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

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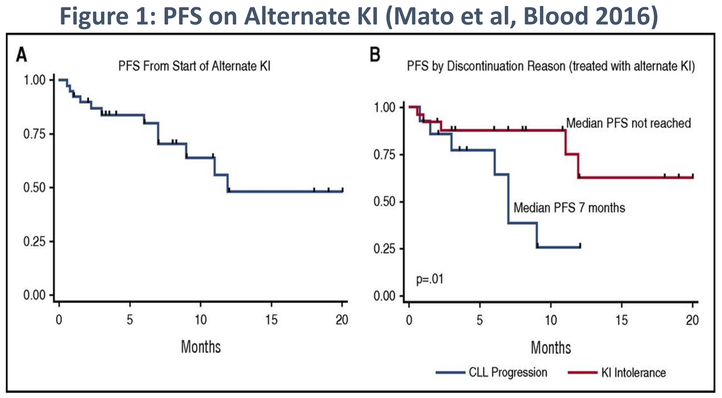
Rationale

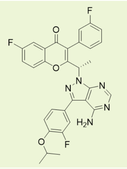
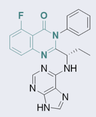
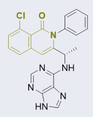
- Kinase inhibitor (KI) therapies such as ibrutinib are generally well tolerated, although intolerance is the most common reason for discontinuation in practice (~50% of discontinuations, Mato et al, Blood 2016). Data showed that KI-intolerant patients (pts) can be successfully treated with an alternate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

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



- Umbralisib (TGR-1202) is a next generation, highly specific PI3Kδ inhibitor, with a unique structure and activity profile distinct from other PI3Kδ inhibitors in development, including prolonged half-life that enables once-daily dosing

Significant structural differences compared to other PI3Kδi

Umbralisib (TGR-1202)	Idelalisib (GS-1101)	Duvelisib (IPI-145)
		
Delta	Delta	Delta/Gamma
QD	BID	BID

- Once-daily TGR-1202 has been well-tolerated with a discontinuation rate due to AEs of < 8% as demonstrated in an integrated safety analysis of 165 previously-treated pts, including 43 pts with CLL (Burris et al, ASCO 2016)

AE's Reported in ≥ 20% of Pts (n = 165)				
Adverse Event	All Grades		Grade 3/4	
	N	%	N	%
Diarrhea	78	**47%**	5	**3%**
Nausea	74	**45%**	2	**1%**
Fatigue	61	**37%**	5	**3%**
Vomiting	44	**27%**	0	**0%**
Neutropenia	34	**21%**	30	**18%**

- 13% of pts had a TGR-1202 dose reduction
- Colitis reported in < 1.5% of pts
- Grade 3/4 AST/ALT increase was 3% (8% all grades), predominantly observed above the Phase 3 dose
- Grade 3/4 pneumonia occurred in 5% of patients (8% all grades)

Key Objectives

PRIMARY ENDPOINT:

- To determine the Progression-Free Survival (PFS) of TGR-1202 in CLL pts who were intolerant to prior BTK and/or PI3K-delta inhibitors

SECONDARY ENDPOINTS:

- To evaluate the Overall Response Rate and Duration of Response of TGR-1202 in pts who were intolerant to prior BTK and/or PI3K-delta inhibitors
- To evaluate Time to Treatment Failure with TGR-1202 as compared to the prior KI therapy in pts with CLL
- To evaluate the safety profile of TGR-1202 as compared to the safety profile of the prior KI therapy in pts with CLL

Study Design/Methods

DESIGN:

- Phase II, multicenter, single-arm trial of TGR-1202 in CLL patients requiring therapy who are intolerant to prior KI therapy (**NCT02742090**)
- Enrollment: Up to 55 patients who have discontinued prior therapy with a BTK or PI3K-delta inhibitor due to intolerance

Prior KI Therapy: BTK or PI3Kδ

Discontinuation due to Intolerance within prior 12 months

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 Grade ≥ 2 non-hematological toxicities as a cause of discontinuation; and/or
- ≥ 1 Grade ≥ 3 non-hematological toxicity; and/or
- ≥ 1 Grade 3 neutropenia with infection or fever; and/or
- Grade 4 hematological toxicities AND the toxicities persist to the point that the investigator chose to discontinue therapy due to toxicity NOT progression.

