Idelalisib Therapy

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

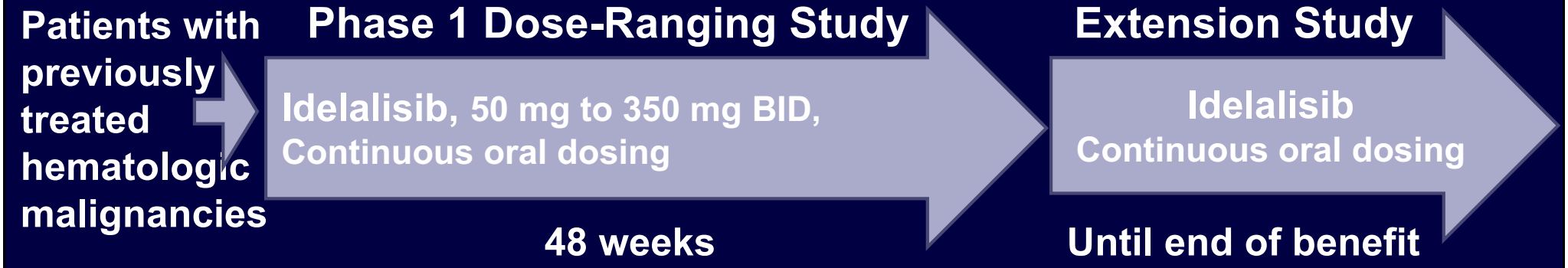
Idelalisib

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

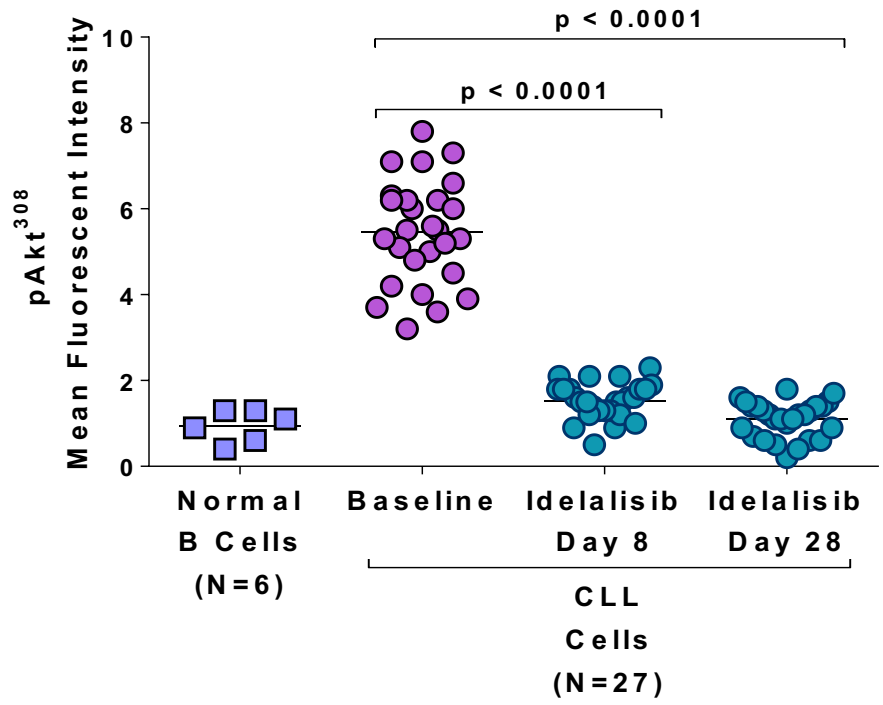
Endpoints:

- Dose selection
- Safety
- Pharmacodynamics
- Pharmacokinetics
- Efficacy

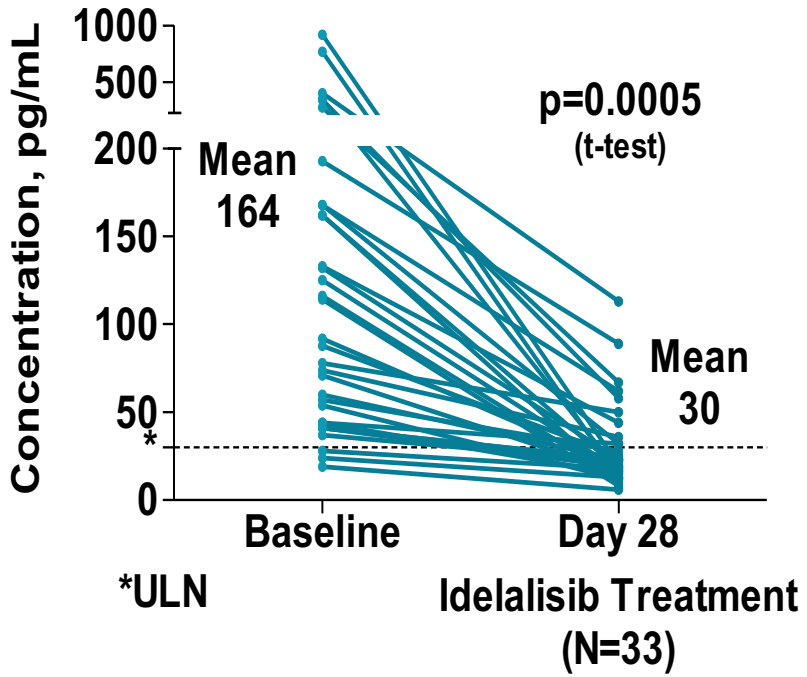
Brown et al. Blood. 2014 May 29; 123 (22): 3390-7

Effective Target Inhibition and Cytokine Reduction in CLL

Phospho-Akt Levels



CXCL13 Plasma Levels



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

Marked Reductions in Peripheral Lymphadenopathy Were Observed

Pretreatment | With IdelalisibTreatment

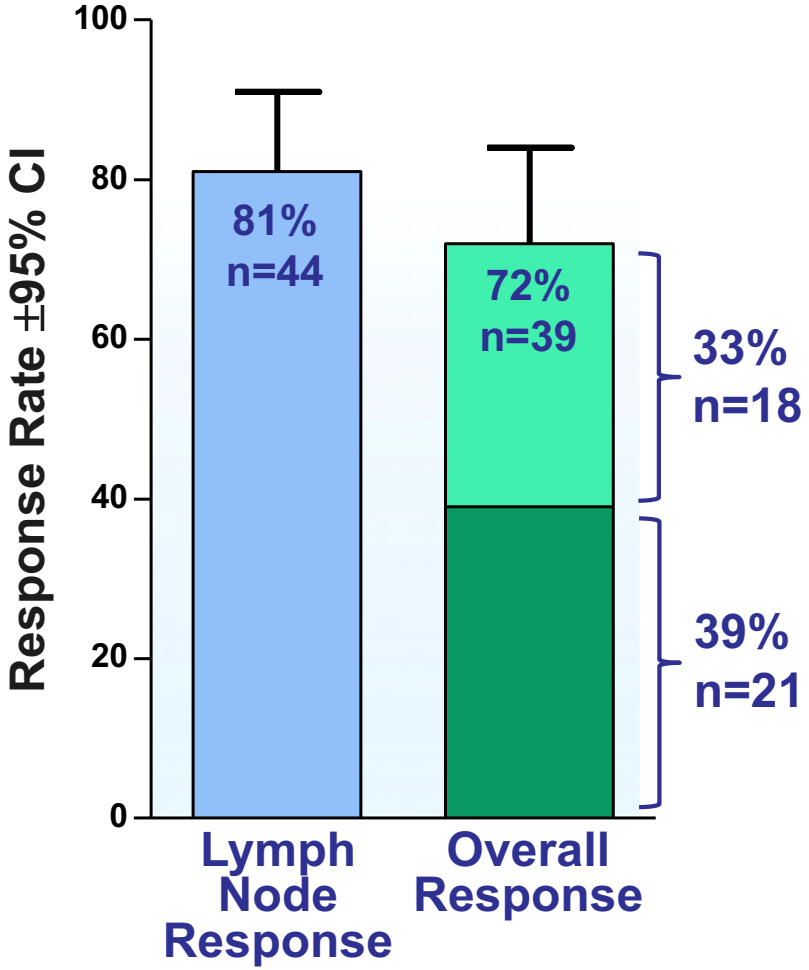
38-year-old patient with refractory CLL and 5 prior therapies

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		

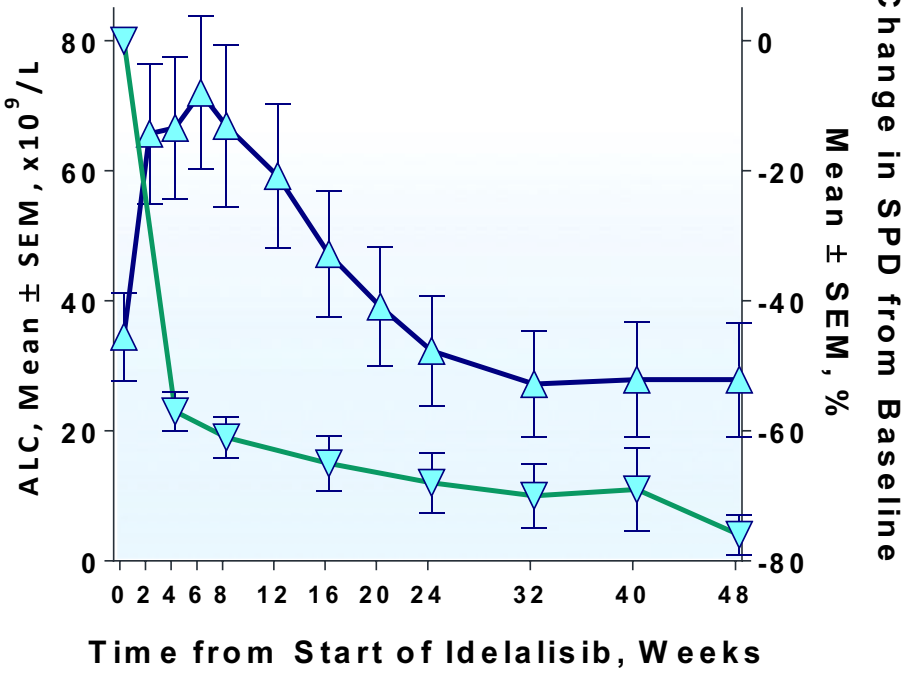
Brown et al. Blood. 2014 May 29; 123 (22): 3390-7

