Clinical Activity and Safety Profile of TGR-1202, a Novel Once-Daily PI3Kδ Inhibitor, in Patients with CLL and B-Cell Lymphoma

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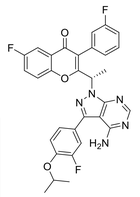
Background

- 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 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

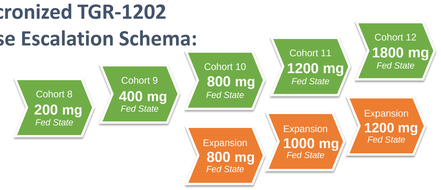
[1]Flinn et al. 2009, [2]Porter et al. 2012

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, Hodgkin's lymphoma (HL), and select other B-cell 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 in dose-escalation cohorts only

Results

Demographics

Evaluable for Safety (n)	81		
Evaluable for Efficacy† (n)	63		
Median Age, years (range)	65 (22 – 85)		
Male/Female	53/28		
Histology	21 CLL	6 MCL	
	22 FL	5 MZL	
	14 DLBCL	9 HL	
	2 WM	1 HCL	1 T-Cell
Median ECOG	1		
Prior Therapies, median (range)	3 (1 – 14)		
Patients with ≥ 3 Prior Therapies (%)	46 (57%)		
Patients Refractory to Prior Therapy (%)	40 (49%)		

† Patients treated with 800 mg of initial formulation or higher, and any micronized dose level of which the following were excluded: 4 were Too Early To Evaluate, 2 Non-Compliant (both at 1800 mg), 3 removed per investigator discretion, and 1 Failed Inclusion/Exclusion (baseline Richter's Transformation)

Safety

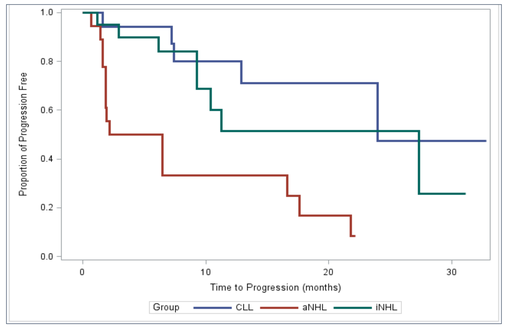
Adverse Events in TGR-1202 Treated Patients

All Events in >10% of Pts (N=81)				
AE	All Grades		Gr. 3/4	
	N	%	N	%
Nausea	34	42%	1	1%
Diarrhea	33	41%	2	2%
Fatigue	25	31%	3	4%
Rash	22	27%	4	5%
Headaches	20	25%	1	1%
Cough	19	23%	0	0%
Vomiting	18	22%	0	0%
Constipation	12	15%	1	1%
Decreased Appetite	12	15%	0	0%
Hypokalemia	12	15%	4	5%
Anemia	11	14%	7	9%
Dizziness	11	14%	0	0%
Dyspnea	11	14%	4	5%
Pyrexia	10	12%	0	0%
Abdominal Pain	9	11%	0	0%
Arthralgia	9	11%	0	0%
Insomnia	9	11%	0	0%

- 38 patients have been on study over 6 cycles, and 22 patients have been on study over 12 cycles
- TGR-1202 has been well-tolerated, with limited Gr. 3/4 events and no significant time dependent trends in AEs observed
- Grade 3/4 AST/ALT increase was 2% (4% all grades)
- 6 patients (7%) have come off study due to an adverse event
- 4 patients (5%) had Grade 3 pneumonia, 2 of which were considered as possibly related to TGR-1202, none resulted in discontinuation from study
- Of the 81 pts treated, no events of colitis have been observed to date

