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EVEREST-1: Initial safety data from a seamless phase 1/2 study of A2B530, a logic-gated Tmod CAR T-cell therapy, in patients with solid tumors associated with CEA expression also exhibiting HLA-LOH

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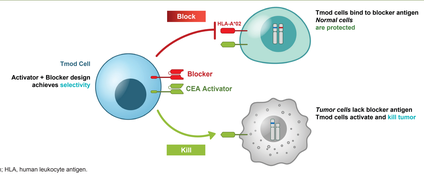
BACKGROUND AND STUDY OBJECTIVES

- 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 (**Figure 1**) [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 [5]; for patients who are germline HLA-A*02 heterozygous, loss of the allele may occur in tumor cells, known as loss of heterozygosity (LOH), which can be detected using Tempus next-generation sequencing (NGS)
- EVEREST-1 (NCT05736731) is a seamless, phase 1/2, open-label, nonrandomized study to evaluate the safety and efficacy of A2B530 in adults with solid tumors

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

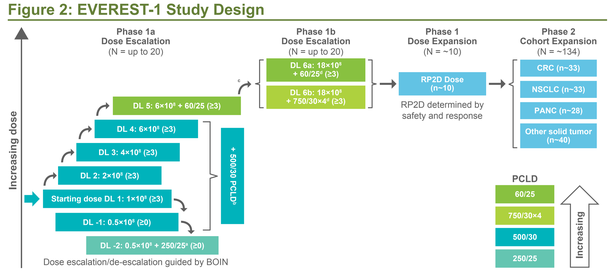


CEA, carcinoembryonic antigen; HLA, human leukocyte antigen.

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 non-small cell lung cancer (NSCLC), colorectal cancer (CRC), pancreatic cancer (PANC) or other solid tumors associated with CEA expression
- Participants 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 participants undergo leukapheresis and, when clinically appropriate, CAR Ts are manufactured for the EVEREST-1 study
- 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 2**); 9 to 40 participants will be included in the dose-escalation

Figure 2: EVEREST-1 Study Design



ᵃIf dose de-escalation to dose level -2 occurs and dose level -2 is deemed safe, dose escalation of cell dose will be evaluated through dose levels 1–4 with 250/25 PCLD. ᵇIf toxicities are observed relative to 500/30 PCLD, the SRT may recommend reduction to 250/25 PCLD if necessary. ᶜCohorts shown are priority for enrollment, additional dose levels may be explored. ᵈLow dose IL-2 may be introduced after at least 3 participants have been treated without a DLT.
AE, adverse event; BOIN, Bayesian optimal interval design; CRC, colorectal cancer; DL, dose level; DLT, dose-limiting toxicity; NSCLC, non-small cell lung cancer; PANC, pancreatic cancer; PCLD, preconditioning lymphodepletion; RP2D, recommended phase 2 dose.

RESULTS

- The first participant was dosed in EVEREST-1 in May 2023 and, as of September 1, 2024, 14 participants have been enrolled (**Table 1**)

Table 1: Participant Demographics and Baseline Characteristics

Characteristic	Participants (N = 14)
Gender, n (%)	
Female	6 (42.7)
Male	8 (57.1)
Median age (range), years	
Female	61 (46–76)
Male	58 (34–70)
Cancer type, n (%)	
PANC	4 (29)
CRC	10 (71)
Median prior lines of anti-cancer therapy (range)	
PANC	2 (1–3)
CRC	2 (1–6)
Race, n (%)	
White	11 (79)
Asian	1 (7)
Other	2 (14)
Ethnicity, n (%)	
Hispanic	2 (14)
Not Hispanic	12 (86)

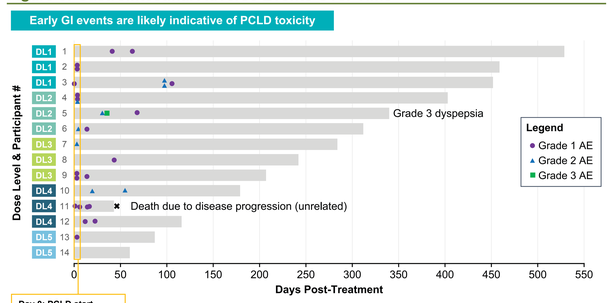
CRC, colorectal cancer; PANC, pancreatic cancer.

- A2B530 was successfully manufactured for all participants, and all participants received A2B530 infusion
- Dose level (DL) 1 to 5 have been administered, with 3 participants at each through DL 4 and 2 participants at DL 5
- Two participants with pancreatic cancer are at 1-year post-infusion, and dose-escalation is ongoing

Safety

- Lymphodepleting chemotherapy has been well tolerated
  - Neutropenia nadired at days 7-10, with recovery in all participants, and no significant anemia or thrombocytopenia was observed
- There have been no dose-limiting toxicities, grade >3 serious adverse events (SAE), nor neurotoxicity related to A2B530; most gastrointestinal (GI) adverse events (AE) were grade 1 or 2 (**Figure 3**)
  - One participant in DL 2 (2×10^8 cells) had grade 2 cytokine release syndrome (CRS), which resolved with supportive therapy. Later, the diagnosis of CRS was confounded by a positive blood culture from the participant's central line, which was determined to be *Klebsiella*; antibiotics were initiated
  - A 71-year-old female in DL 2 with metastatic PANC received gastric radiation 28 days before A2B530 administration. The participant was admitted to the hospital on post infusion Day 24 with grade 3 dyspepsia that was preceded by peak serum IFNγ, TNFα, and granzyme B. The event resolved in 3 days with medical management. The participant had a confirmed partial response at day 30 and month 6 by central evaluation (per Response Evaluation Criteria in Solid Tumors v1.1 on non-irradiated tumors)
- There have been no safety issues in participants at their 1-year follow-up visits and beyond