Idelalisib: Nodal and Overall Response Rate



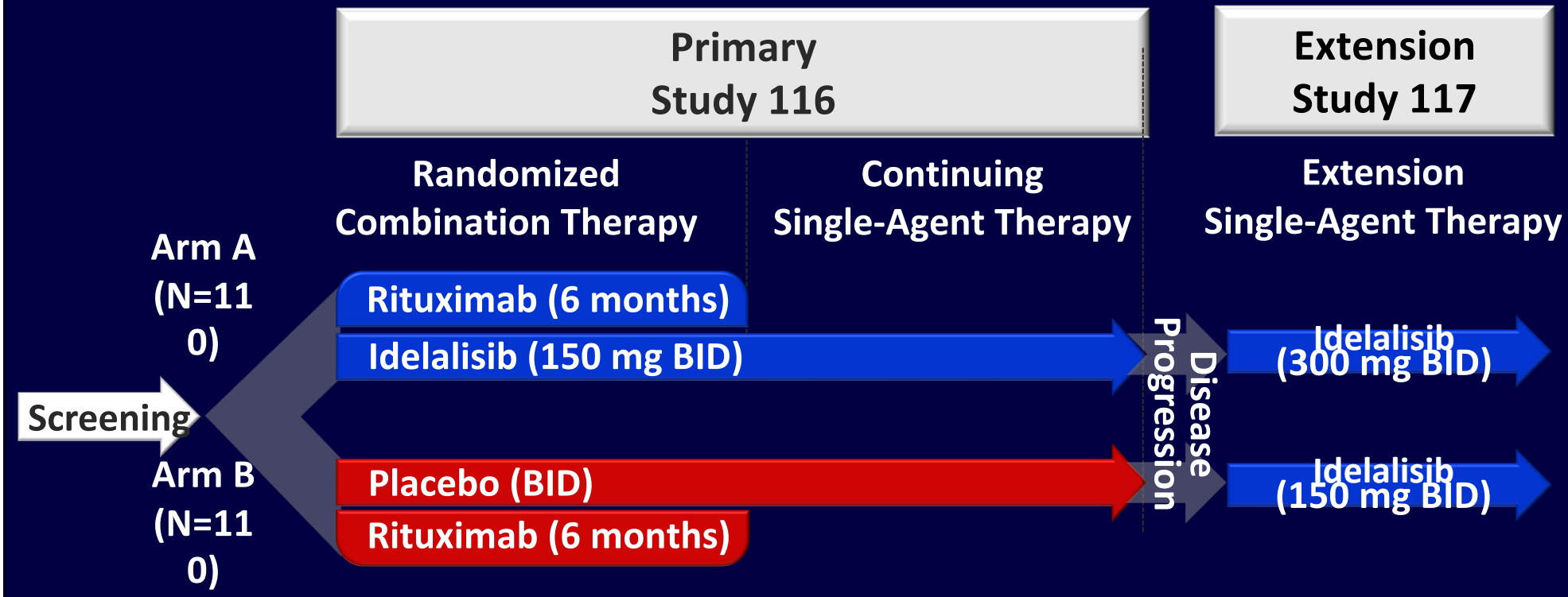
Decrease by ≥50% of nodal SPD
PR with lymphocytosis (Cheson 2012)
PR by IWCLL criteria (Hallek 2008)

ALC and Tumor Burden Over Time



ALC (N=54)
SPD (N=51)

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

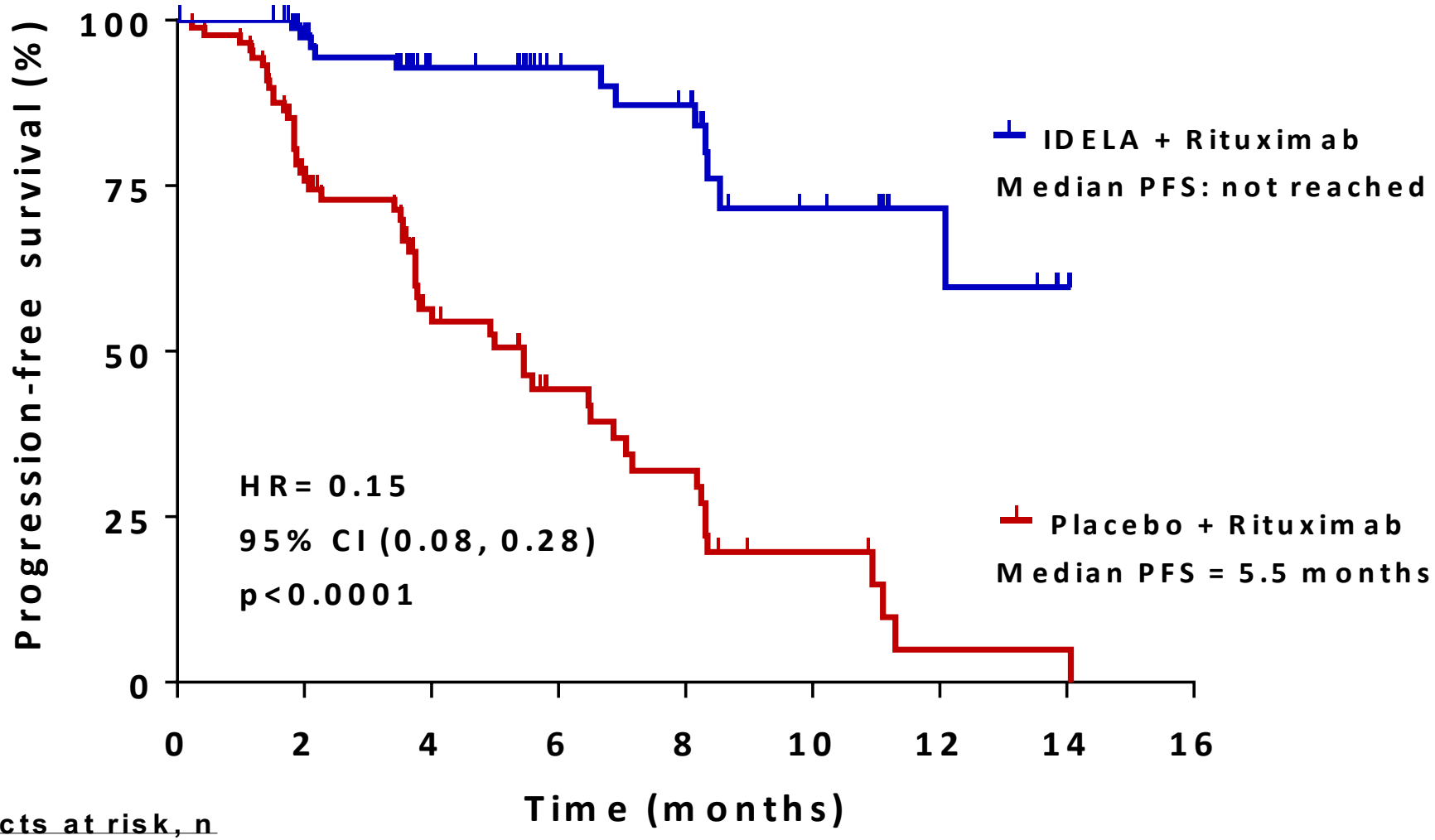
Furman et al N Engl J Med 2014, Mar 13, 370 (11): 997-1007

Baseline Patient Characteristics

	Idelalisib + R N=110	Placebo + R N=110
Male, %	69	62
Median age, y (range)	71 (48-90)	71 (47-92)
Rai stage 0 / I-II / III-IV, %	0 / 31 / 64	1 / 26 / 66
Median years since diagnosis	7.9	8.6
Prior therapies, median (range)	3 (1-12)	3 (1-10)
Cytopenia*, any Grade, Grade 3/4, %	85, 32	88, 39
Total CIRS score >6, %	88	82
Estimated CrCl <60 mL/min, %	44	36
High-risk parameter, %		
Del(17p) and/or *TP53* mutation	42	45
Del(11q)	34	30
Unmutated *IGHV*	83	85
ZAP70+	92	85
CD38+	57	46
ß2-microglobulin >4 mg/L	85	78

*Anemia and/or thrombocytopenia and/or neutropenia.

