014

CT/MRI at baseline, then Q12 weeks, or at PD

Pre-specified interim analysis at 67% of events

Stratification

- 17p deletion and/or TP53 mutation
- IGHV mutation status
- Refractory vs relapsed disease

Endpoints

- Primary: PFS
- Secondary: ORR, nodal response, CR

IGHV, immunoglobulin heavy chain variable region; CR, complete response; ORR, overall response rate; OS, overall survival, PD, disease progression; PFS, progression-free survival.

Results: Response Rates

Study 115: Response Parameters

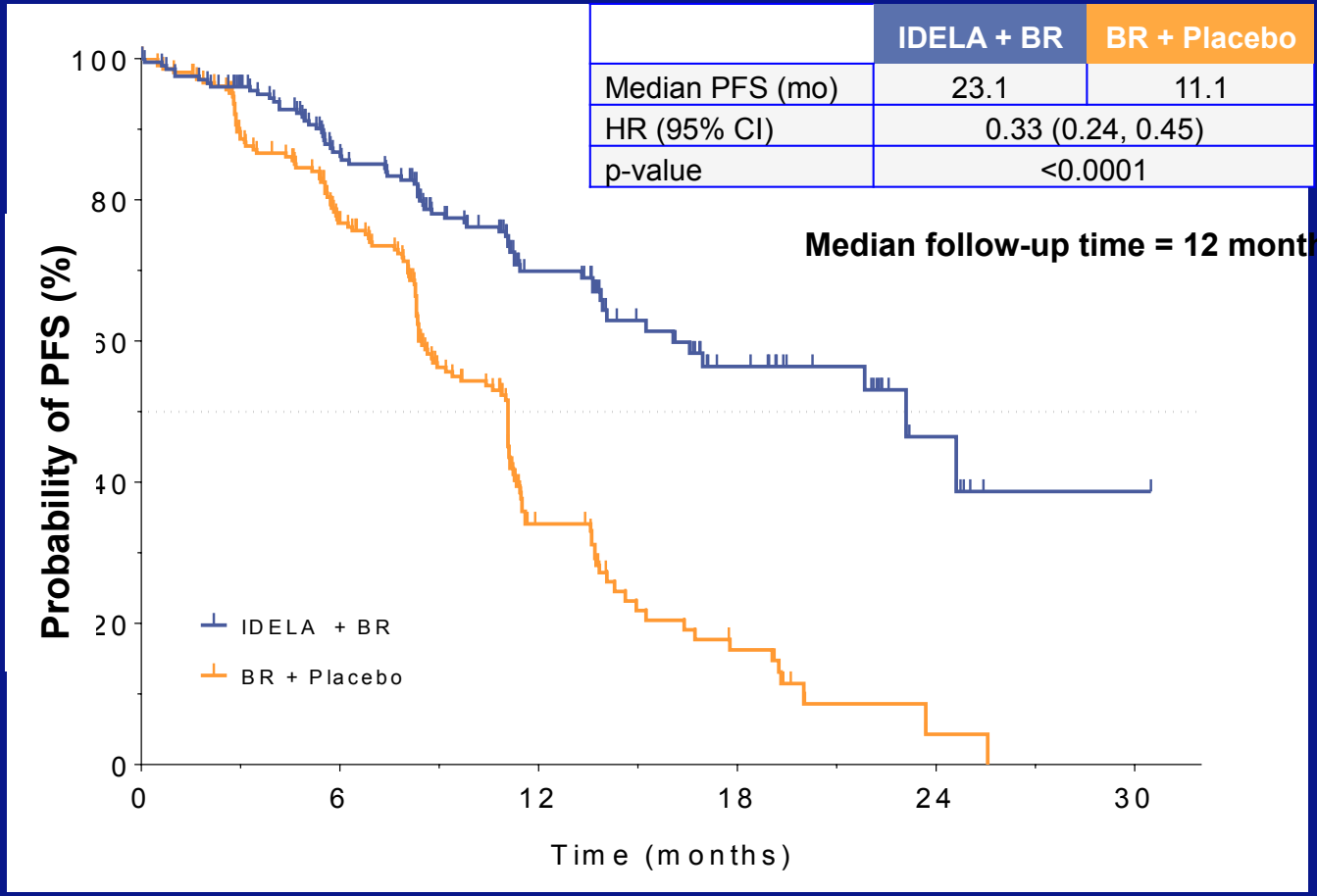
Response Parameter	IDELA + BR n=207 % (95% CI)	BR + Placebo n=209 % (95% CI)
Overall response	68 (61, 74)	45 (38, 52)
CR	5 (2)	0
≥50% reduction in lymph nodes		
Organomegaly response		
Spleen	82 (75, 88)	57 (49, 65)
Liver	56 (46, 66)	40 (31, 50)
Hematologic response		
Hemoglobin	88 (78, 95)	70 (58, 80)
Neutrophils	89 (71, 98)	84 (67, 95)
Platelets	89 (80, 95)	78 (66, 87)

Zelenetz et al. Lancet Oncol 2017 Mar;18(3):297-311

Results: IRC-Assessed PFS

Study 115: Primary Endpoint

	IDELA + BR	BR + Placebo
Median PFS (mo)	23.1	11.1
HR (95% CI)	0.33 (0.24, 0.45)	
p-value	<0.0001	

