Idelalisib in CLL

New Drugs in Hematology

Bologna, 2016

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Disclosures

- Research funding Gilead
- Honoraria for advisory boards Gilead

Questions 2016

- Is idelalisib an efficacious drug?
- Is idelalisib a safe drug?
- When should you consider idelalisib?

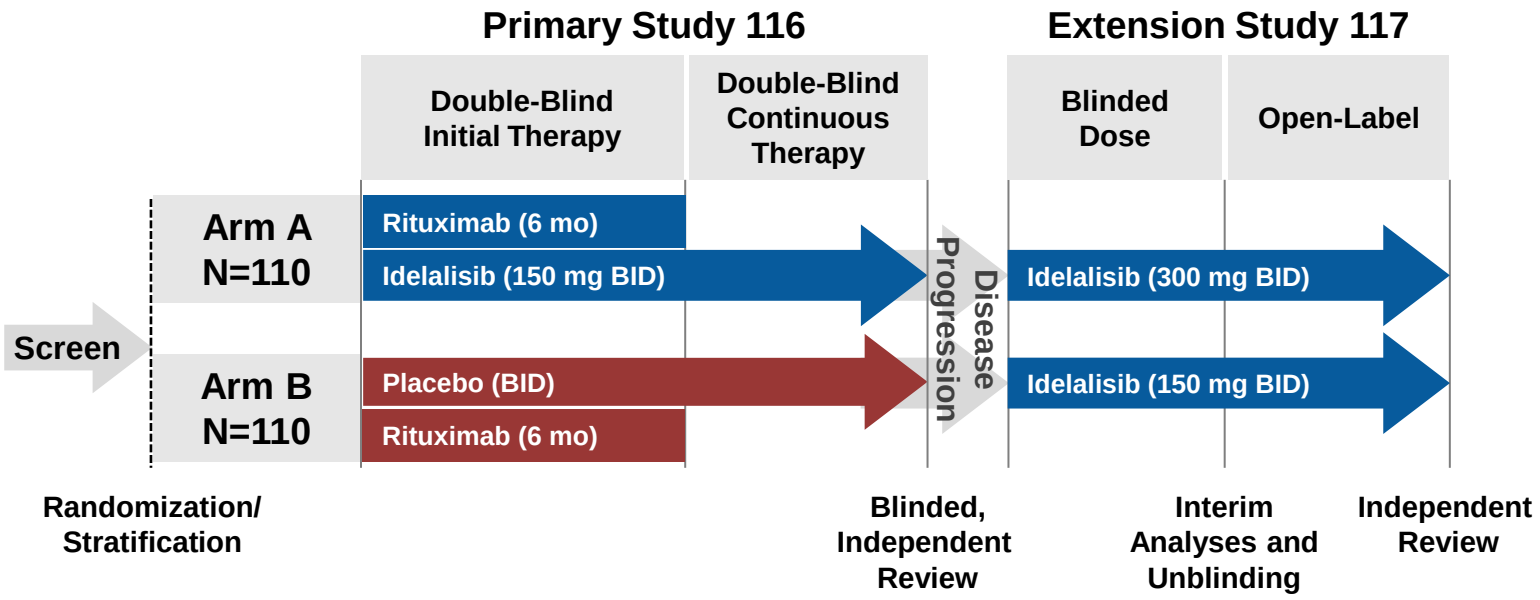
Second Interim Analysis of a Phase 3 Study of Idelalisib (ZYDELIG®) Plus Rituximab for Relapsed Chronic Lymphocytic Leukemia: Efficacy Analysis in Patient Subpopulations with Del(17p) and Other Adverse Prognostic Factors

Jeff P. Sharman,[1] Steven E. Coutre,[2] Richard R. Furman,[3] Bruce D. Cheson,[4] John M. Pagel,[5] Peter Hillmen,[6] Jacqueline C. Barrientos,[7] Andrew D. Zelenetz,[8] Thomas J. Kipps,[9] Ian W. Flinn,[10] Paolo Ghia,[11] Michael Hallek,[12] Bertrand Coiffier,[13] Susan O'Brien,[14] Eugen Tausch,[15] Karl-Anton Kreuzer,[12] Wendy Jiang,[16] Mirella Lazarov,[16] Daniel Li,[16] Thomas M. Jahn,[16] Stephan Stilgenbauer[15]

[1]Willamette Valley Cancer Institute/US Oncology Research, Springfield, OR; [2]Stanford Cancer Institute, Stanford University School of Medicine, Stanford, CA; [3]Weill Cornell Medical College/New York Presbyterian Hospital, New York, NY; [4]Georgetown University Hospital, Washington, DC; [5]Fred Hutchinson Cancer Research Center, Seattle, WA; [6]St. James's University Hospital, Leeds, UK; [7]North Shore-LIJ School of Medicine, New Hyde Park, NY; [8]Memorial Sloan-Kettering Cancer Center, New York, NY; [9]Moores Cancer Center, University of California, San Diego, La Jolla, CA; [10]Sarah Cannon Cancer Institute, Nashville, TN; [11]Università Vita-Salute San Raffaele, Milan, Italy; [12]University of Cologne, Cologne, Germany; [13]Hospices Civils de Lyon, University of Lyon, Pierre-Benite, France; [14]University of Texas MD Anderson Cancer Center, Houston, TX; [15]University of Ulm, Ulm, Germany; [16]Gilead Sciences, Foster City, CA

ASH 2014, San Francisco, CA

Phase 3 Trial of Idelalisib + Rituximab in Relapsed CLL: Subgroup Analysis of High-Risk Groups



	Median Follow-up, months		
	IDELA + R	PBO + R	
1st Interim Analysis	4	4	DMC halted trial (Furman NEJM 2014)
2nd Interim Analysis	6	5	Blind ended (Coutre ASCO 2013) • Arm A continues • Arm B crosses over
Update	13	11	PFS, OS by subgroup analysis

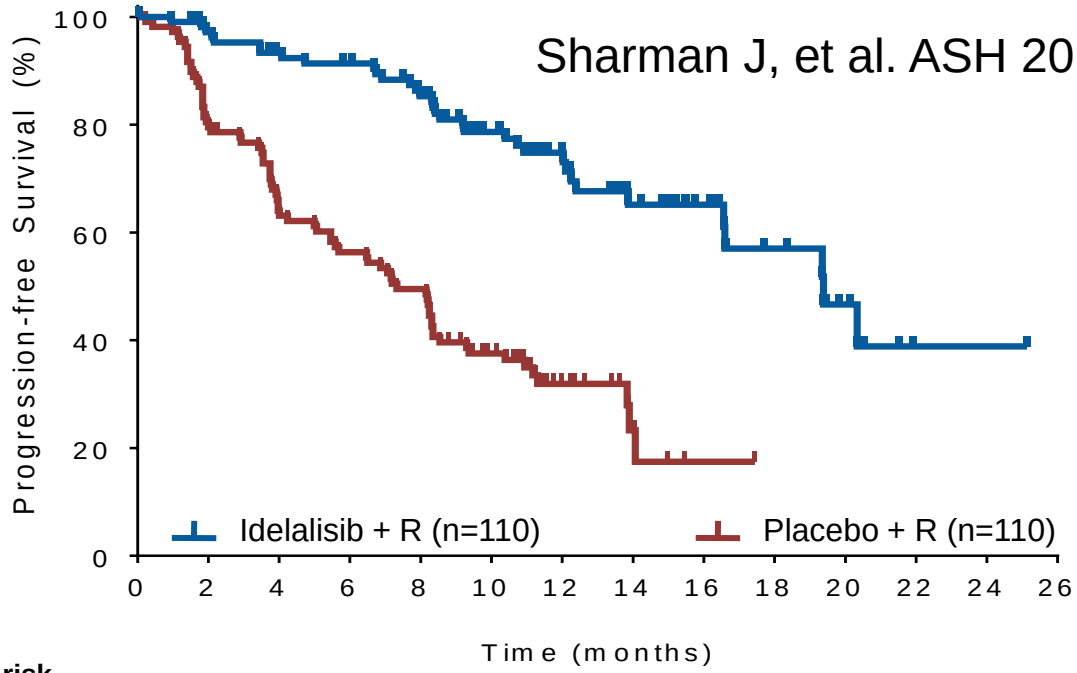
Sharman J, et al. ASH 2014. Abstract 327.

PFS, Including Extension Study*

Idelalisib + R vs Placebo + R

All Patients

Sharman J, et al. ASH 2014. Abstract 327.



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	-	-	-	-

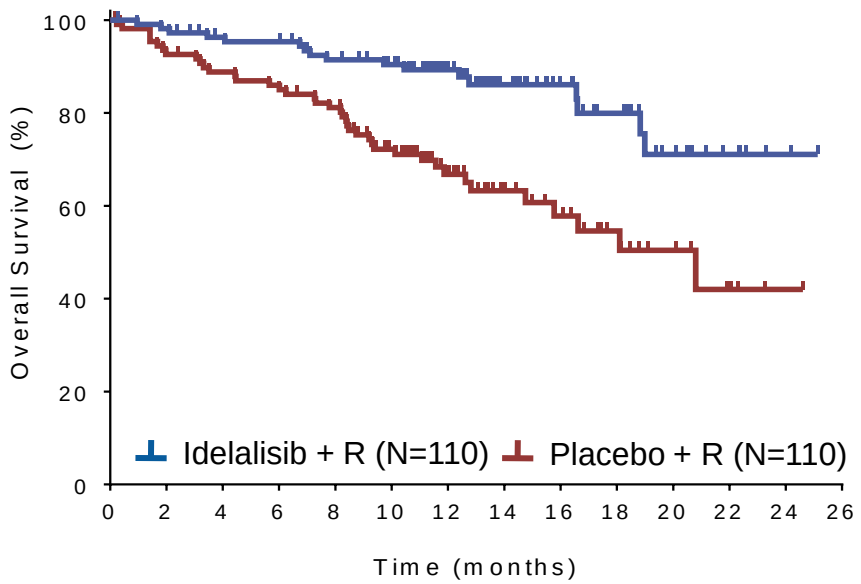
	Median PFS (95% CI)	HR (95% CI)	p-value
IDELA + R	19.4 mo (16.6, –)	0.25 (0.16, 0.39)	<0.0001
PBO + R	7.3 mo (5.5, 8.5)		

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

Overall Survival, Including Extension Study*

Idelalisib + R vs Placebo + R → Idelalisib

All Patients

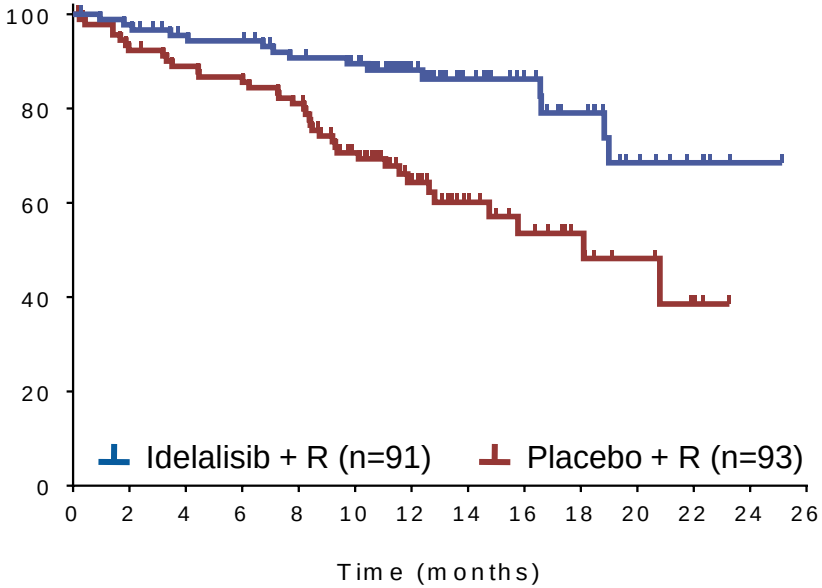


N at risk

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



	91	88	82	81	75	70	48	33	25	19	10	6	2	0
	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 J, et al. ASH 2014. Abstract 327.

