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ORAL ABSTRACTS

704.CELLULAR IMMUNOTHERAPIES: EARLY PHASE AND INVESTIGATIONAL THERAPIES

Promising Safety and Anti-Lymphoma Efficacy of Autologous Pmb-CT01 (BAFFRCAR T Cell) Therapy in a First-in-Human Phase 1 Study

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Introduction: CD19 chimeric antigen receptor (CAR) T cell therapy has revolutionized the treatment landscape of B cell lymphoma. However, a significant number of patients with aggressive B cell lymphoma (aBCL), mantle cell lymphoma (MCL) and follicular lymphoma (FL) still relapse or have refractory disease after autologous CD19CAR T cell therapy, highlighting the urgent unmet need to seek alternative approaches to improve the outcomes. BAFF-R signaling is considered a driver of B cell and malignant growth and survival. This feature may limit the capacity of B cell tumors to evade therapy by loss of BAFF-R expression. Recent work (Qin *et al.*, Sci Transl Med. 2019) has shown that BAFF-R expression is independent of CD19 expression on malignant B cells and that CAR T cells targeting BAFF-R were able to effectively eliminate various B cell malignancies in the preclinical setting. Here we report the initial results from the first 3 patients treated on an ongoing phase 1, first-in-human clinical trial (NCT05370430) evaluating the safety and efficacy of autologous BAFFRCAR T cells in patients with B cell lymphoma.

Study Design and Methods: Our studyis a phase 1, single center, open label, therapeutic trial. PMB-CT01 is a $T_{N}/_{SCM}$-enriched BAFFR.41BB.z.EGFRt-CAR T cell therapy which was previously described (Qin *et al.* Sci Transl Med. 2019). There are 3 dose levels (DL) in the dose escalation phase including $50x10^{6}$ (DL1), $200x10^{6}$ (DL2), and $600x10^{6}$ (DL3) CAR T cells. The lymphodepletion regimen consists of cyclophosphamide 500 mg/m^{2}/day and fludarabine 30 mg/m^{2}/day for 3 days.
The primary endpoints are the incidence of adverse events and the determination of the maximum tolerated dose. Secondary endpoints include disease response, incidence of negative minimal residual disease (MRD), progression-free survival, and overall survival. ASTCT consensus criteria are used to grade cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). Responses are determined by Lugano 2014 (Cheson *et al.*, JCO 2014).

Results: As of July 19, 2023, three patients were enrolled and all received treatment at DL1, $50x10^{6}$ PMB-CT01(BAFFRCAR T cells). The median age was 56 years old (41-75), 100% male. Patients #1 and #2 had MCL and both had received prior treatment with BTK inhibitors, and progressed after CD19CAR T cell therapy. Both patients had bone marrow involvement prior to treatment, and had 4 and 10 prior lines of therapy, respectively. Patient #3 with T cell/histiocyte-rich B cell lymphoma had received 3 prior lines of therapy and his lymphoma was negative for both CD19 and CD20. All 3 patients developed grade 1 CRS only. All CRS events resolved with 2 doses of tocilizumab given to patient #1 and 1 dose to patient #2. Patients #1 and #2 also developed grade 1 ICANS which were self-limited and resolved without pharmacologic intervention. No dose-limiting toxicity (DLT) was observed. Infection was seen in patient #2 with viral pneumonia at month 3.
All 3 treated patients responded to treatment. The overall response rate was 100% including MRD-negative complete response (CR) by flow cytometry and next-generation sequencing (NGS) in patient #1 and by flow cytometry in patient #2, and partial response (PR) in patient #3. All responses are ongoing at 8 months (patient #1), 4 months (patient #2) and 1.5 months (patient #3), respectively. Figure 1 shows the clearance of lymphoma cells in the bone marrow of the first patient 28 days post-CAR T cell infusion. Robust CAR T cell expansion was observed in all 3 patients with peak of expansion (between $2.1x10^{6}$ and $8.9x10^{6}$ copies/ml of blood) on day 12 (patient #1) and day 14 (patients #2 and #3) (Figure 1).

Conclusions: PMB-CT01(BAFFRCART cell) treatment at DL1 was safe and demonstrated potent anti-lymphoma activity with a 100% ORR (2 CR, 1 PR) in patients with poor prognosis. CRS and ICANS were all grade 1 and reversible.Enrollment is ongoing at DL2, and additional clinical and correlative analyses will be presented at the meeting.

