Background

TGR-1202 is a next generation PI3Kδ inhibitor with a unique structure and activity profile distinct from other PI3Kδ inhibitors in development including:

- A prolonged half-life and accumulation that enables once-daily dosing
- A differentiated safety profile from other PI3Kδ inhibitors in development, notably with respect to hepatic toxicity and colitis

Single agent activity for TGR-1202 has been observed in a variety of hematologic malignancies, including a 94% nodal response rate in relapsed/refractory Chronic Lymphocytic Leukemia (Burris et al, ASH 2015)

TGR-1202 is currently in registration directed studies for patients with CLL and Diffuse Large B-cell Lymphoma (DLBCL)

Rationale for Study TGR-BV-107

- Brentuximab vedotin (BV) monotherapy is active in pts with relapsed and refractory Hodgkin’s lymphoma with a 73% ORR (32%, CR), however the duration of response varies significantly between patients achieving a CR compared to those achieving a PR (BV Preclinical Information)

- The combination of TGR-1202 and BV has demonstrated strong synergy in pre-clinical studies (Locatelli et al, Leukemia 2016)

- Co-administration of TGR-1202 and BV resulted in marked mitotic arrest and in increase in cell death in 3 Hodgkin’s lymphoma cell lines (Fig. 1)

Study Design

Study TGR-BV-107 (NCT02164006) is a Phase Ib/II study of TGR-1202 in combination with the anti-CD30 antibody-drug conjugate, brentuximab vedotin, in patients with previously treated Hodgkin’s Lymphoma:

- 3+3 design evaluating two doses of TGR-1202 (120 mg and 400 mg) and two doses of brentuximab vedotin in continuous 21-Day Cycles

- Dose-limiting toxicities (DLTs) assessed in Cycle 1 prior to escalation

- Phase Ib expansion at optimal dose

Study Objectives & Eligibility

- Primary Objective: Safety and Maximum Tolerated Dose (MTD)
- Secondary Objective: Efficacy (Overall Response Rate & Progression-Free Survival)

Key Eligibility Criteria:

- Histologically confirmed Hodgkin’s Lymphoma (HL)
- Disease status defined as refractory or relapsed after autologous stem cell transplantation (ASCT) or at least two prior multi-agent chemotherapy regimens in patients not candidates for ASCT
- Prior exposure to brentuximab vedotin is allowed provided patient did not stop therapy due to toxicity
- Patients with Grade 2 or greater peripheral neuropathy excluded

- 2 patients discontinued due to AE (1 G3 pancreatitis, and 1 G3 diarrhea occurring 11 days following treatment initiation), both the event of G3 diarrhea and a separate event of G3 rash met the criteria for DLTs at the 600mg TGR level

Conclusions

- The goal of this Phase 1 study was to assess combinability of TGR-1202 + brentuximab vedotin, and to assess the ability for the combination to drive complete response rate compared to that historically seen with BV monotherapy

- Data from this Phase 1 study suggests that the combination of TGR-1202 + brentuximab vedotin exhibits an acceptable tolerability profile and is clinically active

- Responses were observed in patients with advanced Hodgkin’s lymphoma, including responses in 60% of patients previously refractory to brentuximab vedotin

- 45% of patients on this study achieved a complete response, including two patients previously refractory to brentuximab vedotin monotherapy

Further studies evaluating this combination are warranted