Primary Endpoint: Progression-Free Survival

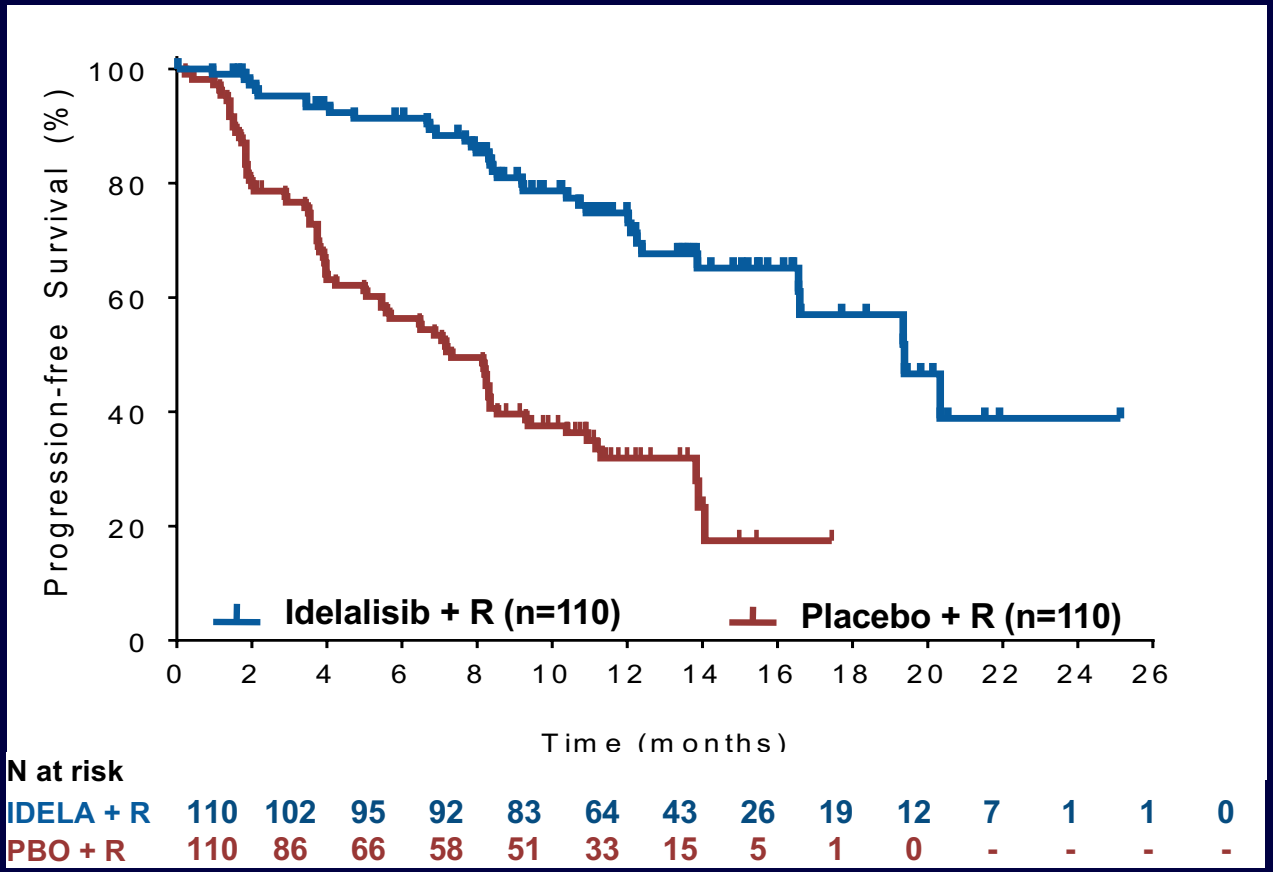


Subjects at risk, n

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

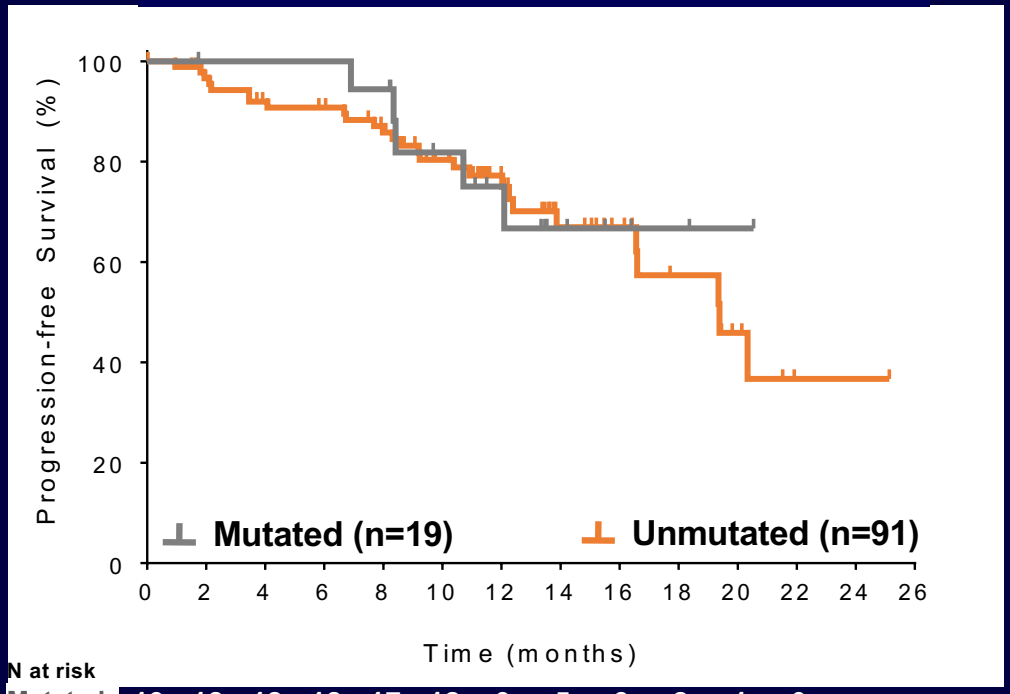


	Median PFS (95% CI)	HR (95% CI)	p-value
IDELA + R	19.4 mo (16.6, –)	0.25 (0.16, 0.39)	<0.0001
PBO + R	7.3 mo (5.5, 8.5)		

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

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

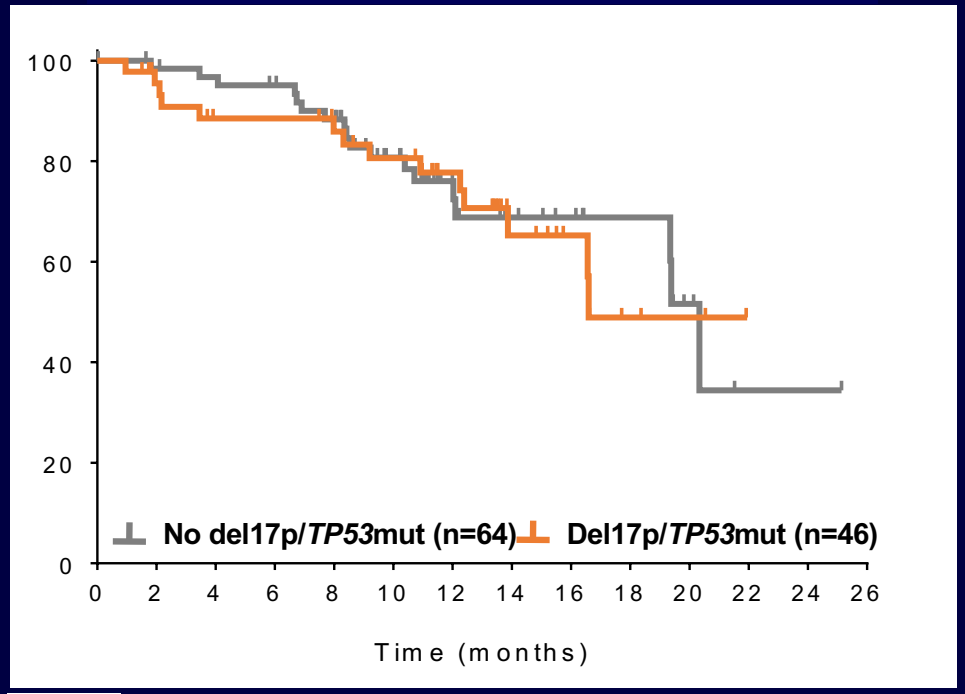
IGHV: Unmutated vs Mutated



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



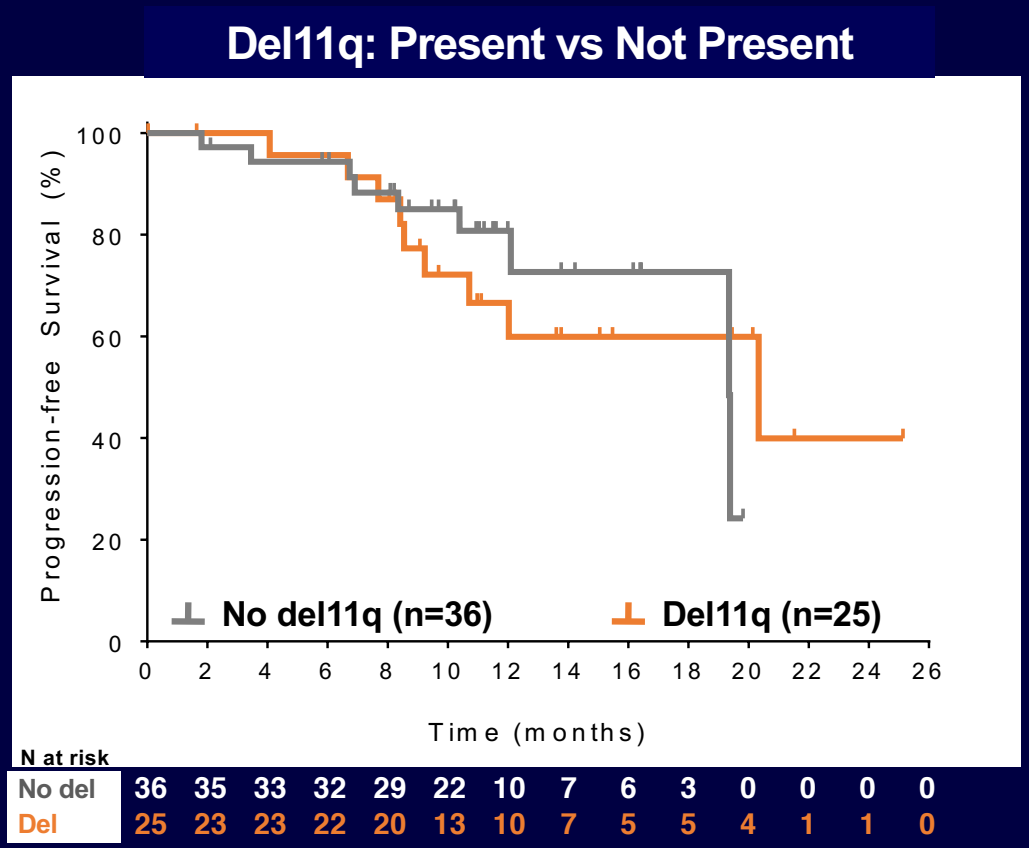
No del	64	61	59	59	52	37	21	14	11	8	4	1	1	1
Del	46	41	36	36	33	30	22	12	8	4	3	0		

	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. J Clin Oncol. 2019 Jun 1;37(16): 1391-1402.