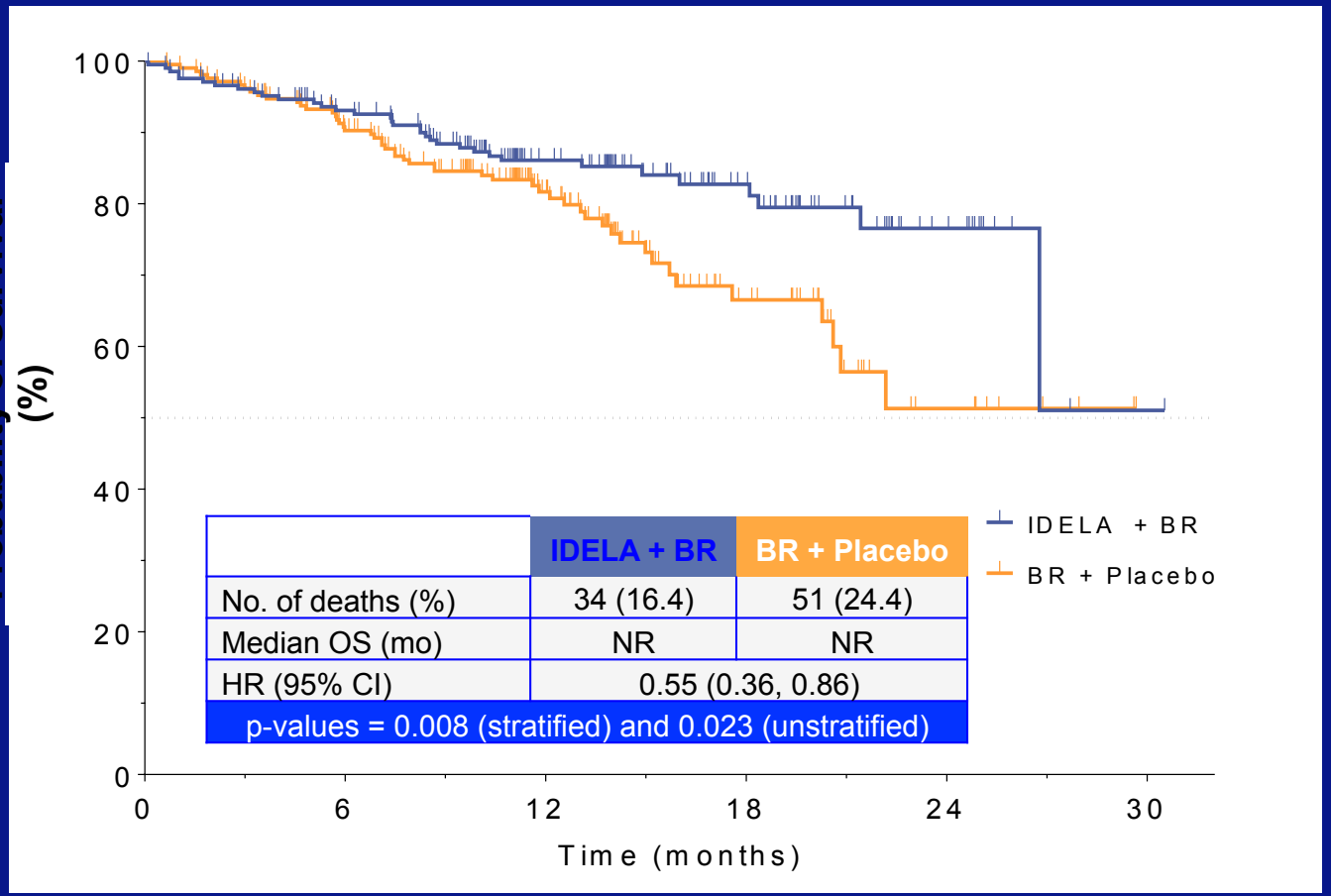


No. at risk (events)						
IDELA + BR	207 (0)	154 (25)	74 (51)	27 (61)	6 (63)	1 (64)
BR + Placebo	209 (0)	145 (46)	36 (111)	11 (126)	1 (131)	0 (132)

- HR, hazard ratio; IRC, independent review committee.

Results: Overall Survival

Secondary Endpoint



	IDELA + BR	BR + Placebo
No. of deaths (%)	34 (16.4)	51 (24.4)
Median OS (mo)	NR	NR
HR (95% CI)	0.55 (0.36, 0.86)	
p-values = 0.008 (stratified) and 0.023 (unstratified)		

No. at risk (events)						
IDELA + BR	207 (0)	181 (14)	104 (27)	52 (30)	13 (33)	1 (34)
BR + Placebo	209 (0)	180 (20)	93 (35)	33 (47)	8 (51)	0 (51)

Results: AEs (>10% of patients)

