A Phase 2 Study to Assess the Safety and Efficacy of Umbralisib (TGR-1202) in Patients with Chronic Lymphocytic Leukemia (CLL) who are Intolerant to Prior BTK or PI3Kδ Inhibitor Therapy

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Presented at the 15th International Conference on Malignant Lymphoma
Lugano, Switzerland ● June 18 – 22, 2019

15-ICML

15th International Conference on Malignant Lymphoma
Palazzo dei Congressi, Lugano, Switzerland, June 18-22, 2019

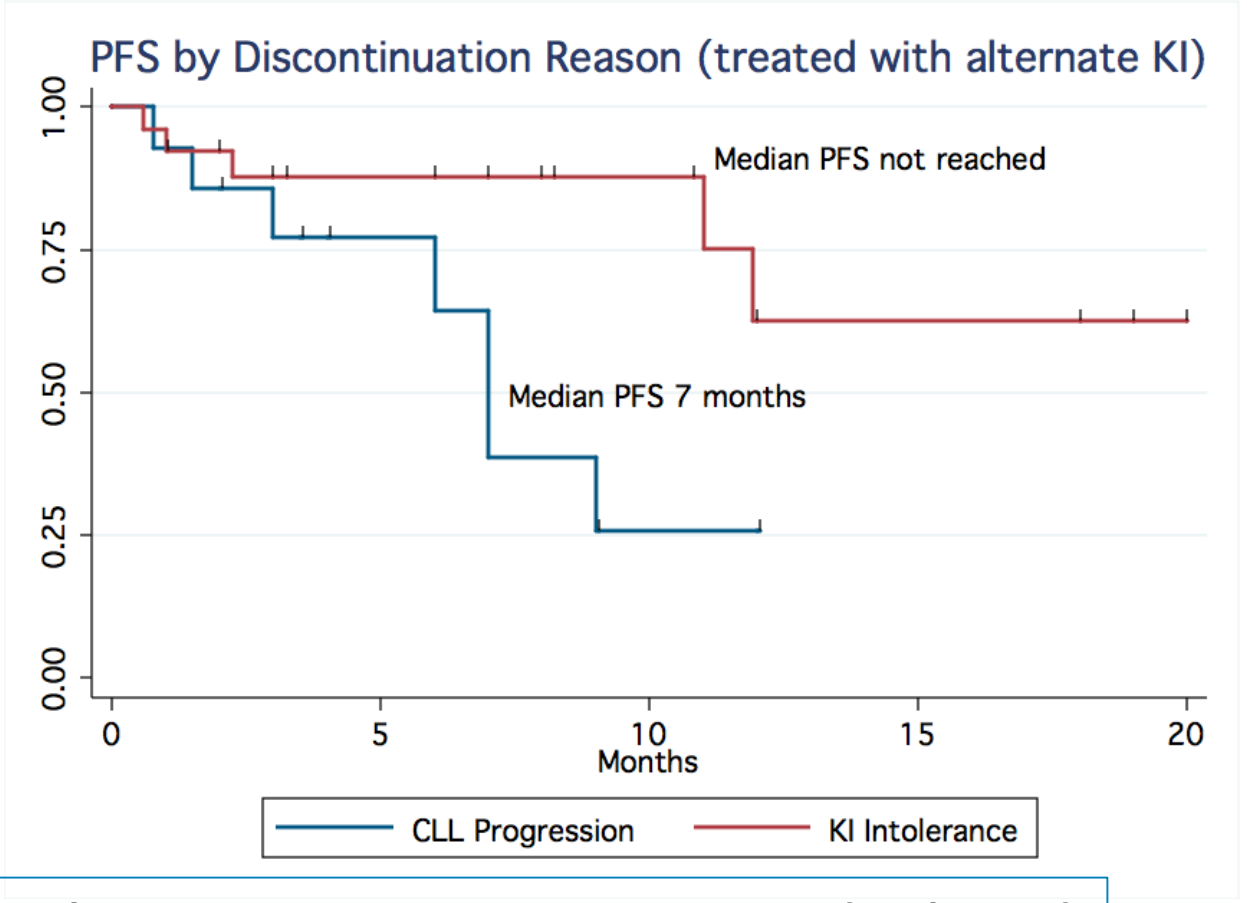
Conflict of Interest Disclosure – Anthony Mato, MD

