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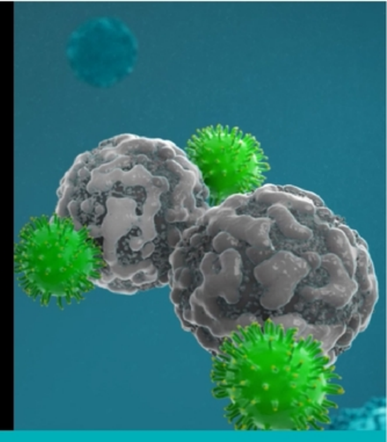
EVEREST-1: A seamless phase 1/2 study of A2B530, a carcinoembryonic antigen (CEA) logic-gated Tmod CAR T-cell therapy, in patients with solid tumors associated with CEA expression also exhibiting human leukocyte antigen (HLA)-A*02 loss of heterozygosity (LOH)



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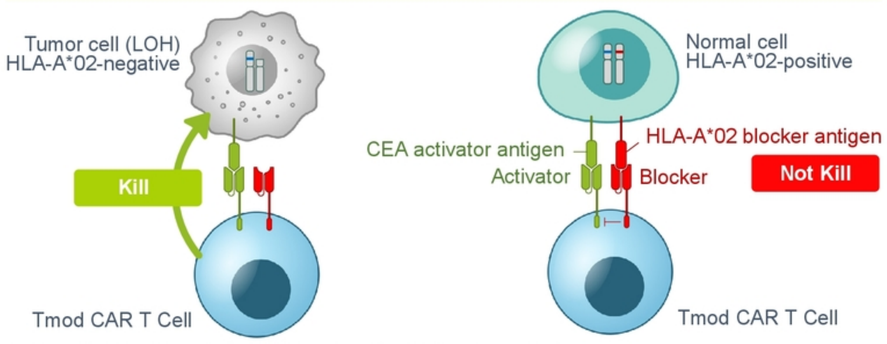
BACKGROUND AND STUDY OBJECTIVES

- 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 engagers targeting CEA, which is normally expressed in epithelial cells and can be upregulated in gastrointestinal and lung tumors, have been hampered by on-target, off-tumor toxicity [1,2]
- A2B530 is a CEA-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**) [3,4]
  - The activator receptor recognizes CEA 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) [5], which can be detected using Tempus next-generation sequencing (NGS; **Table 1**)
- EVEREST-1 (NCT05736731) is a seamless, phase 1/2, open-label, nonrandomized study to evaluate the safety and efficacy of A2B530 in adult patients with solid tumors

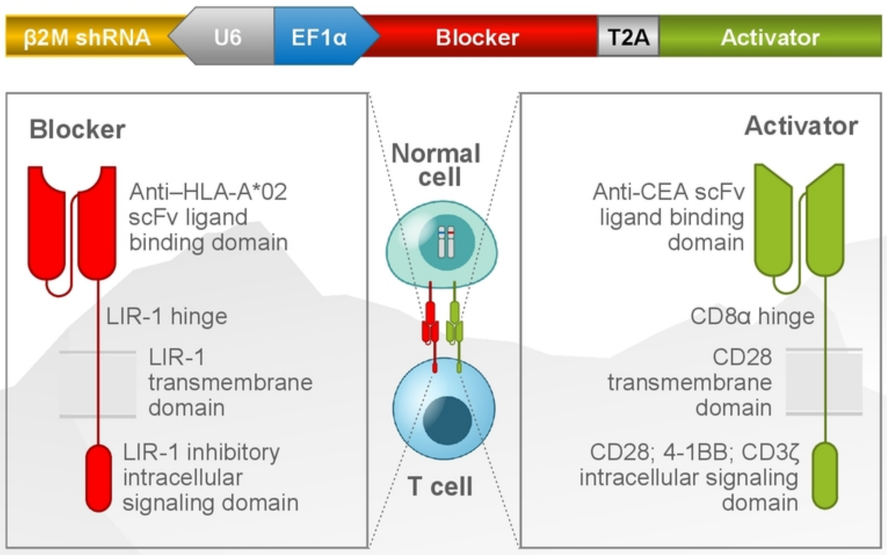
STUDY RATIONALE

Figure 1. Logic-Gated CAR T Therapy With the Goal to Reduce Toxicity: CEA (Activator) and HLA-A*02 (Blocker) [3]



CAR, chimeric antigen receptor; CEA, carcinoembryonic antigen 5; HLA, human leukocyte antigen; LOH, loss of heterozygosity.