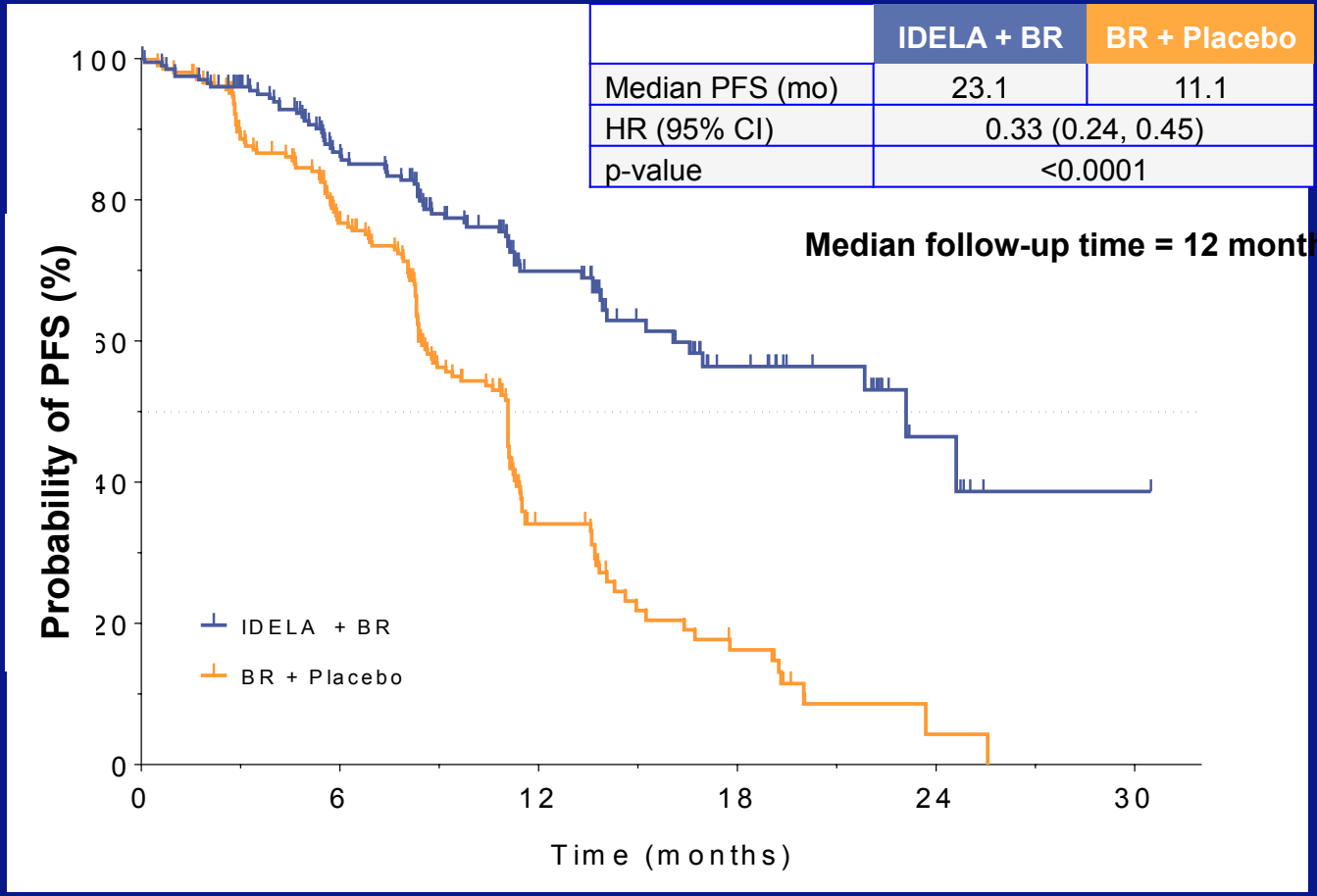
Study 115

Adverse Event	IDELA + BR, n=207		BR + Placebo, n=209	
	Any Grade n (%)	Grade ≥3 n (%)	Any Grade n (%)	Grade ≥3 n (%)
Neutropenia	131 (63)	124 (60)	112 (54)	96 (46)
Pyrexia	86 (42)	14 (7)	63 (30)	7 (3)
Diarrhea	73 (35)	15 (7)	45 (22)	4 (2)
Nausea	56 (27)	2 (1)	72 (34)	2 (1)
Anemia	53 (26)	30 (15)	47 (23)	25 (12)
Thrombocytopenia	46 (22)	27 (13)	49 (23)	24 (12)
Febrile neutropenia	45 (22)	42 (20)	14 (7)	12 (6)
Cough	44 (21)	1 (<1)	46 (22)	2 (1)
Fatigue	42 (20)	7 (3)	52 (25)	5 (2)
Pneumonia	36 (17)	23 (11)	23 (11)	13 (6)
Rash	33 (16)	6 (3)	25 (12)	0
Vomiting	32 (16)	2 (1)	30 (14)	2 (1)
Constipation	32 (16)	1 (<1)	35 (17)	0
ALT increased	31 (15)	22 (11)	3 (1)	1 (<1)
Infusion-related reaction	30 (15)	5 (2)	48 (23)	4 (2)
Upper respiratory tract infection	28 (14)	2 (1)	23 (11)	3 (1)
Arthralgia	25 (12)	2 (1)	16 (8)	0
Chills	23 (11)	0	14 (7)	0
Dyspnea	22 (11)	5 (2)	28 (13)	9 (4)
Asthenia	22 (11)	1 (<1)	20 (10)	5 (2)
Decreased appetite	20 (10)	4 (2)	15 (7)	0
Headache	20 (10)	1 (<1)	22 (11)	1 (<1)

Results: IRC-Assessed PFS

Study 115: Primary Endpoint

	IDELA + BR	BR + Placebo
Median PFS (mo)	23.1	11.1
HR (95% CI)	0.33 (0.24, 0.45)	
p-value	<0.0001	



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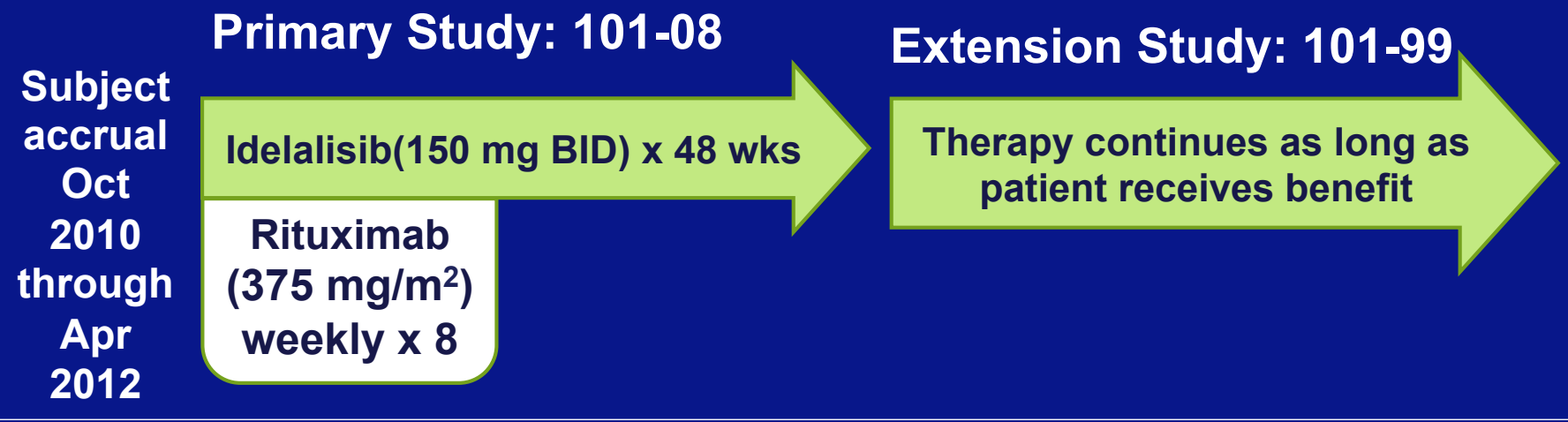
- HR, hazard ratio; IRC, independent review committee.

Phase 2 Single Arm, Open Label Study of Idelalisib + Rituximab in Frontline CLL

Study Schema



Eligibility
- Age ≥ 65 years
- Treatment naive CLL requiring therapy (IWCLL 2008)
- No exclusions for cytopenias

Disease assessment
- Investigator determined
- Weeks 0, 8, 16, 24, 36, 48 and per SOC thereafter

Endpoints
- Primary: ORR
- Secondary: DOR, PFS, Safety

O'Brien et al Blood 2015 Dec 17;126(5):2686-94

Idelalisib + Rituximab: Response

	All Patients		Del(17p) and/or TP53 mutation	
	N = 64	(%)	N = 9	(%)
Complete Response	12	(19)	3	(33)
Partial Response	50	(78)	6	(67)
Stable Disease	0		0	
Progressive Disease	0		0	
Not Evaluable	2	(3)	0	
Overall Response	62	(97)	9	(100)

- Median Time to Response 1.9 months
- 24/26 patients with B symptoms resolved by week 16

No on-study progression

O'Brien et al Blood 2015 Dec 17;126(5):2686-94

Patient Disposition

	All Patients N=64
Received study drug, n (%)	**64 (100)**
Completed 8 weeks	62 (97)
Completed 48 weeks (primary study)	43 (67)
Ongoing (as of Aug 1, 2014)	22 (34)
Discontinued*	**42 (66)**
Adverse event	27 (42)
Disease progression	5 (8)
Death	4 (6)
Withdrew consent	3 (5)
Elected not to enter extension	2 (3)
Investigator request	1 (2)

***23 patients (36%) discontinued before entering extension at 48 weeks; 19 (30%) discontinued after entering extension study.**

Idelalisib + Rituximab: In Frontline CLL

Adverse Events Leading to Discontinuation

Patients, n (%)*	Treatment Duration			Total n=23
	<24 wk n=10	24-48 wk n=6	>48 wk n=11	
Diarrhea/colitis	0	4	8	12 (19)
Respiratory disorders	6	0	1	7 (11)
Rash	3	0	0	3 (5)
Infection	1	2	0	3 (5)
Anemia	1	1	0	2 (3)
ALT/AST	1	0	0	1 (2)
Other	2	4	2	8 (13)

*Patients may have >1 AE.