- Employment or leadership position:	N/A
- Consultant or advisory role:	TG Therapeutics, Pharmacyclics, Abbvie, Johnson and Johnson, Acerta / AZ, DTRM BioPharma, Sunesis, Celgene, Verastem, Pfizer
- Stock ownership:	N/A
- Research:	TG Therapeutics, Pharmacyclics, Abbvie, Johnson and Johnson, Acerta / AZ, Regeneron, DTRM BioPharma, Sunesis, Loxo
- Other remuneration:	N/A

Background / Rationale

- Kinase inhibitor (KI) therapies are generally well tolerated, although intolerance is the most common reason for discontinuation in practice (~20% discontinuation rate due to AE)[1]
- AEs leading to BTK and PI3Kδ discontinuation are non-overlapping
- Retrospective data show that KI-intolerant patients can be successfully treated with an alternate KI

Discontinuation due to intolerance	
US series TN ibrutinib	63% of discontinuations
US series R/R ibrutinib	50% of discontinuations
UK series R/R ibrutinib[2]	43% of discontinuations
US series R/R idelalisib	52% of discontinuations

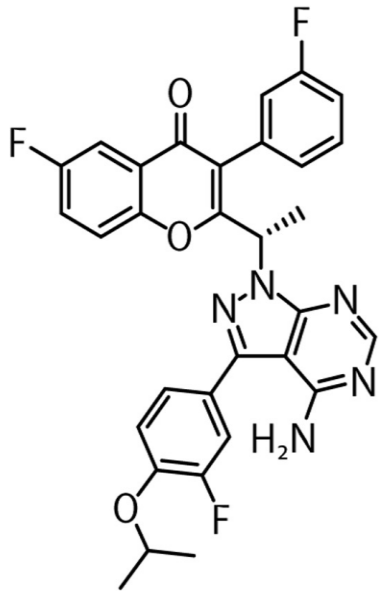
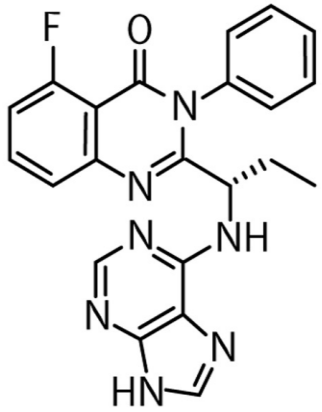
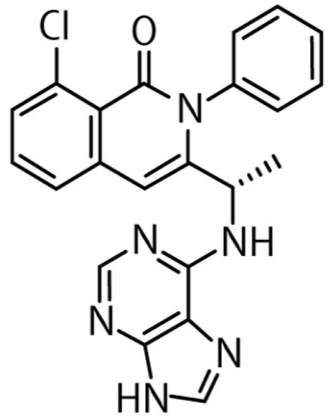


Patients who discontinue a KI due to intolerance represent an unmet medical need

[1]Mato et al., Blood 2016, Annals Oncology 2017; [2]Follows, et al., Haematologica 2016

Umbralisib (TGR-1202)

- Next generation PI3Kδ inhibitor, with a unique structure and improved tolerability[1]
  - Improved selectivity to PI3Kδ isoform
  - Inhibition of CK1ε
    - Potential regulator of Treg count and function
  - Ongoing long-term safety analyses demonstrate low rates of immune-mediated toxicity[2]
- Oral – once daily administration
- Phase 3 dose: 800 mg QD

	Umbralisib	Idelalisib	Duvelisib
			
Isoform		**K_d (nM)**	
PI3Kα	>10 000	600	40
PI3Kβ	>10 000	19	0·89
PI3Kγ	1400	9·1	0·21
PI3Kδ	6·2	1·2	0·047
CK1ε	180	>30 000	>30 000

