EVEREST-1: A SEAMLESS PHASE 1/2 STUDY OF CEA LOGIC-GATED TMOD CAR T-CELL THERAPY (A2B350) IN PATIENTS WITH SOLID TUMORS ASSOCIATED WITH CEA EXPRESSION ALSO EXHIBITING HLA LOSS OF HETEROZYGOSITY (LOH)

Background
Chimeric antigen receptor (CAR) T-cell therapy has demonstrated clinical efficacy in hematologic malignancies; however, implementation of these therapies in solid tumors has been challenging due to a lack of tumor-specific targets that discriminate cancer from normal cells. Previous studies using carcinoembryonic antigen (CEA) T-cell receptors and T-cell engagers have resulted in dose-limiting, off-target, off-tumor toxicities. EVEREST-1 (NCT05736731) is a seamless, phase 1/2, open-label, nonrandomized study to evaluate the safety and efficacy of A2B350, a logic-gated CEA-targeting Tmod CAR T-cell therapy, in adult patients. Tmod CAR T-cell therapy addresses challenges of on-target, off-tumor toxicity by combining a CAR-activating receptor with a blocking receptor to discriminate tumor from normal cells (figure 1). The activator receptor recognizes CEA on the surface of both tumor and normal cells. CEA is normally widely expressed in epithelial cells, particularly of the gastrointestinal (GI) system and can be upregulated in GI and lung tumors. Specificity for tumor cells is provided by a blocker that recognizes human leukocyte antigen (HLA) A*02, which is absent on tumor cells with HLA-A*02 LOH. LOH for HLA-A*02 is observed in solid tumor malignancies and can be detected using the Tempus next-generation sequencing testing. With this definitive discriminator target, A2B350 can potentially provide a therapeutic window to treat patients with CEA-expressing solid tumors exhibiting HLA LOH.

Methods
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. BASECAMP-1 eligible patients undergo leukapheresis and, when clinically appropriate, their banked T cells are manufactured for the EVEREST-1 study (figure 2). The key inclusion criteria include histologically confirmed recurrent, unresectable, locally advanced, or metastatic cancers that are associated with CEA expressions, non-small cell lung (NSCLC), colorectal (CRC), or pancreatic (PANC) cancers. Patients should have received ≥1 line of prior therapy (eg, checkpoint inhibitor, molecular-targeted, or chemotherapy). The primary objective of phase 1 is to evaluate the safety and tolerability of A2B350 in patients with NSCLC, CRC, and PANC, and to identify the maximum tolerated dose and recommended phase 2 dose (RP2D). The dose expansion phase will confirm RP2D and collect biomarker data to further characterize A2B350. Trial Registration NCT05736731.

REFERENCES

Ethics Approval
This study was approved by site IRBs.

Abstract 634 Figure 1 CEA CAR Tmod Single Vector Construct

B2M shRNA, 2D microspleen short-hairpin RNA; CAR, chimeric antigen receptor; CD8, cluster of differentiation 8; CEA, carcinoembryonic antigen; EF1α, elongation factor-1α; HLA, human leukocyte antigen; LIR, leukocyte immunoglobulin-like receptor; scFv, single-chain variable fragment; T2A, frameshift vector 2A.

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Abstract 634 Figure 2  Everest-1 Study Design

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