Deaths

- 5 deaths
  - Pneumonia/sepsis (n=1); pneumonia/metastatic melanoma (n=1); pneumonitis (n=2); myocardial infarction (n=1)

O'Brien et al Blood 2015 Dec 17;126(5):2686-94

Diarrhea/Colitis

- 27 patients (42%) developed Grade ≥3 diarrhea/colitis
  - Onset at median 9.5 months (range 3–29)
  - Dosing interrupted or discontinued in 21 patients
  - 11 patients received a corticosteroid (budesonide or prednisone)
- 21 patients rechallenged following idelalisib dose interruption or had dose reduced to 100 mg BID
  - 12 patients (44% of 27 affected) were subsequently able to maintain dosing for minimum of 120 days

The Connection Between p110δ and Tregs

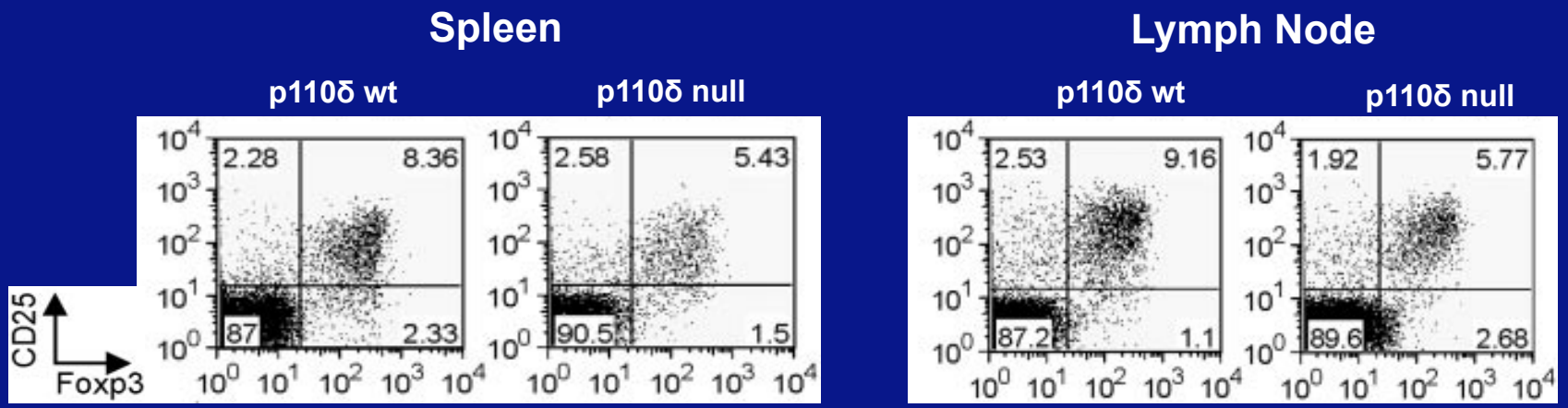
- Mice with genetic inactivation of p110δ develop an autoimmune colitis

  Okkenhaug *Nature* 2002

- Mutations that disrupt Treg function in mice and humans lead to autoimmune syndromes with hepatitis, enteritis, and pneumonitis

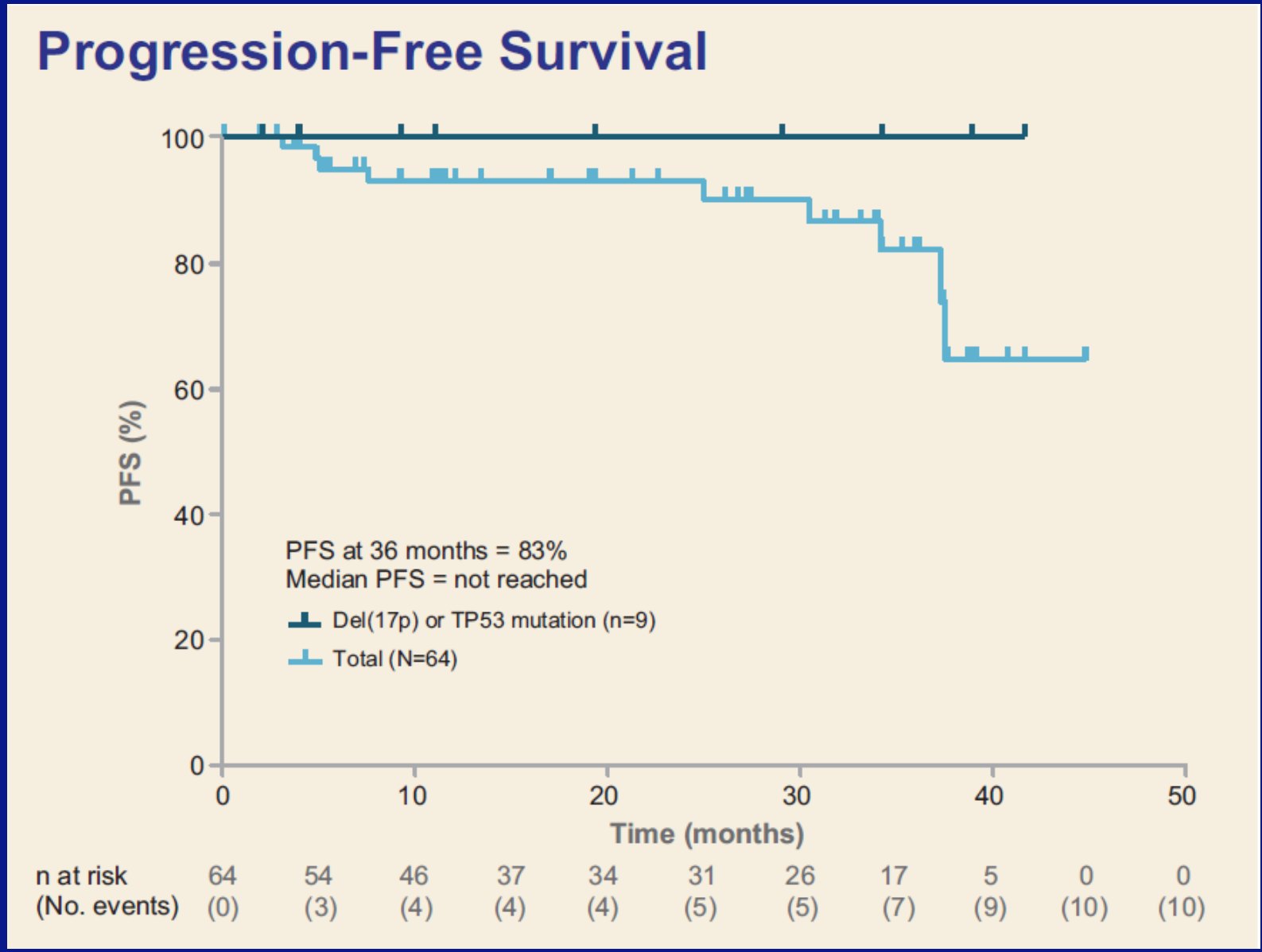
  Torgerson *J Allergy Clin Immunol* 2007
  Godfrey *Am J Path* 1991

- Mice with genetic inactivation of p110δ have decreased numbers and function of regulatory T cells



