TPS2677 Poster Session

Logic-gated, allogeneic Tmod chimeric antigen receptor T-cell (CAR T) therapy targeting epidermal growth factor receptor (EGFR) in advanced solid tumors with human leukocyte antigen (HLA) loss of heterozygosity (LOH): DENALI-1 trial.

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Background: Despite the success in hematologic malignancies, CAR T therapies face significant challenges in solid tumors due to the lack of tumor-specific targets that distinguish cancer from normal cells. EGFR plays a critical role in oncogenesis across several cancers and is often upregulated (TCGA 2022). While monoclonal antibodies targeting EGFR have demonstrated efficacy, these approaches are often limited by on-target, off-tumor toxicities, such as skin rash, which constrains dose escalation and efficacy (Macdonald, et al. *J Am Acad Dermatol*. 2015). A2B395 is an allogeneic, logic-gated, EGFR-targeted Tmod CAR T therapy designed to address these limitations and provide a convenient and consistent off-the-shelf option. This therapy incorporates 2 CARs: an activator targeting EGFR, and a blocker targeting HLA-A*02. The activator recognizes EGFR on both tumor and normal cells, while the blocker inhibits CAR T activity against normal cells with preserved HLA expression and decreases the risk for graft-versus-host disease (Hamburger, et al. *Mol Immunol*. 2020). To address potential host-vs-graft response, an shRNA expression module targeting B2M is included in the Tmod construct, which significantly reduces major histocompatibility complex class I levels and subsequent host immune response (DiAndreth, et al. *Clin Immunol.* 2022). Importantly, the Tmod system is modular and adaptable to multiple targets. Initial data on autologous Tmod CAR T therapy suggest reduced off-tumor toxicity and encouraging clinical efficacy (Grierson, et al. SITC 2024. Abstract 588). A2B395 represents a novel approach for EGFR-expressing solid tumors with HLA-A*02 LOH. **Methods:** DENALI-1 (NCT06682793) is a phase 1/2, open-label, nonrandomized study evaluating the safety and efficacy of A2B395 in adults. Patients are enrolled through BASECAMP-1 (NCT04981119), a master prescreening study that identifies patients with HLA LOH at any time in the course of their disease via next-generation sequencing (Tempus AI, Inc.). Key inclusion criteria include histologically confirmed recurrent unresectable, locally advanced, or metastatic cancers associated with EGFR expression, including colorectal, non-small cell lung, squamous cell head and neck, triple negative breast, and renal cell cancers. Patients must have received ≥1 line of prior therapy, such as a checkpoint inhibitor, molecular targeted therapy, or chemotherapy. The primary objective of phase 1 is to evaluate safety, tolerability, and the recommended phase 2 dose (RP2D) using a Bayesian optimal interval design for dose escalation. The dose-expansion phase will confirm RP2D and collect biomarker data. Phase 2 will assess overall response rate per RECIST v1.1. Clinical trial information: NCT06682793. Research Sponsor: A2 Biotherapeutics, Inc.