[1]Burris et al., Lancet Oncology 2018; [2]Davids et al., EHA 2018

Study Design

- **Study design:** Phase II, multicenter, single-arm trial of umbralisib monotherapy in CLL patients who are intolerant to prior KI therapy and warranting therapy per investigator discretion (NCT02742090)

- **Enrollment**: Up to 50 patients who have discontinued prior therapy with a BTK or PI3Kδ inhibitor due to intolerance
  - Study was fully accrued as of June 2018

- **Correlative studies:** Peripheral blood samples were collected at screening for central analysis of high-risk cytogenetics / mutations and BTK/PLCgamma2 mutations

Study Objectives and Key Eligibility

- Primary Objective
  - PFS of umbralisib in CLL pts intolerant to prior BTK / PI3Kδ inhibitors
- Secondary Objectives
  - Time to Treatment Failure with umbralisib as compared to prior KI therapy
  - Safety profile of umbralisib as compared to the prior KI therapy
- Key Eligibility
  - CLL pts whose prior therapy with a BTK inhibitor (ibrutinib, acalabrutinib) or a PI3Kδ inhibitor (idelalisib, duvelisib) was d/c due to intolerance within 12 mos of C1/D1
  - Meets study KI Intolerance definition
  - Off prior KI for at least 14 days following discontinuation w/o disease progression
  - ANC > 1,000/µL, platelet count > 30,000/µL

Study Design – Definition of KI Intolerance

Intolerance is defined as unacceptable toxicity where, in the opinion of the investigator, treatment should be discontinued in spite of optimal supportive care as a result of one of the following:

- 2 or more Grade ≥ 2 non-hematological toxicities; OR
- 1 or more Grade ≥ 3 non-hematological toxicity; OR
- 1 or more Grade 3 neutropenia with infection or fever; OR
- Grade 4 heme toxicity which persists to the point that the investigator chose to stop therapy due to toxicity NOT progression

Toxicity must have resolved to ≤ Grade 1 prior to umbralisib dosing

Demographics

Evaluable for Safety, n	51
Evaluable for PFS†, n	50
Measurable Disease at Study Entry, n	36
Median Age, years (range)	70 (48 – 96)
Male/Female	28 / 23
ECOG, 0/1/2	23 / 24 / 4
17p del and/or TP53 mutated, n (%)	12 (24%)
11q del, n (%)	9 (18%)
IGHV Unmutated, %	65%
Bulky Disease, n (%)	21 (41%)
Prior Therapies, median (range)	2 (1 – 7)
Prior BTK inhibitor, n	44 (86%)
Prior PI3K inhibitor, n	7 (14%)
Median Time on Prior KI, mos (range)	9 (0.7 – 38 mos)
Median Time from D/C of Prior KI to Enrollment, mos (range)	3 (1 – 12)
Required Tx within 6 mos of Prior KI, n (%)	39 (76%)

Median follow-up 14 months as of data cutoff

Gene	CLL related variants
ATM	11 (24%)
BTK	1 (2%)
NOTCH 1	4 (9%)
PLCG2	2 (4%)
SF3B1	7 (15%)
TP53	9 (20%)

Data available for 46/51 pts

†1 patient with confirmed Richter's Transformation at enrollment (not eligible); excluded from PFS analysis

Adverse Events Leading to Prior KI Intolerance

Intolerant AE on Prior TKI	Grade 2 (n)	Grade 3 (n)	Grade 4 (n)	Total # of events (n)
Rash	6	8		14
Arthralgia	3	5	1	9
Atrial Fibrillation	5	2	1	8
Bleeding	1	3		4
Fatigue	2	2		4
Anorexia/Weight Loss	3			3

