Phase 1/2 study of zilovertamab and ibrutinib in mantle cell lymphoma (MCL) or chronic lymphocytic leukemia (CLL).

Hun Ju Lee, Michael Y. Choi, Tanya Siddiqi, Joanna Meehan Rhodes, William G. Wierda, Iris Isufi, Joseph M. Tuscano, Nicole Lamanna, Suki Subbiah, Jean Louise Koff, Lori Ann Leslie, Alec Goldenberg, Gina G. Chung, Salim Yazji, Yao Wang, James Bradley Breitmeyer, Michael Wang, Catriona Jamieson, Thomas J. Kipps; The University of Texas MD Anderson Cancer Center, Department of Lymphoma/Myeloma, Houston, TX; Moores Cancer Center, University of California San Diego, La Jolla, CA; Department of Hematology and Hematopoietic Cell Transplantation, City of Hope National Medical Center, Duarte, CA; Karches Center for Oncology Research, The Feinstein Institute for Medical Research, Northwell Health, Manhasset, NY; MD Anderson Cancer Center, Houston, TX; Division of Hematology, Department of Internal Medicine, Yale School of Medicine, New Haven, CT; University of California, Davis, CA; Herbert Irving Comprehensive Cancer Center, Columbia University, New York, NY; LSU Health Science Center, New Orleans, LA; Winship Cancer Institute of Emory University, Atlanta, GA; Lymphoma Research Division, John Theurer Cancer Center, Hackensack, NJ; Manhattan Hem Onc Associates, New York, NY; The Christ Hospital, Lindner Center for Research and Education, Cincinnati, OH; Oncternal Therapeutics, Inc., San Diego, CA; Department of Lymphoma and Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Zilovertamab (Zilo) is a humanized monoclonal antibody that inhibits the tumor promoting activity of ROR1 and has demonstrated additive/synergistic activity with many anti-cancer agents, including ibrutinib (Ibr). Methods: Patients (Pts) with relapsed or refractory (RR) MCL or treatment-naïve (TN) or RR CLL were enrolled. In Part 1 (Dose Escalation), multiple doses were examined. Zilo 600 mg IV starting q2wks x3 then q4wks + Ibr qD was selected as the recommended dosing regimen for use in Part 2 (Expansion) and Part 3 (CLL only, Zilo+Ibr vs. Ibr alone). Results: As of 18Jan2022 data cutoff, 26 evaluable RR MCL pts, including pts who received prior Ibr (5) or auto-SCT (7), and 34 evaluable CLL pts (12 TN and 22 RR) were enrolled into Parts 1&2. In Part 3, 22 evaluable pts were randomized (2:1) to receive either Zilo+Ibr (15) or Ibr (7). Safety: Treatment-emergent adverse events (TEAEs) (≥30%, N = 84), regardless of relationship, included fatigue (41.7%), contusion (39.3%), and diarrhea (38.1%). Most common (≥5%) Grade ≥3 TEAEs included hypertension (10.7%), pneumonia (7.1%), atrial fibrillation, fatigue, and neutropenia (all 6.0%). Grade ≥3 neutrophil decrease observed in 9.4% or 17.6%, platelet decrease in 12.5% or 2.9%, or hemoglobin decrease in 9.4% or 0% of pts with MCL or CLL, respectively in Parts 1&2. Investigators scored TEAEs as due to Ibr in 78.1% or 85.3%, or to Zilo in 15.6% or 23.5% of pts with MCL or CLL, respectively. Efficacy (MCL): Objective response rate (ORR) was 80.8% (34.6% CR, 46.2% PR). ORR for pts with prior Ibr was 80% (2CR, 2PR) and median duration of response (mDOR) was 13.7 months (M) (95%CI: 11.93, NE). ORR was 100% in pts who had prior SCT +/- CAR-T (5CR, 2PR), and mDOR was 34.1 M (95% CI 13.84, NE). Overall median PFS (mPFS) was 35.9 M (95% CI: 17.3, NE) at median follow-up of 15.0 M. For MCL pts with TP53 aberrancy (6), Ki67 > 30% (13), ≥ 3 prior lines of therapies (4), blastoid histology (3), bulky disease ≥5 cm (4), intermediate MiPib (6), or high MiPib (11), the mPFS (in M) was 17.3 (95% CI: 2.85, NE), Not Reached (NR) (95% CI: 2.85, NE), 35.9 (95% CI: 16.52, NE), NR (min 9.18, max 27.87), 36.6 (95% CI: 0.03, NE), 35.8 (min 9.30, max 35.9) or 16.5 (95% CI: 2.72, NE). Efficacy (CLL): In Parts 1&2 ORR was 91.2% (8.8% CR, 82.3% PR/PR-L), and 8.8% had stable disease (SD). At median follow-up of 31.4 M, mDOR was 33.5 M and mPFS was NR (95% CI: 36.3, NE); the mPFS (in M) for pts with 1, 2, or ≥ 3 prior therapies was NR (min 19.3, max 41.3), NR (min 19.3, max 36.8) or 36.3 (95% CI: 15.7, NE). At median follow-up of 21.1 M in Part 3, mPFS was NR for TN or RR in both Zilo+Ibr and Ibr arms. Conclusions: Zilo+Ibr is well-tolerated. Striking responses were observed in MCL pts, with mPFS of 35.9 M (95% CI: 17.3, NE) and CR of 34.6%, which compares favorably to mPFS of 12.8 M (95% CI 8.5, 16.6) and CR of 20% reported for single agent Ibr (Rule 2017). For CLL, ORR and PFS compare very favorably to Ibr monotherapy data (Byrd 2019). Clinical trial information: NCT03088878. Research Sponsor: Oncternal Therapeutics, Inc, Other Foundation.