All toxicity must have resolved to ≤ Grade 1 prior to TGR-1202 dosing

TGR-1202 800 mg daily

Key Eligibility Criteria

- Confirmed diagnosis of CLL as per the iwCLL (Hallek 2008) criteria requiring therapy
- Prior therapy with a BTK inhibitor (ibrutinib, acalabrutinib, or other) or a PI3K-delta inhibitor (idelalisib, duvelisib, or other) which was discontinued due to intolerance within 12 months of the time of treatment initiation of TGR-1202. Reasons for intolerance are listed in table below.
- Meets KI Intolerance as defined in schema above
- Patients must be off prior KI for at least 14 days following discontinuation without documented disease progression
- Adequate organ system function:
  - ANC > 1,000/µL & platelet count > 30,000/µL
- No prior TGR-1202 exposure
- No prior autologous stem cell transplant within 3 months. No prior allogeneic hematologic stem cell transplant within 1 year, and excluded entirely if there is active graft versus host disease

Non-Hematological Toxicities by KI Class	
BTK Toxicities	**PI3K Toxicities**
Atrial fibrillation	Pneumonitis
Hypertension	Transaminitis
Bleeding	Rash
Arthralgia	Colitis
Rash	Infection
Diarrhea	
Infection	
Pneumonitis	
Any additional grade ≥ 2 non-heme toxicity not listed will be evaluated by the study chair	

Evaluation

EFFICACY EVALUATION:

- During the study period, all patients are evaluated for response by CT and/or MRI during Cycles 3, 6, 9, 12 and then at least every 6 cycles thereafter (+/- 14 day window)
- Patients continue treatment until disease progression, unacceptable toxicity, or the end of the study (3 years after enrollment)

CENTRAL LAB:

- Peripheral blood samples are collected at screening and analyzed by central lab for cytogenetics (17p del, 11q del, TP53 mut) and BTK/PI3K resistance and activating mutations/deletions of prognostic value. In addition, a Buccal Swab is being collected at screening.

CORRELATIVE STUDIES (UPENN Lab):

- Peripheral blood samples are collected prior to TGR-1202, after 28 days, and at disease progression for correlative analyses to identify markers associated with KI intolerance.

Currently Enrolling Sites

University of Pennsylvania *Philadelphia, PA*	**Duke Cancer Center** *Durham, NC*
University of Rochester *Rochester, NY*	**Dartmouth-Hitchcock Cancer Center** *Lebanon, NH*
Georgetown University *Washington DC*	**Columbia University Medical Center** *New York, NY*
Penn State Hershey *Hershey, PA*	**Clearview Cancer Institute** *Huntsville, AL*
Swedish Cancer Center *Seattle, WA*	**John Theurer Cancer Center** *Hackensack, NJ*

Summary

- Patients who have discontinued prior therapy with a BTK or PI3K-delta inhibitor due to intolerance may be enrolled into this study evaluating TGR-1202 monotherapy at approximately 10-15 sites in the US.
- Planned analysis will include approximately 50 evaluable patients
- The trial commenced 10/1/2016 and is expected to accrue in 12-15 months. As of 6/1/2017, 10 study sites are currently enrolling pts with an additional 4 – 5 sites to be activated.
- This study is registered on clinicaltrials.gov (NCT02742090).

Acknowledgements

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References

1. Mato et al, Blood 2016
2. Burris et al, ASCO 2016
3. Barr et al, ASCO 2017

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