Abstract # 4373

A Phase I Dose Escalation Study Of TGR-1202, a Novel PI3K-δ Inhibitor For Patients With Relapsed Or Refractory Hematologic Malignancies

TG Therapeutics

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Introduction

- PI3K-δ is highly expressed in cells of hematopoietic origin and is often upregulated in lymphoid malignancies.
- TGR-1202 is a novel, next generation PI3K-δ inhibitor shown to inhibit Akt phosphorylation and induce apoptosis in lymphoma and leukemia cell lines, displaying activity in numerous pre-clinical models with potentially superior pharmacokinetic (PK) properties to other PI3K-δ inhibitors in development, including an extended half-life observed in pre-clinical animal studies.

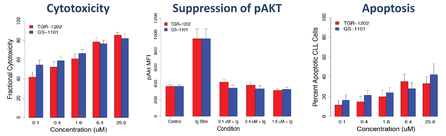
Selectivity of TGR-1202

Fold-selectivity				
Isoform	PI3Kα	PI3Kβ	PI3Kγ	PI3Kδ
TGR-1202	>10000	>50	>48	1
[1]Idelalisib	>300	>200	>40	1
[2]IPI-145	>640	>34	>11	1

[1]Flinn et al. 2009, [2]Porter et al. 2012

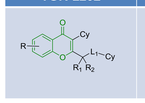
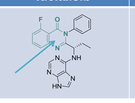
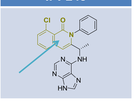
In-Vitro Activity in CLL

- TGR-1202 was compared to idelalisib, a PI3K-δ inhibitor which has displayed clinical activity in a variety of hematologic malignancies, in a blinded *in-vitro* study conducted at Duke University (Friedman et al, ASH 2012) on patient CLL lymphocytes (n=7).
- Data demonstrated equal efficacy of the TGR-1202 and idelalisib with respect to cytotoxicity, apoptosis, and suppression of pAKT.



Structural Design of TGR-1202

- Notably, hepatotoxicity (elevations in ALT/AST) have been reported with other PI3K-δ inhibitors, often necessitating dose delays and/or reductions.
- The chemical structure of TGR-1202 was designed specifically to avoid heterocylic nitrogen moieties in the backbone of the molecule, known to interact with hepatic enzymes, in an effort to mitigate the observed class effect of hepatotoxicity.

TGR-1202	Idelalisib	IPI-145
		

Study Design

- Study TGR-1202-101 (NCT01767766) is an ongoing first-in-human, Phase I study of TGR-1202 in patients with relapsed or 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 escalation in 100% increments up to 800 mg, followed by up to 50% increments thereafter
- *Intra-patient dose escalation allowed for patients in previous cohorts following establishment of safety at higher doses*

Dose Escalation Schema

Cohort 1 50 mg → Cohort 2 100 mg → Cohort 3 200 mg → Cohort 4 400 mg → Cohort 5 800 mg → Cohort 6 1200 mg → Cohort 7 1800 mg *OPEN* → Cohort 8 TBD

Study Objectives

Primary

- To determine the Safety, 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)

Exploratory

- To assess correlative biomarkers including cytokines, T-cell subsets, and molecular aberrations

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 on prior therapies)
- Adequate organ system function as measured by: ANC ≥ 750 cells/μL; platelets ≥ 50 K/μL
- ECOG performance status ≤ 2
- Patients with prior therapy with any drug that specifically inhibits PI3K and/or mTOR are excluded

Demographics

Evaluable for Safety (n)	22
Evaluable for Efficacy (n)	19
Median Age, years (range)	62 *(28 – 82)*
Male/Female	18/4
Histology	10 CLL, 5 iNHL, 3 HL, 1 SLL, 1 MCL, 1 HCL, 1 DLBCL
ECOG 0/1/2	11/12/0
Prior Therapies, median (range)	2.5 *(1 – 13)*
Patients with ≥ 3 Prior Therapies (%)	11 (50%)
Patients with prior Rituximab-Chemo	100%

iNHL – indolent non-Hodgkin's Lymphoma; HL – Hodgkin's Lymphoma; MCL – Mantle Cell Lymphoma; HCL – Hairy Cell Leukemia; DLBCL – Diffuse Large B-Cell Lymphoma