Adverse Events in ≥15% of Patients

Idelalisib + R vs Placebo + R → Idelalisib

AE by Preferred Term	IDELA + R (N=110)				PBO + R → IDELA (N=108)			
	Any Grade, %		Grade ≥3, %		Any Grade, %		Grade ≥3, %	
	2nd IA	Update	2nd IA	Update	2nd IA	Update	2nd IA	Update
Any AE	96	98	64	80	98	100	52	78
Pyrexia	35	44	3	6	17	32	1	3
Diarrhea/Colitis	21	42	6	16	16	44	–	13
Fatigue	26	36	5	5	28	43	3	5
Cough	17	34	1	2	28	44	2	2
Nausea	26	31	–	2	21	36	–	1
Chills	21	26	2	2	16	22	–	–
Infusion reaction	19	20	–	–	30	32	4	4
Constipation	13	19	–	–	11	21	–	1
Decreased appetite	12	19	–	2	10	17	2	3
Pneumonia	10	18	8	13	13	31	9	20
Dyspnea	13	17	3	6	19	25	3	5
Rash	10	17	1	3	5	12	–	1
Vomiting	13	17	–	–	8	21	–	1
Upper respiratory infection	7	15	2	1	11	24	2	2
Edema, peripheral	10	15	–	–	9	19	2	3
Night sweats	11	14	–	2	10	20	–	–
Asthenia	7	12	1	–	9	19	4	6
Abdominal pain	7	10	1	2	9	19	1	2

Sharman J, et al. ASH 2014. Abstract 327.

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

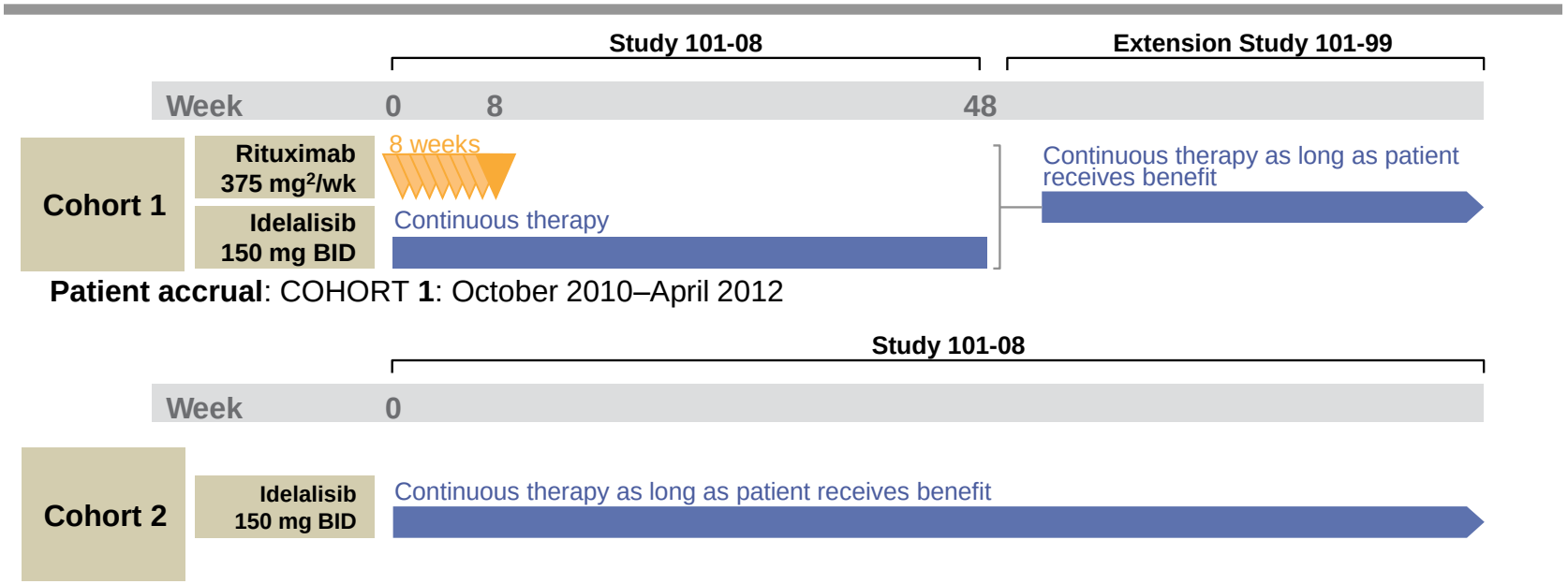
Sharman J, et al. ASH 2014. Abstract 327.

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

Idelalisib for 1L CLL: Sequential Cohort Design



Population:	Disease Assessments:	Study Objectives:
Previously untreated CLL or SLL requiring therapy (iwCLL guidelines, 2008)	Weeks 0, 8, 16, 24, 36, and 48, and per standard of care thereafter	Primary: ORR in patients aged ≥65 years with previously untreated CLL or SLL
Measurable disease	Response assessment per iwCLL 2008	Secondary: DOR, PFS, safety
Age ≥65 years	Investigator choice of CT scan or physical exam	
No exclusions for cytopenias		

Phase 2, single-arm, open-label study and extension study (ClinicalTrials.gov NCT01203930 and NCT01090414, respectively)

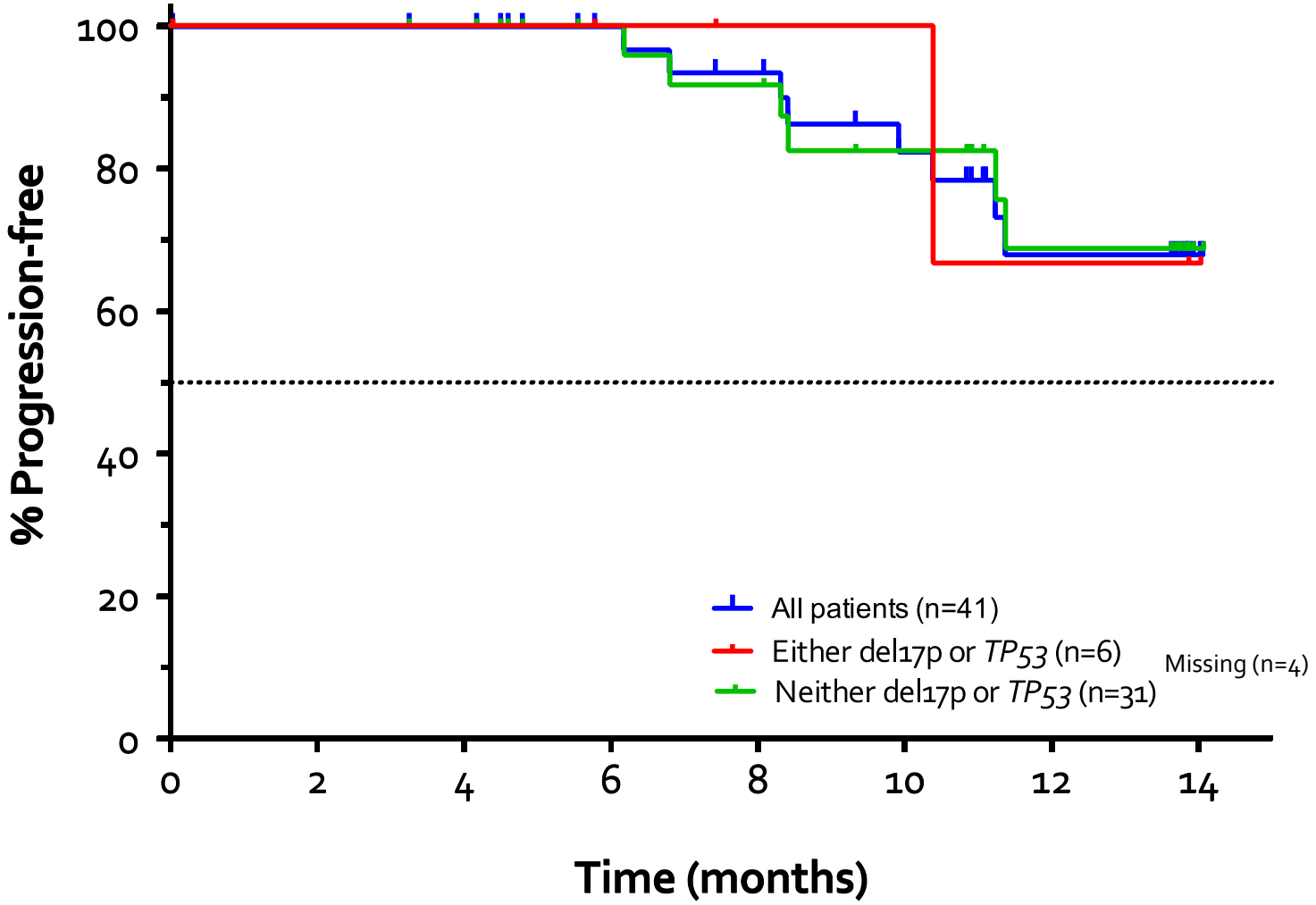
101-08: Best Response

	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)