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



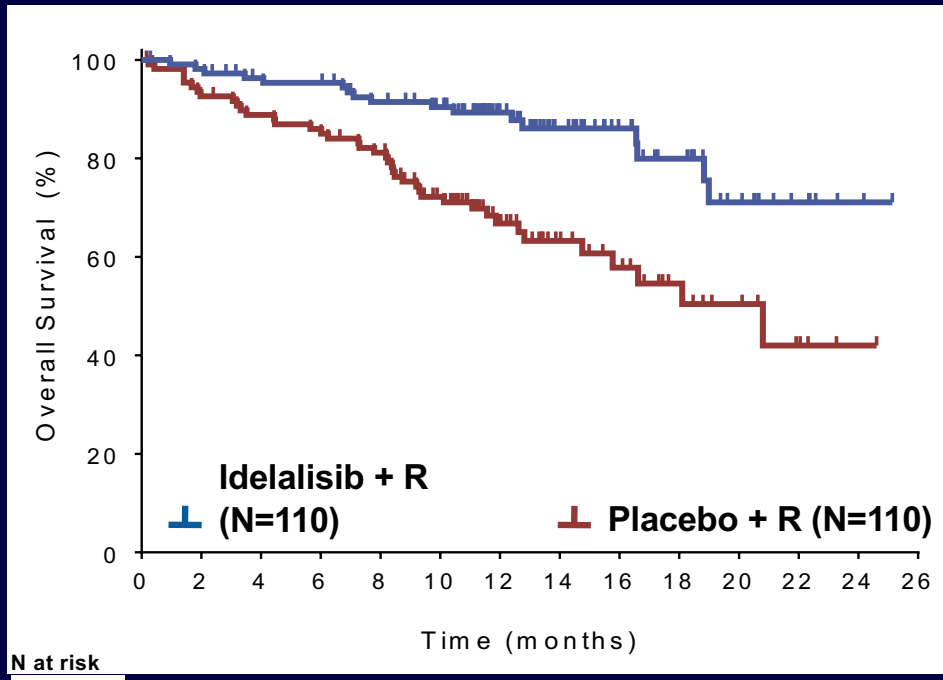
	Median PFS (95% CI)	p-value
No del	19.4 mo (12.1, –)	0.84
Del	20.3 mo (9.2, –)	

*Including extension study

Sharman et al. J Clin Oncol. 2019 Jun 1;37(16): 1391-1402.

Overall Survival, Including Extension Study*
Idelalisib + R vs Placebo + R → Idelalisib

All Patients

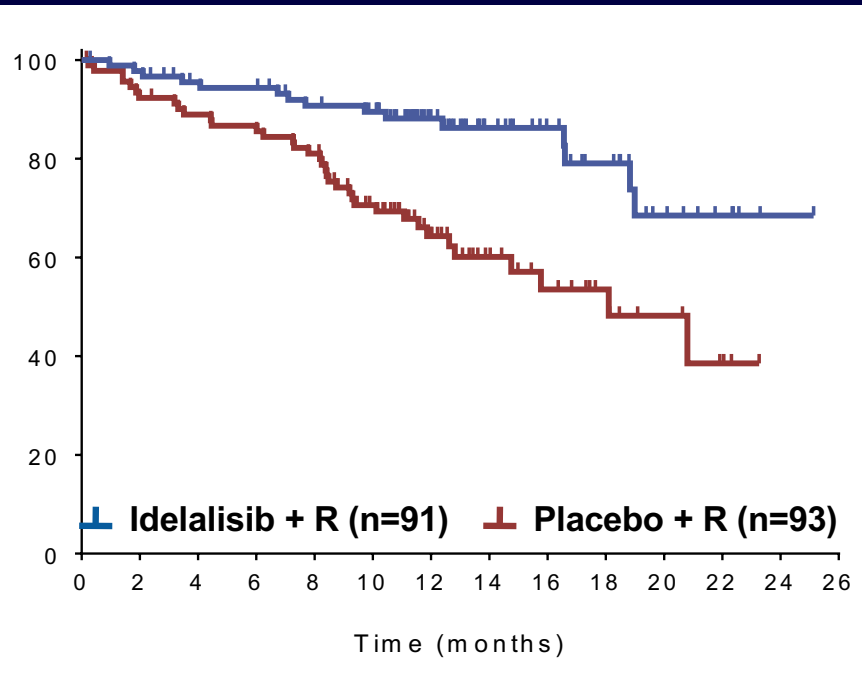


N at risk

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

	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, –)		

IGHV Unmutated



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
NR (19.0, –)	0.35 (0.19, 0.6)	0.0003
18.1 mo (14.8, –)		

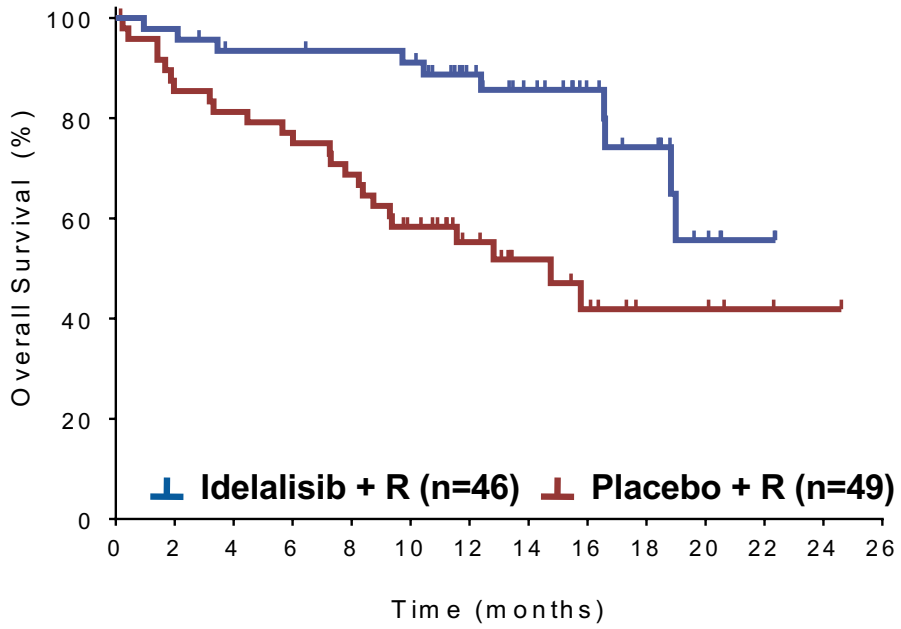
*As randomized, including cross-over

Sharman et al. J Clin Oncol. 2019 Jun 1;37(16): 1391-1402.

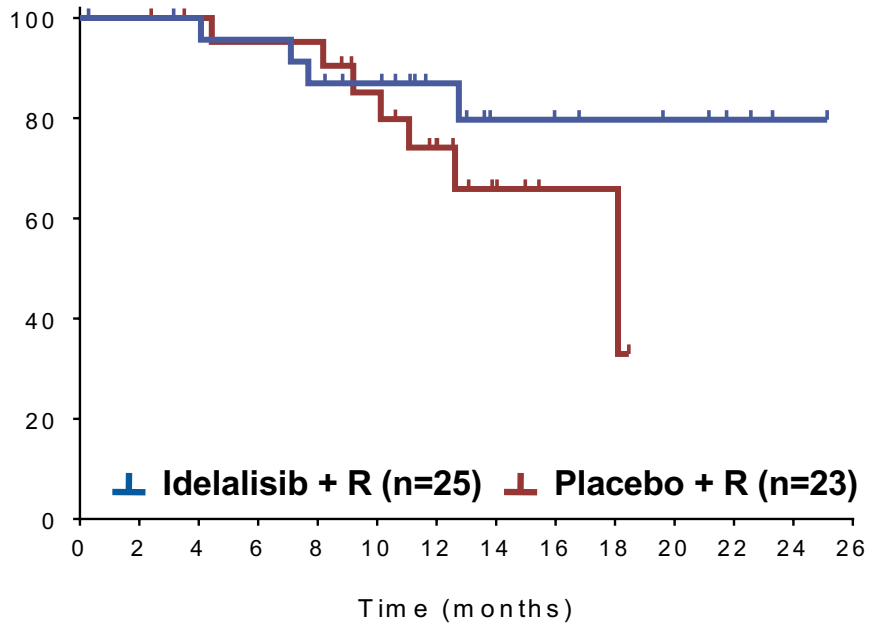
Overall Survival, Including Extension Study*

Idelalisib + R vs Placebo + R → Idelalisib

Del17p/TP53 Mutation (Either)



Del11q Positive



N at risk																									
IDELA + R	46	45	41	41	40	39	30	23	16	12	5	2	0		25	24	23	22	20	17	12	8	7	6	5	3	1	0
PBO + R	49	41	39	37	33	25	17	11	8	4	4	2	1	0	23	23	21	20	20	16	11	5	2	2	0			