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



The Tmod CAR construct is designed for safety with the LIR-1 inhibitory blocker [6] transcribing before the anti-CEA activator

β2M shRNA, beta-2-microglobulin short-hairpin RNA; CAR, chimeric antigen receptor; CD, cluster of differentiation; CEA, carcinoembryonic antigen 5; EF1α, elongation factor-1α; HLA, human leukocyte antigen; LIR, leukocyte immunoglobulin-like receptor; scFv, single-chain variable fragment; T2A, thosea asigna virus 2A.

Table 1. Frequency of HLA-A LOH in Advanced Tumors [7]

	Tempus HLA-A LOH advanced disease real-world
Average, % (n)	16.3 (10,867)
Pancreatic cancer, % (n)	19.6 (675)
Colorectal cancer, % (n)	15.6 (1854)
NSCLC, % (n)	23.1 (1915)

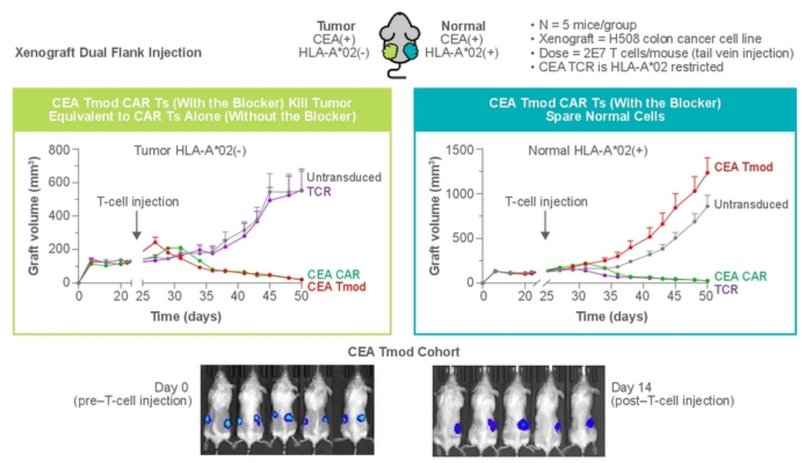
HLA, human leukocyte antigen; LOH, loss of heterozygosity; NSCLC, non-small cell lung cancer.

STUDY RATIONALE (CONTINUED)

Nonclinical Data

- Nonclinical studies of A2B530 demonstrated improved selectivity and a therapeutic safety window with comparable efficacy to National Cancer Institute (NCI) benchmark CEA T-cell receptor (**Figure 3**)
  - Approximately 2 weeks after cell infusion, A2B530 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 CEA-targeted CAR Ts experienced regressions of both tumor and "normal" grafts

Figure 3. CEA Tmod CAR T (A2B530) In Vivo Study Demonstrates Potency Comparable to NCI Benchmark CEA TCR [1,5]

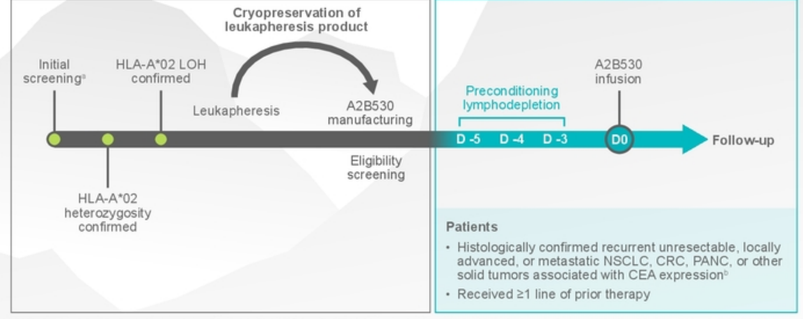


CAR T, chimeric antigen receptor T cell; CEA, carcinoembryonic antigen 5; HLA, human leukocyte antigen; NCI, National Cancer Institute; TCR, T-cell receptor.