Progression-Free Survival

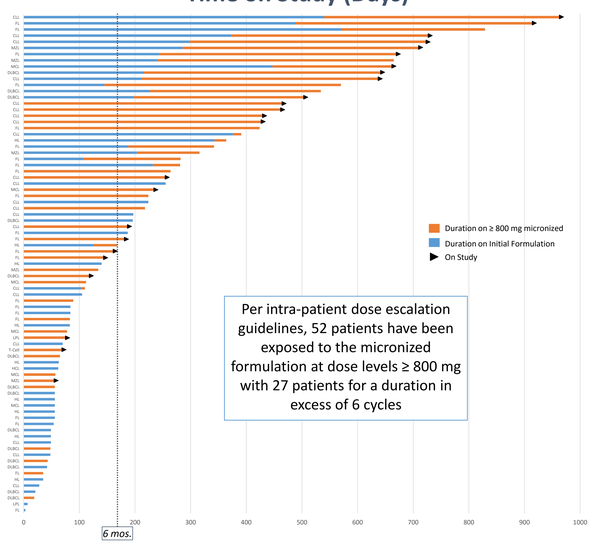
Kaplan-Meier Plot of PFS



- Median PFS:
  - CLL: 23.98 months (95% CI: 7.4, NR)
  - iNHL (FL & MZL): 27.3 months (95% CI: 9.28, NR)
  - aNHL (DLBCL & MCL): 4.33 months (95% CI: 1.88, 16.6)

Duration of Exposure

Time on Study (Days)

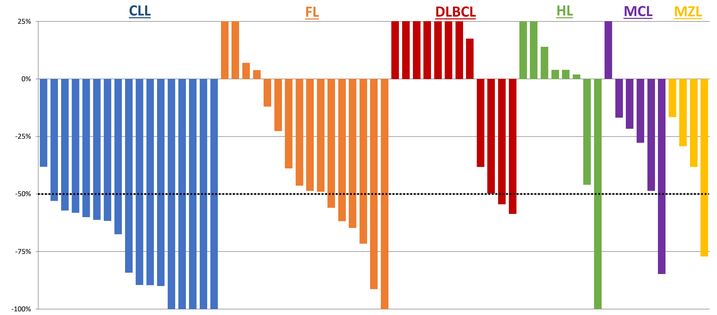


Per intra-patient dose escalation guidelines, 52 patients have been exposed to the micronized formulation at dose levels ≥ 800 mg with 27 patients for a duration in excess of 6 cycles

- Longest patient has been on study for over 34 cycles (2.5+ years)
- 27% of patients have been on study for over 12 cycles

Overall Efficacy

Best Percent Change from Baseline in Disease Burden
Patients Evaluable for Efficacy (n=63)



- 94% of CLL patients (16/17) achieved a nodal PR, remaining patients still on study pending further evaluation
- 59% of CLL patients (10/17) achieved a response per iwCLL (Hallek 2008) criteria
- Clinical activity observed in follicular lymphoma, with 75% of patients (12/16) demonstrating tumor reductions, and a preliminary 38% ORR (6/16), with an additional 2 patients achieving 49% reductions in tumor burden
- Similar to activity seen in CLL, tumor reductions in indolent lymphoma have shown improvement over time

Conclusions

- TGR-1202 is a once-daily PI3Kδ inhibitor with single agent activity observed in patients with a variety of relapsed/refractory hematologic malignancies
- Long term safety has been well characterized with many patients on daily TGR-1202 for over 12 cycles, upwards of 34+ cycles (2.5+ years)
  - To date, no events of colitis have been observed
  - No long term trends in toxicity have been observed
- Adverse event profile to date appears differentiated from other PI3Kδ inhibitors, especially with respect to hepatic-toxicity and colitis
- Marked single-agent activity has been observed at doses ≥ 800 mg of initial formulation or any dose of micronized formulation, in patients with:
  - Relapsed refractory CLL, with a 94% nodal response rate and an ORR of 59% based on iwCLL (Hallek 2008) criteria; and
  - Relapsed refractory FL, including a preliminary ORR of 38% with median tumor reductions of ~48%, and many patients on study pending further efficacy assessments
- Safety and activity profile supports combination therapy with other novel targeted agents (including ublituximab, ASH Abstract #1538)
- TGR-1202 is now in Phase 3 for patients with CLL (UNITY-CLL Study)

COI: **Flinn:** *Celgene Corporation*. **Fenske:** *Millennium/Takeda*; *Celgene*; *Seattle Genetics*; *Pharmacyclics*. **Deng:** *TG Therapeutics, Inc.*; *Seattle Genetics*. **Kuhn:** *TG Therapeutics, Inc.*; *Otsuka American Pharmaceutical*; *Azaya Therapeutics*. **Miskin & Sportelli:** *TG Therapeutics, Inc.:* Employment , Equity. **Vakkalanka:** *Rhizen Pharmaceuticals SA:* Employment , Equity. Authors not listed had no relevant conflicts of interest to disclose

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