

### BASECAMP-1: LEVERAGING HLA LOSS OF HETEROZYGOSITY IN SOLID TUMORS BY NGS TO IDENTIFY PATIENTS WITH RELAPSED SOLID TUMORS FOR FUTURE CEA AND MSLN LOGIC-GATED TMOD™ CAR T-CELL THERAPY

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**Background** Solid tumors comprise >90% of cancers. Non-small cell lung cancer (NSCLC), metastatic colorectal cancer (CRC), and pancreatic cancer are the leading causes of cancer-related mortality (5-year overall survival: 26%, 15%, and 11%, respectively).<sup>1</sup>

Chimeric antigen receptor (CAR) T-cell therapy has demonstrated clinical efficacy in hematologic malignancies.<sup>2,3</sup> However, translating engineered T-cell therapies to solid tumors has proven to be challenging due to a lack of tumor-specific targets that can discriminate cancer cells from normal cells. Previous studies using carcinoembryonic antigen (CEA) T-cell receptors and mesothelin (MSLN) CARs resulted in dose-limiting on-target, off-tumor toxicities.<sup>4,5</sup>

To create a therapeutic safety window, Tmod CAR T-cell therapy utilizes dual-signaling receptors to create a robust logic gate capable of killing tumor cells, while leaving healthy cells intact.<sup>6,7</sup>

The 2 receptors in Tmod CAR T-cell therapy comprise an activator that recognizes an antigen on the surface of tumor cells that may also be present on normal cells, such as CEA and MSLN, and a blocker that recognizes a second surface antigen from an allele lost only in tumor cells (figure 1).<sup>8,9</sup>

Human leukocyte antigen (HLA) loss of heterozygosity (LOH) offers a definitive tumor versus normal discriminator target for CAR T-cell therapy.<sup>10</sup> The frequency of HLA LOH among advanced NSCLC, CRC, and pancreatic cancers in the Tempus real-world dataset is 16.3% with a range of 15.6%-23.1%.<sup>11</sup> LOH can be reliably detected using the Tempus xT-Onco next-generation sequencing (NGS) assay.<sup>12,13</sup> Different activator/blocker combinations can be engineered with the Tmod platform technology and may be applied to T cells and natural killer cells in autologous and allogeneic settings.

BASECAMP-1 is a currently enrolling observational study with key objectives: 1) To identify patients with somatic HLA LOH eligible for Tmod CAR T-cell therapy, and 2) Subsequent apheresis and manufacturing feasibility for the future EVEREST CEA or MSLN Tmod CAR T-cell studies.

**Methods** BASECAMP-1 (NCT04981119) patient eligibility has 2 parts (figure 2): 1) Patients will be initially screened to identify germline HLA-A\*02 heterozygosity by central NGS. If HLA-A\*02 heterozygosity is confirmed, primary archival tumor tissue will be analyzed for somatic mutations by xT-Onco NGS testing; 2) If the tumor demonstrates HLA-A\*02:01 LOH and the patient is eligible after screening, the

patient will undergo apheresis. Banked T cells will be available for the autologous EVEREST Tmod CAR T-cell therapy interventional study to reduce waiting time at relapse.

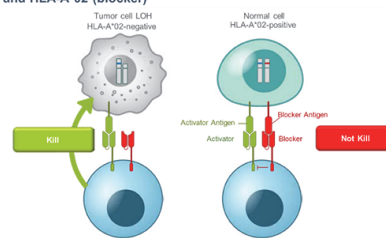
Trial Registration ClinicalTrials.gov, NCT04981119

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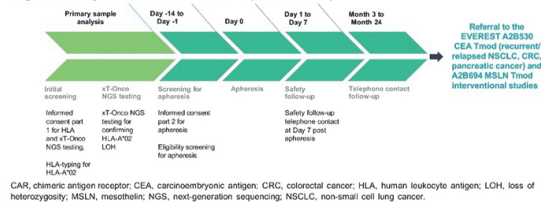
**Ethics Approval** The study was approved by site IRBs

**Figure 1. Logic-gated CAR T with the goal to reduce toxicity: CEA and MSLN (activators) and HLA-A\*02 (blocker)**



**Abstract 639 Figure 1**

**Figure 2. Study schema for BASECAMP-1 (NCT04981119)**



CAR, chimeric antigen receptor; CEA, carcinoembryonic antigen; CRC, colorectal cancer; HLA, human leukocyte antigen; LOH, loss of heterozygosity; MSLN, mesothelin; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer.

**Abstract 639 Figure 2**

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