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ORAL ABSTRACTS

623.MANTLE CELL, FOLLICULAR, AND OTHER INDOLENT B CELL LYMPHOMAS: CLINICAL AND EPIDEMIOLOGICAL

A Multicenter Phase 2 Trial of Zanubrutinib, Obinutuzumab, and Venetoclax (BOVen) in Patients with Treatment-Naïve, *TP53*-Mutant Mantle Cell Lymphoma

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Background: *TP53*-mutant mantle cell lymphoma (MCL) is associated with poor survival outcomes with chemoimmunotherapy (Eskelund, Blood 2017) with median progression-free survival (PFS) of 0.9 years and median overall survival (OS) of 1.8 years. There is no standard frontline treatment for this high-risk subset. The combination of Bruton's tyrosine kinase (BTK) inhibition and BCL2 inhibition were synergistic and active in relapsed, refractory MCL, including in patients with *TP53* mutation (Tam, NEJM 2018). Obinutuzumab, ibrutinib, and venetoclax were well tolerated and efficacious in relapsed and untreated MCL patients (Le Gouill, Blood 2021). We hypothesized that treatment with zanubrutinib (Zanu), Obinutuzumab (Obin), and venetoclax (Ven) (BOVen) would be well-tolerated and efficacious in untreated *TP53*-mutant MCL.
Methods: In this multicenter, investigator-initiated phase 2 trial (NCT03824483), eligible patients had previously untreated MCL with *TP53* mutation (of any variant allele frequency) and ECOG PS ≤2, ANC >1, PLT >75, HGB ≥9 (unless if due to MCL). BOVen is administered in 28-day cycles: Zanu 160 mg PO BID starting D1; Obin 1000 mg IV D1 or split D1-2, 8, 15 of C1, D1 of C2-8; Ven ramp up initiated C3D1 (target 400 mg QD). Treatment duration is 2 years at minimum and the primary endpoint is 2-year PFS. Response was assessed using Lugano criteria (Cheson, JCO 2014). PFS and OS were estimated using the Kaplan-Meier method. Peripheral blood minimal residual disease (PB-MRD) assessment was performed using the Adaptive clonoSEQ ® assay. After 24 cycles, Zanu and Ven can be discontinued if MRD undetectable ($<10^{-6}$) complete remission (CR) is achieved. With subsequent PB-MRD monitoring, patients can be retreated if clinical progression or MRD detectability ($>10^{-6}$). Adverse events (AE) were assessed per CTCAE v5.
Results: All 25 planned patients have been enrolled (May 15, 2023 data cut). The median age on study was 65 years (range 29 - 82); 76% were male (19/25); various histologic subtypes were included (15 conventional MCL, 5 non-nodal leukemic, and 5 blastoid variant); 100% stage IV (25/25); by MIPI: 68% high risk (17/25), 28% intermediate (7/25), and 4% low risk MIPI score (1/25); 67% Ki67 ≥30% (14/21); 33% Ki67≥50% (7/21); 100% *TP53* mutation, and 48% 17p deletion (12/25).
Treatment was overall well-tolerated. The most common treatment-related AEs (≥20%) were predominantly low-grade and manageable, including diarrhea (52%), neutropenia (28%), infusion-related reaction (24%), bruising (20%), COVID-19 infection

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(20%), nausea (20%), thrombocytopenia (20%), and rash (20%). The grade 3 or higher treatment-related AEs were neutropenia (12%), infusion-related reaction (8%), COVID-19 (8%), diarrhea (4%), transaminitis (4%), thrombocytopenia without bleeding (4%), and rash (4%). Detailed toxicity data will be presented in future.

Median follow-up was 16.1 months. There were 5 progressions and 4 deaths on study (2 COVID-related, 1 post-operative aspiration pneumonia, 1 unknown cause), see Figure 1. All deaths occurred in patients who were in ongoing response at time of death. The best overall response rate was 95% (24/25) with 88% (22/25) achieving a CR. At C3 post Zanu-Obin, 68% (n=17/25) achieved PET-CR and post cycle 3, 5 patients converted to a PET-CR (Figure 1). The 1-year PFS and overall survival (OS) were 84% (95% CI: 71%, 100%) and 96% (95% CI: 89%, 100), respectively. The 16-month PFS and OS were 75% (95% CI: 60%, 95%) and 87% (95% CI: 75%, 100%), respectively. The 16-month PFS and OS for patients less than 65 years of age (n=9) were both 100%. Seven patients completed 24 treatment cycles. Of these, 71% (5/7 pts) were in CR and MRD undetectable (treatment discontinued) and 29% (2/7 pts) were in CR and MRD detectable (continued treatment). Outcomes post C24 will be presented in future. At 10^{-6} MRD sensitivity level, 7 (28%) of 23 patients had undetectable MRD at C3 and 16 (100%) of 16 patients at C13.

