TGR-1202, a Novel Once Daily PI3Kδ Inhibitor, Demonstrates Clinical Activity with a Favorable & Differentiated Safety Profile as a Single Agent and in Combination with a Novel Glycoengineered anti-CD20 mAb, Ublituximab, in Patients with Rel/Ref CLL

Susan O'Brien, MD,1 Howard A. Burtiss III, MD,2 Manish Patel, MD,1 Jan Burger, MD, PhD,2 Timothy Fenske, MD,2 Owen A. O'Connor MD, PhD,2 Danielle Brande, MD,3 Marshall T. Schreeder, MD,1 Hari P. Miskin, MS,3 Peter Sportelli,2 Ian Flinn, MD, PhD2

1University of California Irvine, Irvine, CA; 2Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN; 3Sarah Cannon Research Institute/Florida Cancer Specialists, Sarasota FL; 4MD Anderson Cancer Center, Houston, TX; 5Medical College of Wisconsin, Milwaukee, Wi; 6Columbia University Medical Center, New York, NY; 7Duke University Medical Center, Durham, NC; 8Clearview Cancer Institute, Huntsville, AL; 9TG Therapeutics, Inc., New York, NY

TGR-1202

- PI3Kδ is highly expressed in cells of hematopoietic origin and is often upregulated in lymphoid malignancies
- 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 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
- Marked single agent activity for TGR-1202 has been demonstrated in CLL and indolent and aggressive NHL (ASCO/EHA/ICML 2015)

Ublituximab

- Ublituximab (TG-1101) is a novel, chimeric monoclonal antibody (mAb) targeting a unique epitope on the CD20 antigen, and glycoengineered to enhance affinity for all variants of FcyRIIA receptors, thereby demonstrating greater antibody-dependent cellular cytotoxicity (ADCC) activity than rituximab and ofatumumab
- Two Phase I trials of single agent ublituximab in patients with relapsed/refractory CLL reported response rates of 67% (ASCO 2014) and 45% (EHA 2013), with rapid and sustained lymphocyte depletion.

Study Designs

TGR-1202 Single Agent

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

TGR-1202 in Combination with Ublituximab

Study EUTX-TGR-103 (NCT02006485) is an ongoing Phase Ib/II trial evaluating the combination of ublituximab + TGR-1202 in patients with relapsed or refractory NHL and CLL.

Treatment Schedule:
- Efficacy is assessed Week 8, and every 12 weeks thereafter. After Month 12, all patients remain on TGR-1202 single agent

Results

TGR-1202 Single Agent

Demographics

- CLL Patients Evaluated for Safety (n): 66
- CLL Patients Evaluated for Efficacy (n): 21
- Median Age, years (range): 64 (46 - 78)
- Male/Female: 15/6
- ECOG 0/1/2: 6/15/0
- Prior Therapies, median (range): 2 (1 - 8)
- Pts with 3 or Prior Therapies (%): 29%

Efficacy (CLL n=16)

- 88% of CLL patients (14/16) achieved a partial response, with 2 patients still on study pending further evaluation
- 63% of CLL patients (10/16) achieved a response per IWCLL (Hallek 2008) criteria

Duration of Exposure

- Time on Study (Days)

Best Percent Change from Baseline in Nodal Size

TGR-1202 in Combination with Ublituximab

Demographics

- CLL/SLL Patients Evaluated for Safety (n): 55
- CLL/SLL Patients Evaluated for Efficacy (n): 13
- Median Age, years (range): 65 (35 - 80)
- Male/Female: 10/4
- ECOG 0/1/2: 2/12/0
- Prior Therapies, median (range): 2 (1 - 8)
- Pts with ≥ 3 Prior Therapies (%): 43%

Safety

- Related AE’s in ≥ 5% of Patients (n = 66)

Related AE’s in ≥ 5% of Patients (n = 55)

Adverse Event

All Grades Grade 3/4

N % N %

Diarrhea 20 30% 1 2%
Nausea 15 23% -
Fatigue 13 20% 2 3%
Vomiting 13 20% -
Decreased Appetite 7 11% -
Neuropenia 6 9% 5 8%
Dizziness 5 8% -
Oliguria 4 6% -
Headache 4 6% -
Flush 4 6% 1 2%

AE profile on all enrolled pts (including NHL)
- 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 in study for ≥ 6 months
- 3 patients (<5%) have come off study due to an adverse event: pulmonary infection, Legionnaire’s disease, and fatigue
- GI related adverse events have been primarily mild and transient

Conclusions

- TGR-1202 is a once-daily PI3Kδ inhibitor with a single agent activity observed in patients with a variety of relapsed/refractory hematologic malignancies, including CLL, and a differentiated safety profile from other PI3Kδ-inhibitors, especially with respect to hepatic-toxicity and colitis to date
- Safety and activity profile supports combination therapy with other novel targeted agents
- TGR-1202 in combination with ublituximab is well tolerated and highly active
- Amongst both studies, Grade 3/4 adverse events and discontinuations due to adverse events have been limited (<5%)
- Safety profile of the combination supports additional multi-drug combination regimens; triple therapy combinations adding novel agents to ublituximab and TGR-1202 are ongoing (including ibritinib: ASCO 2015 Abstract #8501) with additional triple therapy studies planned
- International Phase III studies for TGR-1202 both as a single agent and in combination with ublituximab are planned

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