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

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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), 26.6 (95% CI: 0.03, NE), 35.9 (min 8.30, 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 31.3, 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.