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

TG Therapeutics

Anthony R. Mato, MD[1], Stephen J. Schuster, MD[2], Nicole Lamanna, MD[3], John M. Pagel, MD, PhD[4], Ian W. Flinn, MD, PhD[5], Jacqueline Barrientos, MD[6], James A. Reeves, MD[7], Bruce D. Cheson, MD[8], Paul M. Barr, MD[9], Suman Kambhampati, MD[10], Frederick Lansigan, MD[11], Jeffrey J. Pu, MD, PhD[12], Alan Skarbnik, MD[13], Gustavo Fonseca, MD[14], Jakub Svoboda, MD[2], Colleen Dorsey, RN, BSN[1], Nicole M. LaRatta, MPH[2], Hanna Weissbrot, BS[3], Eline T. Luning Prak, MD, PhD[15], Patricia Tsao, MD, PhD[15], Andrea Sitlinger, MD[16], Dana Paskalis[17], Peter Sportelli, BS[17], Hari P. Miskin, MS[17], Michael S. Weiss[17], Danielle M. Brander, MD[16]

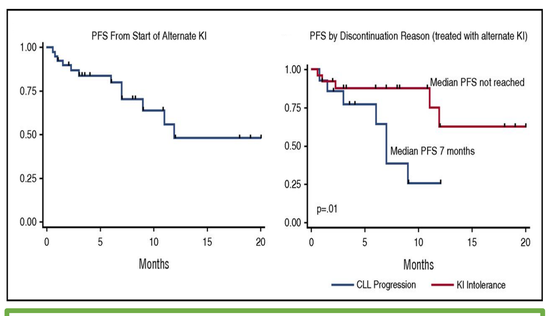
[1]CLL Program, Leukemia Service, Memorial Sloan Kettering Cancer Center, New York, NY, [2]University of Pennsylvania, Abramson Cancer Center, Philadelphia, PA, [3]New York-Presbyterian Columbia University Medical Ctr, New York, NY, [4]Swedish Cancer Institute, Seattle, WA, [5]Tennessee Oncology/Sarah Cannon Research Institute, Nashville TN, [6]Northwell Health/CLL Research and Treatment Program, New Hyde Park, NY, [7]Florida Cancer Specialists South/Sarah Cannon Research Institute, Fort Myers, FL, [8]Georgetown University Hospital Lombardi Comprehensive Cancer Center, Washington, DC, [9]Wilmot Cancer Institute, University of Rochester, Rochester, NY, [10]Sarah Cannon Research Institute at Research Medical Center, Kansas City, MO, [11]Dartmouth-Hitchcock Medical Center, Lebanon, NH, [12]Penn State Health, Hershey, PA, [13]John Theurer Cancer Center, Hackensack, NJ, [14]Florida Cancer Specialists North/Sarah Cannon Research Institute, St. Petersburg, FL, [15]Clinical Immunology Laboratory at the Hospital of the University of Pennsylvania, Philadelphia, PA, [16]Duke University Medical Center, Durham, NC, [17]TG Therapeutics, Inc., New York, NY, United States

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
- Ibrutinib interruptions ≥ 8 days can negatively affect PFS[2]
- Retrospective data show that KI-intolerant patients can be successfully treated with an alternate KI

PFS on Alternate KI[1]

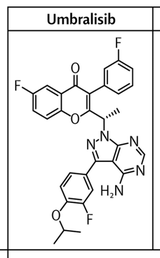
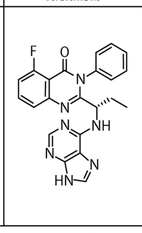
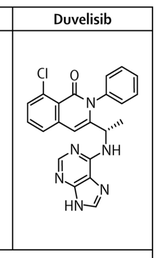


Patients who discontinue a KI due to intolerance represent an unmet medical need

Umbralisib (TGR-1202)

- Umbralisib (TGR-1202) is a next generation PI3Kδ inhibitor, with a unique structure and activity profile distinct from other PI3Kδ inhibitors, including:
  - A differentiated safety profile from other PI3Kδ inhibitors, notably with respect to hepatic toxicity and colitis observed to date;
  - Oral, once-daily (QD) dosing;
  - High selectivity to the δ isoform of PI3K; and
  - Also targets casein kinase-1 epsilon (CK-1ε), a protein which may inhibit regulatory T-cell function

Comparison of Structure and Kinase Inhibition Profile[3]

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]Mato et al., Blood 2016, Annals Oncology 2017; [2]Barr et al., Blood 2017; [3]Burris et al., Lancet Oncology 2018

Study Design

Study TGR-1202-201

- Phase II, multicenter, single-arm trial of umbralisib monotherapy in CLL pts who are intolerant to prior KI therapy (NCT02742090)
- Enrollment: Up to 50 patients who have discontinued prior therapy with a BTK or PI3Kδ inhibitor due to intolerance
- All patients received umbralisib 800 mg oral, once-daily (QD)
- Peripheral blood samples were collected at screening for central analysis of high-risk cytogenetics and BTK/PI3K mutations/deletions
- Study fully accrued as of June 2018

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;
- 1 or more Grade ≥ 3 non-hematological toxicity;
- 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 initiation of umbralisib dosing

Study Objectives

Primary Objective

- To determine the PFS of umbralisib in CLL pts intolerant to prior BTK / PI3Kδ inhibitors

Secondary Objectives

- To evaluate the ORR and duration of response (DOR) of umbralisib.
- To evaluate Time to Treatment Failure with umbralisib as compared to prior KI therapy.
- To evaluate the safety profile of umbralisib as compared to the prior KI therapy.