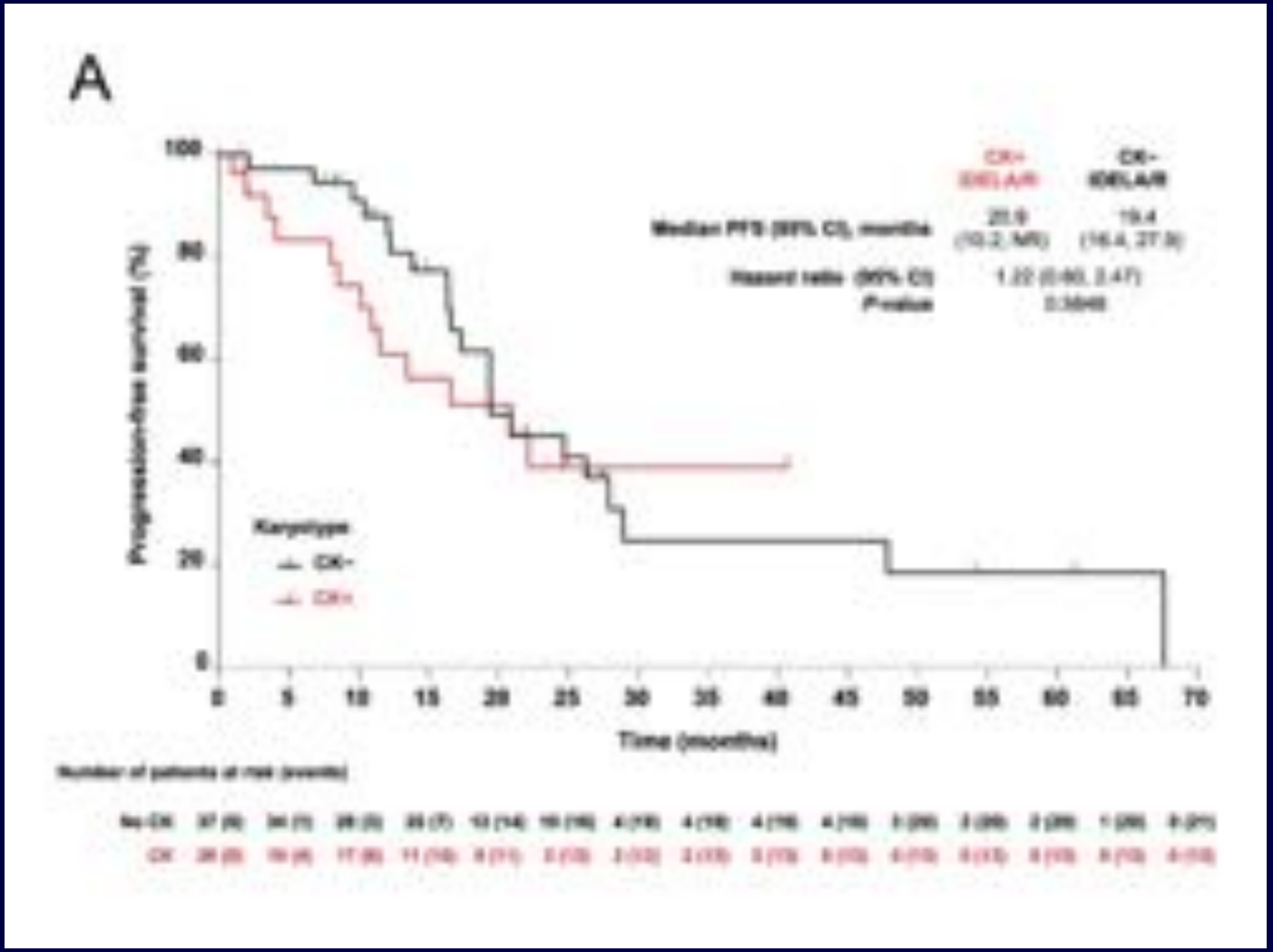
	Median OS (95% CI)	HR (95% CI)	p-value
IDELA + R	NR (18.8, –)	0.31 (0.15, 0.65)	0.001
PBO + R	14.8 mo (8.4, –)		

Median OS (95% CI)	HR (95% CI)	p-value
NR (–, –)	NA	0.21
18.1 (11.1, –)		

*As randomized, including cross-over

Sharman et al. J Clin Oncol. 2019 Jun 1;37(16): 1391-1402.

Progression Free Survival in Patients +/- Complex Karyotype in the Idelalisib Arm



Kreuzer et al. Leukemia. 2019 Aug 19.

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

Select Lab Abnormalities
Idelalisib + R vs Placebo + R → Idelalisib

	Idelalisib + R (N=110)				Placebo + R → Idelalisib (N=108)			
	Any Grade, %		Grade ≥3, %		Any Grade, %		Grade ≥3, %	
	2nd IA	Update	2nd IA	Update	2nd IA	Update	2nd IA	Update
ALT/AST elevation	40	49	9	6	20	53	1	6
Neutropenia	60	66	37	41	60	68	27	43
Anemia	29	33	7	8	32	50	17	24
Thrombocytopenia	19	29	11	14	32	40	18	20

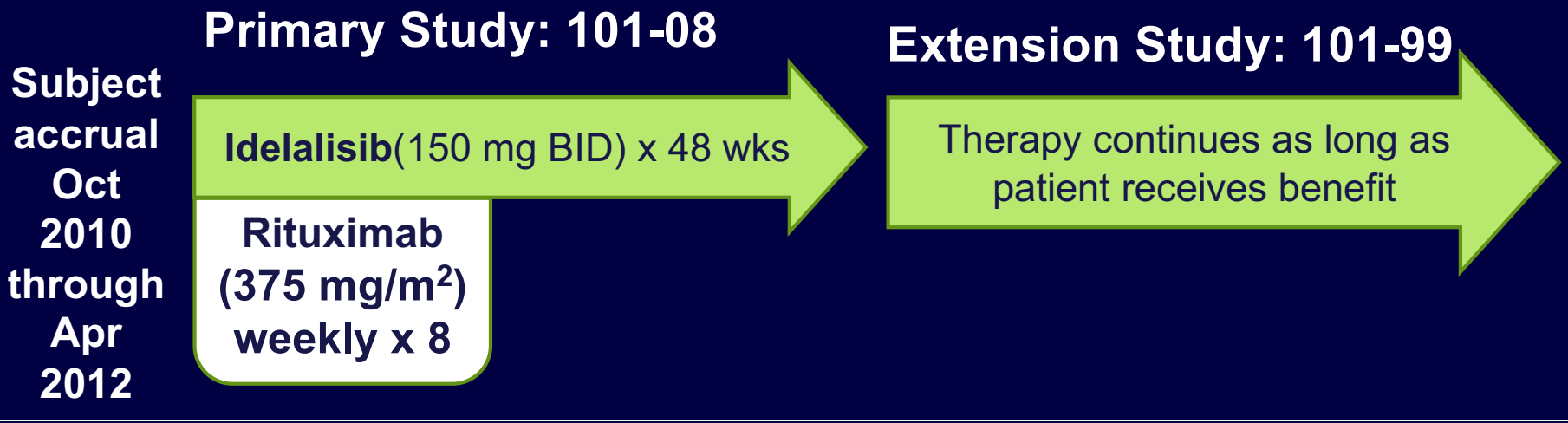
Sharman et al. J Clin Oncol. 2019 Jun 1;37(16): 1391-1402.

Summary and Conclusions

- Phase 3 subgroup analysis demonstrates comparable efficacy of idelalisib + rituximab in the presence or absence of high-risk genomic alterations like unmutated *IGHV*, del17p/*TP53* mutation and del11q
- Overall survival is significantly better for patients on idelalisib + rituximab despite cross-over in extension design
- Idelalisib + rituximab has a manageable safety profile in patients with relapsed/refractory CLL

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(25):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

O'Brien et al. Blood. 2015 Dec 17;126(25):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

A Phase 2 Study of Idelalisib Monotherapy in Previously Untreated Patients ≥65 Years With Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

Andrew D. Zelenetz,[1] Nicole Lamanna,[2] Thomas J. Kipps,[3] Steven E. Coutre,[4] Susan M. O'Brien,[5] Jaime Graves,[6] Wei Ye,[6] Ronald L. Dubowy,[6] Ian W. Flinn[7]

[1]Memorial Sloan-Kettering Cancer Center, New York, NY; [2]Columbia University Medical Center, New York, NY; [3]University of California, San Diego Moores Cancer Center, La Jolla, CA; [4]Stanford University School of Medicine, Stanford, CA; [5]The University of Texas MD Anderson Cancer Center, Houston, TX; [6]Gilead Sciences, Inc, Foster City, CA; [7]Sarah Cannon Research Institute, Nashville, TN

IWCLL 2015

101-08: Cohort 2 Best Response

	All Patients	TP53 mut or del(17p)*	TP53 normal*
N	41	6	31
Complete Response, n (%)	0	0	0
Partial Response, n (%)	28 (68)	4 (67)	22 (71)
PR with Lymphocytosis**, n (%)	7 (17)	1 (17)	5 (16)
Stable Disease, n (%)	3 (7)	0	3 (10)
Progressive Disease, n (%)	0	0	0
Not Done, n (%)	3 (7)	1 (17)	1 (3)
Overall Response, n (%)	35 (85)	5 (83)	27 (87)

- **Median time to response for all patients was 1.9 months**
- **Baseline B symptoms in 15/19 patients resolved at 8 weeks**

* 4 Subjects with missing del(17p)/TP53 data

** Subjects not meeting IWCLL 2008 criteria

101-08: Cohort 2 Treatment Emergent Adverse Events in ≥ 20% of Patients

Adverse Event	n (%) with any Grade	n (%) with Grade ≥3
Any Adverse Event	41 (100)	34 (83)
Diarrhea/Colitis	22 (54)	11 (27)
Rash*	21 (51)	4 (10)
Nausea	13 (32)	0
Pyrexia	13 (32)	1 (2)
Constipation	11 (27)	0
Fatigue	11 (27)	3 (7)
ALT/AST increased	10 (24)	9 (22)
URTI	10 (24)	0
Thrombocytopenia	9 (22)	4 (10)

