Multicenter Phase II Trial of Zanubrutinib, Obinutuzumab, and Venetoclax (BOVen) in Treatment-Naïve Chronic Lymphocytic Leukemia: 5-Year Follow up, Retreatment Outcomes, and Impact of MRD Kinetics (ΔMRD400)

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Background:
Venetoclax-obinutuzumab induces durable undetectable MRD at ≤10-4 (uMRD4) in treatment-naïve CLL (MRD4-free survival of 21 months [mo] for patients (pts) with uMRD4) (Al-Sawaf JCO 2021). Zanubrutinib is a second-generation BTKi with superior PFS and safety compared with ibrutinib (Brown NEJM 2023). BOVen (zanubrutinib, obinutuzumab, venetoclax) was well-tolerated with frequent uMRD in pts with previously untreated CLL (Soumerai Lancet Haem 2021). In the initial report, response kinetics defined as ΔMRD400 (≥400-fold reduction in peripheral blood [PB] MRD level by immunosequencing from baseline to cycle 5 day 1) predicted more durable uMRD4 despite less time on therapy. Herein, we present 5-year follow-up of BOVen in treatment-naïve CLL, safety and efficacy of retreatment with zanubrutinib-venetoclax, and the impact of ΔMRD400 on outcomes.

Methods:
In this multicenter, phase 2 trial (NCT03824483), eligible pts had CLL/SLL requiring first-line treatment (iwCLL 2018), ECOG PS ≤2, ANC ≥1,000/μl and PLT ≥75,000/μl (PLT ≥20,000 and no ANC requirement if due to CLL). Informed consent was obtained from all pts.

BOVen was administered in 28-day cycles: Zanubrutinib 160 mg by mouth (PO) twice daily starting D1; Obinutuzumab 1000 mg intravenously (IV) on D1 (split D1-2 if ALC ≥25,000/ul or LN ≥5cm), 8, and 15 of C1, and D1 of C2-8; Venetoclax ramp up started on C3D1 (target 400 mg PO daily). Treatment consisted of

8-24 cycles with duration determined by MRD (flow cytometry; MRD-FC). PB MRD-FC was assessed every 2 mo. Therapy was discontinued 2 mo after confirmed uMRD4 in both PB and BM (primary endpoint). Thereafter, pts with recurrent MRD-FC >1% or iwCLL progressive disease (PD) had option for retreatment with zanubrutinib-venetoclax for 12-24 cycles (discontinue after 12 retreatment cycles if uMRD4 in PB and BM).

Adverse events (AE) were assessed per CTCAE v5. Median MRD4-free survival (M4FS) was calculated from EOT to MRD4 conversion (≥10-4) (Kaplan–Meier method). ΔMRD400 was evaluated by immunosequencing (Adaptive ClonoSEQ).

Results:
The study accrued 52 pts (3/2019-10/2019; 7/2020-4/2021): median age 62 (range, 23-77), 75% (39/52) male, 71% (37/52) IGHV unmutated, 17% (9/52) del17p/TP53M. All pts are evaluable for safety and 50 are evaluable for efficacy. The median follow-up is 57 mo (range, 4-63).

With a median treatment duration of 10 cycles (interquartile range [IQR] 8-14), 96% (48/50) achieved uMRD4 in PB, and 92% (46/50) achieved uMRD4 in both PB and BM after a median of 8 mo (IQR 6-11.5). ΔMRD400 was achieved in 60% (21/35) pts (analysis pending in remaining pts).

Of 46 pts who met MRD-FC criteria to end treatment, the median M4FS was 34 mo (95% CI 23-NR) with 12- and 24-mo M4FS of 83% and 62% (95% CI: 72-94% and 49-78%), respectively. The median M4FS was longer in ΔMRD400 achievers (51 v 23 mo, log-rank p<0.001) despite less therapy (median 8 v 12 cycles).

Sixteen pts received zanubrutinib-venetoclax retreatment for MRD ≥1% alone (n=4) or with PD (n=12) after a median treatment-free interval of 29 mo (range, 7-54). The median retreatment follow-up is 14 mo (range, 1-38). Of 12 pts who were retreated after PD, the overall response rate was 92% (11/12). Of 13 retreatment pts with repeat MRD-FC testing, 6 (46%) are uMRD4 in PB. Of 11 retreatment pts who were evaluable for ΔMRD400 with initial treatment and for retreatment MRD response, those who achieved ΔMRD400 with initial treatment appeared more likely to achieve PB uMRD4 with retreatment (75% [3/4] v 29% [2/7]).

The most common initial treatment AEs (all-cause) were fatigue (59.6%), thrombocytopenia (59.6%), neutropenia (57.7%), diarrhea (51.9%), bruising (48.1%), cough (38.5%), nausea (36.5%), anemia (36.5%), and infusion-related reaction (36.5%). The most common grade ≥3 AEs were neutropenia (26.9%), thrombocytopenia (7.7%), lung infection (5.8%).

The most common retreatment AEs (all-cause) were upper respiratory infection (43.8%), COVID-19 (37.5%), cough (25%), diarrhea (25%), fatigue (25%), but grade ≥3 AEs were uncommon (neutropenia in 1 pt).

No laboratory/clinical TLS occurred on study (Howard criteria).

Conclusion:
Five-year follow up of the BOVen regimen demonstrates frequent uMRD4 in PB (96%) and BM (92%), and uMRD4 was durable with a median MRD4-free survival of 34 mo. Retreatment with zanubrutinib-venetoclax was also well-tolerated and effective. A phase 2 trial of BOVen with ΔMRD400-directed treatment duration is ongoing.