Disposition

Disposition, n (%)	N = 22
Continuing on Study	12 (55%)
Range on Study	1 - 9+ Months
Discontinued	10 (45%)
Disease Progression	9 (41%)
Adverse Event	0
Death	1

- MTD has not been reached through 1200 mg QD
- Dose escalation is ongoing, currently enrolling patients at 1800 mg QD
- One death occurred on study in a CLL patient in Cohort 5 (diagnosis of Legionnaires' disease, deemed unrelated to TGR-1202 therapy). Patient had marked reduction in femoral chain and inguinal lymphadenopathy and nodal response (>90% reduction by physical exam), but expired prior to first scheduled CT scan

Safety

Definite, Probable, or Possibly Related AEs (N=22)

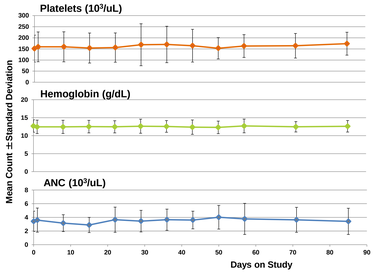
Adverse Event, n	Grade 1 & 2 (>5% of patients)	Grade 3 (all events)
Diarrhea	4	-
Neutropenia	-	1
Rash	-	1
Thrombocytopenia	-	1

- One DLT observed at 800 mg QD: Gr. 3 Rash deemed possibly related to TGR-1202. Rash resolved upon temporarily holding study drug and concomitant medications, and did not reappear upon re-challenge at the same TGR-1202 dose level.
- Of the 22 evaluable patients, one (CLL patient in Cohort 3 – 200 mg QD) was dose reduced due to an event of Gr. 3 neutropenia
- Notably, no hepatotoxicity and no Gr. ≥ 3 GI related toxicity observed

Gr. 3 & 4 Reported AEs – Any Causality (N=22)

Adverse Event, n	Grade 3	Grade 4
Dyspnea	1	-
Neutropenia	2	-
Rash	2	-
Thrombocytopenia	1	-
Lung Infection	1	-

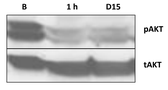
Effect of TGR-1202 on Peripheral Blood Counts (N=18)



- TGR-1202 did not negatively impact patient platelet, hemoglobin, or neutrophil counts

Pharmacodynamics

TGR-1202 Causes Rapid Inhibition of pAKT



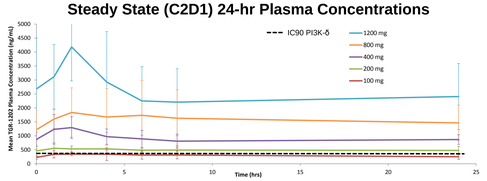
B: C1D1 pre-dose
1 h: C1D1, 1h post-dose
D15: pre-dose on C1D15

Isolated Peripheral Blood Mononuclear Cells (PBMC) were lysed in buffer containing protease and phosphatase inhibitors. Lysate was loaded on gel and probed with phophorylated AKT (pAKT) antibodies. Blot stripped and re-probed with total AKT (tAKT) antibodies.

- Data displays representative blot of a CLL patient from Cohort 4 (400 mg QD). pAKT expression level at baseline (pre-dose), 1 hour post dosing on Day 1, and pre-dose on Day 15 are shown, indicating marked reduction in pAKT 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

