differentiation state and enrich cellular stemness.² This would enhance TILs in vivo anti-tumor activity and prolong their survival. Elucidating TILs and their relations with tumor's PD-L1 expression would allow clinicians to appropriately recognize sarcoma's tumor immune environments and select the most desirable infiltrates for superior ACT.

Ethics Approval The study was approved by Mount Sinai Hospital's Ethics Board, approval number 01-0138-U.

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A POTENT AND OFF-THE-SHELF ONK CELL THERAPY PRODUCT TARGETS HER2+ CANCER CELLS AND RESISTS SUPPRESSIVE TUMOR MICROENVIRONMENT

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Background Autologous or allogeneic natural killer (NK) cells possess efficient cytotoxicity against tumor cells without severe side effects such as CRS or graft-versus-host disease (GvHD). In addition to chimeric antigen receptor (CAR) strategy, antibody-cell conjugates (ACC) platform provides more efficient way to arm NK cells with binding specificity and enhanced potency against target cells. In this work, we develop a NK cell therapy product ACE1702, a novel NK cell line oNK conjugated with trastuzumab, and assess its potency against HER2+ solid tumors.

Methods oNK cells were covalently conjugated with monoclonal antibody Trastuzumab after sublethal irradiation by our patented antibody-cell conjugates (ACC) platform to become our cryopreserved final product ACE1702 compliant with current good manufacturing practice (cGMP). Function of ACE1702 was validated by real-time xCELLigence analyzer and MTT assay in vitro. Efficacy of intraperitoneally (ip.) delivered ACE1702 was evaluated in tumor-bearing female immune compromised NSG mice. Characterization of ACE1702 was analyzed by flow cytometry.

Results We demonstrated that the trastuzumab-armed oNK cells, ACE1702, exerted human epidermal growth factor 2 (HER2) binding specificity and enhanced cytotoxicity against various types of cancer cells with different grade of HER2 expressions compared to control oNK cells in vitro. In vivo results in human ovarian cancer cell line SK-OV-3-bearing xenograft mouse model further supported the in vitro observations. Of note, ACE1702 also displayed a better cytotoxicity against HER2+ cancer cells than trastuzumab and its derived antibody-drug conjugate. ACE1702 also remained cytotoxicity against cancer cells in the suppressive tumor microenvironment. Characterization revealed a preferential expression of NK activation receptors, and conjugation of trastuzumab with cell membrane proteins responsible for NK activity capacitated ACE1702 with enhanced cytotoxicity. These results underscore the potency of ACE1702 in eradication of cancer cells.

Conclusions Here we introduced a novel trastuzumab-modified oNK cell product with enhanced specificity against myriad types of HER2+ cancers. Selective conjugation of trastuzumab with membrane proteins contributing to NK activation conferred ACE1702 with enhanced cytotoxicity even in the suppressive tumor microenvironment.

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Trial Registration None

Ethics Approval The animal study was conducted according to protocols approved by the Institutional Animal Care and Use Committee of Muragenics.

Consent None

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ADOPTIVE CELL THERAPY RESPONSE IN MELANOMA IS MEDIATED BY STEM-LIKE CD8 T CELLS

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Background Adoptive T cell therapy (ACT) utilizing ex vivo-expanded autologous tumor infiltrating lymphocytes (TILs) can result in complete regression of human cancers.¹ Successful immunotherapy is influenced by several tumor-intrinsic factors.²⁻³ Recently, T cell-intrinsic factors have been associated with immunotherapy response in murine and human studies.⁴ Analyses of tumor-reactive TILs have concluded that anti-tumor neoantigen-specific TILs are enriched in subsets defined by the expression of PD-1 or CD39.⁶⁻⁷ Thus, there is a lack of consensus regarding the tumor-reactive TIL subset that is directly responsible for successful immunotherapies such as ICB and ACT. In this study, we attempted to define the fitness landscape of TIL-enriched infusion products to specifically understand its phenotypic impact on human immunotherapy responses.

Methods We compared the phenotypic differences that could distinguish bulk ACT infusion products (I.P.) administered to patients who had complete response to therapy (complete responders, CRs, N = 24) from those whose disease progressed following ACT (non-responders, NRs, N = 30) by high dimensional single cell protein and RNA analysis of the I.P. We further analyzed the phenotypic states of anti-tumor neoantigen specific TILs from patient I.P (N = 26) by flow cytometry and single cell transcriptomics.

Results We identified two CD8+ TIL populations associated with clinical outcomes: a memory-progenitor CD39-negative stem-like TIL (CD39-CD69-) in the I.P. associated with complete cancer regression (overall survival, P < 0.0001, HR = 0.217, 95% CI 0.101 to 0.463) and TIL persistence, and a terminally differentiated CD39-positive TIL (CD39+CD69+) population associated with poor TIL persistence post-treatment. Although the majority (>65%) of neoantigen-reactive TILs in both responders and non-responders to ACT were found in the differentiated CD39+ state, CR infusion products also contained a pool of CD39- stem-like neoantigen-specific TILs (median = 8.8%) that was lacking in NR infusion products (median = 23.6%, P = 1.86 x 10⁻⁵). Tumor-reactive stem-like T cells were capable of self-renewal, expansion, and persistence, and mediated superior anti-tumor response in vivo.

Conclusions Our results support the hypothesis that responders to ACT received infusion products containing a pool of stem-like neoantigen-specific TILs that are able to undergo prolific