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EVEREST-2: A seamless phase 1/2 study of A2B694, a logic-gated Tmod CAR T-cell therapy, in patients with mesothelin-expressing solid tumors with human leukocyte antigen-A*02 loss of heterozygosity

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BACKGROUND AND STUDY OBJECTIVES

- Implementation of chimeric antigen receptor T-cell (CAR T) therapies in solid tumors has been challenging due to a lack of tumor-specific targets that discriminate cancer from normal cells; for example, CAR T and T-cell receptor fusion therapies targeting mesothelin (MSLN), which is normally expressed in mesothelial cells, but can be upregulated in colorectal (CRC), ovarian (OVCA), lung, and pancreatic (PANC) cancers, have been hampered by on-target, off-tumor toxicity, including fatal events [1-3]
- A2B694 is an MSLN-directed Tmod CAR T therapy construct that combines a CAR-activating receptor with a leukocyte immunoglobulin-like receptor-1–based inhibitory receptor (LIR-1; blocker) targeting HLA-A*02 to discriminate tumor from normal cells (**Figures 1 and 2**) [4,5]
  - The activator receptor recognizes MSLN on the surface of both tumor and normal cells
  - The blocker receptor recognizes an HLA-A*02 allele: for patients who are germline HLA-A*02 heterozygous, loss of the allele may occur in tumor cells, known as loss of heterozygosity (LOH) [6], which can be detected using Tempus next-generation sequencing (NGS; **Table 1**)
- EVEREST-2 (NCT06051695), the 2nd A2 Bio interventional clinical trial, is a seamless, phase 1/2, open-label, nonrandomized study to evaluate the safety and efficacy of A2B694 in adults with solid tumors

STUDY RATIONALE

Figure 1. Logic-Gated CAR T With the Goal to Reduce Toxicity: MSLN (Activator) and HLA-A*02 (Blocker) [4]

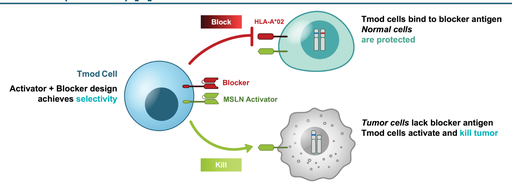
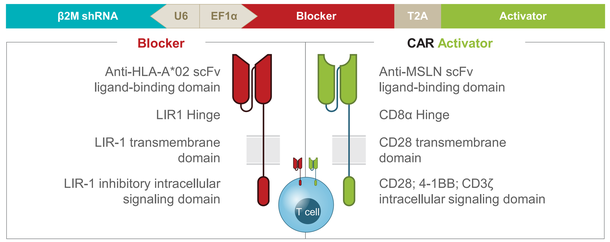


Figure 2. The Structure of Tmod CAR Ts Expressing an MSLN-Targeted Activator and an HLA-A*02-Targeted Blocker



The Tmod CAR construct is designed for safety with the LIR-1 inhibitory blocker transcribing before the anti-MSLN activator

β2M shRNA, beta-2-microglobulin short-hairpin RNA; CAR, chimeric antigen receptor; CD, cluster of differentiation; EF1α, elongation factor 1 alpha; HLA, human leukocyte antigen; LIR, leukocyte immunoglobulin-like receptor; MSLN, mesothelin; scFv, single-chain variable fragment; T2A, thosea asigna virus 2A.

STUDY RATIONALE (CONTINUED)

Table 1. Frequency of HLA-A LOH in Advanced Tumors [8]

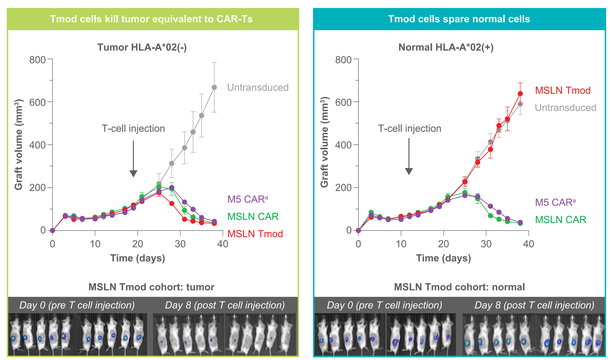
	Tempus HLA-A LOH advanced disease real world
Average, % (n)	16.3 (10,867)
Colorectal cancer, % (n)	15.6 (1854)
Mesothelioma, % (n)	14.3 (7)
NSCLC, % (n)	23.1 (1915)
Ovarian, fallopian tube, primary peritoneal cancer, % (n)	16.0 (569)
Pancreatic cancer, % (n)	19.6 (675)

HLA, human leukocyte antigen; LOH, loss of heterozygosity; NSCLC, non-small cell lung cancer.