STUDY DESIGN

- EVEREST-1 (NCT05736731) is a first-in-human, phase 1/2, multicenter, open-label, nonrandomized study to evaluate the safety and efficacy of a single-dose of A2B530 Tmod CAR Ts in adults with recurrent unresectable, locally advanced, or metastatic cancer with CEA expression
- Patients are enrolled to EVEREST-1 through BASECAMP-1 (NCT04981119), a master prescreening study that identifies patients with HLA LOH at any time in the course of their disease; enrolled patients undergo leukapheresis and, when clinically appropriate, CAR Ts are manufactured for the EVEREST-1 study (**Figure 4**)

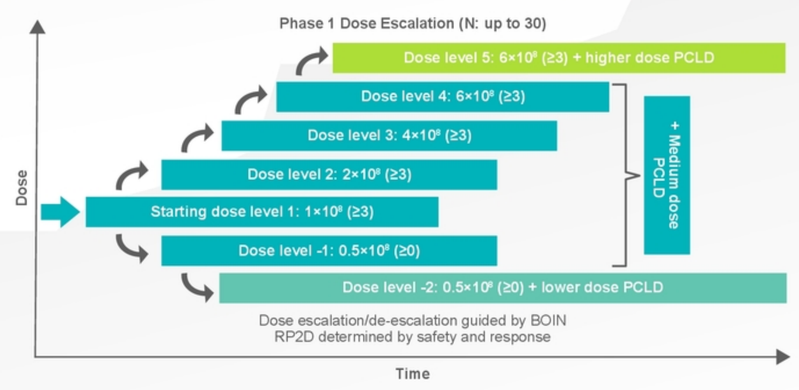
Figure 4. Study Schema: BASECAMP-1 to EVEREST-1



[a] May occur at any point in disease course. [b] For patients with CRC or PANC, CEA assessment will be performed retrospectively, and the result is not needed for enrollment. CAR T, chimeric antigen receptor T cell; CEA, carcinoembryonic antigen 5; CRC, colorectal cancer; HLA, human leukocyte antigen; LOH, loss of heterozygosity; NSCLC, non-small cell lung 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 A2B530 and to determine a recommended phase 2 dose (RP2D; **Figure 5**); 9 to 30 patients will be included in the dose escalation

Figure 5. EVEREST-1 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 cells processing, and with sufficient stored cells available for Tmod CAR T therapy
- Histologically confirmed recurrent unresectable, locally advanced, or metastatic PANC, CRC, NSCLC, or other solid tumors associated with CEA expression; measurable disease is required with lesions of >1.0 cm by computed tomography (soluble CEA is not acceptable as the sole measure of disease)
- 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 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-1 Study Objectives and Endpoints

Objectives
- **Phase 1:** Determine the safety and the optimal dose of A2B530 (after PCLD) in participants with solid tumor disease
- **Phase 2:** Determine the further safety and efficacy of A2B530

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 A2B530
- Serum cytokine analysis

PCLD, preconditioning lymphodepletion.

TRIAL STATUS

- As of May 1, 2024, 10 patients have been enrolled on EVEREST-1
- A2B530 was successfully manufactured for all patients, and all patients have received A2B530 infusion, with the first patient dosed in May 2023 (**Table 2**)
- Dose escalation is ongoing

Table 2. Study Accrual

	Dose Level 1	Dose Level 2	Dose Level 3	Dose Level 4
Patients accrued, n	3	3	3	1
A2B530 successfully manufactured, n (%)	3 (100)	3 (100)	3 (100)	1 (100)
A2B530 infusion received, n	3	3	3	1

SITE LIST

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