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

Abstract # 7530

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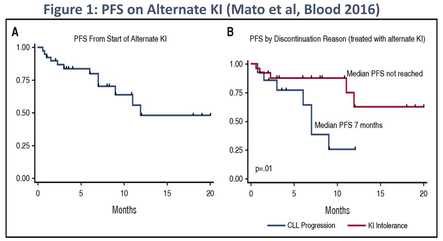
Background / Rationale

- Kinase inhibitor (KI) therapies such as ibrutinib are generally well tolerated, although intolerance is the most common reason for discontinuation in practice (~50% of discontinuations, Mato et al, Blood 2016, Annals Oncology 2017). Data show that KI-intolerant patients (pts) can be successfully treated with an alternate KI (Fig 1). It has also been reported that ibrutinib interruptions ≥ 8 days can negatively affect PFS (Barr et al, Blood 2017). Therefore, pts who discontinue a KI due to intolerance represent an unmet need.
- Fortunately, data suggest that alternate KIs can have non-overlapping toxicity profiles.

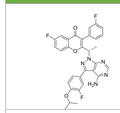
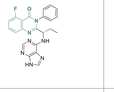
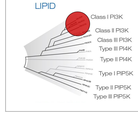
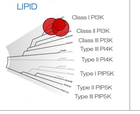
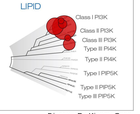
Figure 1: PFS on Alternate KI (Mato et al, Blood 2016)



Umbralisib

- 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;
  - A prolonged half-life that enables once-daily 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 Lipid Kinase Inhibition Profile

Umbralisib	Idelalisib	Duvelisib
		
		

DiscoverRx KinomeScan

Study Design/Methods

- 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.
- Peripheral blood samples were collected at screening for central analysis of high-risk cytogenetics and BTK/PI3K mutations/deletions.

Prior KI Therapy: BTK or PI3Kδ

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 umbralisib dosing

Umbralisib 800 mg daily

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 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.

Results

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 Regimens, median (range)	2 (1 – 7)
Prior BTK inhibitor, n	44 (94%)
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%)
CDKN2A	2 (5%)
MIR-16A	1 (2%)
MLL2	3 (7%)
NOTCH 1	4 (10%)
PLCG2	2 (5%)
RB1	2 (5%)
SF3B1	6 (15%)
SPEN	3 (7%)
TP53	9 (22%)
ZFHX3	1 (2%)

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 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	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

Safety

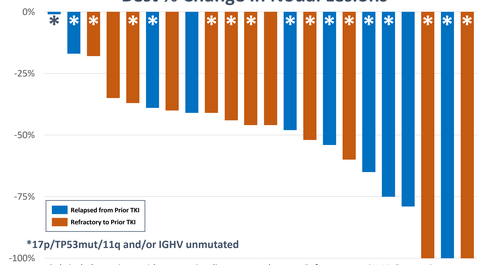
All Grade / All Causality AE's >10% or Grade 3/4 > 5% (N = 47)

Adverse Event	All Grades (n)	% All Grades	Grade 3/4 (n)	% Grade 3/4
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%		

- Of the 19 events of diarrhea, 10 were Grade 1, 6 were Grade 2, and 3 were Grade 3
- 3 (6%) pts had dose reductions (headache, neutropenia, colitis)
- 1 case of colitis reported after 6 weeks on treatment – recovered after 2 week hold, and did not recur on re-challenge at 600 mg daily – patient achieved a Complete Response (17p del) now 16+ months on study
- 6 (13%) pts discontinued treatment due to an umbralisib AE (pneumonia (2), pancreatitis, pneumonitis, dermatitis, rash); 1 was a recurrent AE's that led to prior KI intolerance (rash)
- 2 additional pts had recurrence of an AE that led to intolerance on prior KI, however both recurrences were of lesser severity (diarrhea G1, nausea G1) and neither led to discontinuation / dose-modification of umbralisib
- As of the cut-off date, 47% of pts have been on umbralisib for a longer duration than their prior KI

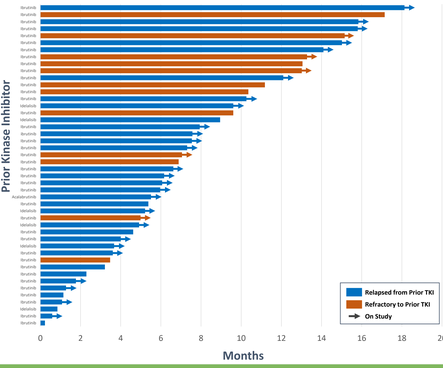
Efficacy

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

Swimmer Plot (Duration of Exposure)



- **PFS:** Median progression-free survival has not been 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 PI3K therapy.
- **Well tolerated:** Only 13% discontinuations due to an AE. Only 1 discontinuation due to a recurrent AE also experienced with prior KI therapy.
- **Significant clinical activity:** In this R/R CLL population, of which 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, **significant clinical activity has been observed** and **median PFS has not been reached.**

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