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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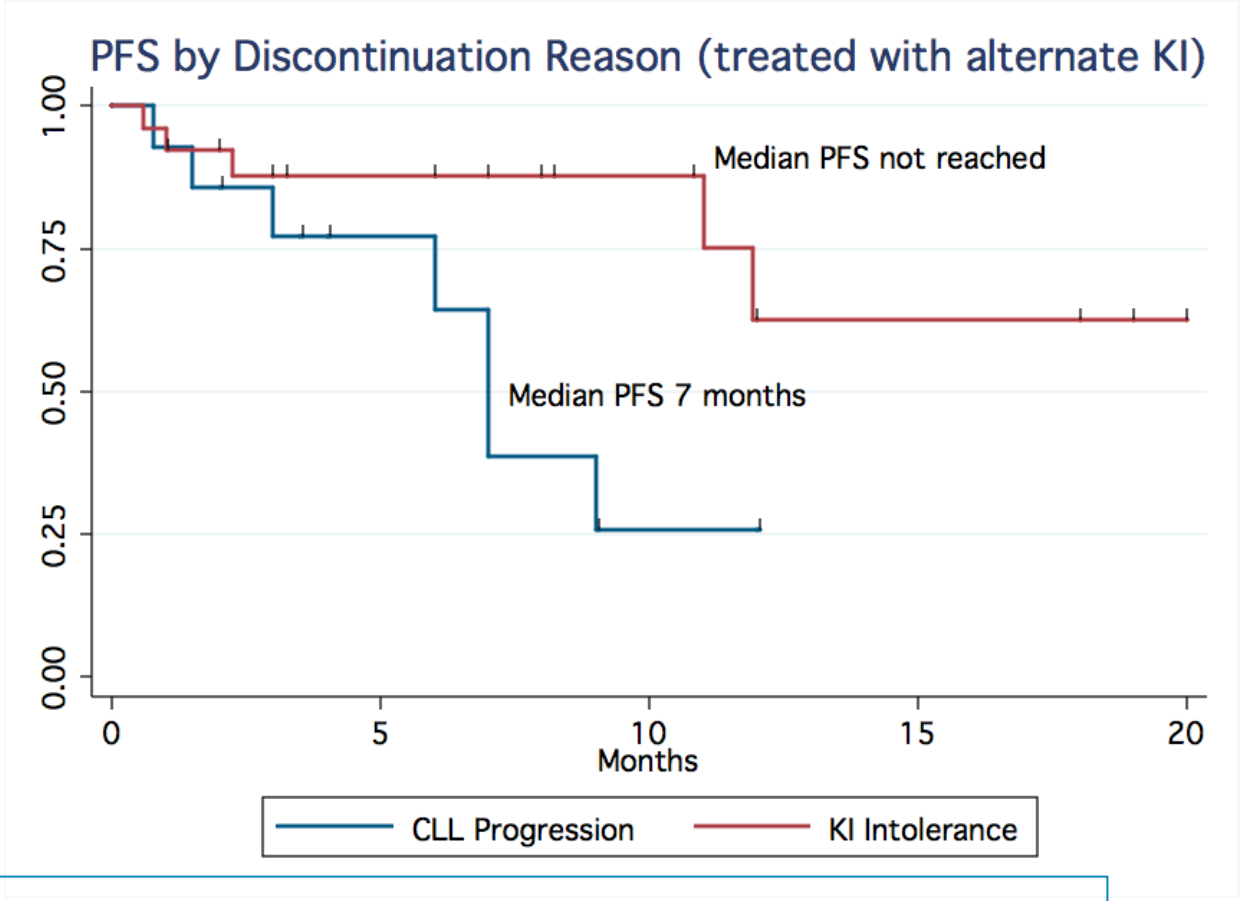
Background / Rationale

- Kinase inhibitor (KI) therapies are generally well tolerated and effective, although intolerance is the most common reason for discontinuation in practice (~50% of discontinuations)[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

