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

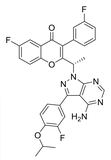
Howard A. Burris III, MD[1,2], Manish R. Patel, MD[1,3], Timothy S. Fenske, MD[4], Owen A. O'Connor, MD, PhD[5], Changchun Deng, MD, PhD[5], Danielle M. Brander, MD[6], Martin Gutierrez, MD[7], Suzanne Jones, PharmD[1], John Kuhn, PharmD[8], Hari P. Miskin, MS[9], Peter Sportelli[9], Swaroop Vakkalanka, PhD[10] and Ian Flinn[1,11]

[1]Sarah Cannon Research Institute, Nashville, TN; [2]Tennessee Oncology, PPLC, Nashville, TN; [3]Florida Cancer Specialists, Sarasota, FL; [4]Medical College of Wisconsin, Milwaukee, WI; [5]Columbia University Medical Center, New York, NY; [6]Duke University Medical Center, Durham, NC; [7]John Theurer Cancer Center at Hackensack University Medical Center, Hackensack, NJ; [8]University of Texas Health Science Center at San Antonio, San Antonio, TX; [9]TG Therapeutics, Inc., New York, NY; [10]Rhizen Pharmaceuticals SA, La Chaux-de-Fonds, Switzerland; [11]Tennessee Oncology, PLLC, Nashville, TN

TG Therapeutics

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

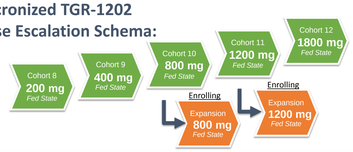
[1]Flinn et al. 2009, [2]Porter et al. 2012

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/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 in dose-escalation cohorts only

Results

Demographics

Evaluable for Safety (n)	66	
Evaluable for Efficacy† (n)	51	
Median Age, years (range)	66 (22 – 85)	
Male/Female	46/20	
Histology	20 CLL	5 MCL
	17 FL	3 MZL
	10 DLBCL	1 HCL
	9 HL	1 WM
ECOG 0/1/2	22/43/1	
Prior Therapies, median (range)	3 (1 – 14)	
Patients with ≥ 3 Prior Therapies (%)	36 (55%)	
Patients Refractory to Prior Therapy	34 (52%)	

† Patient's evaluable for efficacy included only 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 Fasted), 1 removed per investigator discretion, and 1 Failed Inclusion/Exclusion (Richter's Transformation prior to entry)

Safety

Adverse Events in TGR-1202 Treated Patients

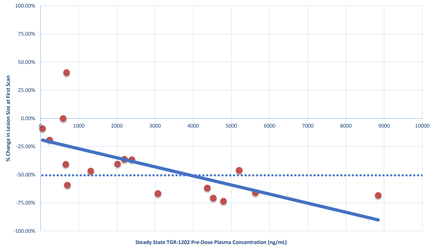
All Events in >10% of Pts (N=66)				
AE	All Grades		Gr. 3/4	
	N	%	N	%
Nausea	27	41%	0	0%
Diarrhea	21	32%	1	2%
Fatigue	21	32%	2	3%
Headache	15	23%	0	0%
Vomiting	15	23%	0	0%
Cough	14	21%	0	0%
Decreased Appetite	11	17%	0	0%
Rash	11	17%	3	5%
Constipation	9	14%	1	2%
Hypokalemia	9	14%	3	5%
Anemia	8	12%	5	8%
Dizziness	8	12%	0	0%
Dyspnea	8	12%	3	5%
Neutropenia	8	12%	7	11%
Pyrexia	8	12%	0	0%
Abdominal Pain	7	11%	0	0%

- TGR-1202 has been well-tolerated, with limited Gr. 3/4 events and no significant dose or time dependent trends in AEs observed with 31 patients on study 6+ months
- 3 patients (< 5%) have come off study due to an adverse event, none of which for hepatic toxicity, colitis, or pneumonitis
- GI related adverse events have been primarily mild and transient