* 4 Subjects with missing del(17p)/TP53 data
** Subjects not meeting IWCLL 2008 criteria

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

101-08: Cohort 2 Progression Free Survival



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

101-08: Cohort 2 Treatment-Emergent Laboratory Abnormalities

Lab Abnormality	n (%) with Increase to Grade ≥3
Transaminase elevations	8 (20)
Neutropenia	7 (17)
Anemia	2 (5)
Thrombocytopenia	2 (5)

EHA-S433

Safety of Idelalisib in B-Cell Malignancies: Integrated Analysis of Eight Clinical Trials

Steven Coutre,[1] Jacqueline Barrientos,[2] Jennifer Brown,[3], Sven De Vos,[4] Richard Furman,[5] Michael Keating,[6] Susan O'Brien,[7] John Pagel,[8] Jeff Sharman,[9] Andrew Zelenetz,[10] Terry Newcomb,[11] Yoonjin Cho,[11] Christopher Aguilar,[11] Lyndah Dreiling[11]

[1]Stanford Cancer Institute, Stanford University School of Medicine, Stanford, California, USA; [2]Hofstra North Shore-LIJ School of Medicine at Hofstra University, Hempstead, New York, USA; [3]Dana-Farber Cancer Institute, Boston, Massachusetts, USA; [4]UCLA's Jonsson Comprehensive Cancer Center, Los Angeles, California, USA; [5]New York-Presbyterian/Weill Cornell Medical Center, New York, New York, USA; [6]The University of Texas MD Anderson Center, Houston, Texas, USA; [7]University of California, Irvine/Chao Family Comprehensive Cancer Center, Orange, California, USA; [8]Fred Hutchinson Cancer Research Center, Seattle, Washington, USA; [9]US Oncology Network/Willamette Valley Cancer Institute, Springfield, Oregon, USA; [10]Memorial Sloan-Kettering Cancer Center, New York, New York, USA; [11]Gilead Sciences, Inc., Foster City, California, USA

20th Congress of EHA, Vienna, Austria

Clinical Trials Included in Analysis

Study No.	N	Drug Regimen	ClinicalTrials.gov
101-02	191	Dose-ranging monotherapy	NCT00710528[1-3]
101-07	232	Dose-ranging combination therapies	NCT01088048
101-08	64	Idelalisib 150 mg BID + rituximab	NCT01203930
101-09	125	Idelalisib 150 mg BID	NCT01282424[4]
101-10	13	Idelalisib 150 mg BID	NCT01306643
101-11	25	Idelalisib 150 mg BID	NCT01393106
101-99	NA*	Continued idelalisib after parent study	NCT01090414
312-0116	110	Idelalisib 150 mg BID + rituximab	NCT01539512[5]

*101-99 is a long-term extension study that enrolls eligible patients from Studies 02, 07, 08, and 10; safety data from this study are included herein, but patients are not counted twice in the overall safety population.

1. Brown JR, et al. Blood 2014;123:3390-7; 2. Flinn IW, et al. Blood 2014;123:3406-13; 3. Kahl BS, et al. Blood 2014;123:3398-405; 4. Gopal AK, et al. N Engl J Med 2014;370:1008-18; 5. Furman RR, et al. N Engl J Med 2014;370:997-1007.

Treatments and Patients Evaluated

- Patients received idelalisib alone (50–350 mg BID), or in combination with rituximab, ofatumumab, bendamustine, bortezomib, everolimus, fludarabine, chlorambucil, bendamustine/rituximab, or chlorambucil/rituximab (idelalisib dose 100 or 150 mg BID)
- Most patients (n=696) were heavily pretreated, with relapsed disease
  - 59 patients with CLL and 5 with SLL were treatment naive

Demographics and Disease Subtypes

	Idelalisib Monotherapy n=354	Idelalisib Combination Therapy n=406
Median age, y (range)	64 (21–91)	68 (37–90)
≥65 y, n (%)	167 (47)	274 (68)
Male, n (%)	236 (67)	274 (68)
Race, n (%)		
White	299 (85)	363 (89)
Black or African-American	13 (4)	12 (3)
Other or not reported	42 (12)	31 (8)
Disease type, n		
CLL/SLL	54/41	283/21
FL	119	59
Marginal zone lymphoma	23	5
Waldenstrom's macroglobulinemia	19	0
Other*	98	38

*Mantle cell lymphoma, diffuse large B-cell lymphoma, Hodgkin lymphoma, acute myeloid leukemia, and multiple myeloma.

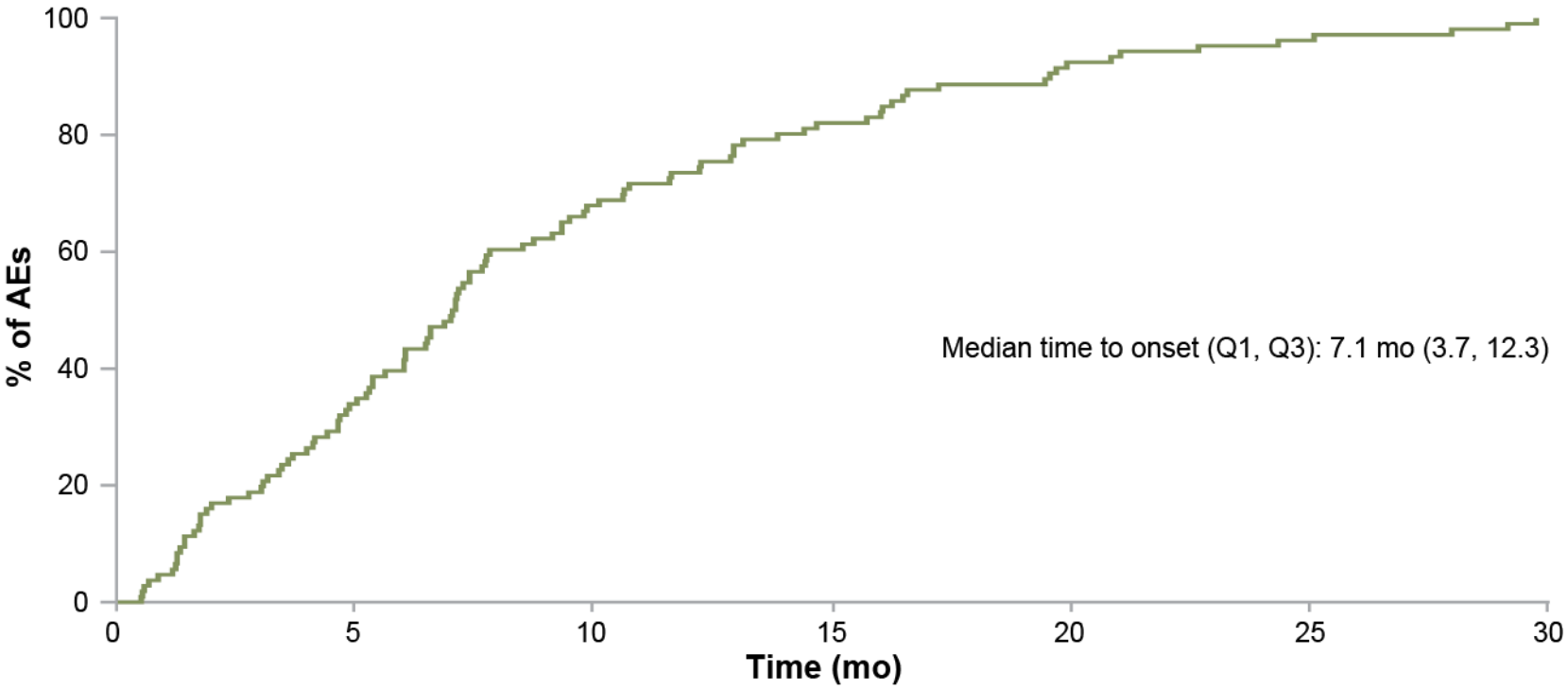
Common Adverse Events (≥ 15% of Patients)

AE, n (%)	Idelalisib Monotherapy n=354		Idelalisib Combination Therapy n=406	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Pyrexia	96 (27)	7 (2)	169 (42)	47 (12)
Diarrhea/colitis	131 (37)	38 (11)	161 (40)	68 (17)
Fatigue	112 (32)	6 (2)	130 (32)	13 (3)
Nausea	91 (26)	5 (1)	125 (31)	30 (7)
Cough	80 (22)	3 (1)	118 (29)	21 (5)
Rash	60 (17)	7 (2)	99 (24)	30 (7)
Chills	49 (14)	0	86 (21)	23 (6)
Pneumonia	47 (13)	40 (11)	74 (18)	56 (14)
Constipation	39 (11)	0	68 (17)	1 (<1)
Dyspnea	43 (12)	7 (2)	68 (17)	10 (3)
Abdominal pain	40 (11)	4 (1)	67 (17)	5 (1)
Vomiting	53 (15)	5 (1)	60 (15)	18 (4)
Decreased appetite	46 (13)	8 (2)	62 (15)	2 (<1)

