THE FUNCTIONAL ACTIVITY OF GAVO-CEL TRUC-T CELLS IS NOT IMPAIRED BY SOLUBLE MESOTHELIN

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Background Gavo-cel is an autologous and HLA-independent T-Cell Receptor Fusion Construct (TRuCTM) T cell therapy that targets mesothelin-expressing tumors and is under Phase 2 evaluation for treatment-resistant MPM, NSCLC, cholangiocarcinoma, and ovarian cancer tumors (NCT03907852). Mesothelin (MSLN) is a 71 kDa GPI-anchored membrane protein that undergoes proteolytic membrane shedding to generate soluble mesothelin-related peptides (sMRPs) whose levels are correlated with tumor burden in MPM. sMRPs contain the juxtamembrane epitope of that is recognized by the MH1 binder domain of the gavo-cel TRuC and whose levels are correlated with tumor burden in MPM. Because shed MSLN has been implicated as a potential obstacle to successful anti-MSLN therapies, including cell therapies, we assessed the impact of soluble MSLN (sMSLN) on the function of gavo-cel and or allogeneic anti-MSLN TRuC, MH1gd.

Methods In this study, we generated primary human TRuC-T cells modeling MSLN-targeting clinical agent gavo-cel or that express MH1gd TRuC, and then measured the impact of soluble MSLN on the in vitro activation, cytotoxicity, and cytokine response of gavo-cel or MH1gd during acute and chronic challenge with antigen-expressing tumor cells. We also evaluated whether sMRP in human serum impacts the in vitro cytotoxicity and cytokine response of gavo-cel in response to MSLN-expressing tumor cell lines.

Results High, supraphysiological levels of the full-length shed domain of MSLN, sMSLN, does not impair, block, or disrupt the effector function of gavo-cel or MH1gd TRuC-T cells with respect to in vitro cytotoxicity or cytokine production. Furthermore, gavo-cel demonstrates potent efficacy in vivo in a tumor model characterized by circulating sMSLN.

Conclusions Our data indicate that both gavo-cel and allogeneic MSLN-targeting TRuC-T cells are not susceptible to functional suppression by sMRPs, even at supraphysiological levels that far exceed those found in cancer patients.