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 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.

- 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

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

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

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 and 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

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).

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References

2. Burris et al, ASCO 2016
3. Barr et al, ASCO 2017

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