804 ANTI-TUMOR EFFECT OF A NOVEL Vβ TCR-TARGETING BIFUNCTIONAL AGENT IN COMBINATION WITH ANTI-PD1 IN CHECKPOINT REFRACTORY MURINE LUNG CANCER MODELS

[1]Shantel Angstadt*, [1]Lucas A Horn, [1]Kristen Fousek, [1]Haiyan Qin, [2]Madan Katragadda, [2]Jacques Moisan, [2]Andrew Bayliffe, [1]Jeffrey Schlom, [1]Claudia Palena. [1]*National Cancer Institute, National Institutes of Health, Bethesda, MD, USA*; [2]*Marengo Therapeutics, Cambridge, MA, USA*

Background Lung adenocarcinoma is the leading cause of cancer-related deaths nationally and worldwide. An unmet clinical need exists to overcome therapy resistance in metastatic lung cancer patients treated with the standard of care platinum-based chemotherapy combined with immune checkpoint blockade (ICB) using antibodies against the programmed cell death protein 1 (PD-1) or its ligand (PD-L1). To this end, we are evaluating the anti-tumor efficacy of a novel, bifunctional fusion molecule, mSTAR1302, comprised of an activating antibody that binds the murine variable beta 13 (Vβ13) chain of the T cell receptor (TCR), and is fused to interleukin-2 (IL-2). The Vβ13 TCR T cells were identified as a common subpopulation of tumor infiltrating T cells in various mouse tumor models. We aim to assess the preclinical use of mSTAR1302 in combination with ICB in syngeneic lung cancer models that are resistant to PD-1 blockade and platinum-based chemotherapy.

Methods The CMT64 lung cancer model was characterized for its response to anti-PD1 therapy alone or in combination with cisplatin. Subsequent studies assessed the antitumor activity of mSTAR1302 combined with anti-PD1 therapy delivered three days after mSTAR1302 administration. Tumor volumes, survival, and toxicity data were collected. Additionally, flow cytometry analysis was used to assess Vβ13 TCR T cell expansion and alterations in the tumor microenvironment immune profile.

Results Our initial results demonstrated CMT64 tumor's lack of response to anti-PD-1 or cisplatin alone and a minimal response to the combination. Subsequent experiments evaluated mSTAR1302 plus anti-PD1. While anti-PD1 had no effect, mSTAR1302 monotherapy delayed tumor growth in 50% of mice with no cures observed. The combination mSTAR1302 plus anti-PD-1 demonstrated additive effect leading to delayed tumor growth in 100% of treated mice with complete tumor regression achieved in 50% of mice. Survival of mice in the combination therapy group was significantly increased over that of mice in the monotherapy and control groups. Flow cytometry analysis on tumors showed significant increases in tumor infiltrating CD4, CD8, and NK cell numbers in the combination group, with an expansion of Vβ13 TCR CD8 T cells. Rechallenge experiments and transcriptomics analyses are ongoing to identify the mechanism of action.

Conclusions This study serves as a proof of concept that targeting and expanding Vβ13 TCR tumor infiltrating T cells via mSTAR1302 is a promising approach to treat poorly infiltrated tumors resistant to checkpoint blockade. Future studies will expand testing in additional models, various administration schedules, and the addition of chemotherapy.

Ethics Approval All animal studies were approved by the NIH Intramural Animal Care and Use Committee.

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