Abstract #3040

Posterboard 355

EVEREST-2: Initial data of the logic-gated Tmod chimeric antigen receptor T-cell (CAR T) therapy A2B694 for patients with solid tumors associated with mesothelin (MSLN) expression and with human leukocyte antigen (HLA) loss of heterozygosity (LOH)

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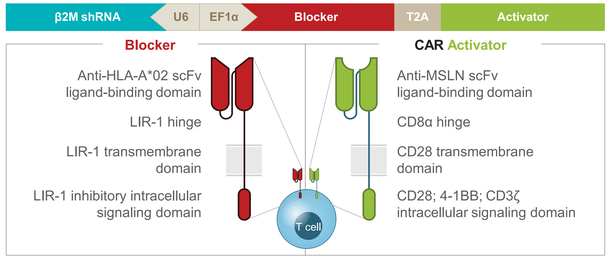
BACKGROUND AND STUDY OBJECTIVES

- Mesothelin (MSLN) is commonly overexpressed in pancreatic (PANC), colorectal (CRC), ovarian (OVCA) and lung cancers, including non-small cell lung cancer (NSCLC) and mesothelioma (MESO), with minimal expression in normal tissues; therefore, it is an attractive target for T-cell–mediated anticancer therapy
- However, chimeric antigen receptor T-cell (CAR T) and T-cell receptor fusion therapies targeting MSLN have been hampered by on-target, off-tumor toxicity, including fatal events [1–3]
- A2B694 is a MLSN-directed Tmod CAR T 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]
  - The activator receptor recognizes MSLN on the surface of both tumor and normal cells
  - The blocker receptor recognizes an HLA-A*02 allele that is present in normal cells and lost in tumor cells; thus, eligible patients for Tmod are germline HLA-A*02 heterozygous and have loss of heterozygosity (LOH) in their tumor cells
  - The frequency of HLA-A LOH in advanced solid tumors is approximately 16% and can be detected using Tempus xT next-generation sequencing (NGS)
- 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 adult patients with solid tumors

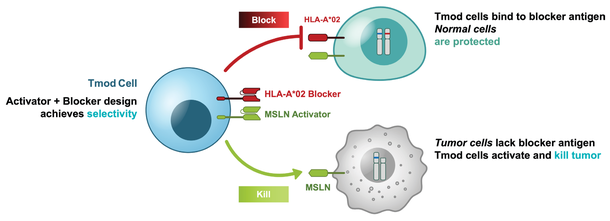
Figure 1: The Structure of Tmod CAR Ts Expressing a MSLN-Targeted Activator and an HLA-A*02-Targeted Blocker



The Tmod CAR construct is designed for safety with the LIR-1 inhibitory blocker transcribing before the anti-MSLN activator, minimizing the chance that the activator is expressed without the blocker

β2M shRNA, beta-2-microglobulin short-hairpin RNA; CAR T, chimeric antigen receptor T-cell; 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.

Figure 2: Logic-Gated CAR T Therapy With the Goal to Reduce Toxicity: MSLN (Activator) and HLA-A*02 (Blocker) [4]

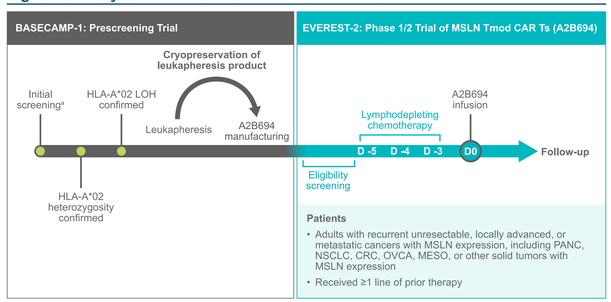


CAR T, chimeric antigen receptor T-cell; HLA, human leukocyte antigen; MSLN, mesothelin.

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, including PANC, NSCLC, CRC, OVCA, MESO, or other solid tumors 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 3**)

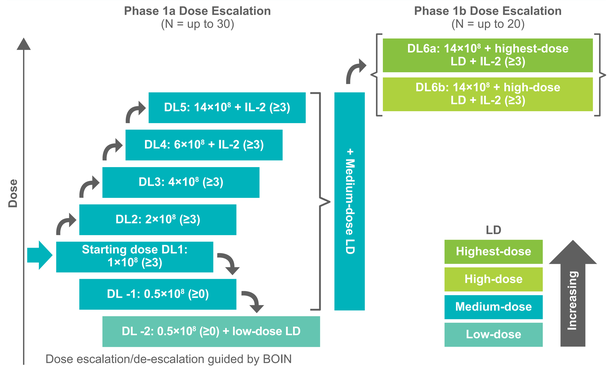
Figure 3: Study Schema: BASECAMP-1 to EVEREST-2



[a] May occur at any point in disease course.
CAR T, chimeric antigen T-cell; 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 to assess the safety and tolerability of A2B694 and to determine a recommended phase 2 dose (RP2D; **Figure 4**)
- Dose escalation was started at 1×10^8 Tmod positive cells (dose level [DL] 1) and will increase up to 14×10^8 in combination with low-dose interleukin [IL]-2 (DL 5).
  - Up to 40 participants will be included in the dose escalation

Figure 4: EVEREST-2 Phase 1 Dose Escalation Study Design



BOIN, Bayesian optimal interval; DL, dose level; IL, interleukin; LD, lymphodepleting chemotherapy; RP2D, recommended phase 2 dose.

