Abstract # 1984

TGR-1202, a Novel Once Daily PI3Kδ Inhibitor, Demonstrates Clinical Activity with a Favorable Safety Profile, Lacking Hepatotoxicity, in Patients with Chronic Lymphocytic Leukemia and B-Cell Lymphoma

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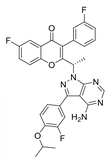
Background

- PI3Kδ is highly expressed in cells of hematopoietic origin and is often upregulated in lymphoid malignancies
- TGR-1202 is a novel, next generation PI3Kδ inhibitor, with a unique structure which contributes to:
  - An extended half-life and accumulation that enables once-daily dosing
  - Differentiated safety profile from other PI3Kδ inhibitors in development, notably absent of hepatic toxicity to date



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

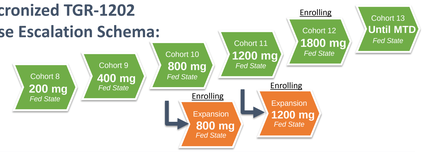
[1]Flinn et al. 2009, [2]Porter et al. 2012

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 dosed orally once-daily (QD) in continuous 28 Day Cycles
- Dose-limiting toxicities (DLTs) assessed in Cycle 1 prior to escalation
- *Intra-patient dose escalation allowed for patients in previous cohorts following establishment of safety at higher doses*

3+3 Dose Escalation Schema:

Micronized TGR-1202 Dose Escalation Schema:



Study Objectives

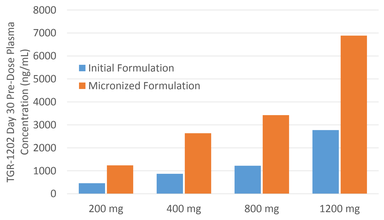
- **Primary:** To determine the Safety, Pharmacokinetics (PK), and Maximum Tolerated Dose (MTD) of TGR-1202
- **Secondary:** To determine the Pharmacodynamics of TGR-1202 and assess Efficacy (overall response rate and duration of response)

Key Eligibility Criteria

- Histologically confirmed B-cell non-Hodgkin lymphoma (NHL), CLL/small lymphocytic lymphoma (SLL), Hodgkin's lymphoma (HL), and select other B-cell lymphoproliferative disorders
- Relapsed after, or refractory to, at least 1 prior treatment regimen with no limit on prior therapies
- ECOG performance status ≤ 2
- Adequate organ system function: ANC ≥ 750/µL; platelets ≥ 50 K/µL
- Patients with prior therapy with any drug that specifically inhibits PI3K and/or mTOR are excluded

Pharmacokinetics

Initial Formulation (Fasting) vs. Micronized Formulation (Fed State)



Results

Demographics

Evaluable for Safety (n)	55	
Evaluable for Efficacy (n)	43	
Median Age, years (range)	62 (22 – 82)	
Male/Female	40/15	
Histology	18 CLL	2 MCL
	15 FL	2 MZL
	9 HL	1 HCL
	7 DLBCL	1 WM
ECOG 0/1/2	19/35/1	
Prior Therapies, median (range)	3 (1 – 14)	
Patients with ≥ 3 Prior Therapies (%)	28 (51%)	
Patients with prior Rituximab-Chemo	44 (80%)	

Efficacy subset includes all patients treated with 800 mg of initial formulation or higher, and any micronized dose level. Not evaluable: 8 patients treated at less than 800 mg initial formulation, 1 Too Early To Evaluate (1200 mg micronized Fed), 2 Non-Compliant (both at 1800 mg Fasted), 1 Failed Inclusion/Exclusion (Richter's Transformation prior to entry)

Safety

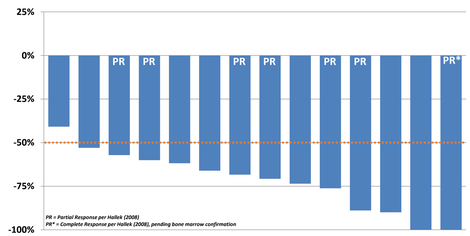
Adverse Events in TGR-1202 Treated Patients