Key Eligibility Criteria

- CLL patients whose prior therapy with a BTK inhibitor (ibrutinib, acalabrutinib) or a PI3Kδ inhibitor (idelalisib, duvelisib) was discontinued due to intolerance within 12 months 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.

Results

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%)

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

Gene	CLL related variants
ATM	11 (24%)
BTK	1 (2%)
NOTCH1	4 (9%)
PLCG2	2 (4%)
SF3B1	7 (15%)
TP53	9 (20%)

Data available for 46/51 pts

- **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

Adverse Event Leading to Prior BTK/PI3K Discontinuation

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
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
Hyperuricemia		1		1
Infection		1		1
Malaise	1			1
Mental Status Change	1			1
Myalgia	1			1
Pericardial Effusion			1	1
Respiratory failure			1	1
Tendonitis			1	1
Thalamic Lesions		1		1
Transaminitis	1			1
TOTAL	39	28	6	73

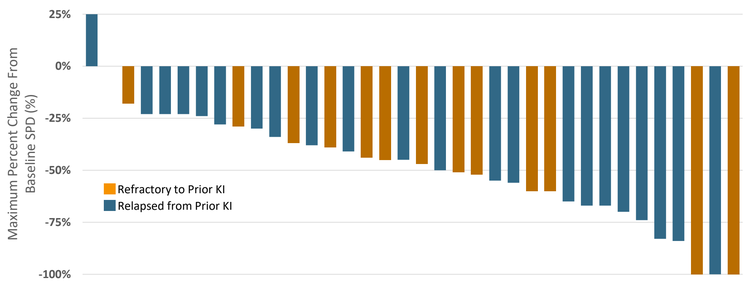
Safety: All Causality Adverse Events in >10% of Patients (N=51)

	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 infection	7	14%		
Vomiting	7	14%		
AST/ALT Increase	6	12%	3	6%

- Median follow up of 15.7 months
- 4 patients had recurrence of an AE that led to prior KI intolerance, however 3 were of lesser severity and did not lead to dose modification of umbralisib, and 1 patient d/c for recurrent rash (prior ibrutinib)
- 1 case of colitis reported after 6 weeks on treatment – 17p del CLL patient. Recovered after 2 week hold, and did not recur on re-challenge at 600 mg daily - 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)

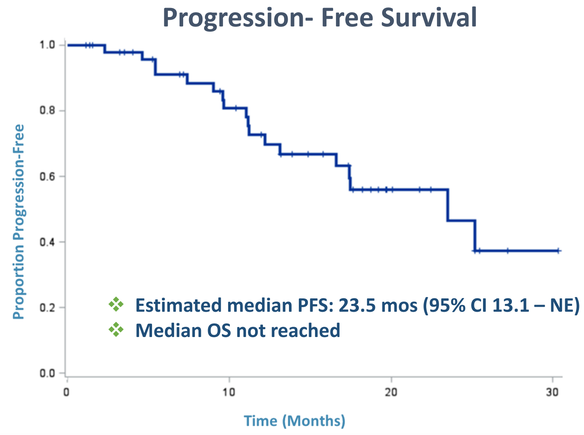
Efficacy

Best % Change in Nodal Lesions

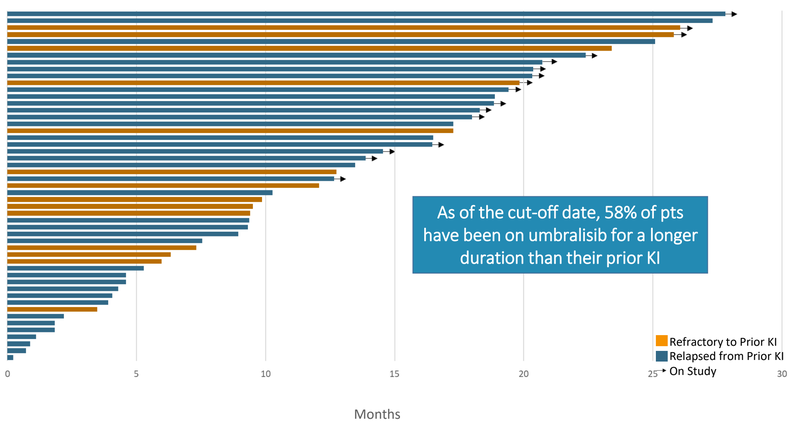


Note: Patients were not required to have relapsed or refractory disease following prior KI discontinuation
Plot only includes patients with measurable disease at study entry (N=36)
Refractory to prior KI: Progression from 14 days to 6 mos post KI; Relapsed from prior KI: Progression after 6 mos post KI

Progression- Free Survival



Duration of Exposure



Conclusions

- **Favorable safety profile:** Umbralisib demonstrates a favorable safety profile in pts intolerant to prior BTK or PI3K 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 months in a high-risk population, and 94% of patients with measurable disease at baseline had a reduction in lymphadenopathy

Presented at the 18th International Workshop on CLL, 20 - 23 September, 2019, Edinburgh, UK