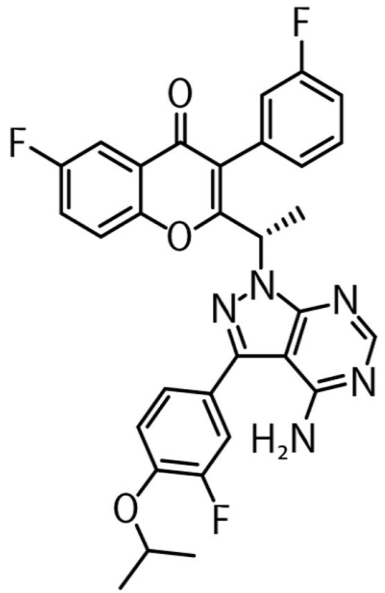
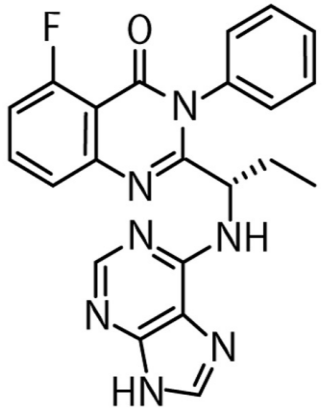
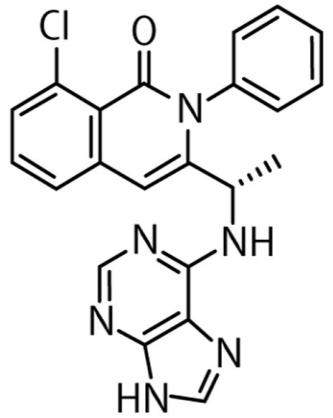


Patients who discontinue a KI due to intolerance represent an unmet medical need

[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
  - **Integrated analysis of long-term safety presented at EHA 2018 demonstrates low rates of immune-mediated toxicity[2]**
  - Not metabolized through CYP3A4: limited medication interactions
- 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 is fully accrued as of June 7, 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	47
Evaluable for PFS†, n	46
Evaluable for Response*	22
Median Age, years (range)	71 (52 – 96)
Male/Female	27 / 20
ECOG, 0/1/2	21 / 22 / 4
17p del, n (%)	7 (15%)
11q del, n (%)	8 (17%)
IGHV Unmutated, n (%)	25 (53%)
Bulky Disease, n (%)	20 (43%)
Prior Therapy, median (range)	2 (1 – 7)
Prior BTK inhibitor, n	40 (85%)
Prior PI3K inhibitor, n	7 (15%)
Median Time on Prior KI, mos (range)	9 (1 – 38)
Median Time from D/C of Prior KI to Enrollment, mos (range)	3 (1 – 12)
Required Tx within 6 mos of Prior KI, n (%)	36 (77%)

Gene	CLL related variants
ATM	9 (22%)
BTK	1 (2%)
NOTCH 1	4 (10%)
PLCG2	2 (5%)
SF3B1	6 (15%)
TP53	9 (22%)

Data available for 41/47 pts

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

*Patients with progressive disease at study entry

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	5	7		12
Arthralgia	3	5	1	9
Atrial Fibrillation	4	2	1	7
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
Bruising	2			2
Diarrhea	1	1		2
Hypertension	2			2
Nausea	2			2
Cough	1			1
Dizziness	1			1
Edema	1			1
GI Toxicity	1			1
Infection		1		1
Malaise	1			1
Mental Status Change	1			1
Myalgia	1			1
Pericardial Effusion			1	1
Respiratory failure			1	1
Thalamic Lesions		1		1
Transaminitis	1			1
TOTAL	**37**	**26**	**5**	**68**