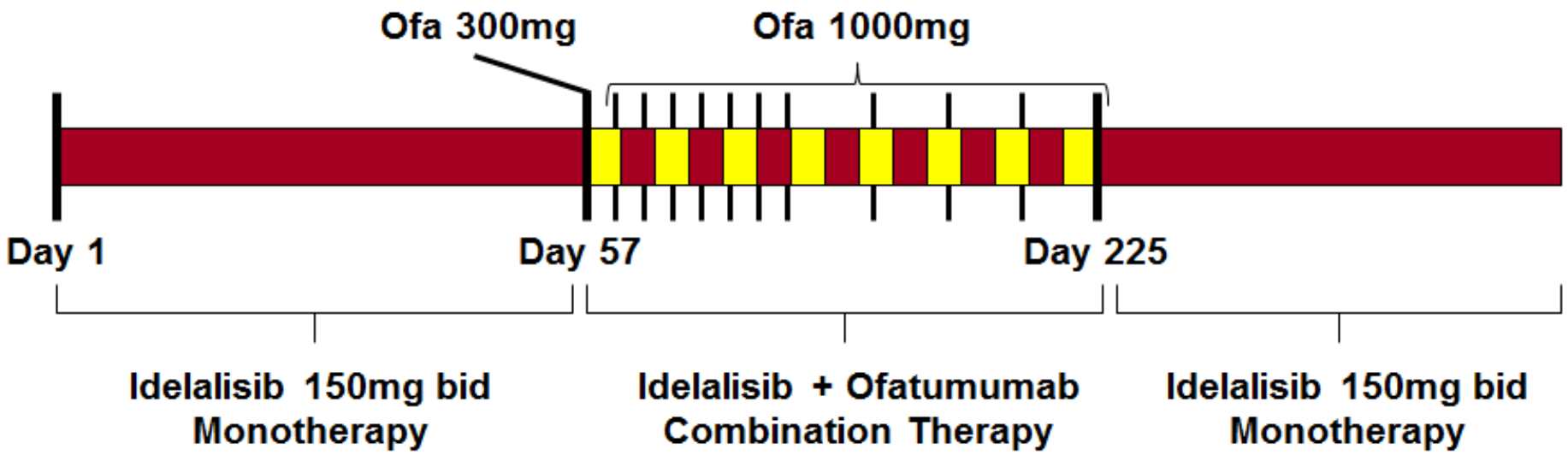
Patton *J Immunol* 2006

Results: PFS



O'Brien et al Blood 2015 Dec 17;126(5):2686-94

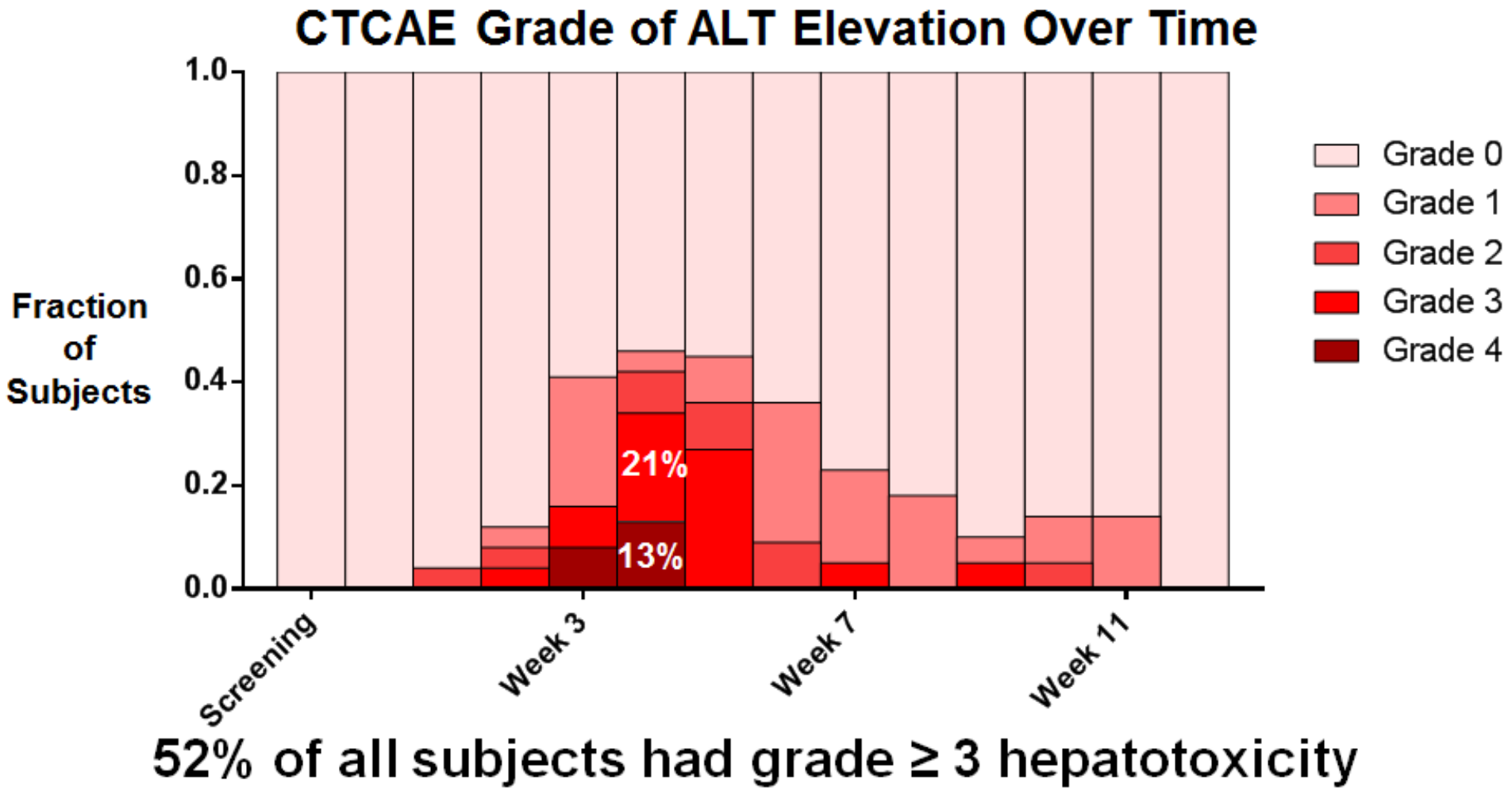
A Phase II Study of Idelalisib + Ofatumumab in Previously Untreated CLL/SLL



- Median time on therapy is 7.7 months (range, 0.7-16.1 months)
- Median follow-up time is 14.7 months (range, 1.2-16.8 months)