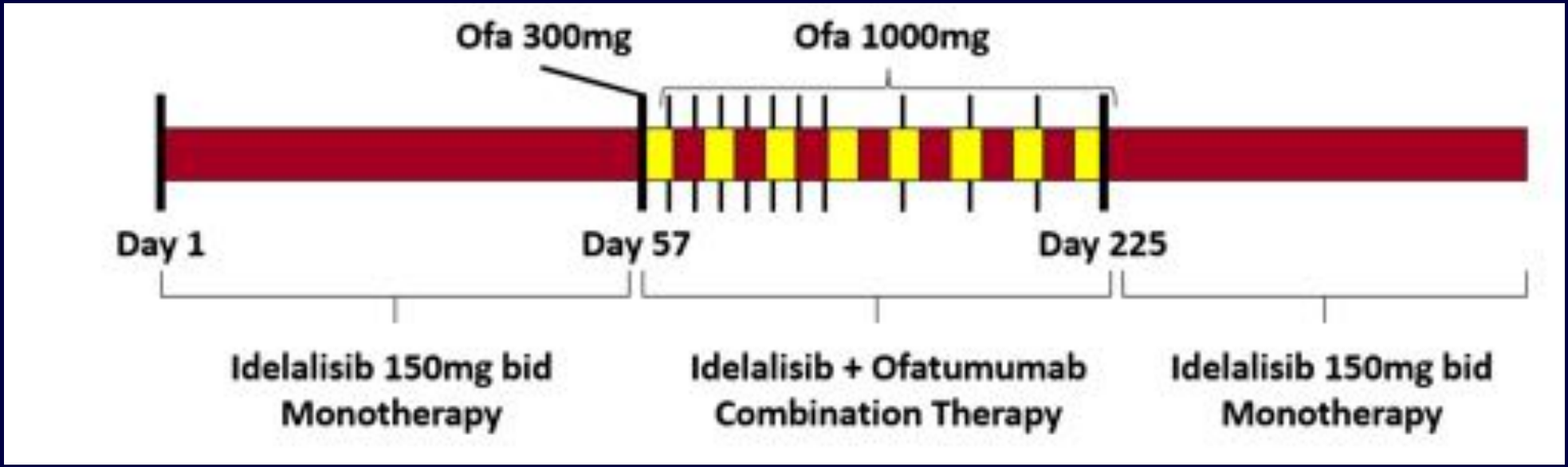
* **All rash related AEs per** Medical Search Term list

Idelalisib Given Front-line for the Treatment of Chronic Lymphocytic Leukemia Results in Frequent and Severe Immune-Mediated Toxicities

Benjamin L. Lampson, Tiago R. Matos, Siddha N. Kasar, Haesook Kim, Elizabeth A. Morgan, Laura Rassenti, Matthew Davids, Thomas Kipps, Joshua Fein, Stacey Fernandes, Jerome Ritz, Jennifer R. Brown

ASH Annual Meeting
December 7, 2015

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



- Trial is currently ongoing with 24 subjects enrolled as of 11/9/2015
- 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 Adv. 2019 Apr 9;3(7):1167-1174.

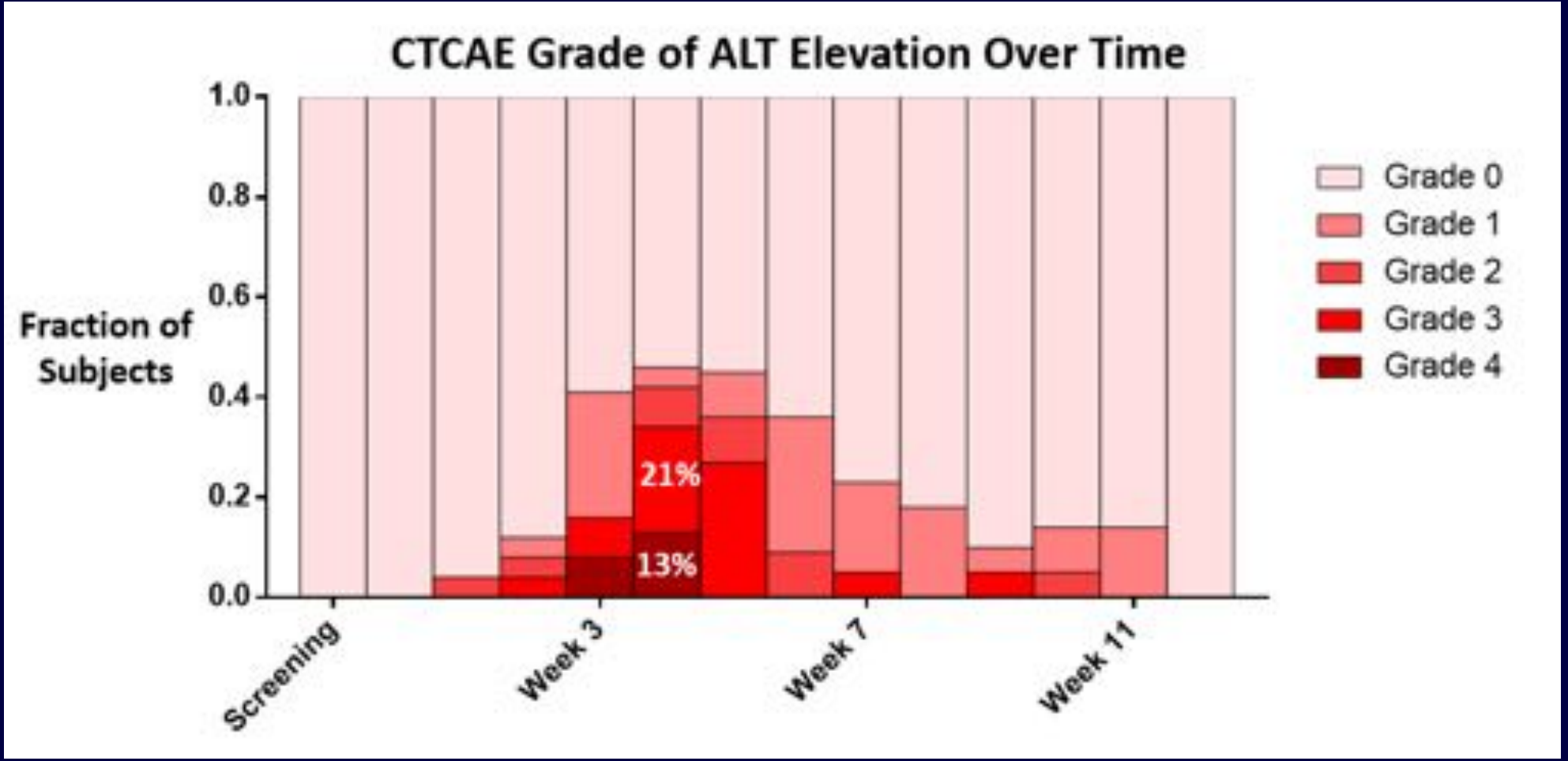
Baseline Characteristics

Total Number Enrolled	24
Male gender	75%
Median Age [range] (years)	67.4 [57.6–84.9]
Prior therapies	0

CLL genetics	
Unmutated IgHV	13 (54%)
Del 17p/TP53 mut	4 (17%)
Del 11q	1 (4%)
Del 13q	13 (54%)

Lampson et al. Blood Adv. 2019 Apr 9;3(7):1167-1174.

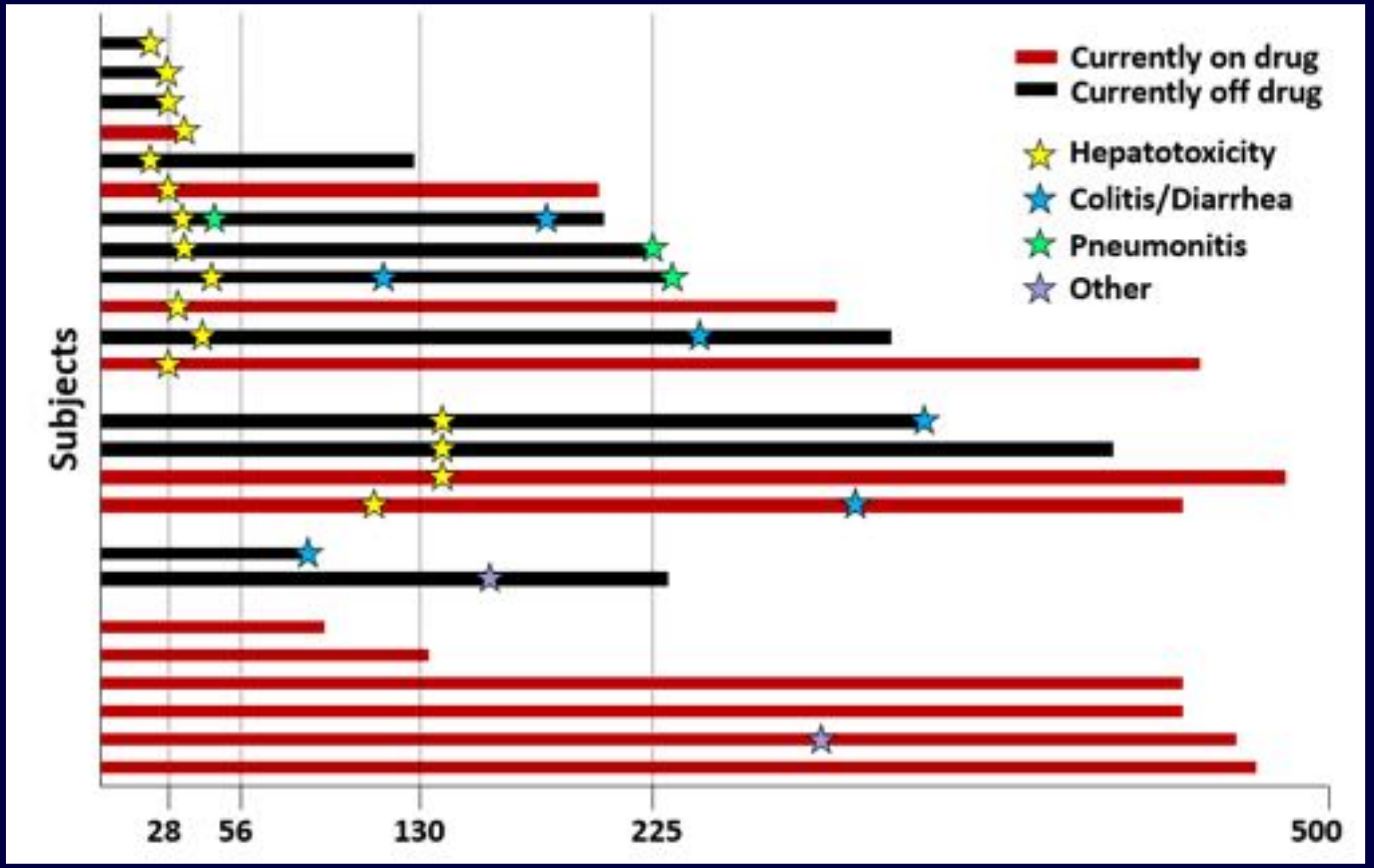
Frequent and Severe Hepatotoxicity



52% of all subjects had grade ≥ 3 hepatotoxicity

Lampson et al. Blood Adv. 2019 Apr 9;3(7):1167-1174.

