BASECAMP-1: Leveraging Human Leukocyte Antigen A (HLA-A) Loss of Heterozygosity (LOH) in Solid Tumors to Identify Patients for Carcinoembryonic Antigen (CEA) and Mesothelin (MSLN) Logic-Gated Tmod Chimeric Antigen Receptor (CAR) T-Cell Therapy

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BACKGROUND
• Metastatic non-small-cell lung cancer and mesotheliomas are throracic malignancies with poor outcomes, with 5-year survival rates of 5% [1].

• Chimeric antigen receptor (CAR) T-cell therapy has demonstrated improved clinical outcomes in hematologic malignancies [2,3]. However, translating engineered T-cell therapies to solid tumors proves difficult due to a lack of somatic alterations that distinguish cancer cells from normal cells. In previous studies, the use of CARs, consisting of extracellular receptor domains and intracellular signaling domains, has been shown to reduce tumor toxicities [4-6].

• Tmod CAR T-cell is a logic-gated cellular therapy that addresses these challenges by leveraging dual receptors capable of killing tumor cells while leaving healthy cells intact [7]. Tmod platform technology is a versatile system that may be applied to T cells and natural killer cells in numerous and novel settings.

 STUDY RATIONALE

Tmod CAR T cells (MSLN Tmod cohort: tumor MSLN Tmod cohort: normal)

A representative example of clinical HLA LOH (Figure 3), where discordance is observed in read coverage of HLA-A*0201 between the tumor and matched normal samples [8].

• HLA-A*0202 D1 LOH can be reliably detected using the Tempus xT clinical diagnostic test (Table 1).

Table 1. Frequency of HLA-A LOH in advanced solid tumors

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>HLA-A LOH frequency (%)</th>
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<tbody>
<tr>
<td>NSCLC</td>
<td>19.1</td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>14.7</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>12.3</td>
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• In vivo studies show that Tmod maintains selectivity:

- Tumor (HLA-A*0202) and “normal” (HLA-A*0201) cells were implanted subcutaneously in NOD scid gamma (NSG) mice. Tmod CAR T cells were administered at baseline when tumor reached 100-150 mm. Approximately 2 weeks following cell injection, Tmod CAR T-cell treated mice (shown in red) experienced selective regression of tumor grafts while “normal” tumor grafts continued to grow. Mice treated with CEA or MSLN CAR T cells (shown in green) experienced regressions of both tumor and “normal” tumor grafts (Figures 5 and 6).

 STUDY DESIGN AND METHODS

Study design:

- In chemotherapy-naïve patients with NSCLC, patients with NSCLC, and patients with NSCLC, the study enrolled patients in the 1B phase (pre-T-cell injection) (Figures 7 and 8).

- Patients with ECOG PS 0-1 were enrolled for Phase 1a (tumor tissue undergoing HLA-typing for HLA-A*0201 LOH).

SITE LIST

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