442-N RNA PRIMED SMAR-T™ CELLS AGAINST MULTIPLE DRIVER MUTATIONS, ALL HLA'S, DESIGNED FOR FIRST LINE THERAPY

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Background Success of immune checkpoint inhibitors, e.g., anti-PD1 antibodies have revolutionized cancer immunotherapy by demonstrating that a patient's own T-cells recognize and treat cancer. The efficacy of PD-1 blockade is driven by recruitment of new T-cells from blood rather than via activation of pre-existing tumor infiltrating lymphocytes.[1] However, anti-PD1 therapy is most effective in ~5% of malignancies i.e., cancers with high mutational burden. Hence, the challenge of addressing most lower mutational burden cancers (the ~95%) needs an alternate treatment strategy.

Methods We address this challenge by using RNA to prime and expand peripheral T-cells to cancer-specific mutations ex-vivo. Using our proprietary, patented, and robust manufacturing method, we can generate T-cell populations reactive to as low as 8 and as high as 40 cancer-specific mutant proteins.

Results In in-vitro cytotoxicity assays, our T-cells have cancer mutation-specific cytotoxicity and do not kill the normal cells. Further, the T-cells express homing receptors enabling them to infiltrate tumors and express high levels of TNFα and IFNγ, which are associated with effective tumor cytotoxicity and pro-inflammatory modification of tumor microenvironment (TME). Additional characterization shows these cells to be predominantly CD4+ and CD8+ T-cells bearing central and effector memory phenotypic with negligible regulatory or exhausted T-cells.

Conclusions We believe our T-cells can be used for cellular therapy in conjunction with, or as an alternative to, immune checkpoint inhibitors to treat lower mutational burden cancers present in most patients.

REFERENCE

1. Yost KE, et al. Nat Med. 2019 Aug;**25**(8):1251–1259.

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