Laboratory Abnormalities

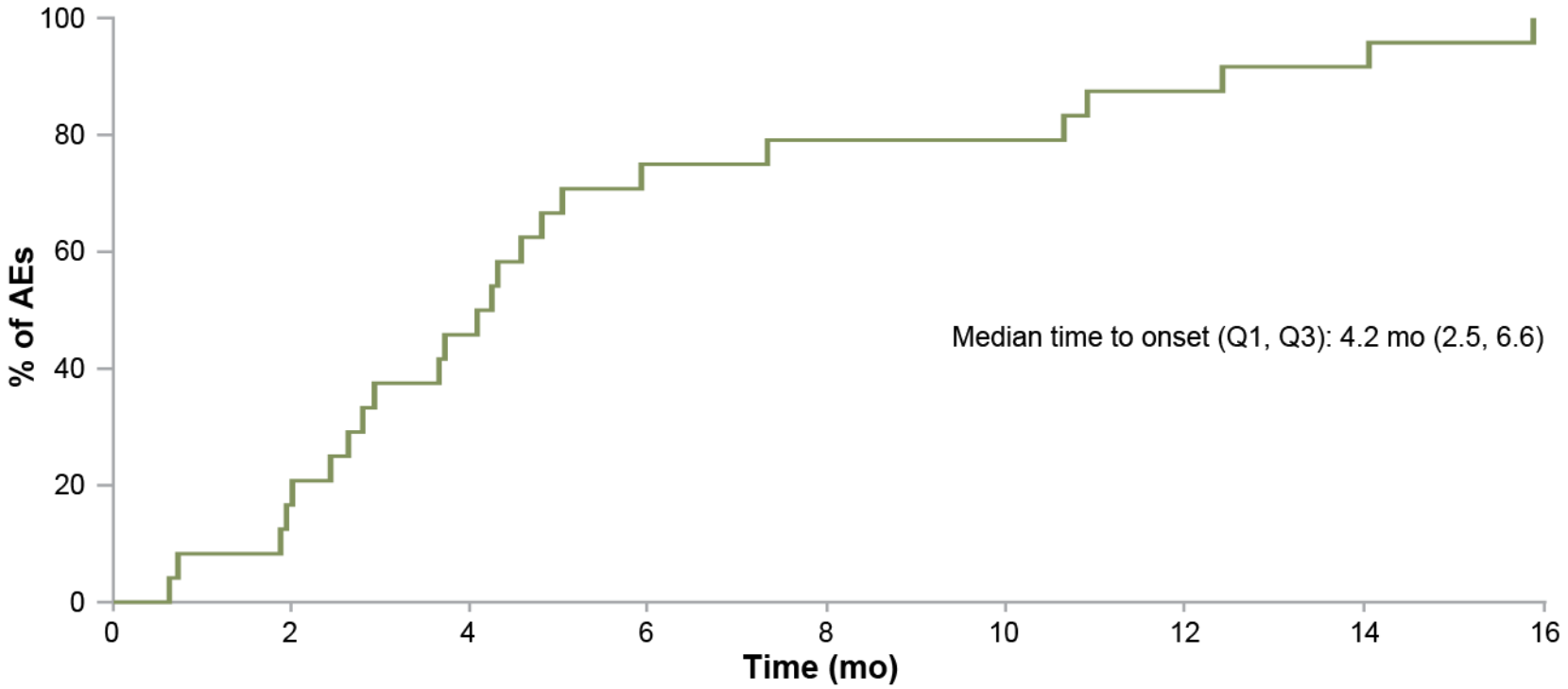
Abnormality, n (%)	Idelalisib Monotherapy n=354		Idelalisib Combination Therapy n=406	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Hematologic				
Neutropenia	162 (46)	83 (23)	234 (58)	151 (37)
Anemia	102 (29)	18 (5)	145 (36)	34 (8)
Thrombocytopenia	94 (27)	37 (11)	143 (35)	50 (12)
Transaminases				
ALT or AST increased	176 (50)	56 (16)	190 (47)	53 (13)

Time to Onset of First Grade ≥3 Diarrhea/Colitis



- Grade ≥3 diarrhea occurred in 106 patients (14%) and was generally a late-onset AE

Time to Onset of First Any-Grade Pneumonitis



- Pneumonitis occurred in 24 patients (3%); most AEs occurred within first 6 months of treatment

New Safety Information (MAR2016)

			+ Idela	Control
*Idela +/- BR	untreated	CLL	N=664 7.4% death	N=402 3.5% death
*Idela +/- R	Prev treated	NHL		
*Idela +/- BR	Prev treated	NHL		
Idela +/- R	2-3 prior therapies	CLL	N=491 23.2% death	N=406 31.5% death
Idela +/- Ofa	2-3 prior therapies	CLL		
Idela +/- BR	2-3 prior therapies	CLL		

*Idela + R untreated NHL, *Idela + R untreated del17p CLL,
*Idela +obinu v Chlor + obinu untreated CLL, *ISTs for untreated

* Trials terminated

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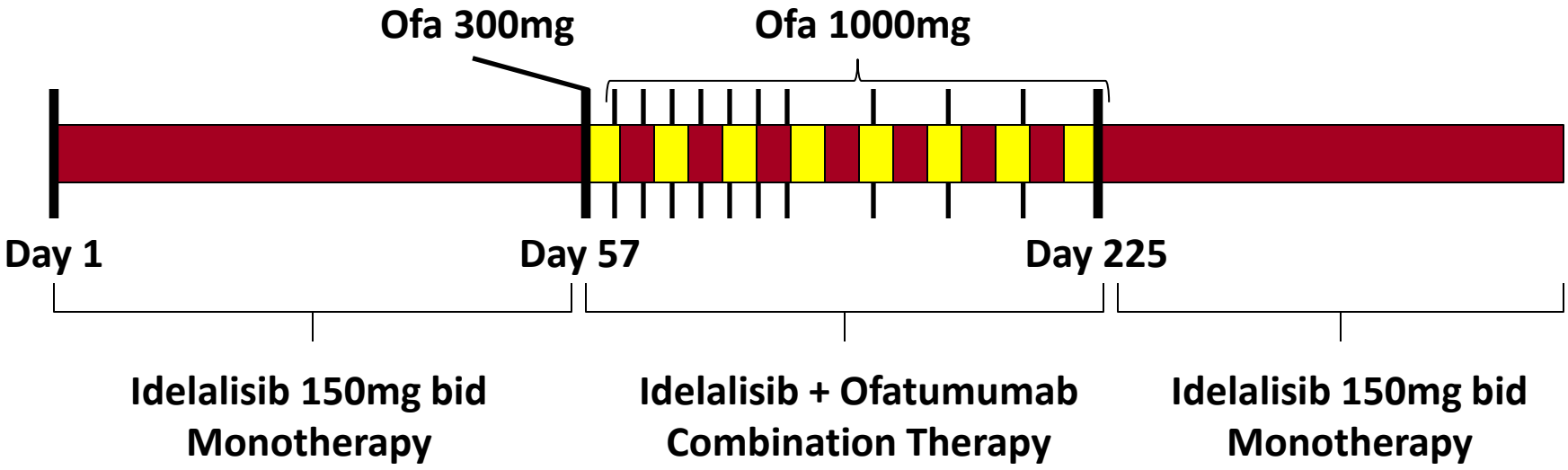
Idelalisib Given Front-line for the Treatment of Chronic Lymphocytic Leukemia Results in Frequent and Severe Immune-Mediated Toxicities