Lampson et al. Blood. 2016 June 14;128(2)195-203

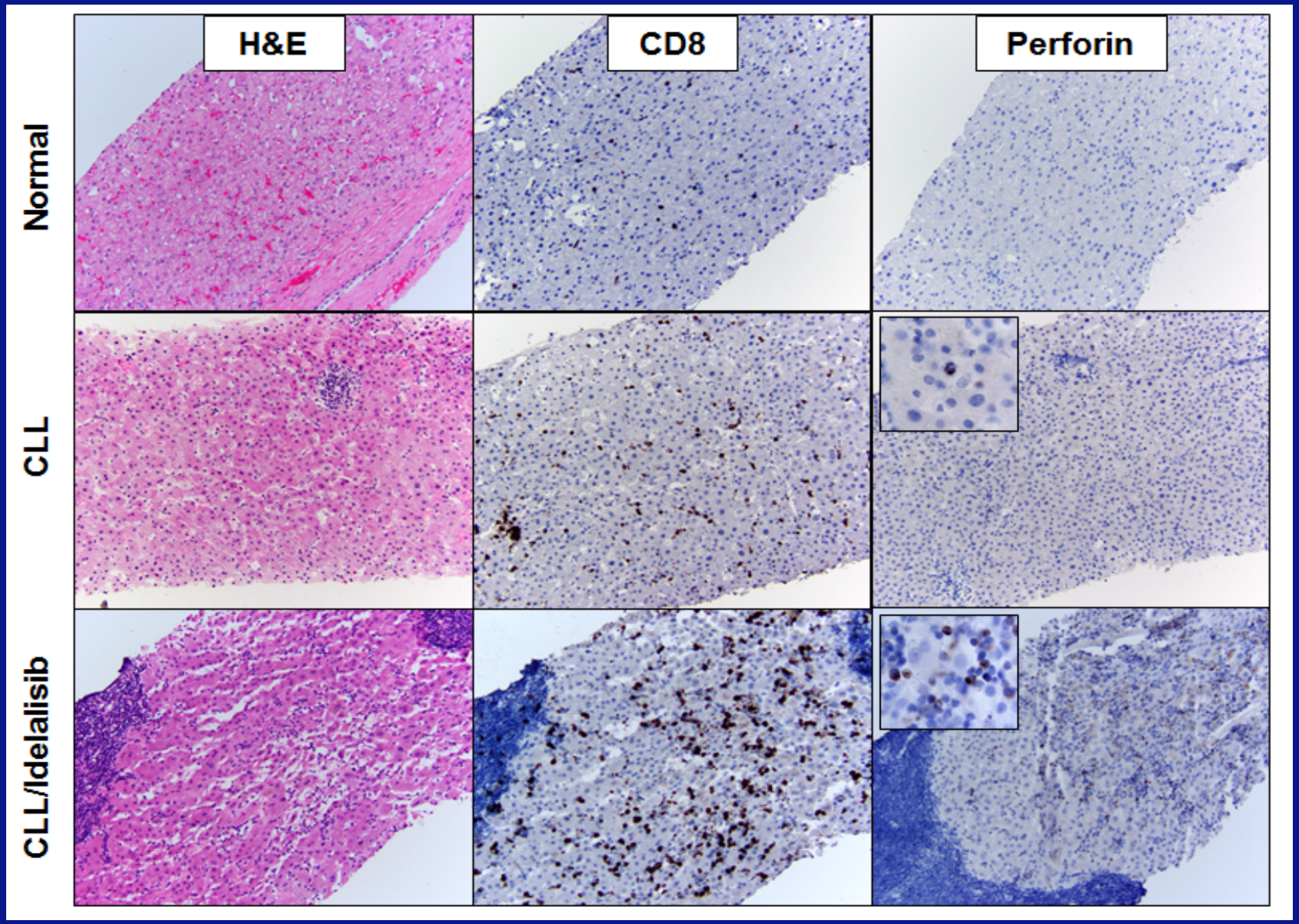
Frequent and Severe Hepatotoxicity



52% of all subjects had grade ≥ 3 hepatotoxicity

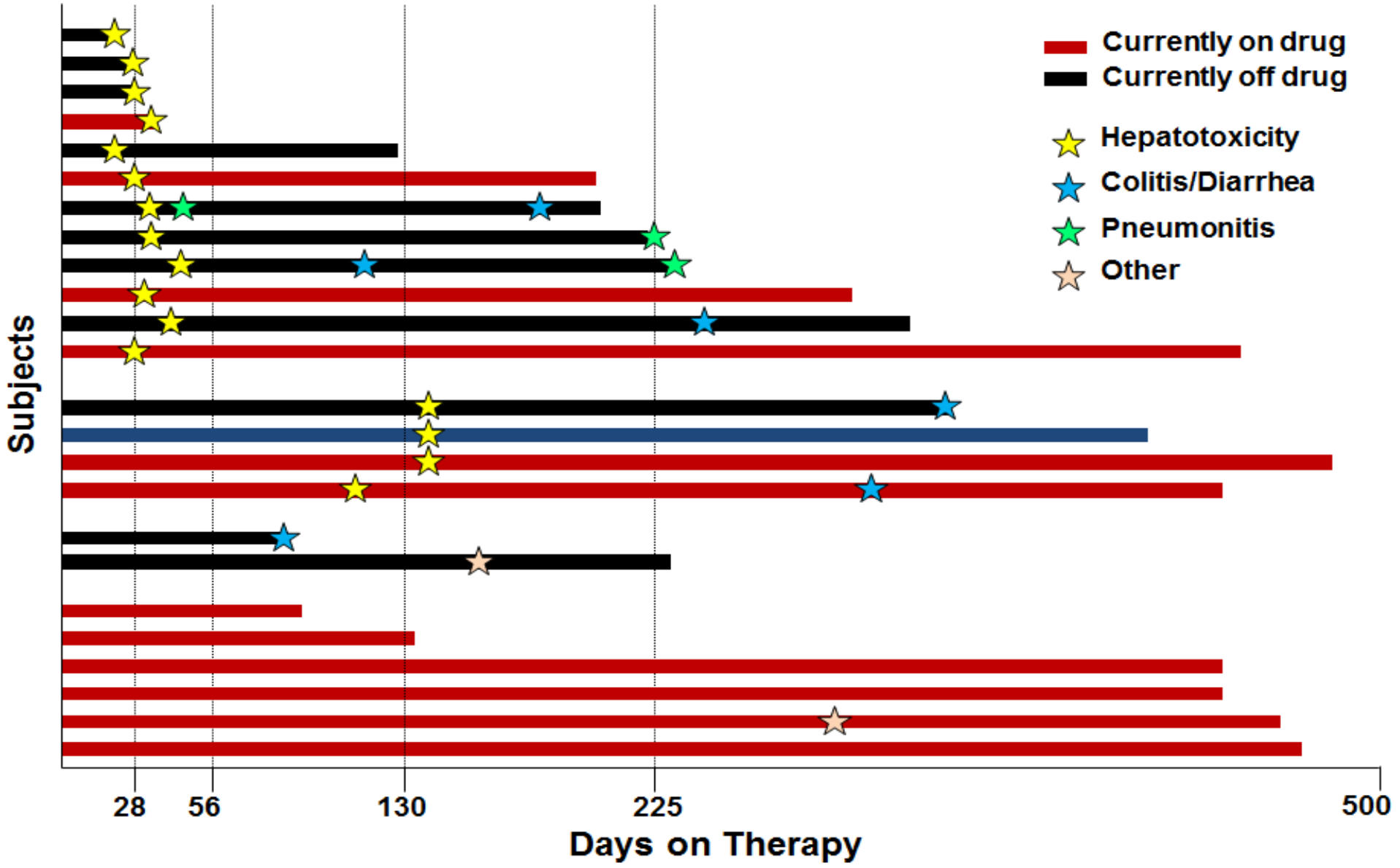
Lampson et al. Blood. 2016 June 14;128(2)195-203