Nonclinical Studies

- Nonclinical studies of A2B694 demonstrated improved selectivity and a therapeutic safety window with comparable efficacy to the MSLN-directed M5 CAR T [2,9]
  - Approximately 2 weeks following cell infusion, A2B694 treated NOD scid gamma mice experienced selective regression of tumor grafts (HLA-A*02-), while "normal" grafts (HLA-A*02+) continued to grow. Mice treated with MSLN-targeted M5 CAR Ts experienced regressions of both tumor and "normal" grafts (**Figure 3**)

Figure 3. MSLN Tmod (A2B694) In Vivo Study Demonstrates Efficacy Comparable to M5 CAR T Benchmark

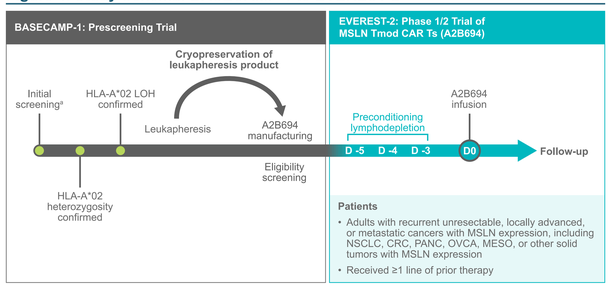


aM5 CAR is a MSLN-directed CAR T therapy that was clinically tested in a phase I trial [2].
CAR, chimeric antigen receptor; HLA, human leukocyte antigen; MSLN, mesothelin; UTD, untransduced T-cells.

STUDY DESIGN

- EVEREST-2 (NCT06051695) is a first-in-human, phase 1/2, multicenter, open-label, nonrandomized study to evaluate the safety and efficacy of a single-dose of A2B694 Tmod CAR Ts in adults with recurrent unresectable, locally advanced, or metastatic cancers with MSLN expression
- Participants are enrolled to EVEREST-2 through BASECAMP-1 (NCT04981119), a master prescreening study that identifies patients with HLA LOH at any time in the course of their disease; enrolled participants undergo leukapheresis and, when clinically appropriate, CAR Ts are manufactured for the EVEREST-2 study (**Figure 4**)

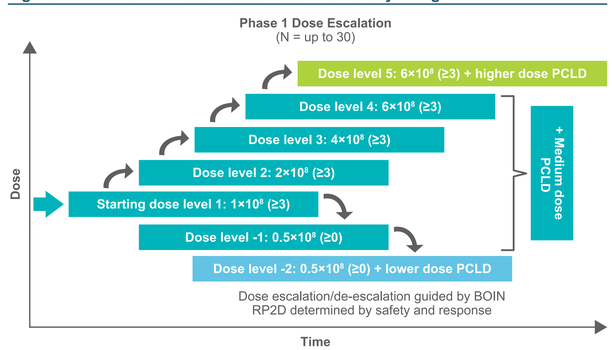
Figure 4. Study Schema: BASECAMP-1 to EVEREST-2



aMay occur at any point in disease course.
CAR, chimeric antigen receptor; CRC, colorectal cancer; HLA, human leukocyte antigen; LOH, loss of heterozygosity; MESO, mesothelioma; MSLN, mesothelin; NSCLC, non-small cell lung cancer; OVCA, ovarian cancer; PANC, pancreatic cancer.

- The phase 1 dose escalation portion of the study employs a Bayesian optimal interval design (BOIN) to assess the safety and tolerability of A2B694 and to determine a recommended phase 2 dose (RP2D; **Figure 5**); up to 30 participants will be included in the dose escalation

Figure 5. EVEREST-2 Phase 1 Dose Escalation Study Design



BOIN, Bayesian optimal interval design; PCLD, preconditioning lymphodepletion; RP2D, recommended phase 2 dose.

STUDY DESIGN (CONTINUED)

Inclusion Criteria

- Appropriately enrolled in the BASECAMP-1 study, with tissue demonstrating LOH of HLA-A*02 by NGS (whenever possible from the primary site), successful apheresis and peripheral blood mononuclear cell processing, and with sufficient stored cells available for Tmod therapy
- Histologically confirmed recurrent unresectable, locally advanced, or metastatic CRC, non-small cell lung cancer (NSCLC), PANC, OVCA, mesothelioma (MESO), or other solid tumors with MSLN expression; measurable disease is required with lesions of >1.0 cm by computed tomography
- Received previous required therapy for the appropriate solid tumor disease as described in the protocol
- Has adequate organ function as described in the protocol
- ECOG performance status of 0 to 1
- Life expectancy of ≥3 months
- Willing to comply with study schedule of assessments including long-term safety follow-up

Figure 6. EVEREST-2 Study Objectives and Endpoints

Objectives
- **Phase 1:** Determine the safety and the optimal dose of A2B694 (after PCLD) in participants with solid tumor disease
- **Phase 2:** Determine the further safety and efficacy of A2B694

Primary Endpoints
- **Phase 1:** Rate of adverse events and dose-limiting toxicities by dose levels; recommended phase 2 dose
- **Phase 2:** Overall response rate

Secondary Endpoints
- Persistence of A2B694
- Serum cytokine analysis

PCLD, preconditioning lymphodepletion.

RESULTS

- The first participant was enrolled on EVEREST-2 in April 2024. Dose escalation is ongoing

SITE LIST

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