326 THE ANTI-TIGIT ANTIBODY M6223 INDUCES SIGNIFICANT ANTI-TUMOR EFFICACY AND IMMUNE RESPONSE VIA MULTIPLE MECHANISMS OF ACTION

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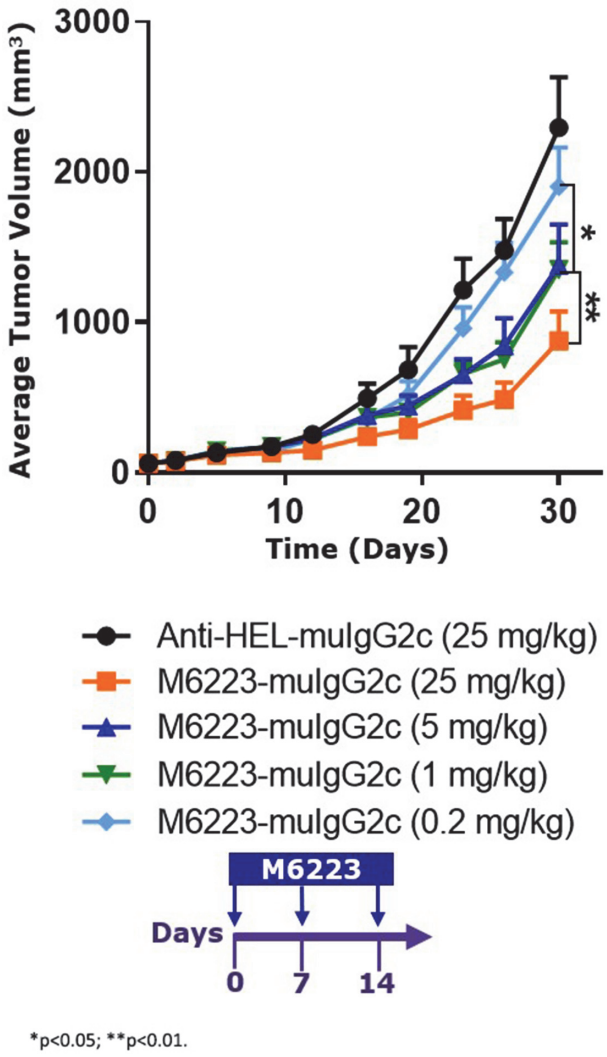
Background M6223 is a fully human antagonistic anti-T cell immunoreceptor with immunoglobulin and ITIM domains (TIGIT) antibody in IgG1 format with Fc-mediated effector function.

Methods The ability of M6223 to block the interaction of TIGIT with its ligands, CD155 and CD112, and the interaction of TIGIT with CD226 was determined by a flow cytometry-based binding assay. The anti-tumor efficacy, immune profile, and effector function of M6223 were investigated in syngeneic tumor models in huTIGIT knock-in mice. M6223 was either formatted with an effector competent mouse IgG2c constant region (M6223-muIgG2c) or formatted with effector null mouse IgG1-D256A constant region (M6223-muIgG1) as two versions of chimeric antibodies for the in vivo studies.

Results M6223 dose-dependently blocked the binding of TIGIT to its ligands, including CD155 and CD112, thereby inhibiting a TIGIT-mediated immunosuppressive pathway. In addition, M6223 interrupted the interaction of TIGIT with the costimulatory receptor CD226. By blocking the interactions, the chimeric protein M6223-muIgG2c showed anti-tumor efficacy in multiple tumor models, including an MC38 tumor model (figure 1), and generated tumor antigen-specific long-term protective immunity in immunocompetent huTIGIT knock-in mice. M6223 monotherapy dose-dependently elevated the ratio of CD8+ cytotoxic T cells to regulatory T cells and the ratio of CD226 to TIGIT expression in immune cells in the tumor microenvironment. We also found that M6223 selectively depleted suppressive and exhausted TIGIT+ immune cell subsets and the anti-tumor activity of effector null M6223-muIgG1 was significantly lost ($p<0.0001$), suggesting that Fc-mediated effector function contributes to M6223 anti-tumor activity. Antibody depletion studies demonstrated that CD8+ T cells and natural killer cells contributed to the anti-tumor activity of M6223 in a complementary manner.



Abstract 326 Figure 1 M6223-muIgG2c displayed dose-dependent anti-tumor efficacy. M6223-muIgG2c displayed dose-dependent anti-tumor efficacy in an MC38 tumor model in hTIGIT knock-in mice.

Conclusions Given that TIGIT blockade can inhibit an immunosuppressive pathway as well as remove the suppression on a costimulatory pathway, M6223 has the potential to induce an anti-tumor immune response by three complementary mechanisms: direct blockade of the TIGIT pathway, stimulation of CD226 dimerization/activation, and depletion of TIGIT+ immune subsets by Fc-mediated effector function. Our data demonstrate that these complementary mechanisms orchestrate

the anti-tumor activity of M6223. A Phase I, first-in-human clinical trial (NCT04457778) is underway to determine the safety, tolerability, maximum tolerated dose and recommended dose for expansion of M6223 as a single agent (Part 1A) and in combination with bintrafusp alfa (Part 1B) in patients with metastatic or locally advanced solid unresectable tumors.

Ethics Approval All animal experiments were performed in accordance with EMD Serono Research & Development Institute, Inc., Billerica, MA, USA, an affiliate of Merck KGaA (protocol 17-008, 20-005) and Wuxi AppTec Animal Care and Use Committee (IACUC) guidelines.

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