Conclusions:BOVen is a well-tolerated, outpatient regimen associated with high response rates and high rates of undetectable MRD in untreated *TP53*-mutant MCL. The early PFS and OS estimates with BOVen compare favorably with historical outcomes of chemoimmunotherapy in this high-risk subset of MCL. Based on this data, BOVen emerges as a promising treatment option for *TP53*-mutant MCL and, therefore, the study was expanded to include an additional 25 (total 50) *TP53*-mutant MCL patients.

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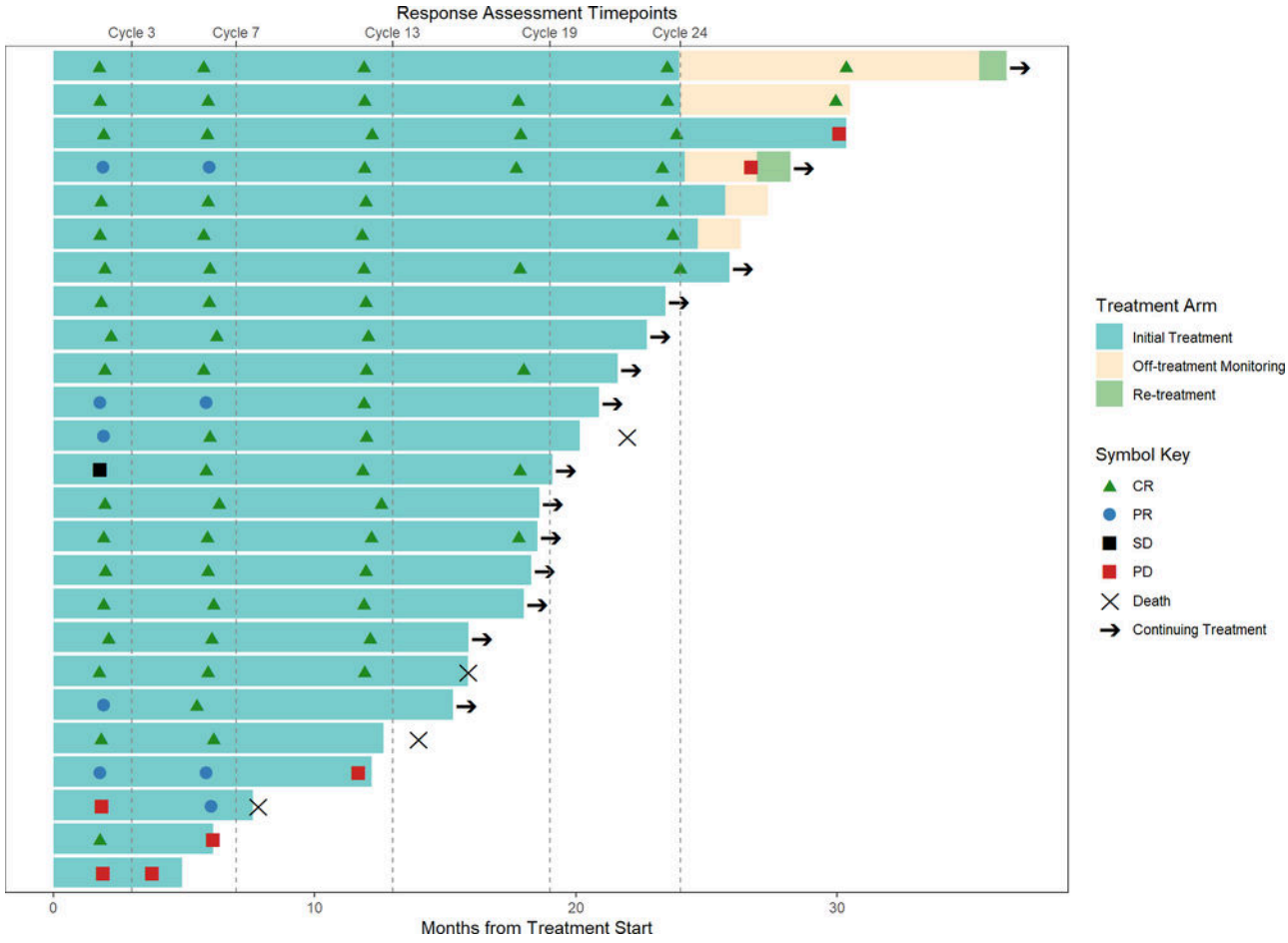

Figure 1

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