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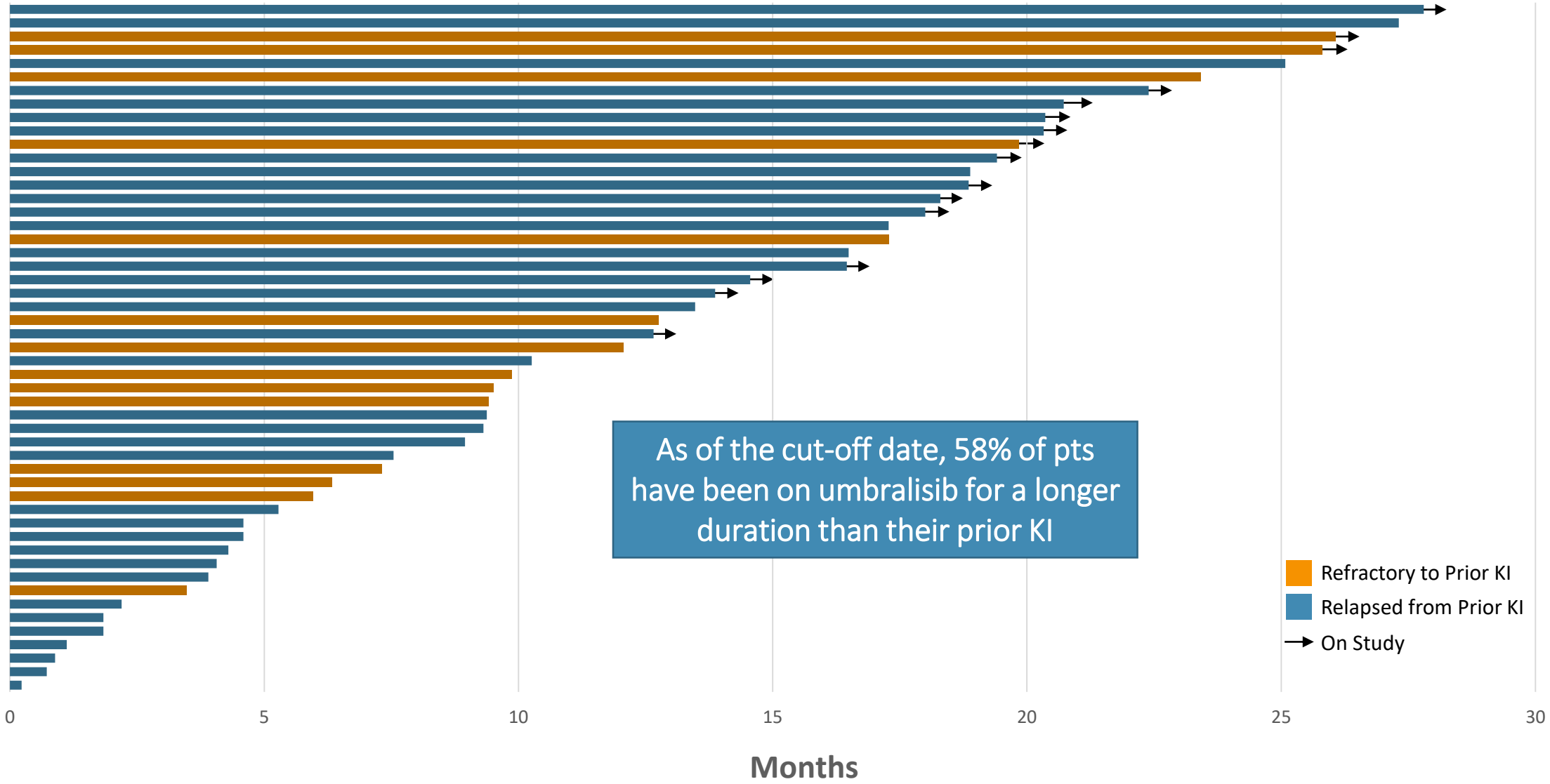
Arthralgia	3	5	1	9
Atrial Fibrillation	5	2	1	8
Bleeding	1	3		4
Fatigue	2	2		4
Anorexia/Weight Loss	3			3