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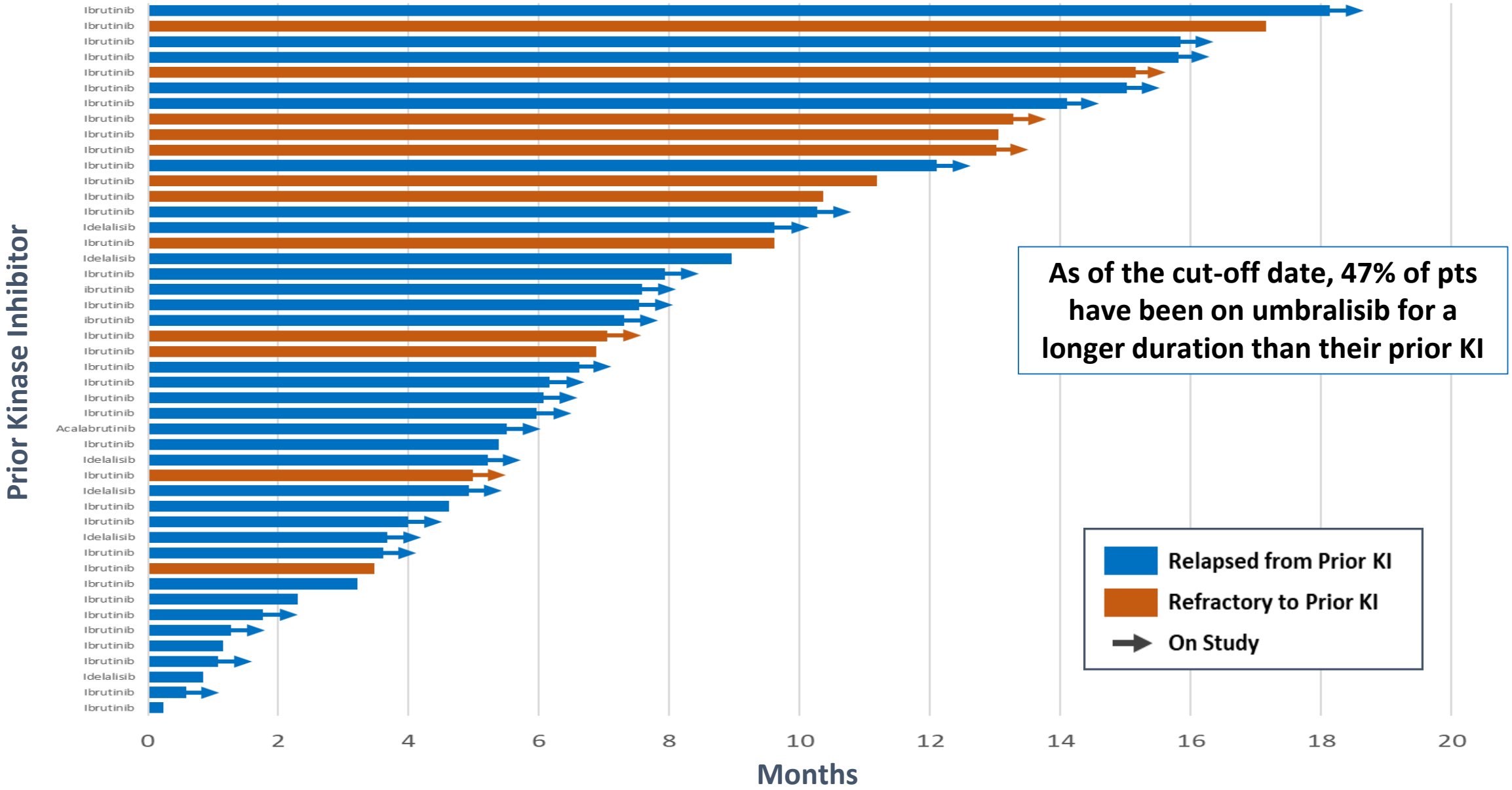
Fatigue	2	2		4
Anorexia/Weight Loss	3			3
Colitis	1	2		3
Congestive Heart Failure	1	1	1	3
Pneumonitis	2	1		3

