A Personalized Approach to Immune Therapies for Cancer: One Drug, One Patient

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Cancer patients responding to immune checkpoint blockade usually bear tumors that are heavily infiltrated by T cells and express a high load of neoantigens, indicating that the immune system is involved in the therapeutic effect of these agents. These observations also strongly support the renewed interest immune therapy strategies, increasingly those that require personalization. One example is personalized determinants on the surface of lymphoma cells which can be used as tumor-specific antigens, and effective vaccination against these targets was demonstrated in a positive controlled Phase III clinical trial (Schuster [Kwak] et al. ***J Clin Oncol* 2011**). The genes encoding these unique determinants can also be cloned and used as a DNA or mRNA vaccines. We recently demonstrated the safety and feasibility of a next-generation DNA neoantigen vaccine in a first-in-human clinical trial of asymptomatic lymphoplasmacytic lymphoma (LPL) patients (Szymura [Kwak] et al. ***Nat Commun*. 2024** Aug 11;15(1):6874). This vaccine, testing early intervention, could shift the current paradigm of clinical management for patients with asymptomatic LPL

Another personalized therapy, chimeric antigen receptor (CAR) T-cells directed against CD19, have redefined treatment paradigms for B-cell malignancies. However, relapse is common and often associated with loss of CD19 expression. Patients who relapse after or are ineligible for CD19-targeted therapies face limited treatment options and poor outcomes. We have developed CAR T cells against the B-cell activating factor receptor (BAFF-R), a functionally important receptor expressed on both normal and malignant B cells. Unlike CD19 and CD20, BAFF-R plays a critical role in B-cell function and survival, making therapeutic escape via downregulation less likely. Importantly, BAFF-R is expressed in human CD19-negative relapse tumors, supporting its relevance in settings where CD19-targeted therapies fail. PMB-CT01 is a novel autologous CAR T cell therapy currently under evaluation in a first-in-human phase 1 study in patients with B cell lymphomas:

Methods: We are conducting a dose-escalation phase 1 trial (NCT05370430) of PMB-CT01 in patients with relapsed/refractory (r/r) B-cell non-Hodgkin lymphomas (B-NHL). The trial has been expanded to a multicenter study. Patients were treated at either dose level 1 (DL1; 50×10^6 CAR T cells) or dose level 2 (DL2; 200×10^6 CAR T cells).

Results: Nine patients have been treated to complete the Phase 1a dose escalation portion of the clinical trial. Diagnoses included stage IV mantle cell lymphoma (MCL; n=6), CD19- and CD20-negative stage III T cell/histiocyte-rich large B-cell lymphoma (THRBCL; n=1), stage II marginal zone lymphoma (MZL; n=1) and stage I/II follicular lymphoma (FL; n=1). Median age was 62 years (range: 41-75), with 8/9 male patients. Patients had received 1-10 prior lines of treatment, including CD19 CAR T cells (n=6) and a CD3/CD20 bispecific antibody (n=2). Three patients were treated at DL1 and six at DL2. No DLTs occurred. All nine patients experienced only grade 1 CRS; two had grade 1 ICANS that resolved without corticosteroids. No grade ≥2 CRS or ICANS events were reported. Seven patients achieved CR and two patient achieved SD at 1 or 3 months post-infusion (80% CR rate). Responses have been durable, with no relapses and ongoing remissions extending up to 37 months (median 17 months; range 3-37 months). Among MCL patients, 4/4 tested were MRD-negative by both high-resolution flow cytometry and next-generation sequencing (NGS) at 1 and ≥6 months post-treatment. Robust CAR T cell expansion was observed in all CR patients. Given the favorable safety profile and durable remissions observed thus far, 200 x 10^6 BAFF-R CAR T cells is

expected to be the recommended dose for the Phase 1b expansion cohorts: 1) Follicular lymphoma; 2) Mantle cell lymphoma (MCL); and 3) Large B-cell lymphoma (LBCL) to further assess safety and efficacy in each subtype.

Conclusions: PMB-CT01 demonstrated an 80% CR rate in r/r B-NHL patients with poor-prognosis features, including CD19-negative disease and prior CD19 CAR T cell therapy. The durability of responses at both dose levels supports BAFFR-CAR T cells as a potentially transformative therapeutic option in patients who have relapsed after CD19-directed therapy. Furthermore, the exceptionally favorable safety profile will accelerate wider adoption of outpatient administration in community oncology centers and potential applications to autoimmune diseases.