A Phase I Trial of TGR-1202, a Next Generation Once Daily PI3K-Delta Inhibitor in Combination with Obinutuzumab Plus Chlorambucil, in Patients with Chronic Lymphocytic Leukemia

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Background

- TGR-1202 is a next generation PI3K inhibitor with a unique structure and activity profile distinct from other PI3K inhibitors in development including:
  - A prolonged half-life (T1/2 = xx) and accumulation that enables once-daily dosing
  - A differentiated safety profile from other PI3K inhibitors in development, notably with respect to hepatic toxicity and colitis to date

Studies Design

Study TGR-GA-106 (NCT02100852) is a Phase I study of TGR-1202 in combination with the glycoengineered anti-CD20 mAb, obinutuzumab, in patients with treatment naive and previously treated CLL.

- 3+1 design evaluating escalating doses of TGR-1202 dosed orally once-daily (QD) in continuous 28 Day Cycles
- Dose-limiting toxicities (DLTs) assessed in Cycle 1 prior to escalation

Study Outcomes & Eligibility

- Treatment Naïve/ Evaluable for Safety (n)
- Evaluable for Efficacy (n)
- Median Age, years (range)
- Male/Female
- ECOG 0/1/2

Safety

Adverse Events in TGR-1202 + O-CHL Treated Patients

- All Events in 20% (FDA y 148)
- All Grades Gr. 3/4
- Neuropenia
- Neutropenia
- Thrombocytopenia
- Diarrhea
- Nausea
- Anemia
- Infusion related reaction
- Insomnia
- ASI increased
- Headache
- ALT increased
- Constipation
- Fatigue
- Vomiting
- Cough
- Dizziness
- Pyrexia
- AK phos increased
- Dysgeusia
- Hypokalemia
- Hypophosphatemia
- Simplicity
- Stomatitis

Efficacy

Overall Response Rate and CR rate

- 7/15 (47%) of treatment naïve patients achieved MRD-negative status with TGR-1202 + O-CHL

- Best % Change in Nodal Size from Baseline

Conclusions

- Data from this ongoing Phase 1 study suggests the triple combination of TGR-1202 + obinutuzumab + chlorambucil demonstrates acceptable tolerability and high activity in patients with treatment naïve and relapsed/refractory CLL.
- In treatment naïve patients, combination therapy resulted in a 100% ORR, with 33% of patients achieving a CR, and 47% of patients achieving MRD negativity.
- Notably, the AE profile observed with TGR-1202 + O-CHL differed from that observed when TGR-1202 was combined with the other glycoengineered anti-CD20 mAb, obinutuzumab, specifically regarding neuropenia (78% vs. 30%), thrombocytopenia (78% vs. <1%), and transaminase elevations (39% vs. 8%) (Luning et al, ASH 2015, Abstract153B).
- TGR-1202 is currently in Phase 3 testing in combination with the glycoengineered anti-CD20 mAb, obinutuzumab, in patients with previously untreated and relapsed/refractory CLL in a randomized trial compared to obinutuzumab + chlorambucil.

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