TGR-1202 Coaxes Rapid Reduction of pAKT

**Primary**
- To determine the Safety, Pharmacokinetics (PK), and Maximum Tolerated Dose (MTD) of TGR-1202
- To determine the Pharmacodynamics of TGR-1202 and assess Efficacy (overall response rate and duration of response) Exploratory
- To assess correlative biomarkers including cytokines, T-cell subsets, and molecular alterations

**Study Objectives**

**Key Inclusion/Exclusion Criteria**
- Histologically confirmed B-cell non-Hodgkin lymphoma (NHL), CLL/small lymphocytic lymphoma (SLL), peripheral T-cell lymphoma (PTCL), and select other B-cell lymphoproliferative disorders
- Refractory to or relapsed after at least 1 prior treatment regimen (no limit for hematologic malignancies)
- Adequate organ system function as measured by ANC ≥ 750 cells/µl, platelet count ≥ 100,000 cells/µl
- ECOG performance status ≤ 2
- Patients with prior therapy with any drug that specifically inhibits PI3K and/or mTOR are excluded

**Abbreviations**
- ECOG: Eastern Cooperative Oncology Group
- TCR: T-cell receptor
- PI3K: Phosphoinositide 3-kinase
- mTOR: Mammalian target of rapamycin
- pAKT: Phospho-Akt

**Dose Escalation Schema**

**Analysis of TGR-1202**

**Study Design**
- **Study 1202-101 (NCT07977766)**: an ongoing first-in-human, Phase I study of TGR-1202 in patients with relapsed/refractory hematologic malignancies
- **TGR-1202 is dosed orally once-daily (QD) in continuous 28 Day Cycles**
- **A 3+3 dose-escalation design was utilized evaluating sequentially higher doses of TGR-1202 after evaluating Cycle 1 dose-limiting toxicities (DLTs)**
- **Cohort 1 starting dose of 50 mg, with dose increments of 50 mg every 28 days up to 300 mg, followed by 50 mg increments thereafter**
- **Patients in previous cohorts are able to dose-escalate once a new dose-level has cleared safety evaluation. As such, all patients on-study are currently being treated at 800 mg QD or higher**

**Pharmacodynamics**
- **Data display representative blot of a CLL patient from Cohort 6 (800 mg QD).**
- **AKT expression level at baseline (pre-dose).**
- **1 hour post-dosing on Day 1, and pre-dose on Day 15 are shown, indicating marked reduction of AKT expression following treatment with TGR-1202**
- **Rapid suppression (within 1 hour) of pAKT was observed after single dose of TGR-1202 at the 400 mg dose level with sustained target inhibition exhibited pre-dose on Day 15**

**Pharmacokinetics**
- **TGR-1202 is rapidly absorbed (C_tmax Time of 2 hrs)**
- **Harmonic mean Cmax on Cycle 1, Day 15 of 85 (89-93) ng/ml**
- **Estimated exposure, AUC of 50 hrs at steady state**
- **A linear relationship (Spearman’s) exists between dose and both AUC (r=0.82) and Cmax (r=0.83)**
- **Steady state levels are reached by Day 15**
- **The average accumulation ratio between Cycle 1, Cycle 2 (AUC and Cmax)**

**Efficacy Results**
- **Of the 4 remaining CLL patients, all had reduction on TGR-1202 therapy**
- **1 nodal PI: 50% reduction in CT scan & B, one unconfirmed—baseline measurement for single target lesion was obtained outside of screening window**
- **1 nodal PI by physical examination exhibited ≥ 50% decrease**
- **CT confirmation not obtained**
- **1 nodal reduction to <10% on CT scan at Week 8**

**Conclusions**
- **TGR-1202 is a well-tolerated PI3K-δ inhibitor with promising signs of clinical activity in the higher dosing cohorts in patients with advanced hematologic malignancies**
- **TGR-1202 displays linear kinetics with levels consistently above the PI3K-δ IC50 by Day 8 at the 800 mg dose level and above. Extended half-life supports once-daily (QD) oral administration of TGR-1202**
- **TGR-1202 safely moved into multiple diseases with dose-escalation completed to date, with no dose-related trends observed, and notably no hematopoietic toxicity and no cardiac effects at current dose levels**
- **Clinical activity observed at higher doses (400 mg and greater), notable responses observed at 800 mg QD level with patients demonstrating a reduction in expression cohort expanded to 800 mg to evaluate additional patients. No MTD has been achieved, and dose escalation continues at the 1200 mg QD dose level**

**Disclosures**
- F. Sportelli, M. Miskin: Employment & Stock Ownership in TG Therapeutics, Inc., New York, NY
- P. Sportelli: Employment & Stock Ownership in TG Therapeutics, Inc., New York, NY
- M. Miskin: Employment & Stock Ownership in TG Therapeutics, Inc., New York, NY
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