LONG-TERM FOLLOW-UP OF MULTICENTER PHASE II TRIAL OF ZANUBRUTINIB, OBINUTUZUMAB, AND VENETOCLAX (BOVEN) IN PREVIOUSLY UNTREATED PATIENTS WITH CLL/SLL

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Background: Venetoclax-obinutuzumab induces durable undetect- able MRD (median time to MRD ≥10-4 of 21 mo) in CLL (Al-Sawaf JCO, 2021) and zanubrutinib is a second-generation BTKi with a favorable safety profile (Brown NEJM 2023). BOVen appeared well- tolerated and achieved frequent uMRD in CLL (Soumerai Lancet Haem 2021), but longer follow-up was needed to evaluate the MRD- driven treatment strategy. Herein, we present the initial report on long-term follow-up of BOVen in CLL.

Methods: In this multicenter phase 2 trial (NCT03824483), eligible pts had CLL/SLL requiring first-line treatment (iwCLL), ECOG PS ≤2, ANC ≥1000, PLT ≥75,000 (ANC ≥0/PLT ≥20,000 if due to CLL). Informed consent was obtained from all pts. BOVen was administered in 28-day (D) cycles (C): Zanubrutinib 160 mg PO twice daily starting D1; Obinutuzumab 1000 mg IV D1 (split D1–2 if ALC ≥25,000 / LN ≥5 cm), D8, D15 of C1, and D1 of C2–8; Venetoclax ramp up initiated C3D1 (target 400 mg PO daily). MRD was evaluated by flow cytometry (MRD-FC) with uMRD defined as ≤10-4 for the primary endpoint. ΔMRD400 was evaluated by immunosequencing (Adaptive ClonoSEQ) in 35/39 (13 pending) and defined as ≥400-fold reduction in peripheral blood (PB) MRD level at C5D1. Treatment consisted of 8–24 cycles (duration determined by pre-specified MRD-FC criteria). Beginning C7D1 then q2 cycles, PB uMRD-FC prompted bone marrow (BM) <14 days. If BM uMRD-FC, PB MRD-FC was repeated after 2 additional cycles. Pts with confirmed uMRD-FC in PB and BM discontinued therapy. All-cause adverse events (AE) were assessed (CTCAE v5). Median time to PB MRD-FC ≥10-4 was calculated from end-of-treatment (EOT; Kaplan–Meier method).

Results: The study accrued 52 pts (3–10/2019; 7–4/2021): median age 61, 75% male, 75% IGHV unmutated, 18.4% del17p/TP53M. All evaluable for safety with 50 evaluable for efficacy. With median follow up of 40 mo (4.1–47.4) and treatment duration of 10 cycles (IQR 8–14), 96% (48/50) were uMRD-FC in PB; 92% (46/ 50) were uMRD in PB and BM after a median 8 mo (IQR

6–11.5). The most common AEs were thrombocytopenia (55.8%), fatigue (55.8%), neutropenia (53.8%), diarrhea (46.2%), bruising (44.2%), infusion related reaction (36.5%). The most common grade ≥3 AE were neutropenia (23.1%), thrombocytopenia (7.7%), lung infection (5.8%). No lab/clinical TLS occurred (Howard). Of 46 pts meeting MRD-FC criteria to end treatment, MRD-FC free survival was 29.8 mo (3.6–35.1; A). Of pts who were PB uMRD-FC and evaluable for ΔMRD400, MRD-FC free survival was longer in ΔMRD400 achievers (NR vs. 18.1 mo, log-rank p = 0.003; B) despite fewer median cycles of therapy (8 vs. 13, p < 0.001).

Conclusion: Long-term follow up of BOVen demonstrate high rates of durable uMRD-FC. A phase II trial of BOVen with ΔMRD400- directed treatment duration is planned, and we hypothesize that longer duration of therapy for pts who do not achieve ΔMRD400 (24 vs. 10 mo) will further improve uMRD duration in these pts.