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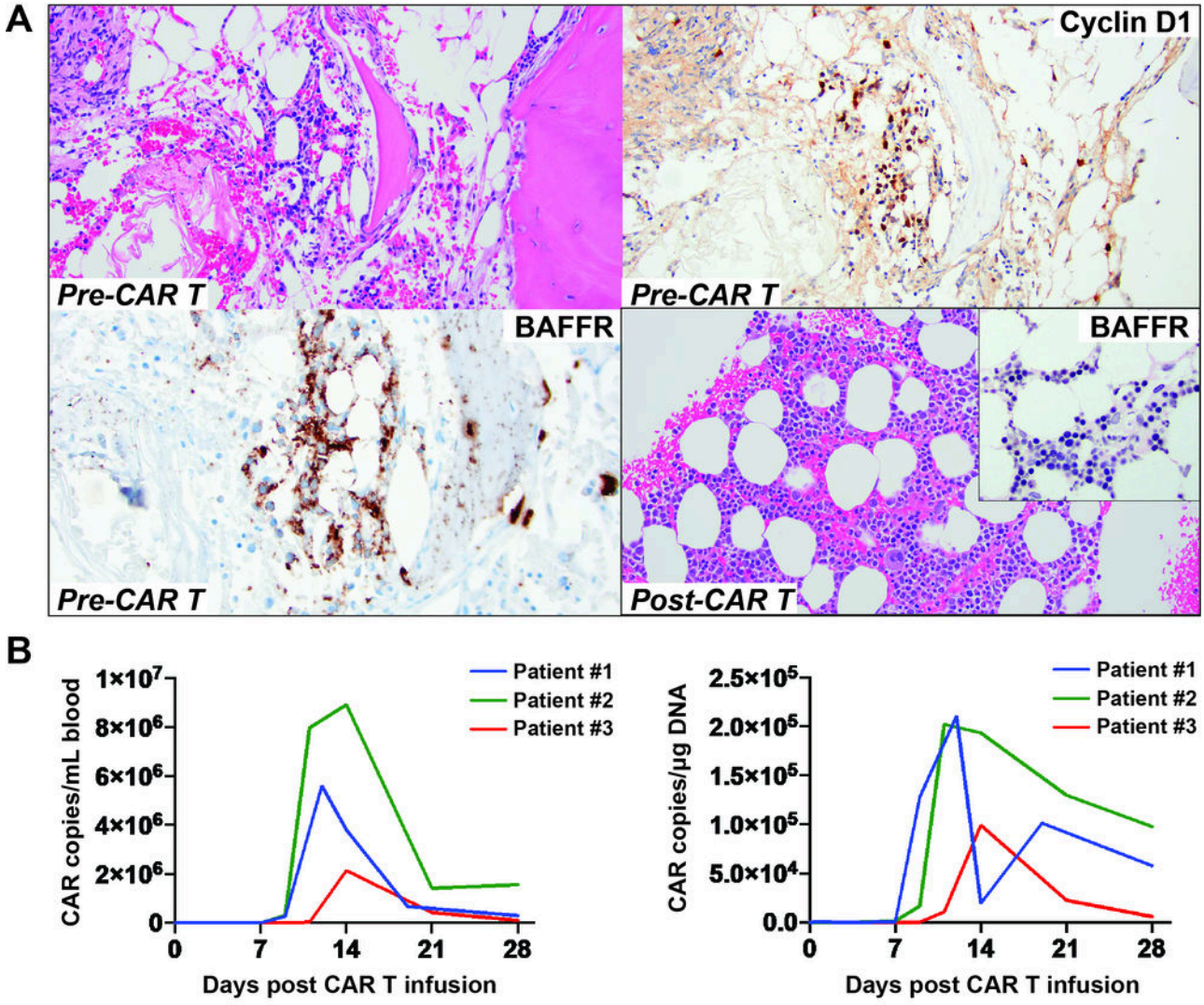

A. Clearance of lymphoma in the bone marrow of Patient #1 (MCL). Staining (H&E, Cyclin D1, BAFFR) is shown before CAR T treatment. Clearance of lymphoma is demonstrated by H&E staining and absence of BAFFR expression (bottom right panel). **B. Post-infusion expansion of CAR T cells in the peripheral blood of the 3 patients.** Copy number is shown per mL of blood and per µg of DNA.

Figure 1

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