Figure 3: Gastrointestinal Adverse Events Over Time

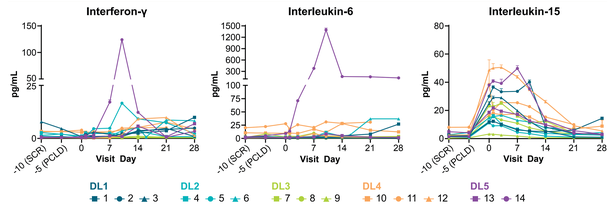


AE, adverse event; DL, dose level; GI, gastrointestinal; PCLD, pre-conditioning lymphodepletion.

Translational

- Few CRS events were observed, which is consistent with low levels of serum cytokines (**Figure 4**)

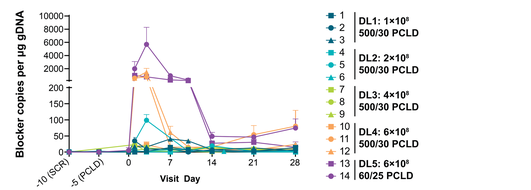
Figure 4: Serum Cytokine Levels



CRS, cytokine release syndrome; PCLD, preconditioning lymphodepletion; SCR, screening.

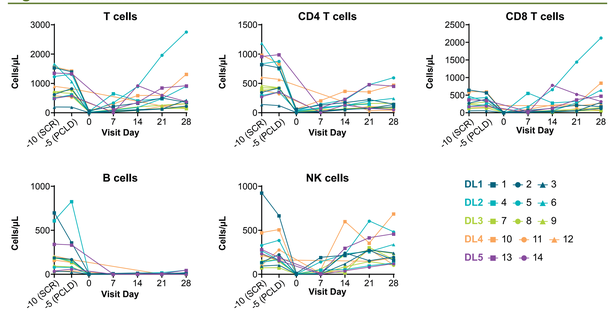
- EVEREST-1 peak expansion shows a possible dose-response (**Figure 5**)

Figure 5: A2B530 Blood Levels vs Time



A2B530 levels in the peripheral blood as measured by ddPCR. Plotted values represent mean and standard deviation from triplicate wells.
ddPCR, droplet digital polymerase chain reaction; DL, dose level; PCLD, preconditioning lymphodepletion; SCR, screening.

Figure 6: Immune Cell Blood Levels Over Time

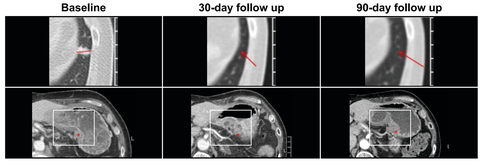


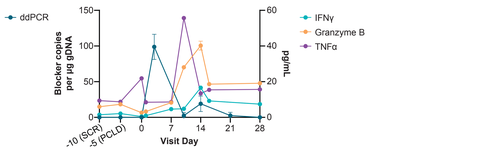
T, B, and NK cells in the peripheral blood were measured at the indicated visit date using a validated flow cytometric assay. The following cell surface markers were used to define each population: T cells [CD45(+)CD3(+)], CD4 T cells [CD45(+)CD3(+)CD4(+)], CD8 T cells [CD45(+)CD3(+)CD8(+)], B cells [CD45(+)CD19(+)] and NK cells [CD45(+)CD3(-)CD16/56(+)].
DL, dose level; PCLD, preconditioning lymphodepletion; SCR, screening.

Efficacy

- Central review has been completed for the 6 participants in DL 1 and 2
- One participant (Patient #5) with pancreatic cancer at DL 2 with detection of Tmod in peripheral blood had a partial response by central review per RECIST1.1 and stable disease by local review (**Figure 7**)

Figure 7: Longitudinal Assessment of a Participant with Pancreatic Cancer (DL 2)





A2B530 levels measured by ddPCR. Plotted values represent mean and standard deviation from triplicate wells. For cytokines, plotted values represent mean and standard deviation from duplicate measurements.
DL, dose level; gDNA, genomic DNA; IFNγ, interferon gamma; PCLD, preconditioning lymphodepletion; SCR, screening; TNFα, tumor necrosis factor alpha.

CONCLUSIONS:

- Treatment with CEA Tmod (A2B530) is safe and tolerable, and the maximum tolerated dose has not been reached
- No dose-limiting toxicities observed throughout dose-escalation in 14 participants
- No significant safety signals attributed in short- or long-term follow-up (including 2 participants at 1 year)
- In studies by NCI and others [1,2] at similar doses, on-target, off-tumor toxicity manifested as colitis and other GI AEs; GI AEs reported in EVEREST-1 suggest that the Tmod blocker is reducing on-target, off-tumor toxicity
- Among the first 6 participants dosed on the lowest doses of A2B530, a partial response was observed by central review in 1 out of 3 participants with pancreatic cancer, showing potential clinical efficacy
- Pharmacokinetic data from the 14 participants treated with DL 1–5 show a potential dose-response
- Dose-escalation continues to determine RP2D

NEXT STEPS

- We are adding additional dose-escalation cohorts in a Phase 1b portion of the study to test higher cell doses; IL-2 may also be added (**Figure 2**)

References

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