Colitis	1	2		3
Congestive Heart Failure	1	1	1	3
Pneumonitis	2	1		3
Respiratory failure			1	1
Tendonitis			1	1
Thalamic Lesions		1		1
Transaminitis	1			1
TOTAL	39	28	6	73

Efficacy & Tolerability: Duration of Exposure



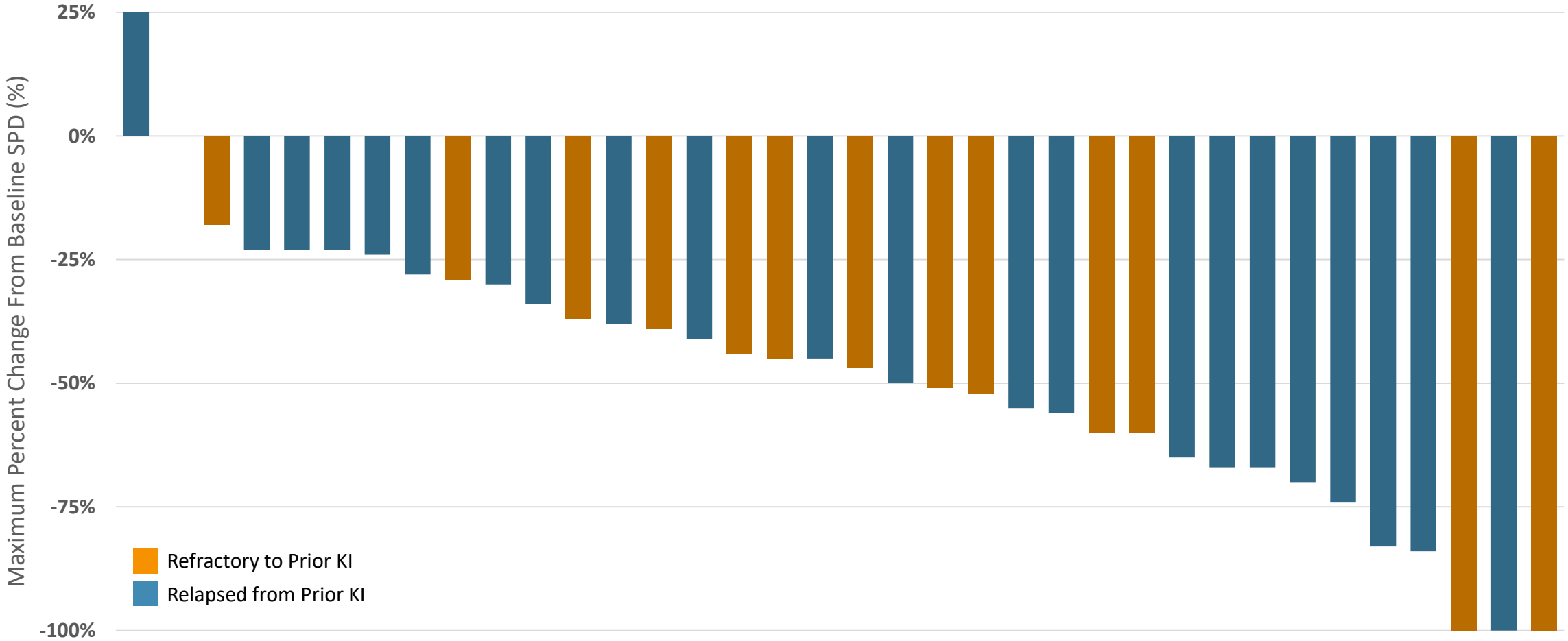
Safety: Umbralisib was well tolerated

- 4 patients had recurrence of an AE that led to prior KI intolerance
  - 3 were of lesser severity and did not lead to dose modification or d/c of umbralisib
  - 1 patient discontinued for recurrent rash (prior ibrutinib)
- 1 case of colitis reported after 6 weeks on treatment – 17p del CLL patient
  - Recovered after 2 week hold
  - Did not recur on re-challenge at 600 mg
  - Patient achieved a CR and on study for 25 months
- No fatal AE's occurred
- 8 pts (16%) had dose reductions allowing them to continue umbralisib therapy
- 6 pts (12%) discontinued treatment due to an umbralisib AE (pneumonitis (2), pancreatitis, pneumonia, dermatitis, rash)