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

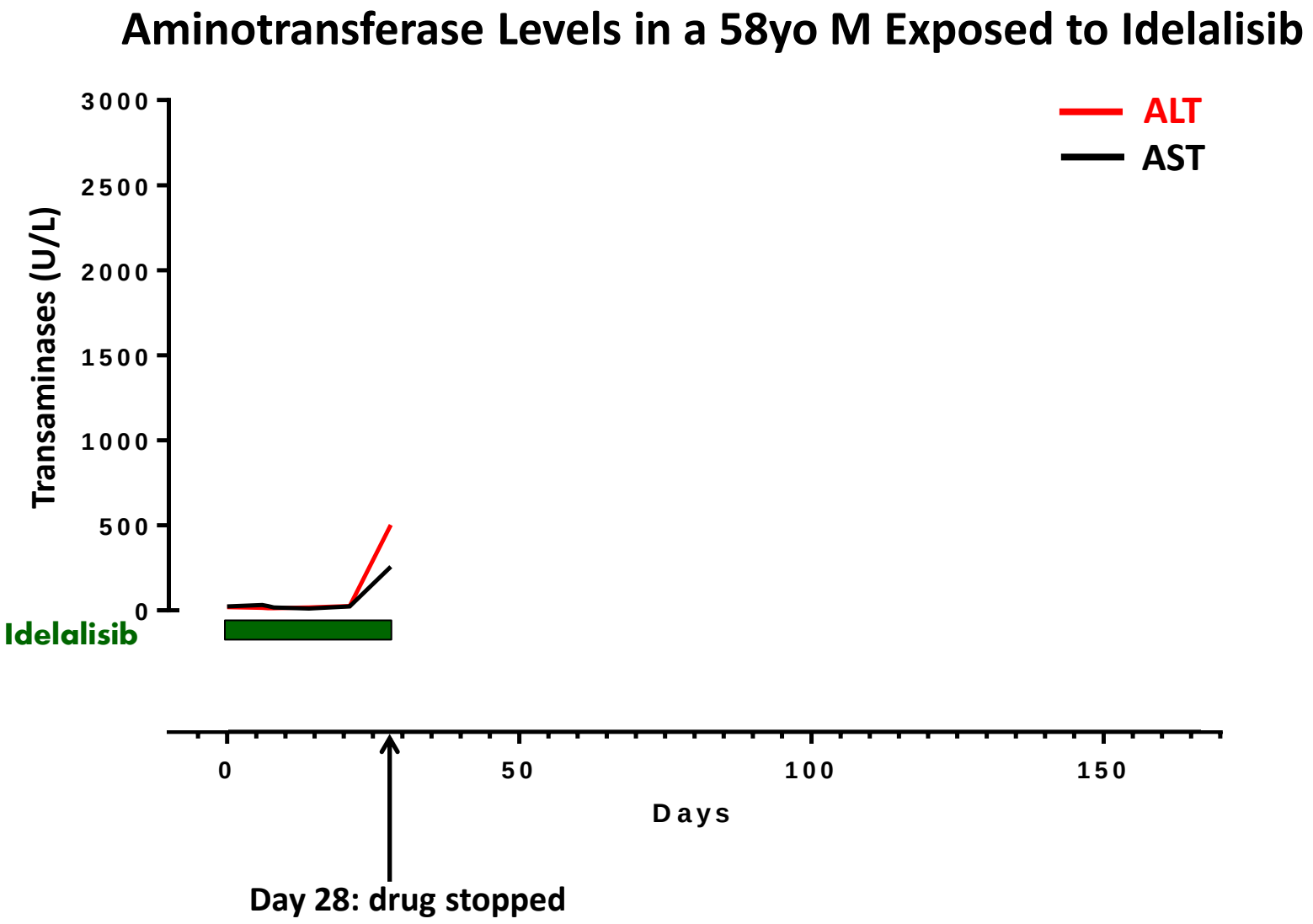
ASH Annual Meeting
December 7, 2015

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

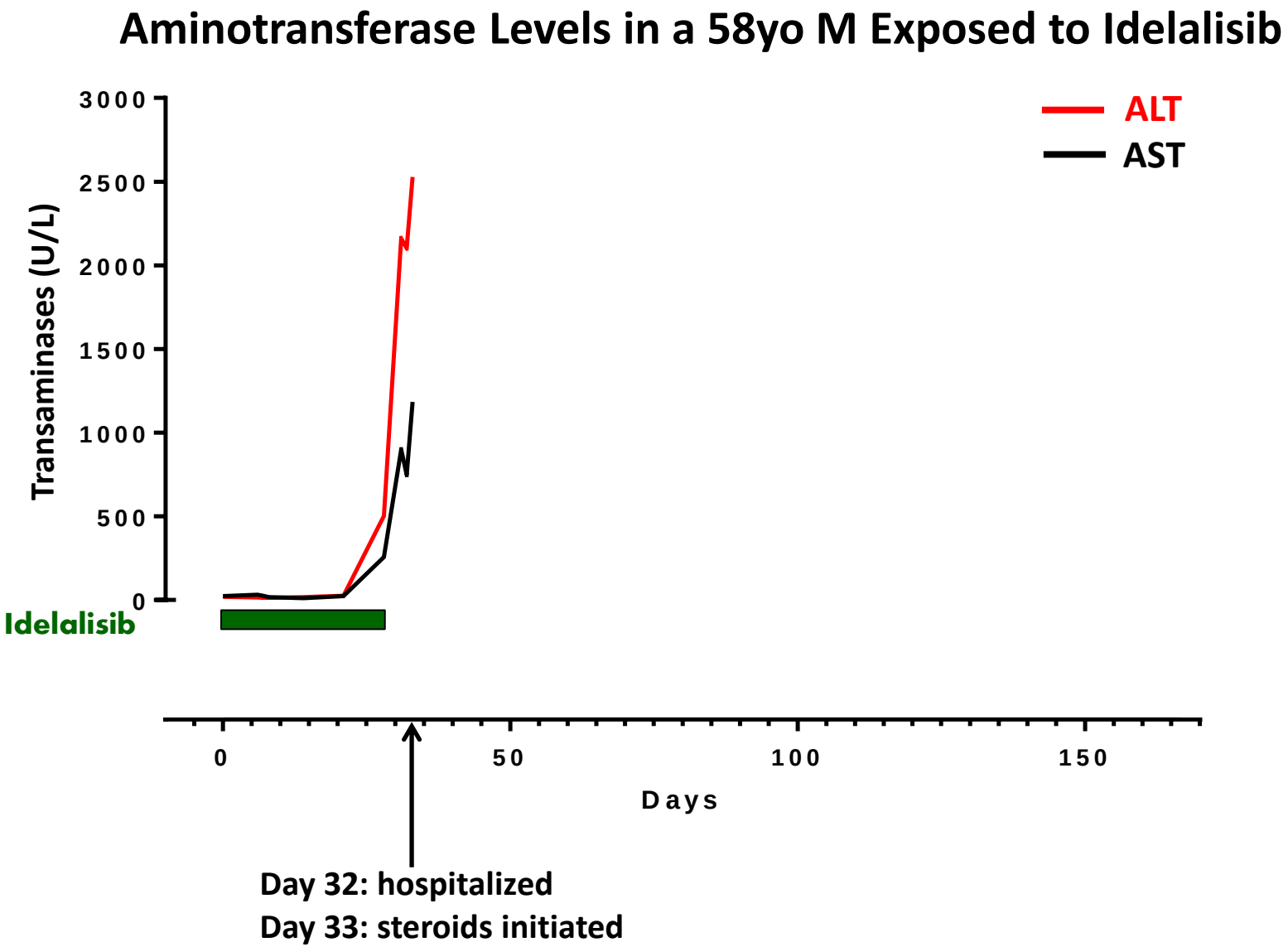


- **Trial is currently ongoing with 24 subjects enrolled as of 11/9/2015**
- **Median time on therapy is 7.7 months (range, 0.7-16.1 months)**
- **Median follow-up time is 14.7 months (range, 1.2-16.8 months)**