All Events (All Causality) in >10% (n=55)	All Grades		Grade 3/4	
	Events	%	Events	%
Diarrhea	17	31%	1	2%
Nausea	16	29%	-	-
Fatigue	14	25%	-	-
Cough	13	24%	-	-
Anorexia	11	20%	-	-
Headache	10	18%	-	-
Vomiting	10	18%	-	-
Rash	9	16%	2	4%
Neutropenia	8	15%	7	13%
Constipation	6	11%	-	-
Dyspnea	6	11%	2	4%
Thrombocytopenia	6	11%	4	7%

- No drug related hepatotoxicity observed
- No events of pneumonitis reported to date
- Diarrhea events have been early and transient, with no events of colitis reported to date (median time on study 6+ months)
- Only 2 patients (< 4%) have come off study due to an adverse event (one unrelated, one possibly related)

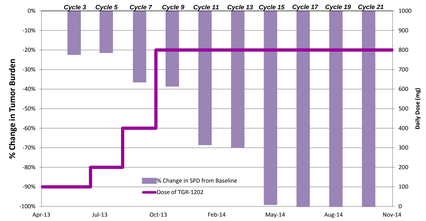
Efficacy in Chronic Lymphocytic Leukemia

Best Percent Change from Baseline in Nodal Size
Evaluable CLL Patients Treated at ≥800 mg of Initial Formulation or any Dose of Micronized Formulation



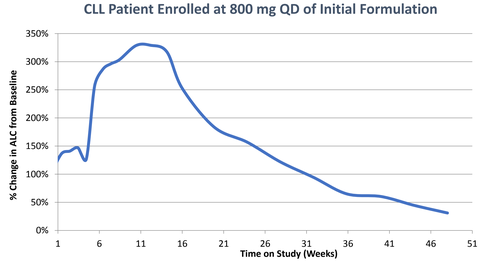
- 93% of CLL patients (13/14) treated at 800 mg or higher achieved a nodal PR (median nodal reduction of 70%)
- Nodal reductions have been shown to improve with time on TGR-1202

Evolving Responses with TGR-1202 in CLL
CLL Patient Enrolled at 100 mg QD of Initial Formulation



- Patients in previous cohorts are allowed to dose-escalate once a new dose level has cleared safety evaluation
- Strong threshold effect seen at 800 mg QD of initial formulation
- Decreasing lymph node SPD correlates with higher TGR-1202 dose levels and extended duration of dosing

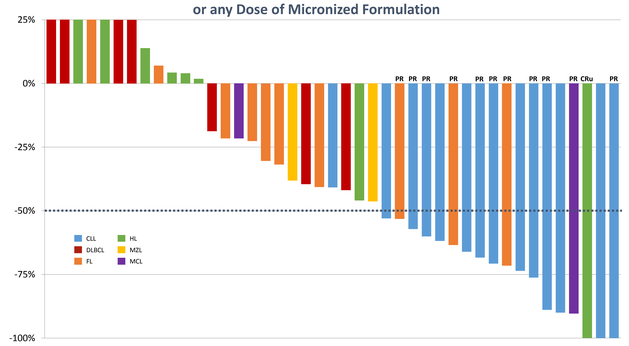
Percent Change from Baseline in Absolute Lymphocyte Count
CLL Patient Enrolled at 800 mg QD of Initial Formulation