Efficacy & Tolerability: Duration of Exposure

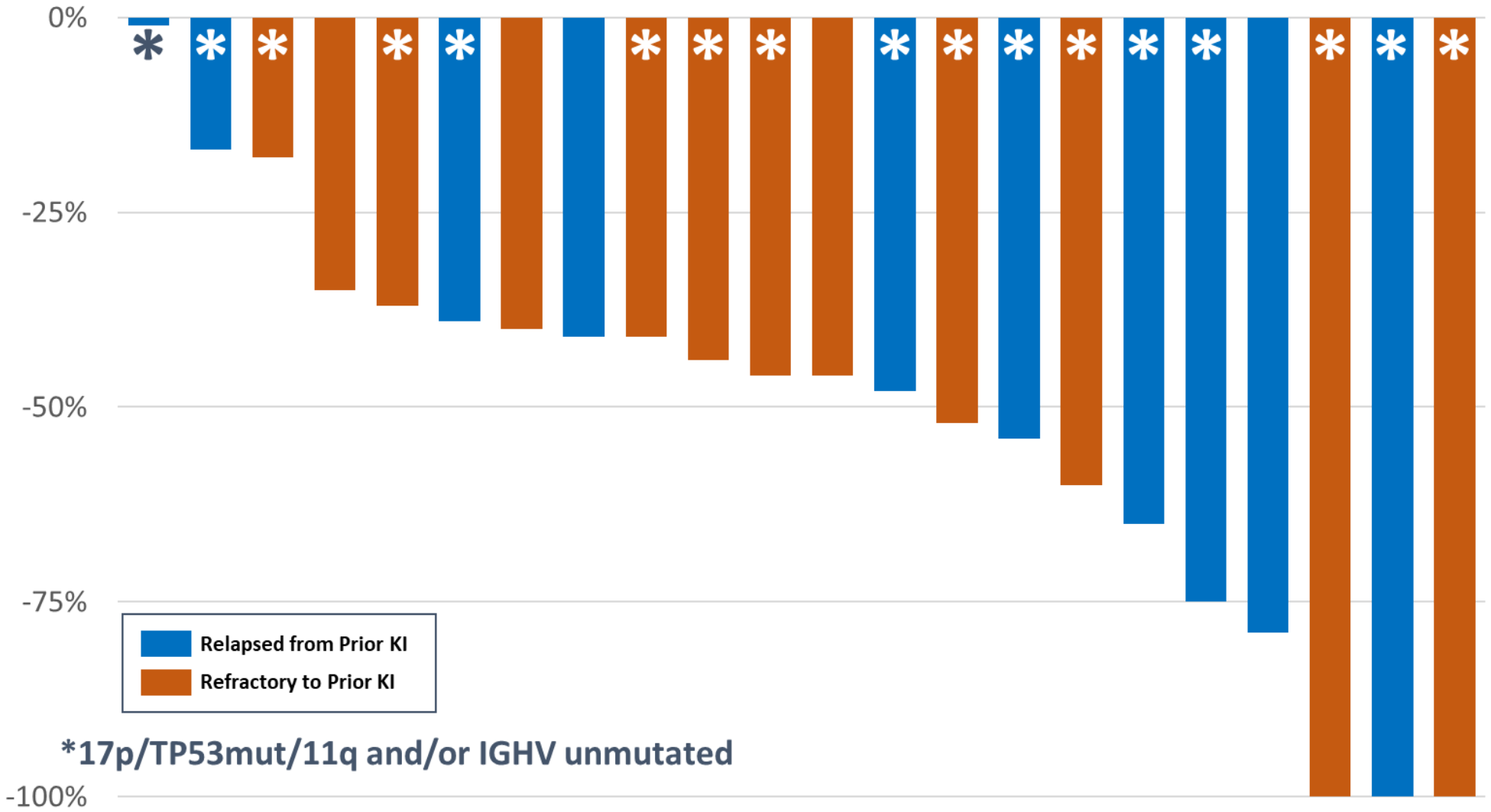


Safety on Umbralisib

- 3 patients had recurrence of an AE that led to prior KI intolerance
  - 2 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 now 16+ months on study
- 3 pts had dose reductions (headache, neutropenia, colitis)
- 6 (13%) pts discontinued treatment due to an umbralisib AE (pneumonia (2), pancreatitis, pneumonitis, dermatitis, rash)