Activated Immune Infiltrate on Liver Biopsy



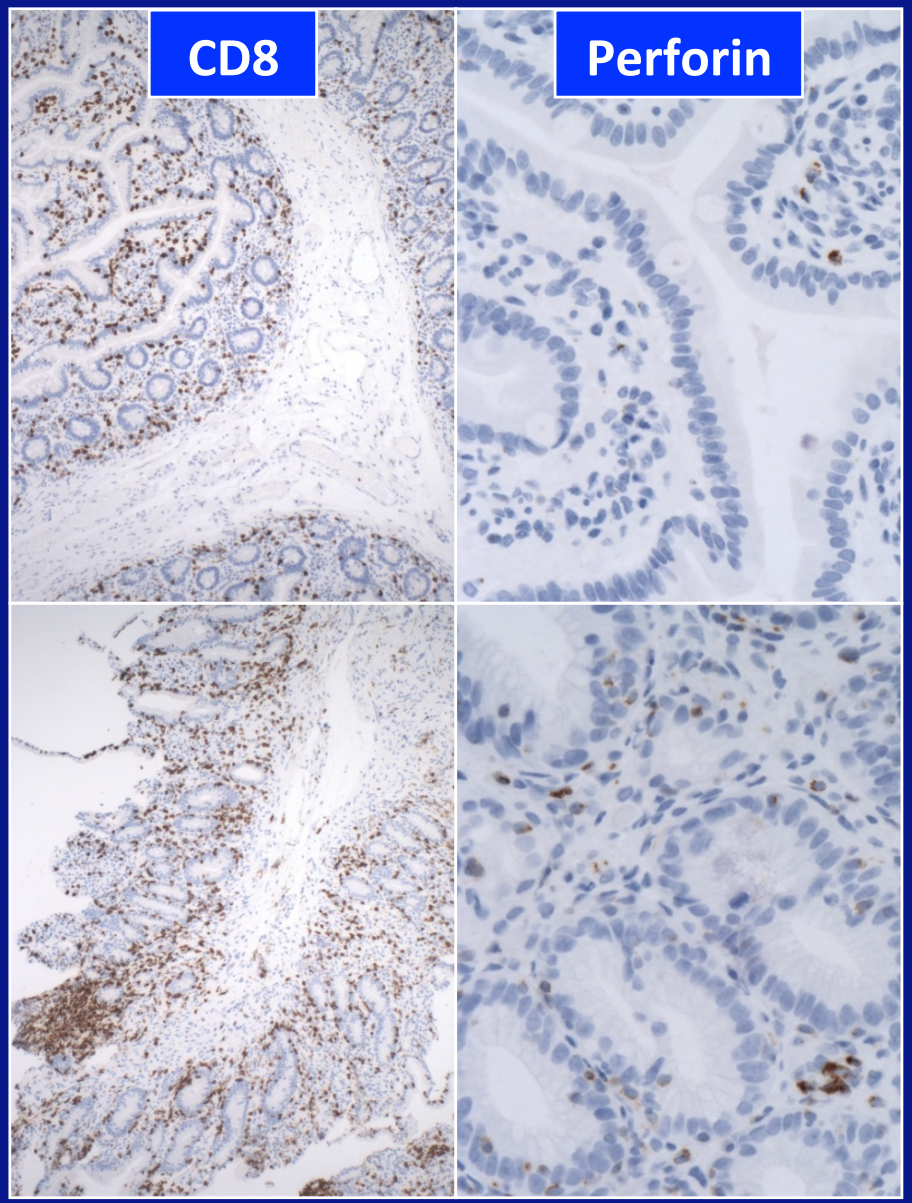
Lampson et al. Blood. 2016 June 14;128(2)195-203