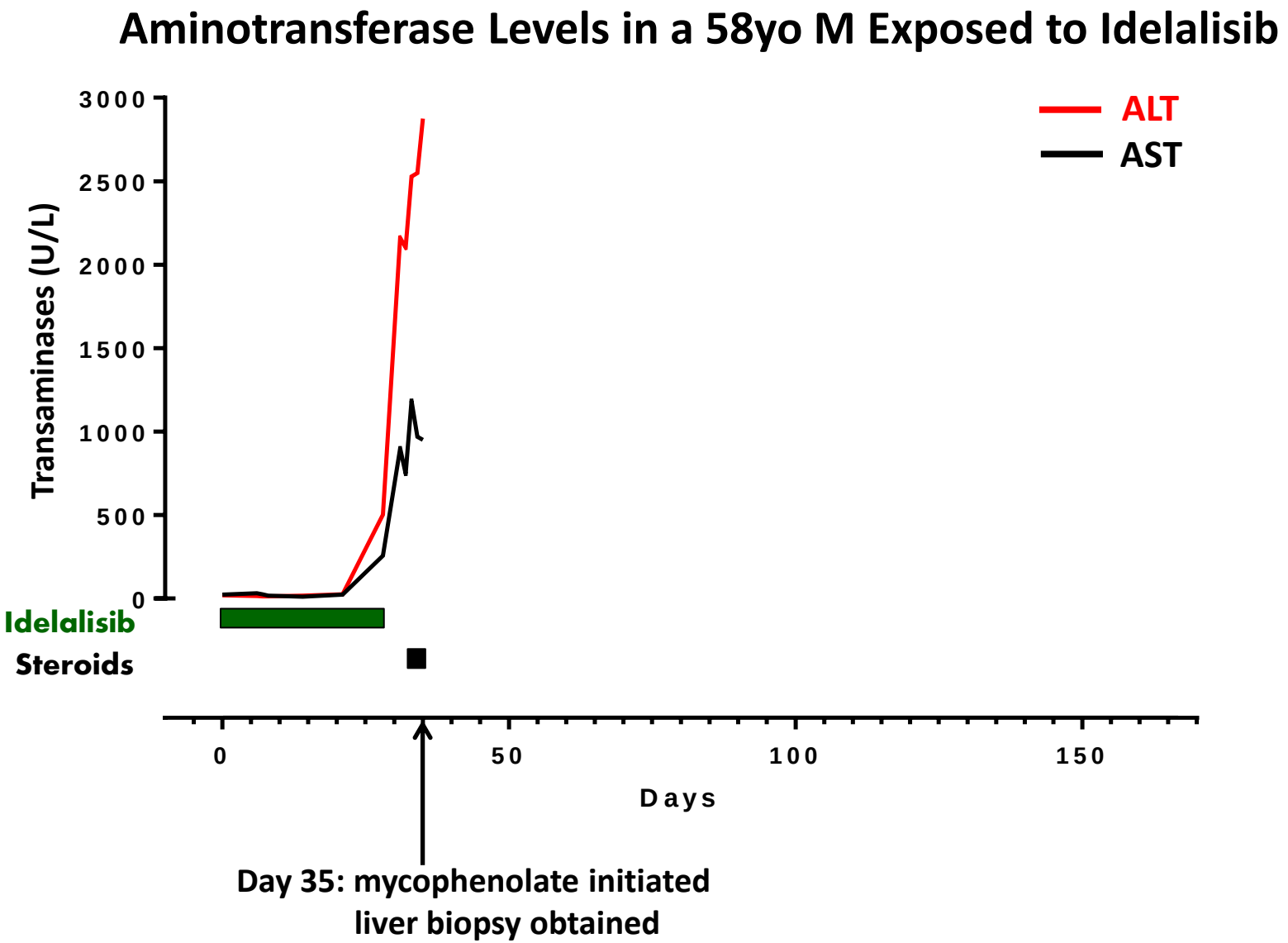
Severe Hepatotoxicity: An Index Case



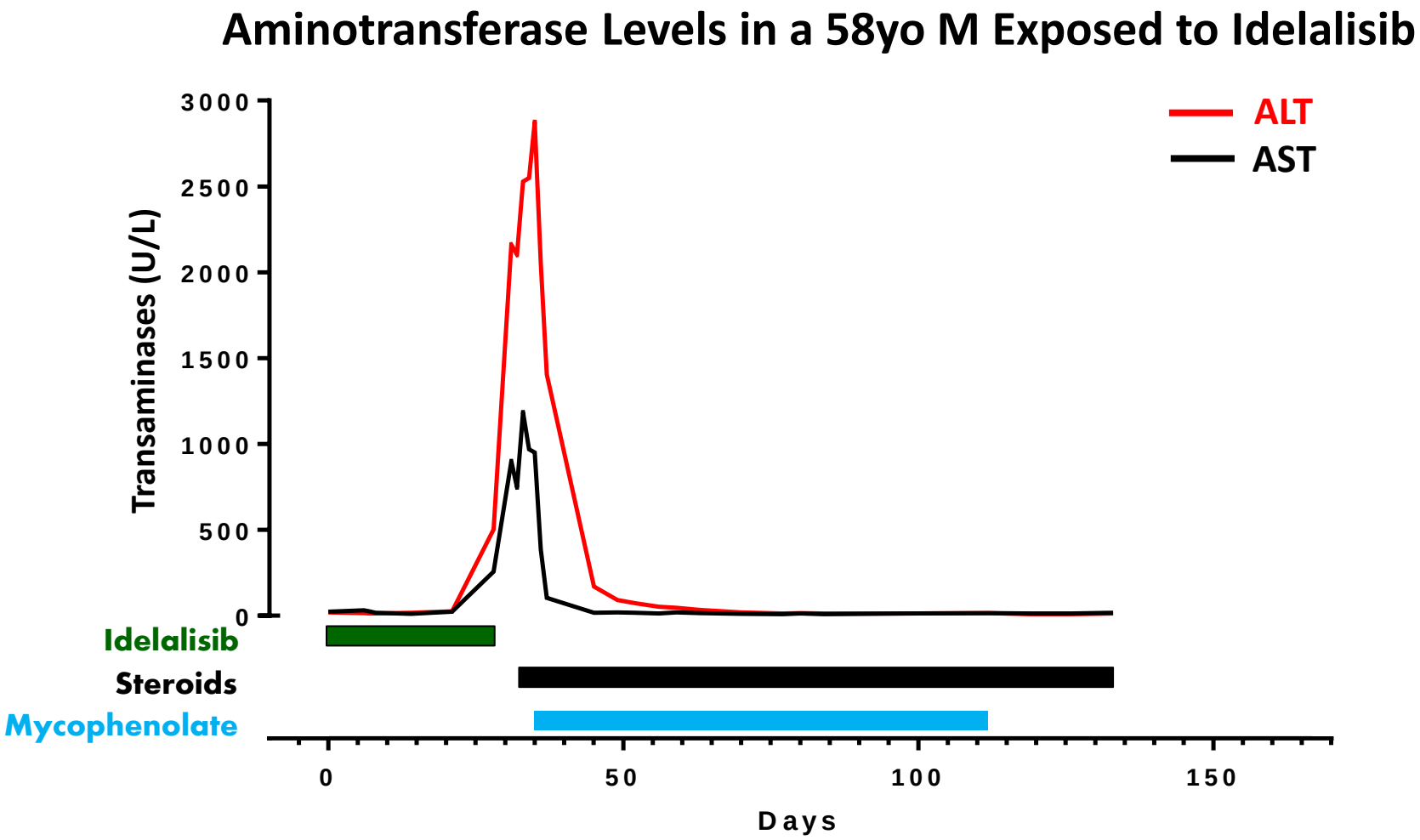
Severe Hepatotoxicity: An Index Case



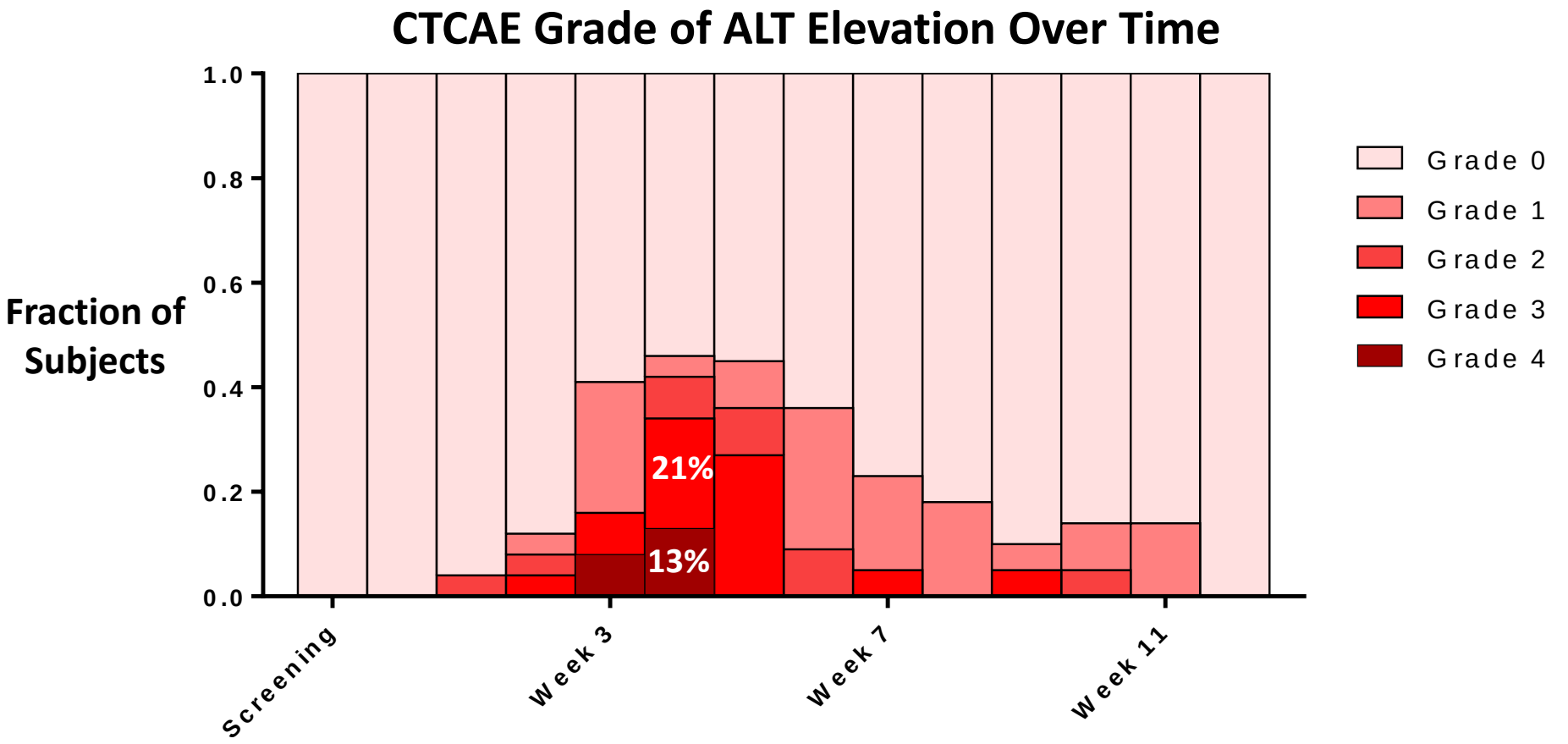
Severe Hepatotoxicity: An Index Case



Severe Hepatotoxicity: An Index Case

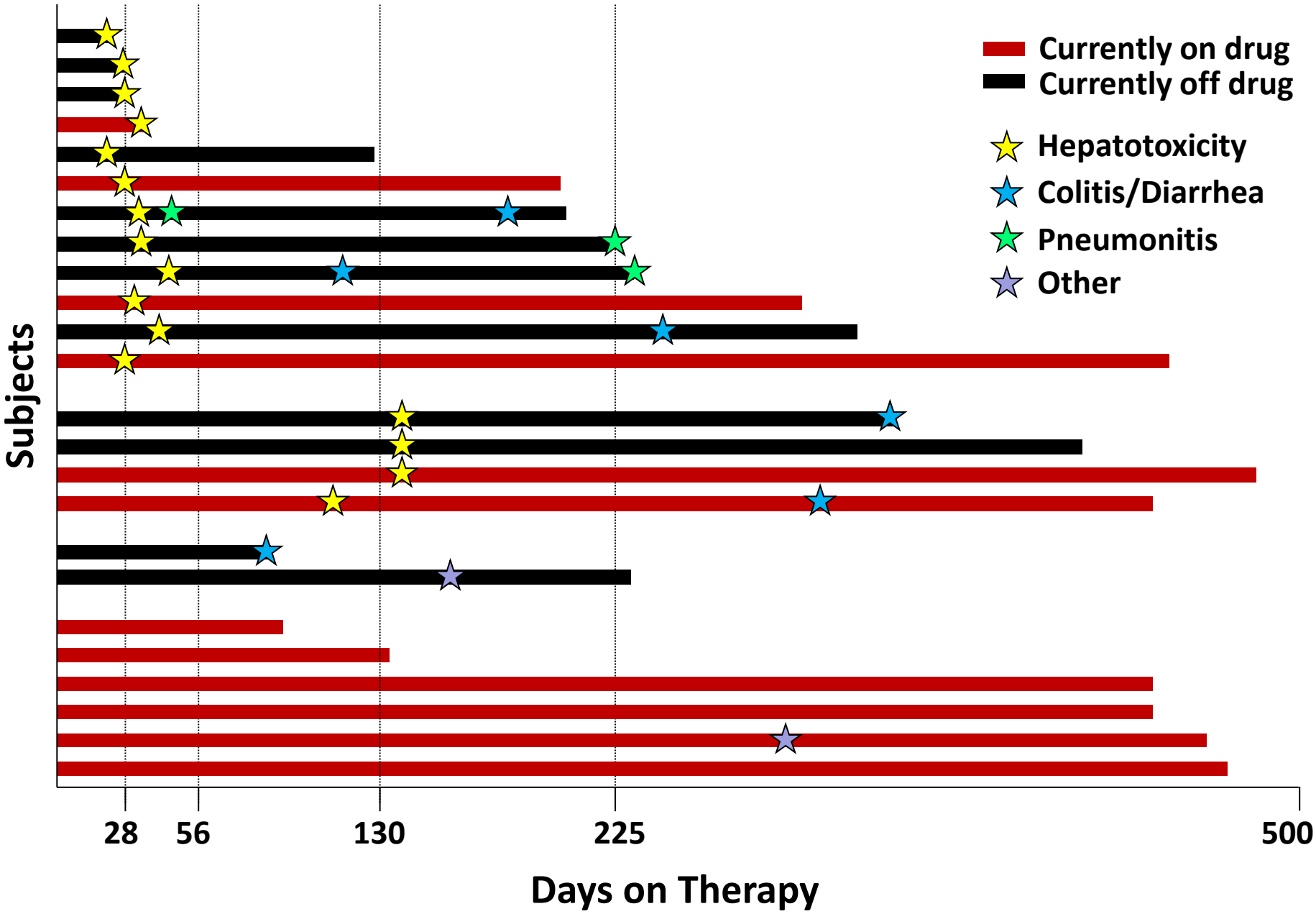


Frequent and Severe Hepatotoxicity



52% of all subjects had grade ≥ 3 hepatotoxicity

Idelalisib Toxicities



Toxicities Are More Common In Less Heavily Pre-treated Patients

	Toxicity Frequency		
	Phase I	Overall Relapsed	Upfront therapy, patients ≥ 65yo
Number of Subjects	54	760	64
Median Prior Therapies	5 (2-14)	≥1	0
Median Age	62.5 (37-82)	66 (21-91)	71 (65-90)
Median Time on Therapy (mos)	15 (0.2-48.7)	-	22.4 (0.8-45.8)
Grade ≥3 Transaminitis	1.9%	14%	23%
Grade ≥3 Colitis/Diarrhea	5.6%	14%	42%
Any grade pneumonitis	5.6%	3%	3%
Reference	Brown *Blood* 2014	Coutre *EHA* 2015	O'Brien *Blood* 2015

