Phase I/II triple therapy study of umbralisib and ublituximab ("U2") combined with checkpoint inhibition in patients with rel/ref CLL and Richter's transformation

Anthony R. Mato, MD,1 Jakub Svoboda, MD,2 Eline T. Luning Prak, MD, PhD,3 Stephen J. Schuster, MD,4 Patricia Y. Tsao, MD, PhD,5 Colleen Dorsey, BSN, RN,6 Lisa M Sarmasti, BSN RN,7 Pamela S. Becker, MD, PhD,8 Danielle M. Brander, MD,8 Mark Geyer MD,9 Jae Park MD,10 Isaac DeOliveira BS,11 Cara M. King, MPH,12 Beth Morrigan13 Jill Elwell5, Katlin Kennard, RN, BSN,14 Lindsey Roskel15 MD, Andrew D. Zeleznets MD,16 Michelle Purdom, PhD, RN,11 Dana Paskalis17 Peter Sportelli, BS,18 Har P Miskin, MSci,19 Michael S. Weiss20 and Mazayar Shadman, MD, MPH21

1CLL Program, Leukemia Service, Division of Hematologic Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY; 2Symphony Program, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA; 3University of Pennsylvania, Department of Pathology and Laboratory Medicine, Philadelphia PA; 4Fred Hutchinson Cancer Research Center, Seattle, WA; 5Duke University Medical Center, Durham, NC; 6TG Therapeutics, Inc., New York, NY

Study Design

- Phase I/II dose-escalation (3+3 design), multicenter study to assess the safety and efficacy of pembrolizumab in combination with umbralisib and ublituximab (U2) in pts with relapsed or refractory CLL and RT (NCT02535286)
- Correlatives: Peripheral blood and/or bone marrow samples were collected at screening, month 2 and month 6

Key Eligibility Criteria

- CLL or RT pts who have progressed on at least one prior therapy
- Mid-study amendment required CLL pts to be BTK refractory (progression on or within 6 mos of prior BTK and RT pts to be chemomunotherapy refractory or not eligible for high-dose chemotherapy
- No limit on # of prior therapy treatment regimens
- ANC > 750/μL, platelet count > 40,000/μL
- Prior exposure to PD-1 or PI3K inhibitor was not an exclusion

Results

Demographics

- Chronic Lymphocytic Leukemia
  - Male/Female
  - ECOG
  - Prior Therapy Regimens, median (range)
  - Prior BTK (inhibitor or antibody), n (%)
  - Refractory to prior BTK
  - Prior RT at time of study entry, n (%)
  - Median follow-up: 28.7 mos

Richter’s Transformation

- Available for efficacy, n
- ORR:
- 0.00
- 0.05
- 0.10
- 0.15
- 0.2
- 0.4
- 0.6
- 0.8
- 1.0
- Thousands/uL

Efficacy: CLL

- ORR: 85% (6/7)
- 80% of BTK refractory responders (4/5) achieved response after U2 induction, prior to addition of pembro

Efficacy: Richter’s Transformation

- 7/8 BTK Refractory

Conclusions

- Triplet combination of umbralisib + ublituximab ("U2") + pembrolizumab was well tolerated
- Immune mediated toxicities were not increased above what would be expected with either umbralisib or pembrolizumab alone
- Responses were durable in BTK refractory, high-risk pts, including two durable CRs in RT pts
- Data suggest that CLL pts who achieve less than CR with a checkpoint inhibitor-containing regimen can achieve durable remissions and that time-limited schedules should be explored
- Maintenance of T-reggs throughout therapy may explain limited autoimmune sequelae
- Enrollment is ongoing in both the CLL (BTK refractory only) and RT cohorts
- Protocol now amended to replace pembrol with novel anti-PD-L1, cosibelimab (TG-1501)

Background / Rationale

- Pre-clinical data supports a major role for the PD-1 and PD-L1/PD-L2 axis in mediating immune evasion in CLL, however, there is a disconnect between pre-existing preclinical data and clinical data with anti-PD1 monotherapy
- A key interation exists between PI3K signaling and immune checkpoint surveillance by which inhibition of PI3K decreases PD-L1 tumor expression, suggesting potential synergistic activity with PD-1 + PI3K blockade

Umbalisib

- Umbalisib (TGR-1202) is a next generation PI3Kδ inhibitor, with a unique structure and activity profile, including:
  - A differentiated safety profile from other PI3Kδ inhibitors;
  - Oral, once-daily (QD) dosing;
  - Inhibition of caspase-1 kinase-1 epsilon (CK-1ε), a protein which may inhibit regulatory T-cell function

Ublituximab

- Ublituximab is a novel, glycoengineered, chimeric monoclonal antibody targeting a unique epitope on the CD20 antigen, and demonstrating greater ADCC activity than rituximab and ofatumumab
- Ublituximab is currently in Phase 3 development in combination with umbralisib for patients with CLL and NHL

Ublituximab Binding Epitope

- Red: Amino acids contributing to ofatumumab binding
  - Yellow: Amino acids essential for rituximab, but not ofatumumab binding
- Purple: Core amino acids of umbralisib epitope

Safety and Disposition

- All Causality Adverse Events in 20% of Patients (n=11)
  - Grade 1
  - Grade 2
  - Grade 3
  - Grade 4/

Correlatives: T-reg population

- Circulating FoxP3+ CD4+ T cell levels do not change significantly in CLL study patients

-circulating Foxp3+ CD4+ T cells vs. time

- Foxp3 Column Analysis (CD3+CD4+Foxp3+ Lymphs, PB)

- Enrollment by Cohort:
  - Pembrol + U2
  - CLL
  - RT

- 1 DLT at 200 mg pembrol dose (transient elevated ALT - resolved); MTD not reached
- 2 Grade 3/4 elevations in 4 patients (20%)
- 2 Grade 3/4 elevations in 4 patients (20%)
- No Grade 3/4 diarrhea and no events of colitis observed
- No Grade 3/4 adverse autoimmune events
- No Grade 3/4 adverse events in 11 mos (23 mos for CLL cohort)
- No patients had their pembrol dose reduced while 3 patients had their umbralisib dose reduced (azithromycin, lansoprazole, omeprazole)