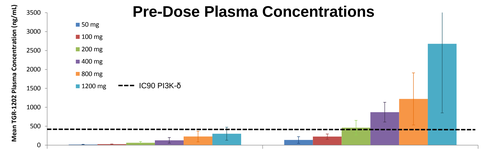
Pharmacokinetics

Steady State (C2D1) 24-hr Plasma Concentrations



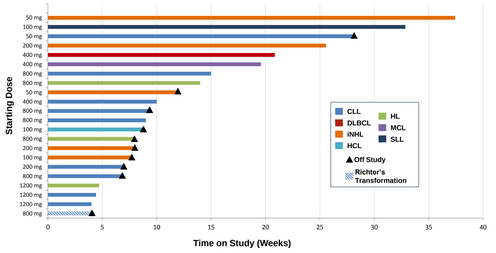
- TGR-1202 is rapidly absorbed (C_1D_1 Tmax of 2 hrs)
- Harmonic mean $t_{½}$ on Cycle 1, Day 1 of 15 (±9.36) hrs
- Estimated effective $t_{½}$ of 50 hrs at steady state
- A linear relationship (Spearman's) exists between dose and both AUC (R = 0.92) and Cmax (R = 0.83)
- Steady-state levels are reached by Day 15
- The average accumulation Cmin ratio between C_1t_{24hr} & C_2t_{0hr} is 8 (±2.65)

Pre-Dose Plasma Concentrations



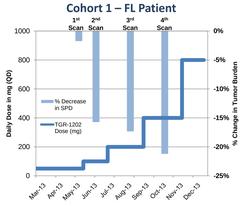
*IC90 value determined from in-vitro whole blood assay

Time on Study

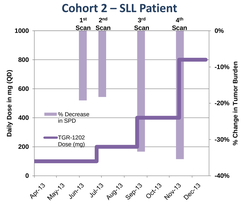


- Patients in previous cohorts are allowed to dose-escalate once a new dose level has cleared safety evaluation. As such, all patients on study are currently being treated at 800 mg QD or higher.
- Below are two examples (FL pt with starting dose of 50 mg and SLL pt with starting dose of 100 mg) displaying decreasing tumor burden correlating with higher TGR-1202 dose levels and extended duration of dosing

Cohort 1 – FL Patient

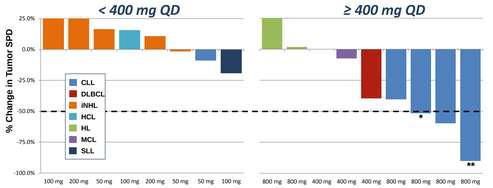


Cohort 2 – SLL Patient



Efficacy Results

% Change in Tumor Size At First Response Assessment

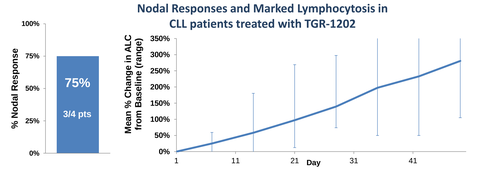


* Unconfirmed, single target lesion obtained outside screening window
** Assessment by Physical Exam only, not confirmed by CT

- Two patients progressed and were removed from study prior to their first efficacy assessment
- Three patients enrolled into Cohort 6 at 1200 mg were too early for response evaluation as of data presentation

CLL Patients at 800 mg

- 5 patients with CLL were enrolled at the 800 mg dose level, of which one patient was removed from study within one Cycle of TGR-1202 due to a Richter's Transformation (determined by investigators to have occurred prior to patient enrollment)



- Of the 4 remaining CLL patients, all had nodal reductions on TGR-1202 therapy
  - 2 nodal PR (> 50% LN reduction) by CT scan at Week 8
    - one unconfirmed—baseline measurement for single target lesion was obtained outside of screening window
  - 1 nodal PR by physical exam (patient exhibited >90% LN decrease); CT confirmation not obtained
  - 1 nodal reduction of 41% by 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 IC90 by Day 8 at the 800mg dose level and above. Extended half life supports once-daily (QD) oral administration of TGR-1202
- TGR-1202 related adverse events have been minimal to date, with no dose-related trends observed, and notably no hepatotoxicity and no Gr. ≥ 3 GI toxicity observed to date
- Clinical activity observed at higher dose levels (400 mg and greater), nodal responses observed at the 800 mg dose level in patients with CLL; expansion cohort opened at 800 mg to evaluate additional patients
- No MTD has been achieved, and dose escalation continues at the 1800 mg QD dose level

Disclosures: P. Sportelli, H. Miskin: Employment & Stock Ownership in TG Therapeutics. S. Vakkalanka: Employment and Stock Ownership in Rhizen Pharmaceuticals. No relevant relationships to disclose for all other authors.