All Causality Adverse Events in >10% of Patients (N=51)

	All Grades		Grade 3/4	
	N	%	N	%
Diarrhea	32	63%	4	8%
Nausea	27	53%		
Thrombocytopenia	13	25%	6	12%
Fatigue	13	25%		
Insomnia	13	25%		
Neutropenia	12	24%	9	18%
Headache	12	24%		
Dizziness	10	20%		
Peripheral Edema	9	18%		
Cough	8	16%		
Rash	8	16%		
Leukocytosis	7	14%	7	14%
Pneumonia	7	14%	6	12%
Anemia	7	14%	2	4%
Pyrexia	7	14%	1	2%
Arthralgia	7	14%		
Contusion	7	14%		
Decreased appetite	7	14%		
Myalgia	7	14%		
Upper respiratory tract infection	7	14%		
Vomiting	7	14%		
AST/ALT Increase	6	12%	3	6%

Efficacy – Best % Change in Nodal Lesions

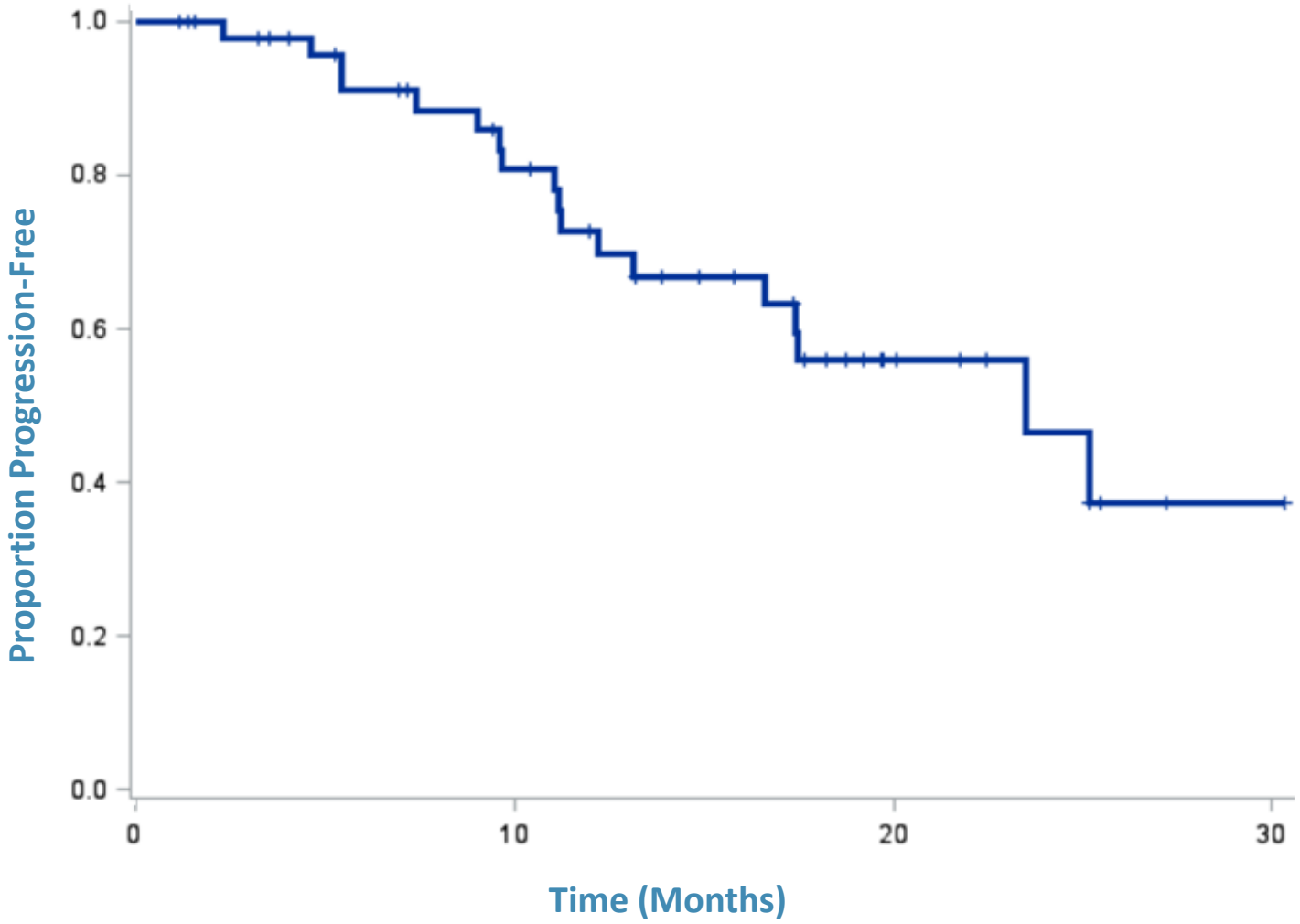


Note: Patients were not required to have relapsed or refractory disease following prior KI discontinuation

Plot only includes patients with measurable disease at study entry

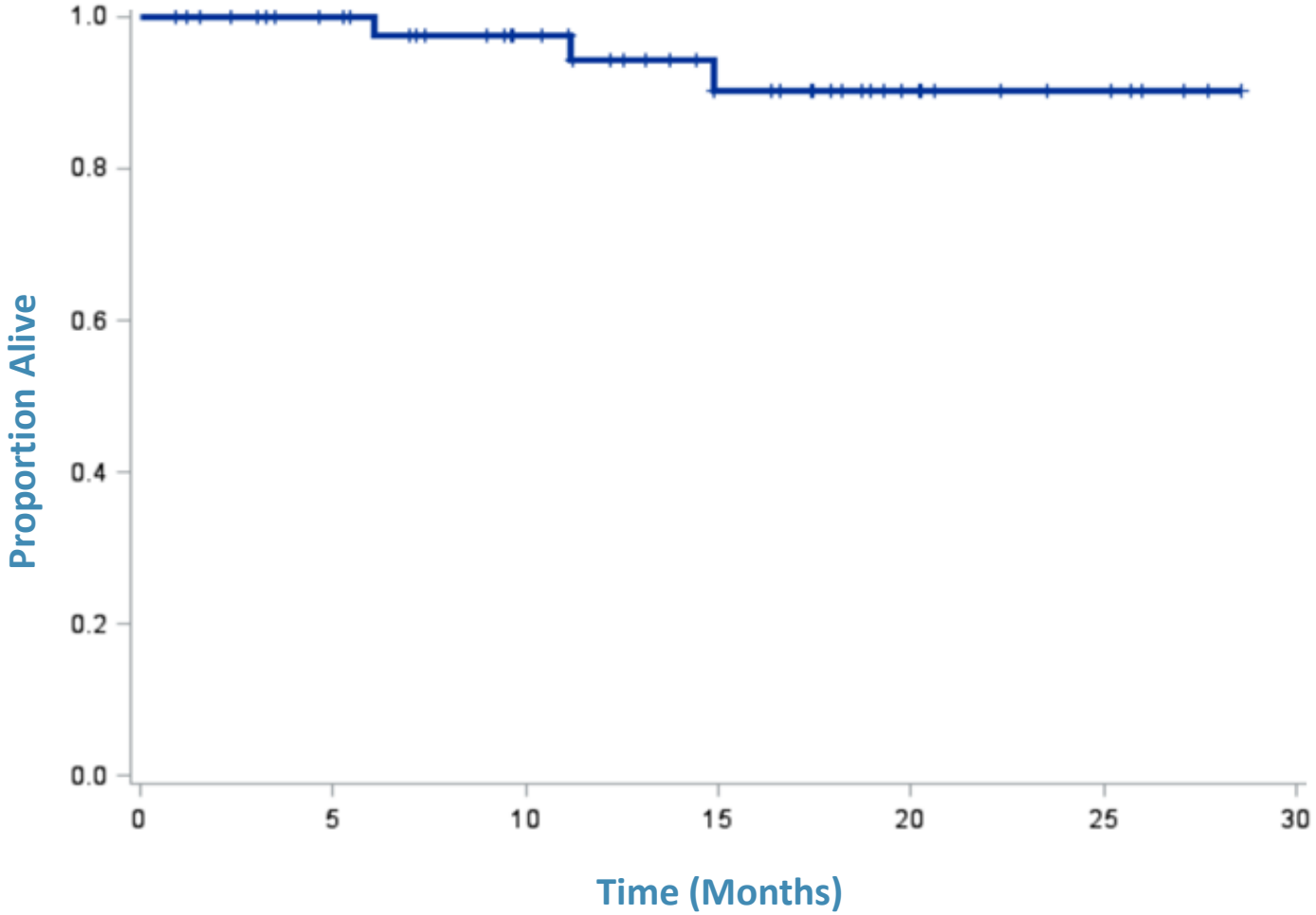
Refractory to prior KI: Progression from 14 days to 6 mos post KI; Relapsed from prior KI: Progression after 6 mos post KI