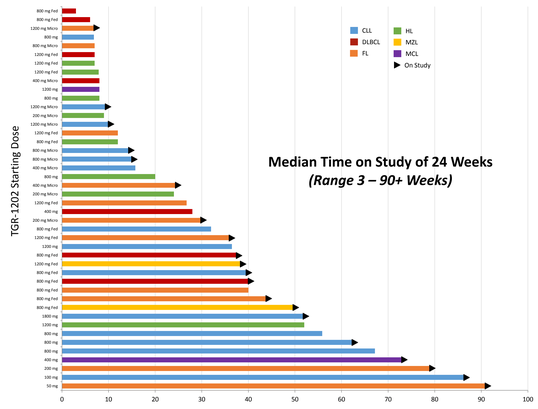
- Nodal reductions were generally accompanied by marked lymphocytosis
- Median time to resolution of lymphocytosis (return to baseline) was confounded by Intra-patient dose escalation in most patients but ranged from ~60 days to 420+ days

Overall Efficacy

Best Percent Change from Baseline in Nodal Size
Evaluable Patients Treated at ≥800 mg of Initial Formulation or any Dose of Micronized Formulation

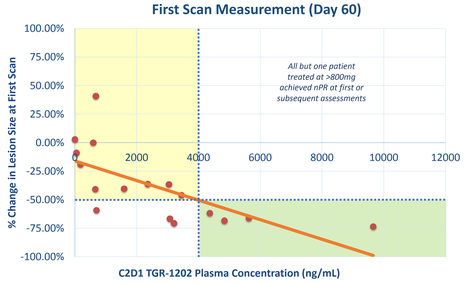


Current Status of Evaluable Patients

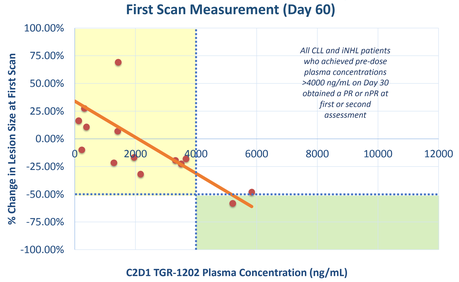


Dose & Exposure Related Response

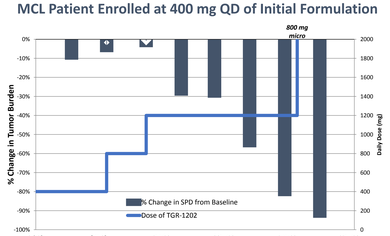
Exposure Response Relationship in CLL
Pre-Dose Plasma Concentration (Day 30) vs. First Scan Measurement (Day 60)



Exposure Response Relationship in Indolent Non-Hodgkin's Lymphoma
Pre-Dose Plasma Concentration (Day 30) vs. First Scan Measurement (Day 60)



Dose Response Relationship in Non-Hodgkin's Lymphoma
MCL Patient Enrolled at 400 mg QD of Initial Formulation



Conclusions

- TGR-1202 is a once-daily PI3Kδ inhibitor with single agent activity observed in patients with a variety of relapsed/refractory hematologic malignancies
- Marked activity has been observed in patients with relapsed/refractory CLL, with a 93% nodal response rate at doses ≥ 800 mg of initial formulation or any dose of micronized formulation. Of these patients, 50% (7/14) achieved a partial response per iwCLL (Hallek 2008) criteria
- TGR-1202 has been well tolerated, with no drug related hepatic toxicity or colitis reported to date, with a median time on study over 6 months and some patients on daily TGR-1202 for 1.5+ years, demonstrating an adverse event profile which is differentiated from other PI3K-delta inhibitors and supports combination therapy
- An exposure response trend was noted in both CLL and NHL, with higher plasma TGR-1202 exposures correlating with increased nodal responses, with all CLL and NHL patients who achieved pre-dose plasma concentrations on Day 30 in excess of 4000 ng/mL obtaining a PR or nPR at first or second assessment
- No MTD has been achieved and dose escalation continues with the micronized formulation with enrollment now restricted in dose escalation to NHL, with CLL patients continuing to be enrolled in expansion cohorts
- Additional studies are ongoing evaluating TGR-1202 in combination with approved and novel agents, with Phase III studies in development

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