High Efficacy and Favorable Safety of CD20-targeted CAR-T Therapy for BTK Inhibitor-refractory Waldenström Macroglobulinemia (WM)/ Lymphoplasmacytic Lymphoma (LPL)

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Background: Chimeric antigen receptor T-cell (CAR-T) therapy is an approved treatment for several B-cell non-Hodgkin lymphoma (B-NHL) histologies but is investigational for Waldenström macroglobulinemia (WM)/lymphoplasmacytic lymphoma (LPL). Minimal data have been reported to date for CAR-T for WM/LPL. MB-106 is a 3rd-generation fully human CD20-targeting CAR-T with high response rates and favorable safety profile in follicular lymphoma and other B-NHLs (Shadman et al., ICML 2023).

Aims: To assess the safety and efficacy of MB-106 for the cohort of WM/LPL patients in our Phase I study.

Methods: We conducted a single-institution study in which patients (pts) with relapsed/refractory B-NHLs including WM/LPL were eligible after confirmation of CD20 expression. Lymphodepletion (LD) consisted of cyclophosphamide + fludarabine. CAR-T cells were administered at one of 4 dose levels (DL): DL1: $3.3x10^5$, DL2: $1x10^6$, DL3: $3.3x10^6$, DL4: $1x10^7$ CAR T cells/kg. A continual reassessment method dose escalation design was used to find the maximally tolerated dose. CAR-T was infused in the outpatient setting except for the first pt of each dose cohort (overnight observation). Initial treatment response was assessed on day 28 and best response by IWWM-11 is reported here. CRS and ICANS were graded per ASTCT criteria.

Results: Between 7/2021-2/2024, 10 pts with WM were treated with MB-106 (1 DL4, 3 DL3 and 6 DL2). The median age was 69.7 yrs (range 51-79), with 7 of 10 male. Median time from diagnosis was 14.5 yrs (range 1-31), and median prior treatment lines was 9 (range 1-12). All 10 pts had BTKi refractory disease (9 ibrutinib, 2 acalabrutinib, 5 zanubrutinib, 1 pirtobrutinib). $MYD88^{L265P}$ was present in 9/10 pts and 1 of 6 tested pts had a CXCR4 mutation. B2M was elevated in 7 of 10 pts; 5 pts had extramedullary disease (PET-avid adenopathy), 4 had splenomegaly, and 8 had anemia (<11 g/dL) at baseline. Median pre-CAR-T IgM was 2461 mg/dL (range 187-6461; ULN 350). By flow cytometry, median marrow involvement by LPL was 22% (range 1.4-74%). Bridging therapy was continuation of BTKi (n=5), bendamustine (n=1), dexamethasone (n=1), or none (n=3). Of 10 pts, 9 developed CRS (5 grade 1, 4 grade 2), and 3 pts received tocilizumab; no pts had grade 3 or 4 CRS. One pt had grade 1 ICANS. One pt each developed pneumonia and enterocolitis before day 28. By IWWM-11, 9 pts responded to treatment (3 CR, 2 VGPR, 4 PR). All pts experienced B cell aplasia. CAR-T expansion and persistence were robust. One pt died from complications of COVID-19 while in remission 7 months after treatment. One pt had PD at day 80 after CAR-T but subsequently had a PR without additional treatment.

Conclusion: CD20 CAR-T therapy (MB-106) for BTKi-refractory WM/LPL shows high efficacy and favorable safety with no grade 3-4 CRS and no grade 2 or higher ICANS. MB-106 has received orphan drug designation by the US FDA for WM, and a multicenter registrational phase 2 study is planned in the US for WM.