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%
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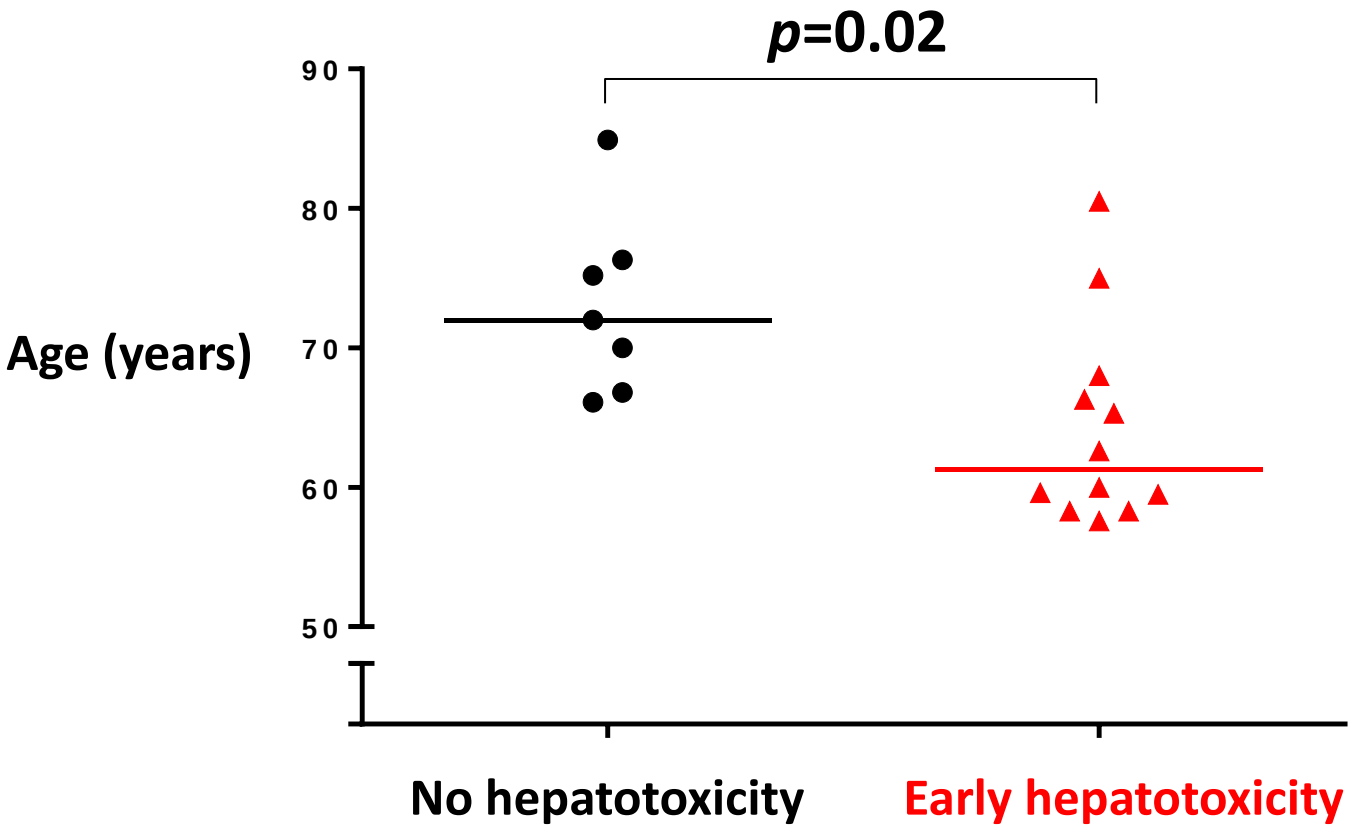
Reference	Brown *Blood* 2014	Coutre *EHA* 2015	O'Brien *Blood* 2015	

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	

Age Is a Risk Factor for Early Hepatotoxicity

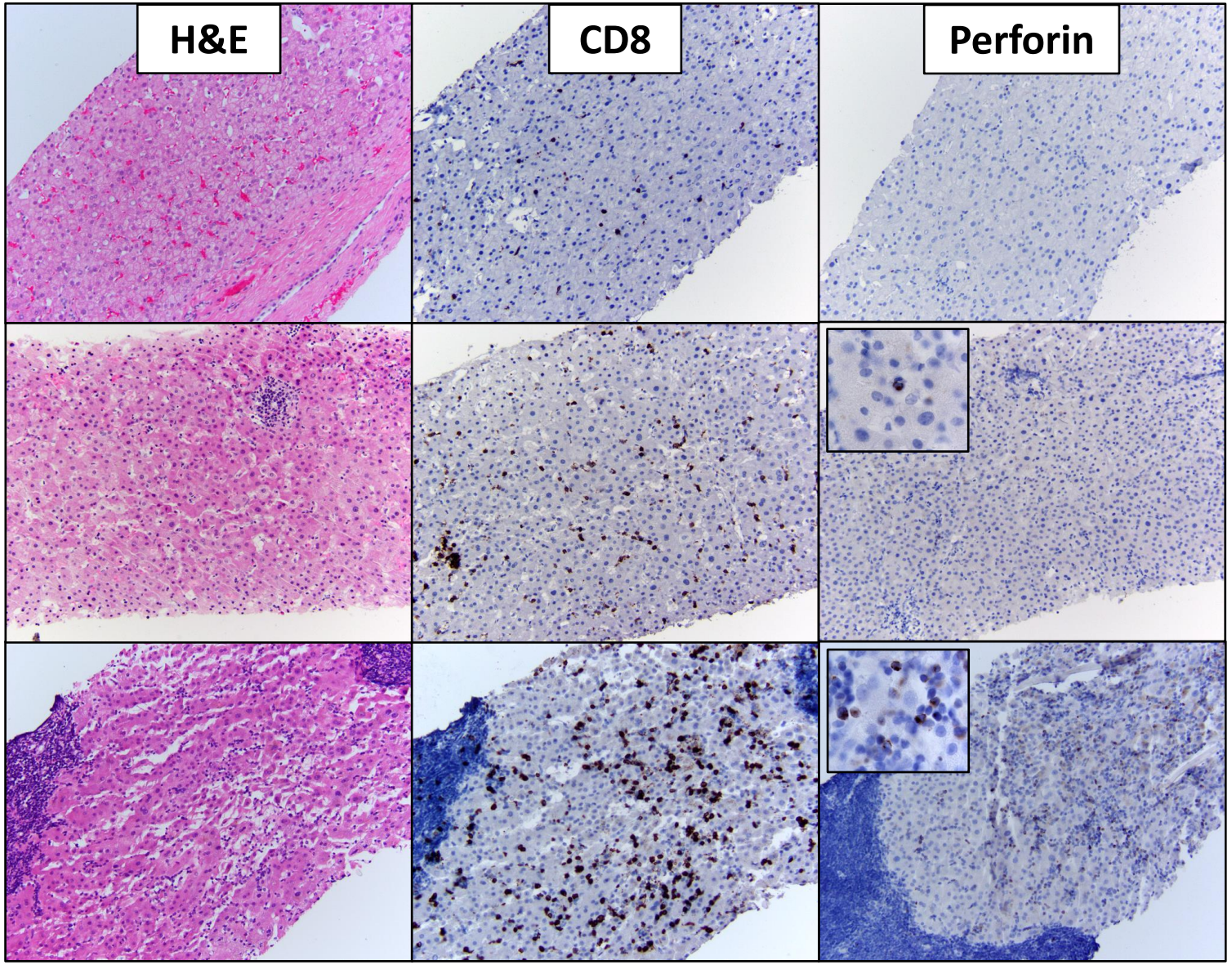


100% of subjects age ≤65 (*n*=7) required systemic steroids for toxicities

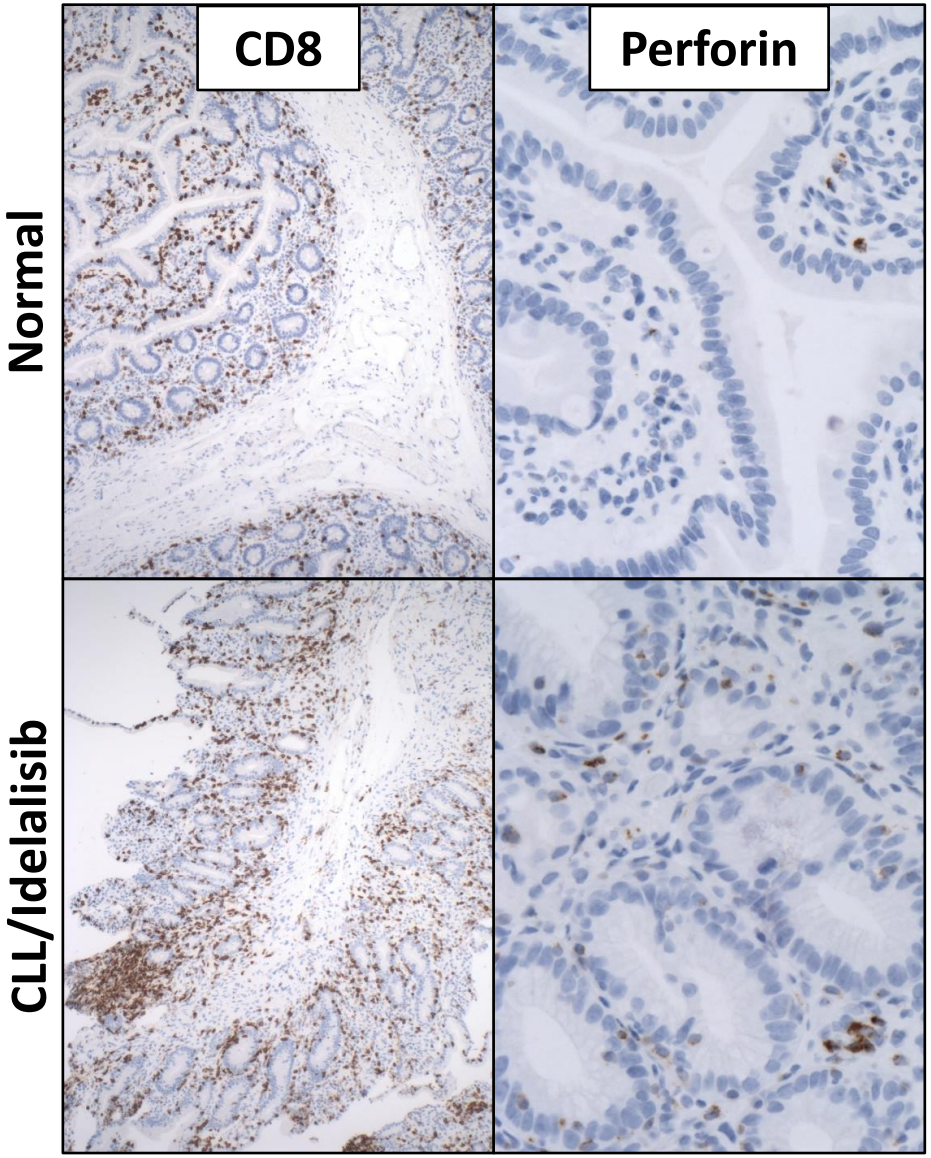
Idelalisib Toxicities Are Likely Due to On-Target Immune Mediated Effects

- Lymphocytic infiltrate on liver biopsy
- Lymphocytic colitis in idelalisib-treated patients
- Toxicity is treatable and preventable with steroids
- Rapid recurrence upon re-exposure to drug
- Preclinical data from mouse models
- Decrease in regulatory T cells on idelalisib

Activated Immune Infiltrate on Liver Biopsy



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

Delayed Development with Rapid Recurrence

12 subjects with grade ≥ 2 transaminitis were re-challenged with the drug after holding for toxicity

