**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 FcγR ligand-dependent clustering.

**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.

**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.

http://dx.doi.org/10.1136/jitc-2021-SITC2021.757