Idelalisib Toxicities



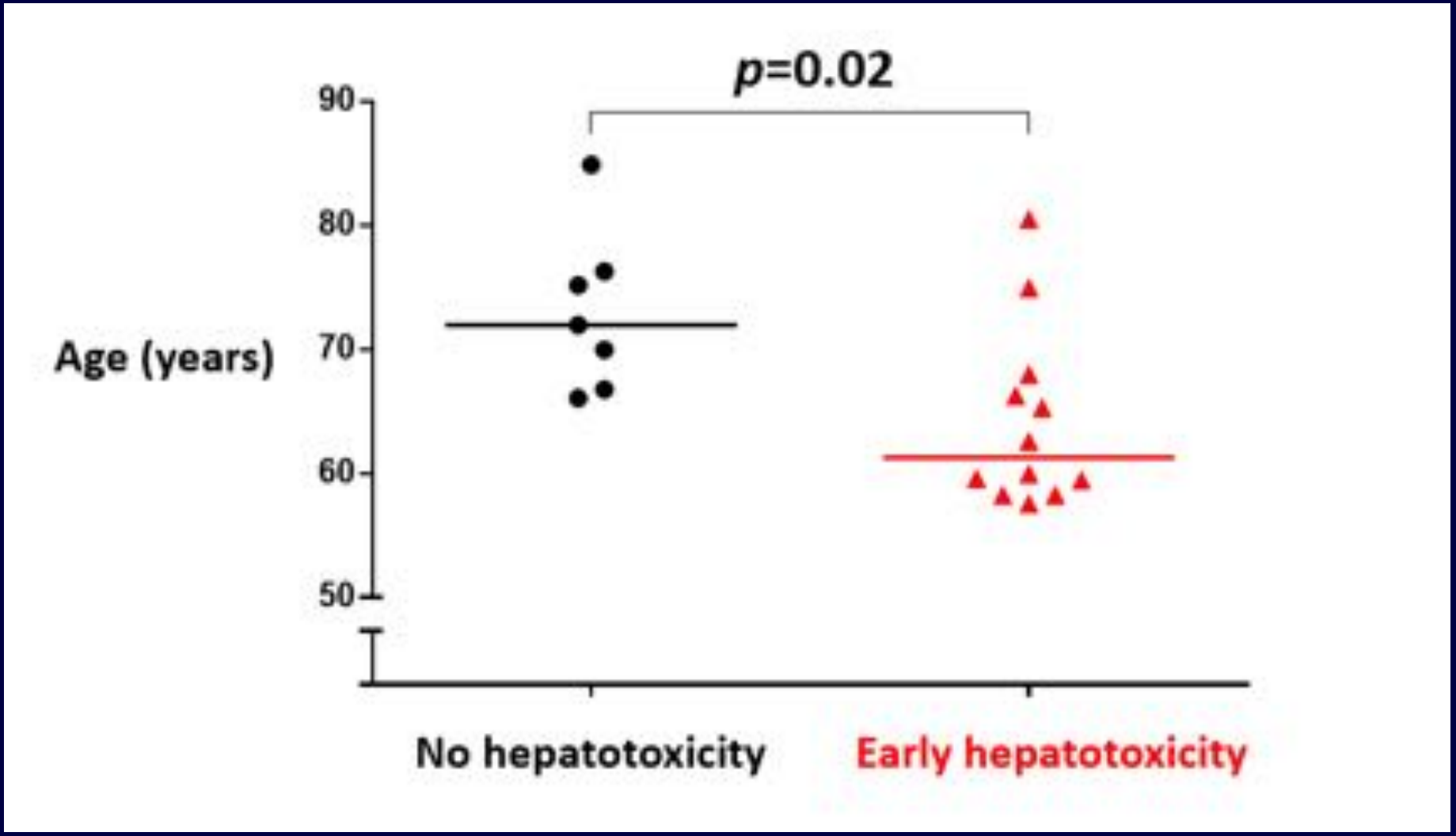
Lampson et al. Blood Adv. 2019 Apr 9;3(7):1167-1174.

Toxicities Are More Common In Less Heavily Pre-Treated Patients

	Toxicity Frequency			
	Phase I	Overall Relapsed	Upfront patients ≥ 65yo	Upfront idela + ofa
Number of Subjects	54	760	64	24
Median Prior Therapies	5 (2-14)	≥1	0	0
Median Age	63 (37-82)	66 (21-91)	71 (65-90)	67.4 (58-85)
Median Time on Therapy (mos)	15 (0.2-48.7)	-	22.4 (0.8-45.8)	7.7 (0.7-16.1)
Grade ≥3 Transaminitis	1.9%	14%	23%	52%
Grade ≥3 Colitis/Diarrhea	5.6%	14%	42%	13%
Any grade pneumonitis	5.6%	3%	3%	13%
Reference	Brown *Blood* 2014	Coutre *EHA* 2015	O'Brien *Blood* 2015	

Lampson et al. Blood Adv. 2019 Apr 9;3(7):1167-1174.

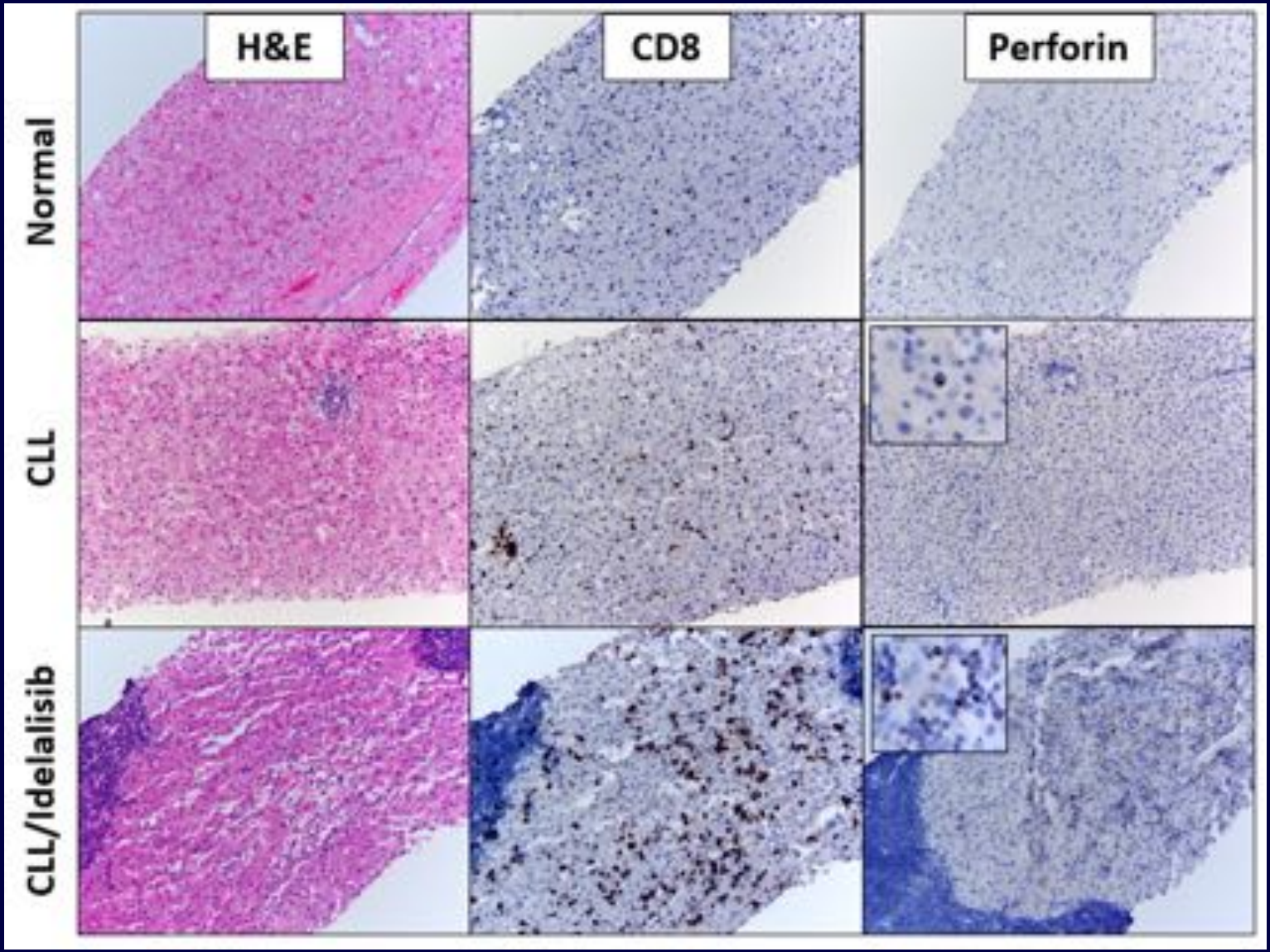
Age Is A Risk Factor for Early Hepatotoxicity



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

Lampson et al. Blood Adv. 2019 Apr 9;3(7):1167-1174.

