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 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

- 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)

- 13% of pts had a TGR-1202 dose reduction

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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

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 allogeneic hematologic 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

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
- Duke Cancer Center
- University of Rochester
- Dartmouth-Hitchcock Medical Center
- Georgetown University
- Columbia University Medical Center
- Penn State Hershey
- Clearview Cancer Institute
- Swedish Cancer Center
- John Theurer Cancer Center

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

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

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