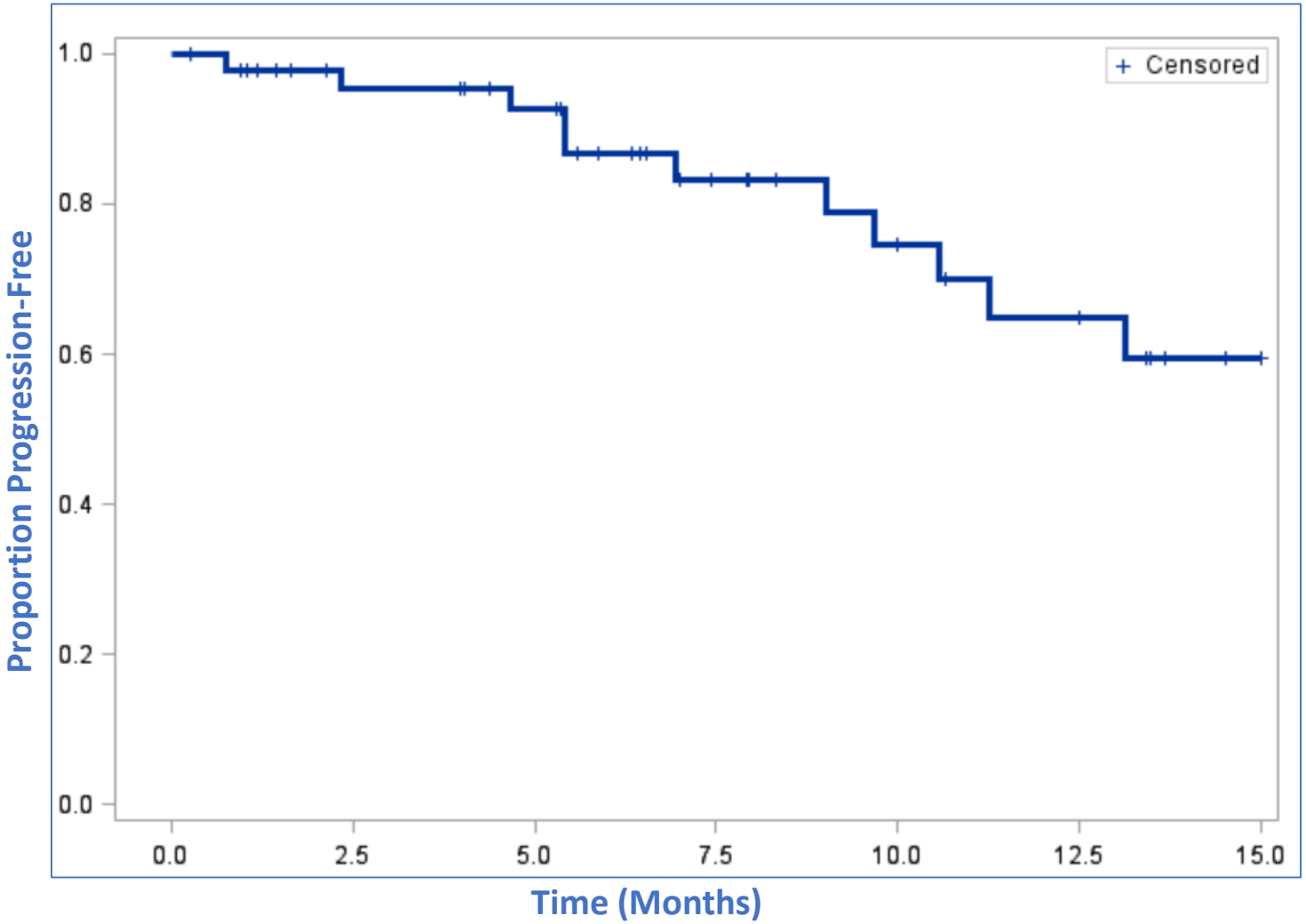
	All Grades		Grade 3/4	
	N	%	N	%
Nausea	20	43%	-	-
Diarrhea	19	40%	3	6%
Thrombocytopenia	12	26%	4	9%
Insomnia	11	23%	-	-
Fatigue	10	21%	-	-
Dizziness	9	19%	-	-
Neutropenia	9	19%	7	15%
Headache	8	17%	-	-
Anemia	6	13%	1	2%
Contusion	6	13%		
Cough	6	13%	-	-
Edema peripheral	6	13%	-	-
Pyrexia	6	13%	1	2%
Arthralgia	5	11%	-	-
Myalgia	5	11%	-	-
Pain in extremity	5	11%	-	-
Paresthesia	5	11%	-	-
Productive Cough	5	11%	-	-
Rash	5	11%	-	-