Activated Immune Infiltrate on Liver Biopsy



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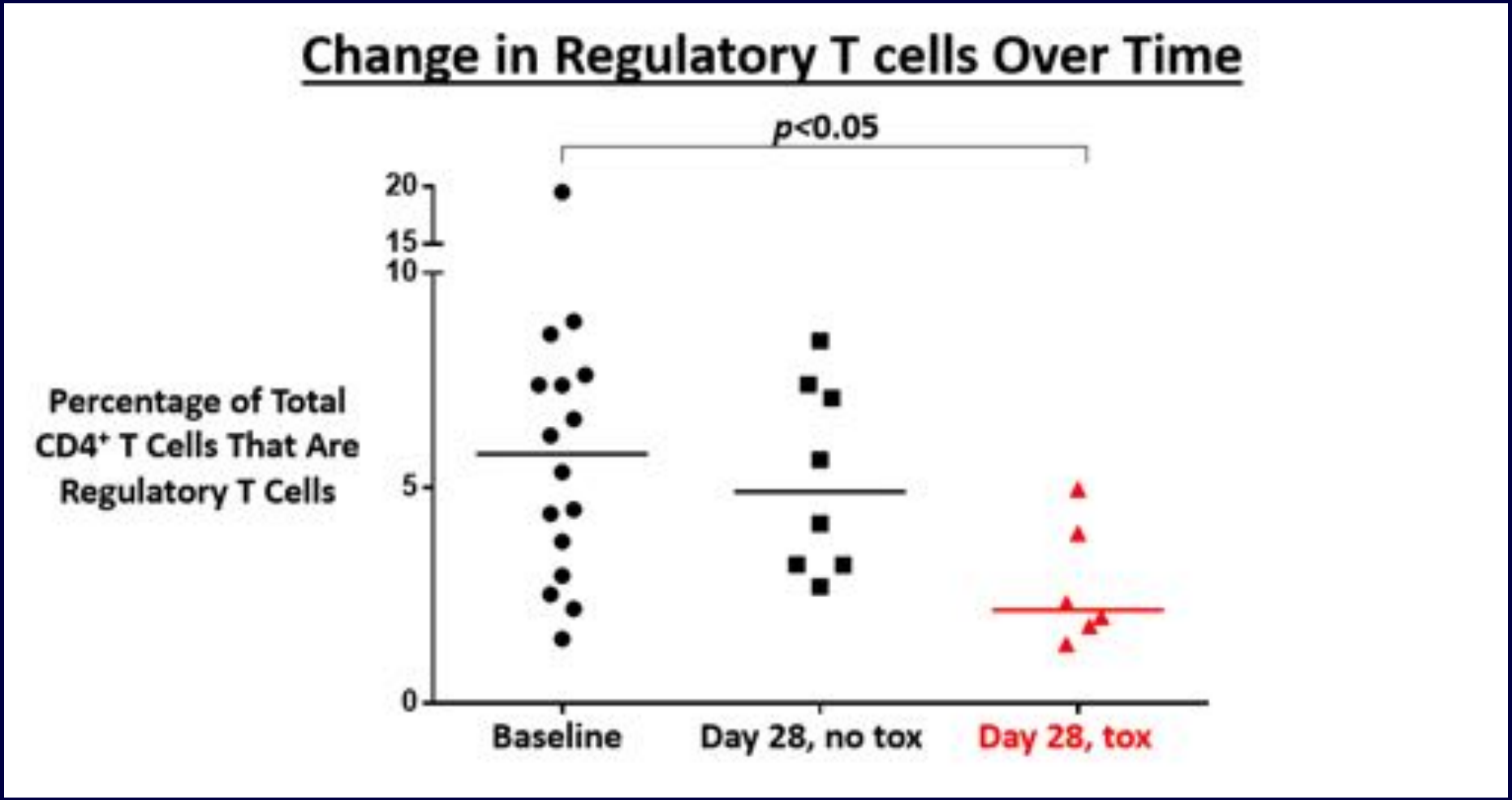
Decrease In Regulatory T Cells While on Therapy



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

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Idelalisib and Ofatumumab in Untreated CLL: Efficacy

Responses	Number
CR	1
PR	21
PRL	2
SD	3
OR	24 (89%)

All patients with SD discontinued with <1 cycle
5/5 patients with TP53 aberrant disease responded
13/13 unmutated responded

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BRIEF COMMUNICATION

AJT

Targeting PI3Kδ function for amelioration of murine chronic graft-versus-host disease

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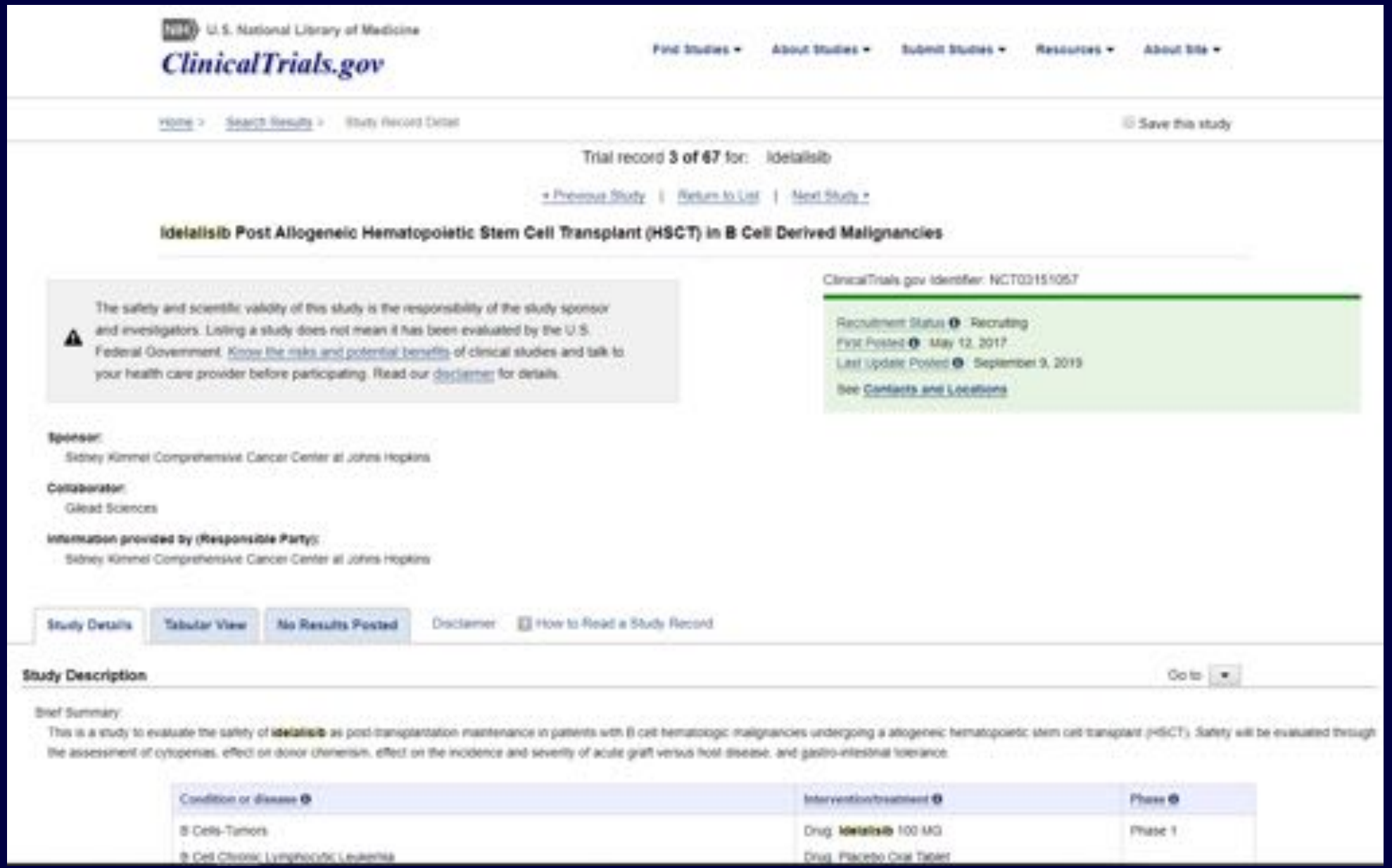
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Idelalisib Post Allogeneic Hematopoietic Stem Cell Transplant (HSCT) in B Cell Derived Malignancies
The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.
ClinicalTrials.gov Identifier: NCT03151057
Recruitment Status Recruiting
First Posted May 12, 2017
Last Update Posted September 9, 2019
See Contacts and Locations
Sponsor:
Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins
Collaborator:
Gilead Sciences
Information provided by (Responsible Party):
Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins
Study Details
Tabular View
No Results Posted
Disclaimer
How to Read a Study Record
Study Description
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Brief Summary:
This is a study to evaluate the safety of idelalisib as post transplantation maintenance in patients with B cell hematologic malignancies undergoing a allogeneic hematopoietic stem cell transplant (HSCT). Safety will be evaluated through the assessment of cytopenias, effect on donor chimerism, effect on the incidence and severity of acute graft versus host disease, and gastro-intestinal tolerance.
Condition or disease
Intervention/treatment
Phase
B Cells-Tumors
Drug: Idelalisib 100 MG
Phase 1
B Cell Chronic Lymphocytic Leukemia
Drug: Placebo Oral Tablet