Exposure-Response Relationship

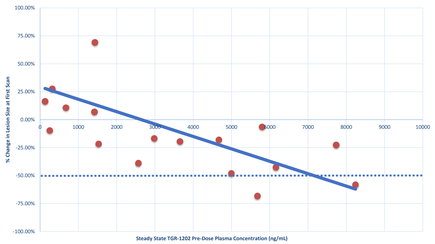
Exposure Response Relationship in CLL

Steady State Plasma Concentration vs. Change in Nodal Size at First Scan



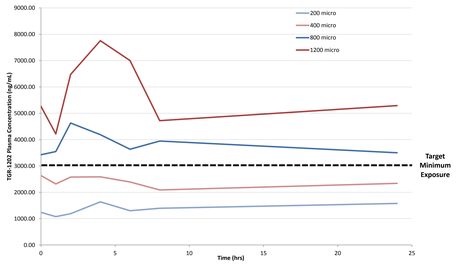
Exposure Response Relationship in iNHL

Steady State Plasma Concentration vs. Change in Nodal Size at First Scan



Pharmacokinetics

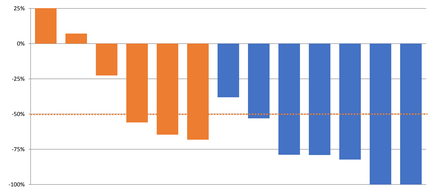
TGR-1202 Steady State (Cycle 2, Day 1) Pharmacokinetics



Efficacy with "Higher Dose" TGR-1202

Best Percent Change from Baseline in Disease Burden

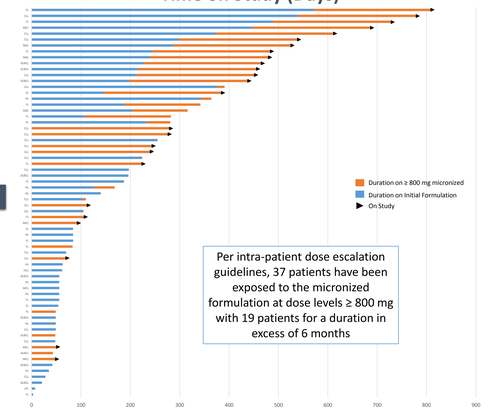
Evaluable CLL & FL Patients Treated at "Higher Doses"



- "Higher Doses" of TGR-1202 (1200 mg initial formulation, or ≥ 600 mg micronized) demonstrated rapid and profound responses
- 86% of CLL patients (6/7) treated at Higher Doses of TGR-1202 achieved a nodal PR (median nodal reduction of ~80%), with remaining patient still on study pending second evaluation
- 50% of FL patients (3/6) treated at Higher Doses of TGR-1202 achieved a PR

Duration of Exposure

Time on Study (Days)



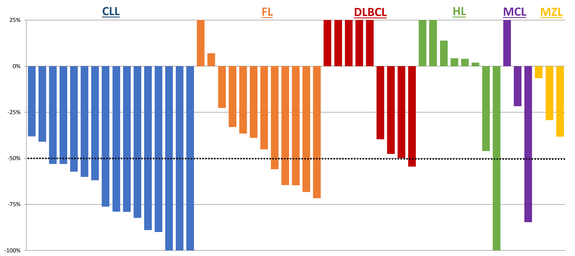
Per intra-patient dose escalation guidelines, 37 patients have been exposed to the micronized formulation at dose levels ≥ 800 mg with 19 patients for a duration in excess of 6 months

- 25 of 37 patients exposed to ≥ 800 mg micronized currently remain on study
  - Median PFS of 9.5+ months amongst these patients

Overall Efficacy

Best Percent Change from Baseline in Disease Burden

Patients Evaluable for Efficacy (N=51)



- 88% of CLL patients (14/16) achieved a nodal PR, remaining 2 patients still on study pending further evaluation
- 63% of CLL patients (10/16) achieved a response per iwCLL (Hallek 2008) criteria
- Clinical activity observed in follicular lymphoma, with 83% of patients (10/12) demonstrating tumor reductions, and a preliminary 42% ORR (5/12)
- Majority of FL patients remain on study awaiting additional efficacy assessments
- 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.
- 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 BCR 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 upwards of 2+ years, demonstrating an adverse event profile which is differentiated from other PI3K-delta inhibitors, especially with respect to hepatic-toxicity and colitis to date.
- 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 88% nodal response rate and an ORR of 63% based on iwCLL (Hallek 2008) criteria; and
  - Relapsed refractory FL, including a preliminary ORR of 42% with the majority 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 ublituximab, ASCO Abstract #8548).
- Expansion cohorts open and enrolling at the 800 mg and 1200 mg dose levels of the micronized formulation with Phase III studies in development and expected to be initiated in 2015

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