RESULTS

- The first patient was dosed in EVEREST-2 in May 2024 and, as of March 31, 2025, 5 patients have been enrolled and have received A2B694 at DLs 1-2 (**Table 1**)
  - One patient in each DL received a half dose because they weighed <50 kg resulting in protocol-specified dose decrease; thus, actual doses received were 0.5×10^8 (n = 1), 1×10^8 (n = 3), and 2×10^8 (n = 1) cells

Table 1: Patient Demographics and Baseline Characteristics

Characteristic	Patients (N = 5)
Gender, n (%)	
Female	4 (80)
Male	1 (20)
Median age (range), years	59 (50-84)
Ethnicity, n (%)	
Hispanic	1 (20)
Not Hispanic	4 (80)
Tumor type, n (%)	
OVCA	3 (60)
PANC	1 (20)
NSCLC adenocarcinoma	1 (20)

NSCLC, non-small cell lung cancer; OVCA, ovarian cancer; PANC, pancreatic cancer.

- A2B694 was successfully manufactured for all patients and all patients received A2B694 infusion

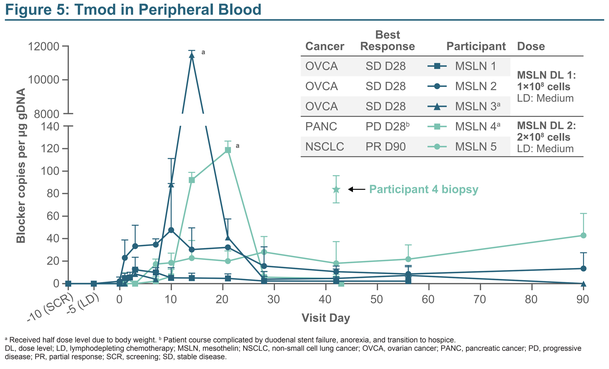
Safety

- Lymphodepleting chemotherapy has been well tolerated with no significant cytopenias observed
- All 5 patients had at least 1 adverse event (AE), the most common included:
  - Decreased appetite (n = 3 [60%], 1 serious)
  - Fatigue (n = 3 [60%])
- There were no dose-limiting toxicities, cytokine release syndrome, or related neurotoxicity
- Long-term follow-up for up to 7.3 months resulted in no new safety signals

Translational

- A2B694 was detected postinfusion in the peripheral blood in all patients (**Figure 5**)
- A2B694 was detected in a tumor biopsy collected on day 42, but not in the concurrently collected blood sample, demonstrating that A2B694 can infiltrate the tumor microenvironment and persist for weeks even when undetectable in the peripheral blood

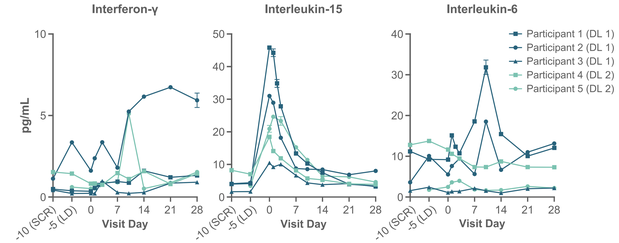
Figure 5: Tmod in Peripheral Blood



[a] Received half dose level due to body weight. [b] Patient course complicated by duodenal stent failure, anorexia, and transition to hospice.
DL, dose level; LD, lymphodepleting chemotherapy; MSLN, mesothelin; NSCLC, non-small cell lung cancer; OVCA, ovarian cancer; PANC, pancreatic cancer; PD, progressive disease; PR, partial response; SCR, screening; SD, stable disease.

- No CRS events were observed, which is consistent with low levels of serum cytokines (**Figure 6**)

Figure 6: Serum Cytokine Levels

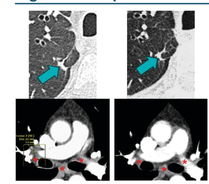


DL, dose level; LD, lymphodepleting chemotherapy; SCR, screening.

Efficacy

- Participant 5 has *KRAS G12V/STK11* commutated NSCLC adenocarcinoma that progressed on carboplatin, pemetrexed, and pembrolizumab. They achieved a partial response at day 90 postinfusion and continue on observation (**Figure 7**)

Figure 7: Response Assessment in Participant with NSCLC



RECIST 1.1	Scan		
Day	Baseline	30	90
Lung target lesion % change	0	0	-30%
Non-target			
Hilar conglomerate[a]	1 >1cm	0 <1cm	0 <1cm
Bone metastasis manubrium	1 >1cm	1 >1cm	1 >1cm
Left flank sub-centimeter	1 <1cm	1 <1cm	1 <1cm

[a] Principal investigator and local radiology considered the hilar conglomerate resolved.
NSCLC, non-small cell lung cancer; RECIST, Response Evaluation Criteria in Solid Tumors.

- Participants 1-3 had stable disease at day 28 and progressive disease by day 90 and participant 4 had progressive disease at day 28

CONCLUSIONS

- Treatment with MSLN Tmod (A2B694) is safe and tolerable, the maximum-tolerated dose has not been reached, and results from the dose escalation phase continue to determine the RP2D
- In studies of other MSLN-targeted CAR T therapies [1–3], AEs such as severe pulmonary toxicity and fatal events were observed; AEs reported in EVEREST-2 suggest that the logic-gated approach was successful at reducing on-target, off-tumor toxicity
- A2B694 showed successful expansion, persistence, and tumor infiltration
- Among the first 5 participants, a partial response was observed in 1 participant with NSCLC, showing potential clinical efficacy

References

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