Efficacy – Progression-Free Survival



- Estimated median PFS: 23.5 months (95% CI 13.1 – NE)

Efficacy – Overall Survival



- Median OS not reached

Conclusions

- Umbralisib demonstrates a *favorable safety profile* in pts intolerant to prior BTK or PI3Kδ therapy
- *Well tolerated:*
  - Only 1 pt (2%) discontinued due to a recurrent AE also experienced with prior KI therapy
  - Only 6 pts 12% discontinued due to an umbralisib AE
- *Significant clinical activity:*
  - **Primary endpoint was met** with a **median PFS of 23.5 mos**
  - **High-risk population:** 76% required treatment within 6 months of prior KI discontinuation, 67% had a high-risk molecular / genetic marker and 6% had an ibrutinib resistance mutation
  - 94% of patients with measurable disease at baseline had a reduction in lymphadenopathy

Acknowledgements

- Thank you to the patients and their families for their participation

- Participating Centers:

  - **University of Pennsylvania Cancer Center**
    - Stephen J. Schuster, MD; Jakub Svoboda, MD; Colleen Dorsey, BSN, RN; Eline T. Luning Prak, MD, PhD; Patricia Tsao, MD, PhD
  - **New York-Presbyterian Columbia University Medical Center**
    - Nicole Lamanna, MD; Hanna Weissbrot, BS
  - **Northwell Health/CLL Research and Treatment Program**
    - Jacqueline C. Barrientos, MD; Kanti R. Rai, MD; Alexis Mark, MS
  - **Florida Cancer Specialists/Sarah Cannon Research Institute**
    - James A. Reeves, MD; Gustavo A. Fonseca, MD
  - **Tennessee Oncology/Sarah Cannon Research Institute**
    - Ian W. Flinn, MD, PhD
  - **Sarah Cannon Research Institute at Research Medical Center**
    - Suman Kambhampati, MD
  - **Duke University Medical Center, Durham**
    - Andrea Sitlinger, MD; Danielle M. Brander, MD
  - **Swedish Cancer Institute**
    - John M. Pagel, MD, PhD
  - **Georgetown Lombardi Comprehensive Cancer Center**
    - Bruce D. Cheson, MD; Chaitra Ujjani, MD
  - **Wilmot Cancer Institute, University of Rochester**
    - Paul M. Barr, MD
  - **Dartmouth-Hitchcock Medical Center**
    - Frederick Lansigan, MD
  - **John Theurer Cancer Center**
    - Alan P. Skarbnik, MD
  - **Upstate Cancer Ctr., Syracuse, NY**
    - Jeffrey J. Pu, MD, PhD