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 PI3K inhibitors in development, notably with respect to hepatic toxicity and coagulation.

Study Design

- Study TGR-1202-101 (NCT01772766) is an ongoing first-in-human, phase 1 study of TGR-1202 in patients with relapsed or refractory hematologic malignancies.
- TGR-1202 was dosed QD continuously 28 Day Cycles.
- Dose-limiting toxicities (DLTs) assessed in Cycle 1 prior to escalation.
- Dose-escalation for patients in previous cohorts following establishment of safety at higher doses.

3+3 Dose Escalation Schemes:

- Cohort 1: 20 mg (N=6) Evaluable for Safety (n=5): 2 DLTs
- Cohort 2: 40 mg (N=6) Evaluable for Safety (n=5): No DLTs
- Cohort 2 Expansion: 60 mg (N=6) Evaluable for Safety (n=5): No DLTs
- Cohort 3: 1200 micro (N=6) Evaluable for Safety (n=5): 1 DLT
- Cohort 4: 1800 mg (N=6) Evaluable for Safety (n=5): 1 DLT
- Cohort 5: 2400 mg (N=6) Evaluable for Safety (n=5): 1 DLT
- Cohort 6: 3600 mg (N=6) Evaluable for Safety (n=5): 1 DLT
- Cohort 7: 6000 mg (N=6) Evaluable for Safety (n=5): 0 DLTs
- Cohort 8: 9000 mg (N=6) Evaluable for Safety (n=5): 0 DLTs
- Cohort 9: 12000 mg (N=6) Evaluable for Safety (n=5): 0 DLTs

Study Objectives

- Primary: To determine the Pharmacokinetics (PK), and Maximum Tolerated Dose (MTD) of TGR-1202.
- Secondary: To determine the Pharmacodynamics of TGR-1202 and assess efficacy (overall response rate and duration of response).

Key Pharmacodynamics

- Micronized TGR-1202 (DLBCL, MZL, CLL/Hodgkin’s Cancer) has been well-tolerated with limited G1/2 events and no significant dose or time dependent trends in AEs observed with 31 patients on study for 6 months.

Conclusions

- TGR-1202 is a once-daily PI3Kδ inhibitor with single agent activity observed in patients with a variety of relapsed/refractory hematologic malignancies.
- An exposure-response trend was noted in both CLL and NHL, with higher plasma TGR-1202 exposures correlating with increased responses; additionally, as with other PI3Kδ pathway inhibitors, responses appear to improve over time with TGR-1202, especially in CLL and FL.
- TGR-1202 has been well tolerated with patients on daily TGR-1202 for up to 3 years, demonstrating an overall adverse event profile which is differentiated from other PI3Kδ inhibitors, especially with respect to hepatic toxicity and coagulation.
- Marked single-agent activity has been observed in patients at doses ≤ 800 mg of initial formulation or any dose of micronized formulation, with:
  - Relapsed refractory CLL, with an 80% ORR in a phase 1 trial in patients involving 42% of patients remaining on therapy with median tumor reductions of 40%, pending further efficacy assessments.
  - Safety and activity profile supports combination therapy with other novel targeted agents (including idelalisib). ASCO Abstract #8584.
  - Expansion cohorts open and enrolling at the 800 mg and 1200 mg dose levels of the micronized formulation with Phase II trials in development and expected to be initiated in 2015.

Pharmacokinetics

- TGR-1202 Steady State (Cycle 2, Day 1) Pharmacokinetics

Exposure-Response Relationship

- Exposure Response Relationship in CLL
- Steady State Plasma Concentration vs. Change in Nodal Size at First Scan

Efficacy with “Higher Dose” TGR-1202

- Best Percent Change from Baseline in Disease Burden
- Evaluable CLL & FL Patients Treated at “Higher Doses”