Idelalisib Toxicities



Lampson et al. Blood. 2016 June 14;128(2)195-203

Immune Infiltrate in Subjects with Colitis

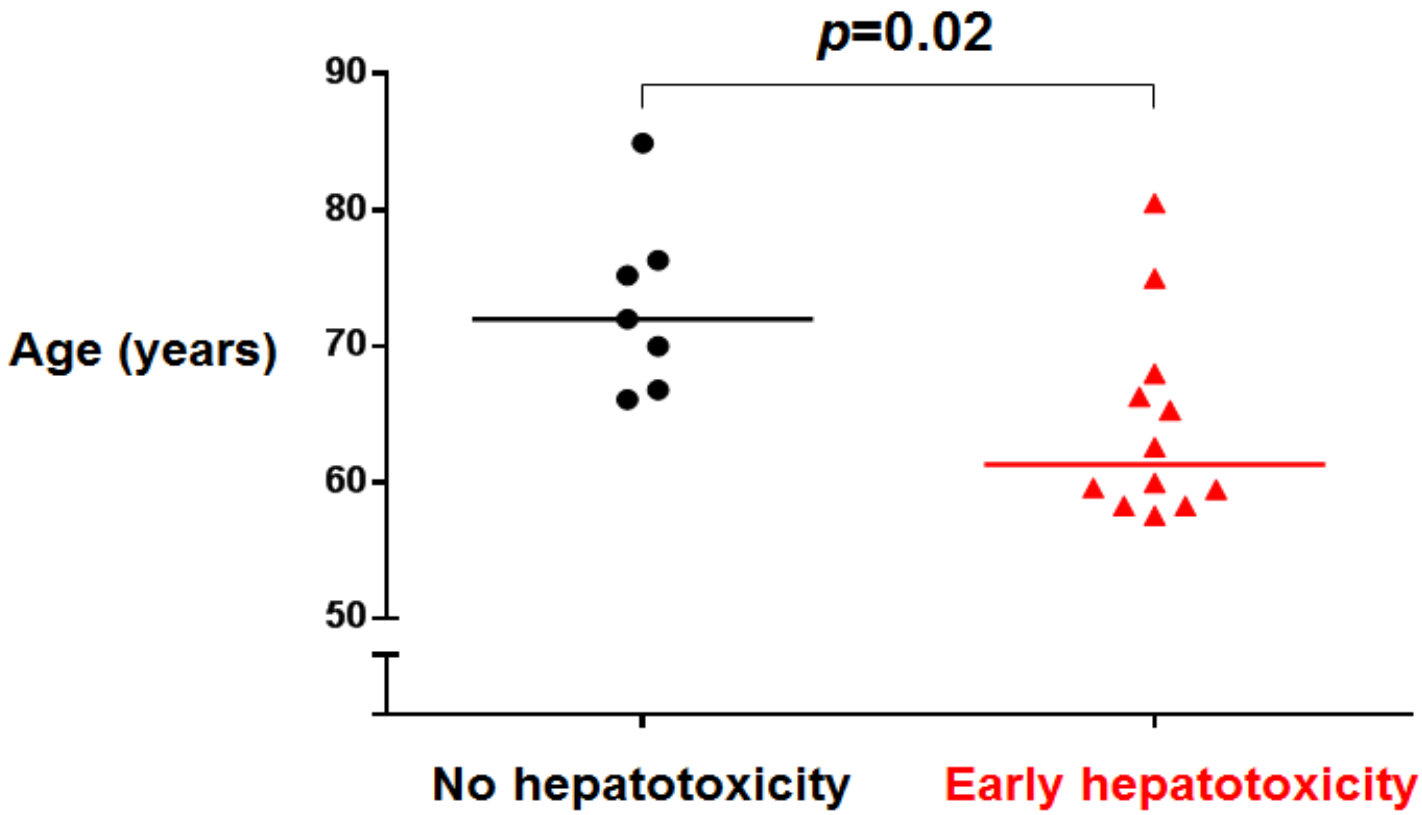


- Intestinal biopsies from patients with idelalisib-related colitis show intraepithelial CD8+ lymphocytosis and crypt cell apoptosis

Weidner *Am J Surg Path* 2015

Louie *Am J Surg Path* 2015

Age Is a Risk Factor for Early Hepatotoxicity

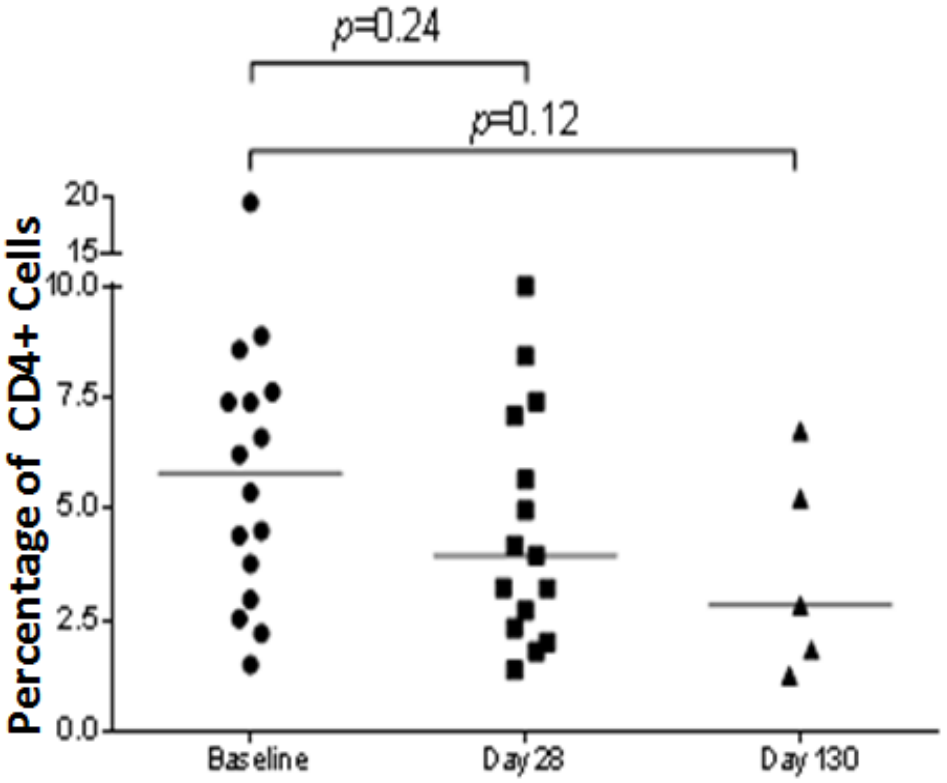


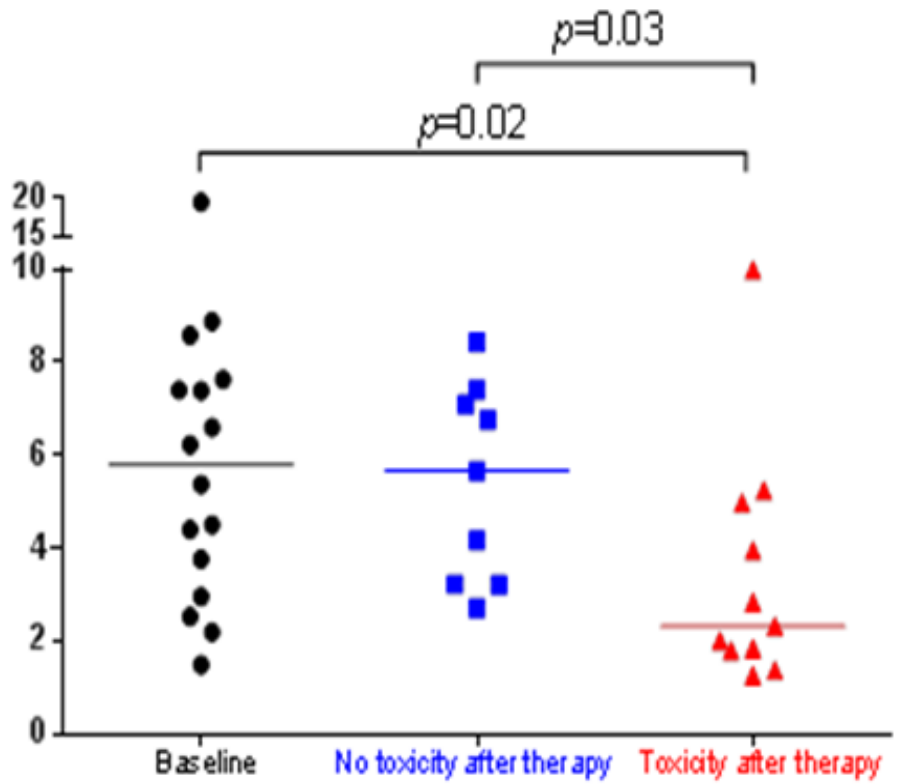
100% of subjects age ≤65 (*n*=7) required systemic steroids for toxicities

Lampson et al. Blood. 2016 June 14;128(2)195-203

Change in Tregs on Therapy

CD3+CD4+CD25hiFOXP3+ T cells





73% (11 out of 15) of subjects with matched samples had a decrease in percentage of regulatory T cells over time

Lampson et al. Blood. 2016 June 14;128(2)195-203

Summary: Idelalisib

- Idelalisib is a highly active drug that is still much needed in B cell malignancies
  - Median PFS 19 mos in patients with high CIRS, short remission duration and 45% 17p deletion
  - No difference based on *IGHV* or 17p status
- Idelalisib as a prototypical PI3Kd inhibitor causes a characteristic pattern of immune-mediated toxicity that is currently unpredictable and may be severe
  - Associated with younger age, less prior therapy, mutated *IGHV* and decrease in Tregs on idelalisib
  - Mouse models support that this is an on target effect
  - Ongoing work to identify clinical and/or immune predictors