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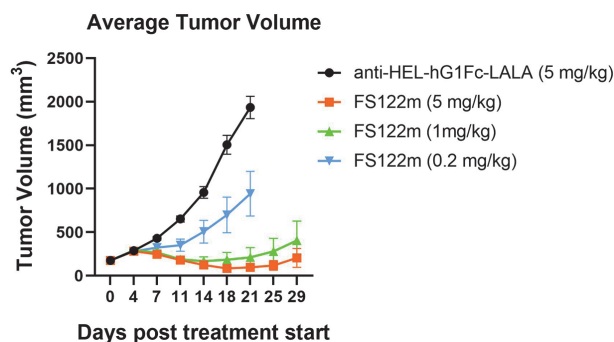
M9657, A NOVEL TUMOR-TARGETED CONDITIONAL ANTI-CD137 AGONIST DISPLAYS MSLN-DEPENDENT ANTI-TUMOR IMMUNITY

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Background The costimulatory receptor CD137 (also known as 4-1BB and TNFRSF9) plays an important role in sustaining effective cytotoxic T cell immune responses and its agonism has been investigated as a cancer immunotherapy. In clinical trials, the systemic administration of the 1st generation CD137 agonist monotherapies, utomilumab and urelumab, were suspended due to either low anti-tumor efficacy or hepatotoxicity mediated by recognized epitope on CD137 and FcγR ligand-dependent clustering.

Methods M9657, a bispecific antibody was engineered a tetra-valent bispecific antibody (mAb2) format with the Fab portion binding to the tumor antigen Mesothelin (MSLN) and a modified CH2-CH3 domain as Fc antigen binding (Fcab) portion binding to CD137. M9657 has a human IgG1 backbone with LALA mutations to abrogate the binding to Fcγ receptor. The biological characteristics and activities of M9657 were investigated in a series of in vitro assays and the in vivo efficacy was investigated in syngeneic tumor models with FS122m, a murine-reactive surrogate with the same protein structure of M9657.

Results M9657 binds efficiently to both human and Cynomolgus CD137 as well as MSLN. In the cellular functional assay, M9657 displayed MSLN- and TCR/CD3 interaction (signal 1)-dependent cytokine release and tumor cell cytotoxicity associated with Bcl-XL activation and immune memory formation. FS122m demonstrated potent MSLN- and dose- dependent in vivo anti-tumor efficacy (figure 1). Comparing with 3H3, a Urelumab surrogate Ab, FS122m displayed an improved therapeutic window with significantly lower for on-target /off-tumor toxicity.



Abstract 757 Figure 1 FS122m displayed dose-dependent anti-tumor efficacy

Conclusions Taken together, M9657 exhibits a promising developability profile as a tumor-targeted immune agonist with potent anti-cancer activity, but without systemic immune activation.

Ethics Approval All animal experiments were performed in accordance with EMD Serono Research & Development Institute (protocol 17-008, 20-005) and Wuxi AppTec Animal Care and Use Committee (IACUC) guidelines.

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