KI Intolerance Study: 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 # 4314

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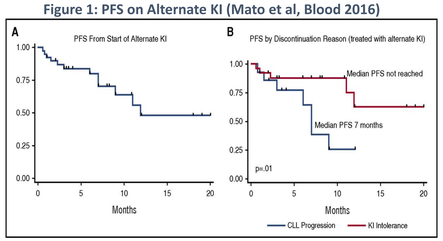
Background / Rationale

- 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). Data shows that KI-intolerant patients (pts) can be successfully treated with an alternate KI (Fig 1). Additionally, it has been reported that KI interruptions ≥ 8 days can shorten Overall Survival (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.

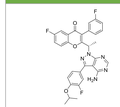
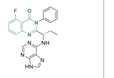
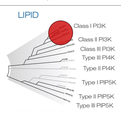
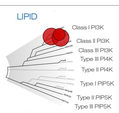
Figure 1: PFS on Alternate KI (Mato et al, Blood 2016)



Umbralisib

- Umbralisib (TGR-1202) is a next generation PI3Kδ inhibitor, with a unique structure and activity profile distinct from other PI3Kδ inhibitors in development, 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 PI3K-delta inhibitor due to intolerance.

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 tox 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 KI Intolerance as defined to the left.
- 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	33
Evaluable for PFS†, n	32
Median Age, years (range)	67 (53 – 96)
Male/Female	18 / 15
ECOG, 0/1/2	13 / 18 / 2
Prior Therapy Regimens, median (range)	2 (1 – 7)
17p del, n (%)	5 (15%)
11q del, n (%)	7 (21%)
IGHV Unmutated, n (%)	16 (48%)
Bulky Disease, n (%)	13 (39%)
Prior BTK, n	30
Prior PI3K, n	3
Median Time on Prior TKI, mos (range)	11 (1 – 38)
Median Time from D/C of Prior TKI to Enrollment, mos (range)	3 (1 – 15)
Requiring treatment within 6 mos of Prior TKI, n (%)	25 (76%)

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

Adverse Event Leading to Prior BTK/PI3K Discontinuation

Intolerant AE on Prior TKI	Grade 2	Grade 3	Grade 4	Total # of Events
Arthralgia	3	4	-	7
Rash	3	4	-	7
A-Fib	3	2	1	6
Diarrhea	2	2	-	4
Anorexia/Weight Loss	3	-	-	3
Bleeding	1	2	-	3
Fatigue	2	1	-	3
Bruising	2	-	-	2
CHF	-	1	1	2
Colitis*	-	2	-	2
Dizziness	1	-	-	1
Edema	1	-	-	1
Hypertension	1	-	-	1
Pericardial Effusion	-	-	1	1
Mental status change	-	1	-	1
Respiratory Failure	-	-	1	1
Transaminitis*	1	-	-	1

- *All 3 events were idelalisib intolerant patients (2 pts colitis and 1 transaminitis)

Safety

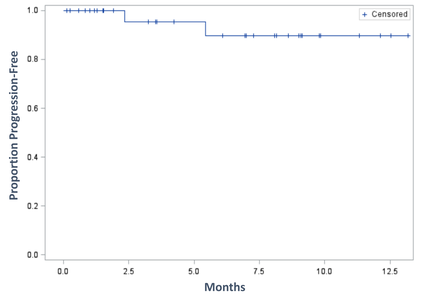
All Grade / All Causality AE's >15% or Grade 3/4 > 5% (N = 33)

Adverse Event	All Grades		Grade 3/4	
	N	%	N	%
Nausea	16	48%	-	-
Diarrhea	14	42%	2	6%
Thrombocytopenia	8	24%	2	6%
Insomnia	8	24%	-	-
Neutropenia	7	21%	6	18%
Fatigue	7	21%	-	-
Peripheral Edema	7	21%	-	-
Cough	6	18%	-	-
Dizziness	6	18%	-	-
Febrile neutropenia	3	9%	3	9%
Hypophosphatemia	2	6%	2	6%

- Mean time on study = 6 mos (range 1 – 13 mos)
- AST/ALT Increase = 3% (One Grade 1 event)
- Of the 14 events of diarrhea, 8 were Grade 1, 4 were Grade 2, and 2 were Grade 3
- 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 remains in Partial Response 10+ months on study
- 2 (6%) pts discontinued treatment due to an umbralisib AE (pancreatitis and rash); neither were recurrent AE's that led to prior KI intolerance
- 2 pts had recurrence of an AE that led to intolerance on their prior TKI, however both recurrences were of lesser severity, and neither led to discontinuation or dose-modification of umbralisib
- 3 (9%) pts had dose reductions (headache, neutropenia, colitis)
- 1 event of pneumonia was reported and deemed not related to umbralisib

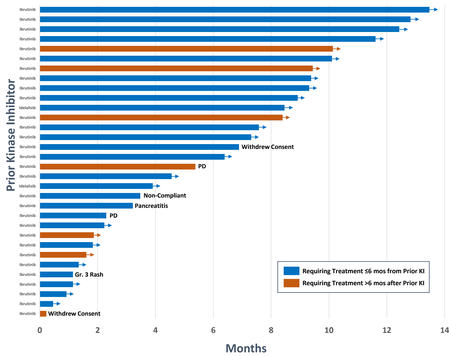
Efficacy

Kaplan-Meier Plot of Progression-Free Survival



- 30/32 patients (94%) remain progression-free with a median time on study of 6 months

Swimmer Plot



Conclusions

- Umbralisib as a single agent demonstrates a favorable safety profile in patients intolerant to prior ibrutinib or idelalisib, with only 2 patients (6%) discontinuing due to an AE, none of which was a recurrent AE from prior TKI therapy.
- In this high-risk group of patients, of which 76% required treatment within 6 months of discontinuation from a prior BTK or PI3K inhibitor, 94% remain progression-free with a median time on study of 6 mos.
- Enrollment continues with up to 50 patients expected in this TKI intolerant patient population.

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