5 were re-challenged while off steroids

4 developed recurrent transaminitis within 1-4 days

grade 4: 1
grade 3: 2
grade 2: 1

7 were re-challenged while on steroids

2 developed recurrent transaminitis within 3-4 days

grade 3: 1
grade 2: 1

The Connection Between p110δ and Tregs

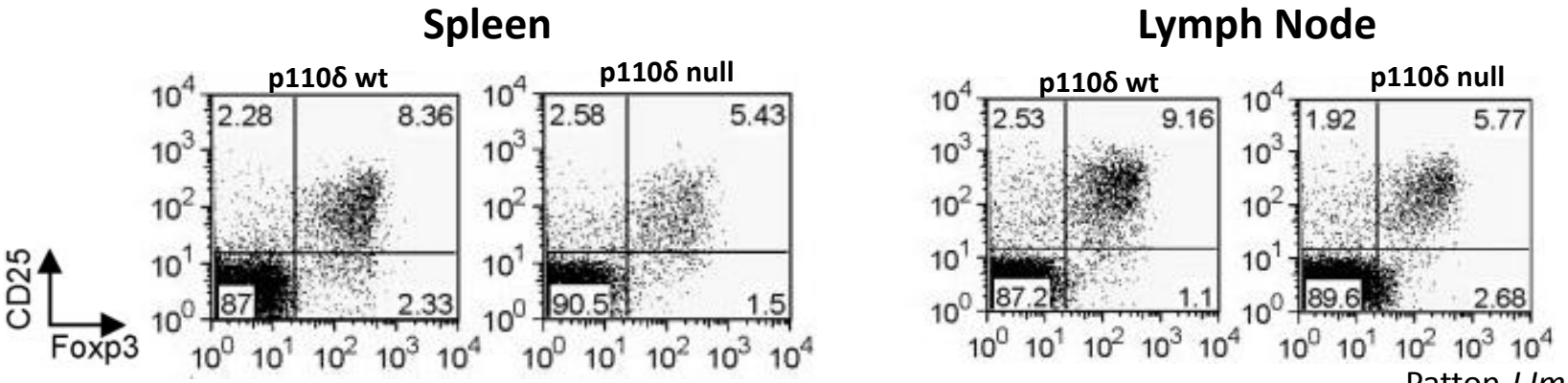
- **Mice with genetic inactivation of p110δ develop an autoimmune colitis**

  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

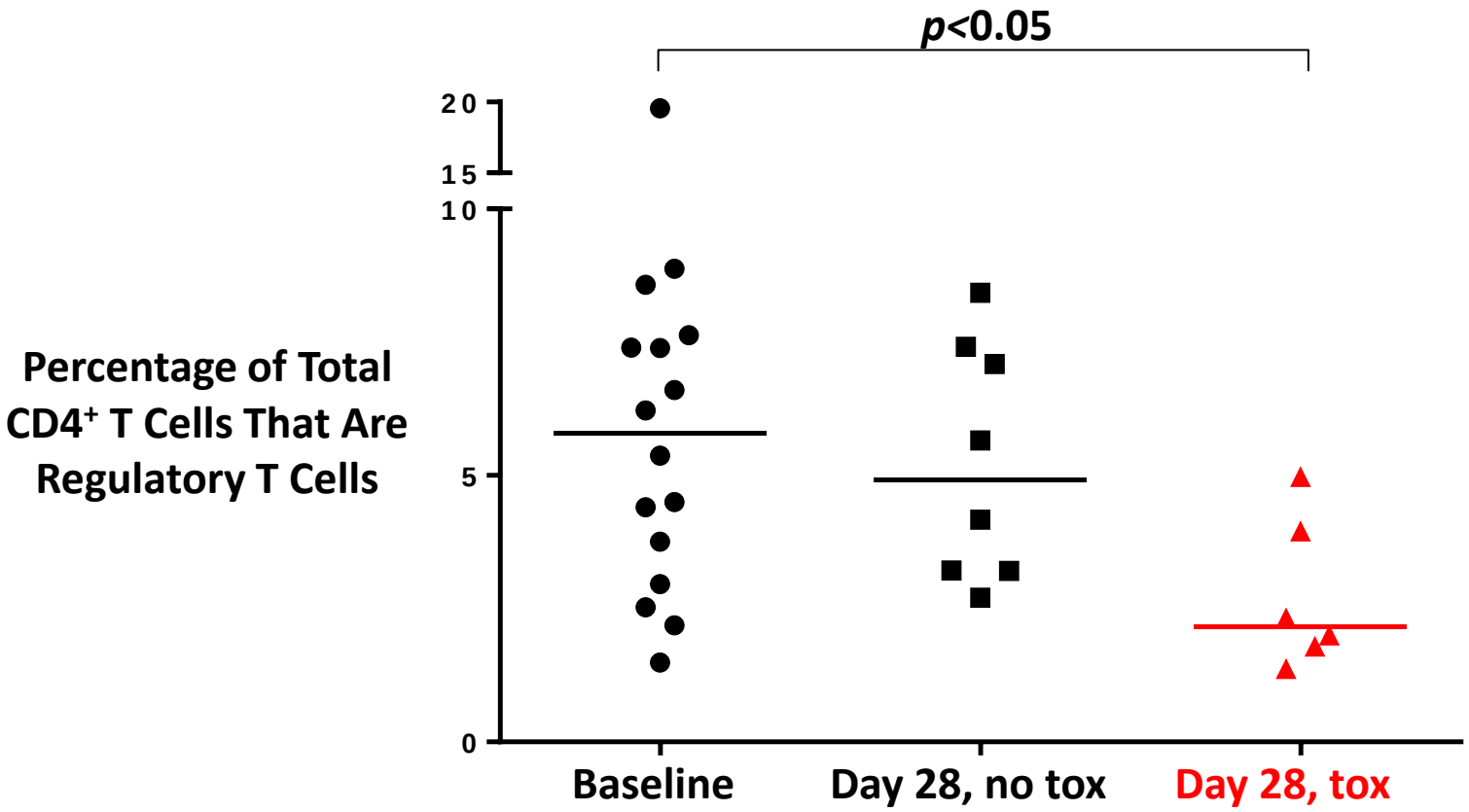
- **Mice with genetic inactivation of p110δ have decreased numbers and function of regulatory T cells**



Patton *J Immunol* 2006

Decrease in Regulatory T Cells While on Therapy

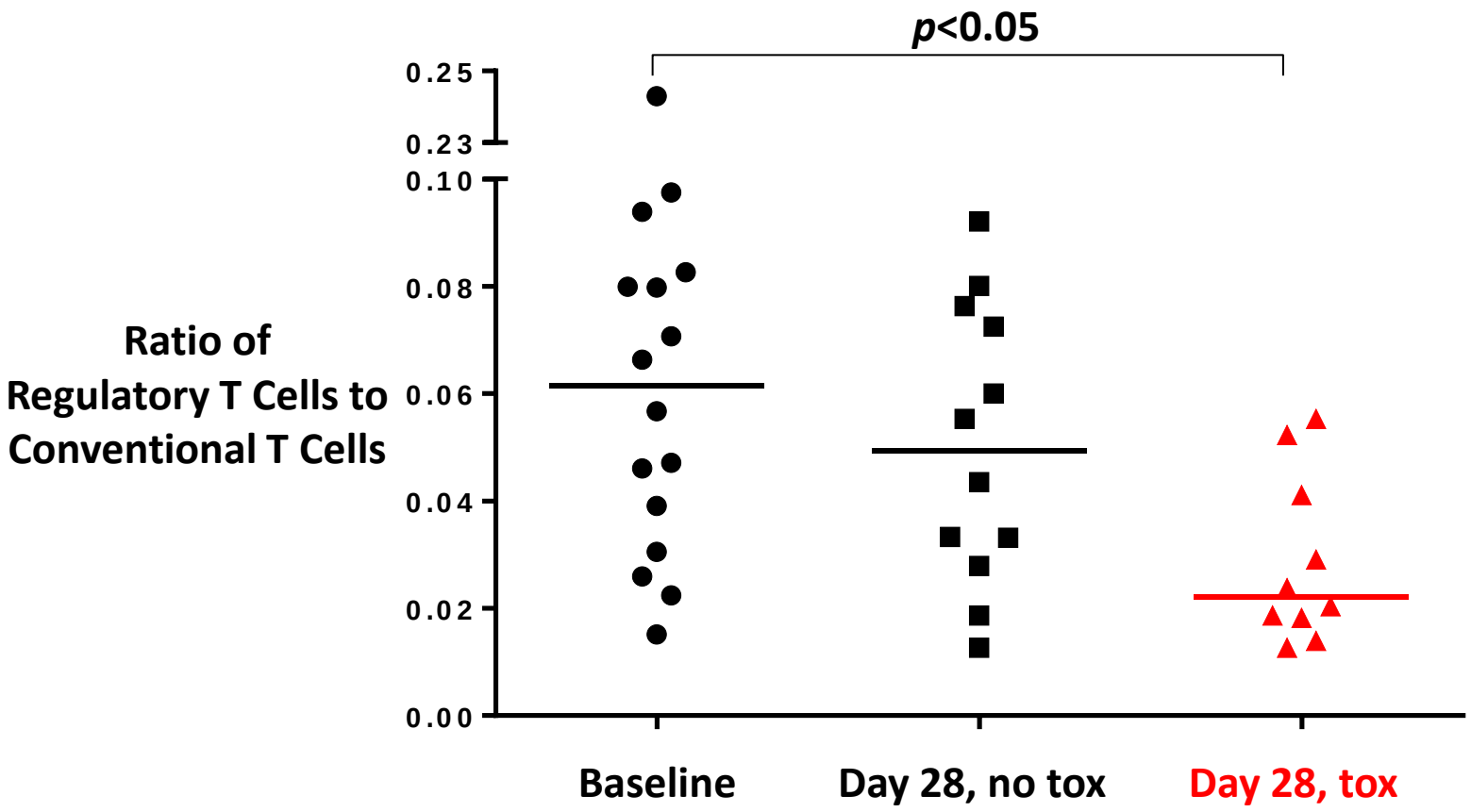
Change in Regulatory T cells Over Time



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

Decrease in Regulatory T Cells While on Therapy

Change in Regulatory T Cell to Conventional T Cell Ratio Over Time



Summary

- **An early fulminant hepatotoxicity develops in a subset of primarily younger patients treated with idelalisib monotherapy in the front-line setting.**

- **Multiple lines of evidence suggest that this early hepatotoxicity is immune-mediated.**

- **The proportion of regulatory T cells in the peripheral blood decreases on idelalisib therapy, providing a possible explanation for the development of early hepatotoxicity.**

Questions 2016

- Yes, idelalisib is a very efficacious drug.
- Idelalisib use is limited by very significant toxicities, particularly in younger, less heavily-pretreated patients.
- Idelalisib should not be used for front-line therapy. It’s use in other clinical settings should be based on a careful assessment of risks/benefit for an individual patient.