Efficacy – Best % Change in Nodal Lesions



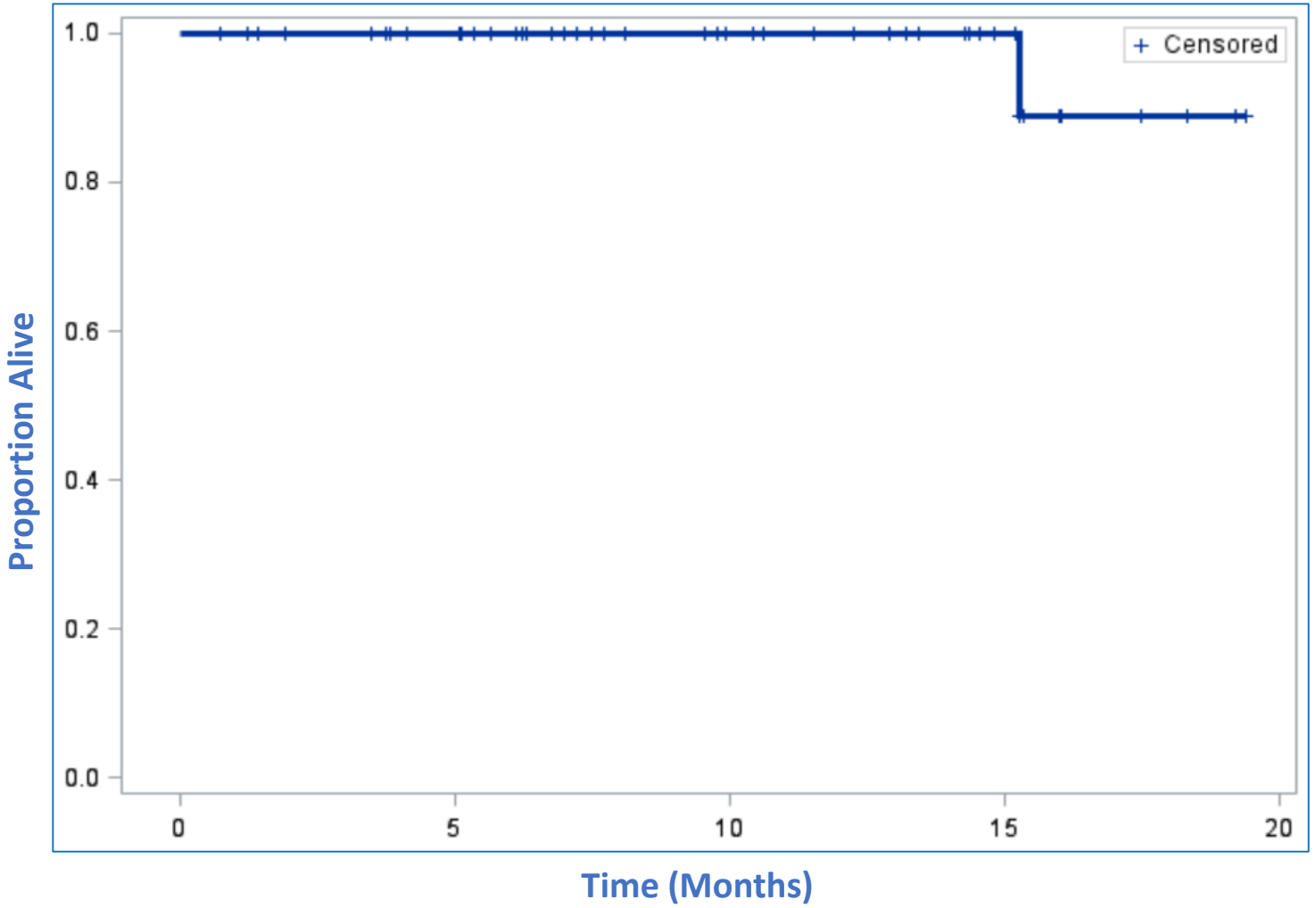
Only includes patients with progressive disease at study entry; Refractory to prior KI: Progression from 14 days to 6 mos post KI; Relapsed from prior KI: Progression after 6 mos post KI

Efficacy – Progression-Free Survival



- Median PFS has not yet reached with a median follow-up of 9.5 months

Efficacy – Overall Survival



- Median OS not yet reached with a median follow-up of 9.5 months

Conclusions

- **Favorable safety profile**: Umbralisib demonstrates a favorable safety profile in pts intolerant to prior BTK or PI3Kδ therapy
- **Well tolerated**:
  - Only 13% discontinued due to an AE
  - Only 1 discontinued due to a recurrent AE also experienced with prior KI therapy suggesting non-overlapping toxicity profile
- **Significant clinical activity**:
  - **High-risk population:** 77% required treatment within 6 months of prior KI discontinuation, 68% had a high-risk molecular / genetic marker and 6% had an ibrutinib resistance mutation
  - Median PFS and OS have not been reached

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    - Nicole Lamanna, MD; Hanna Weissbrot, BS
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