Anti-tumor immunity and efficacy of combination treatment of M6223 and bintrafusp alfa versus the combination of M6223 and anti–PD-L1 in preclinical tumor models

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CONCLUSION

- **The complementary mechanisms of M6223 and bintrafusp alfa, including direct blockade of the TIGIT pathway, stimulation of CD226 dimerization/activation, and depletion of TIGIT+ immune subsets by Fc-mediated effector function, orchestrate antitumor activity in preclinical tumor models**
- **M6223 and bintrafusp alfa combination is being investigated in a Phase I clinical trial (NCT04457778) in patients with metastatic or locally advanced solid unresectable tumors**

BACKGROUND

- T cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domains (TIGIT) is an inhibitory receptor expressed on lymphocytes, and has recently emerged as a target in cancer immunotherapy[1]
- M6223 is a fully human antagonistic anti-TIGIT antibody in immunoglobulin (Ig) G1 format with Fc-mediated effector function
- Preclinical studies have demonstrated that M6223 induces an anti-tumor immune response by complementary mechanisms. These mechanisms include, but are not limited to, direct blockade of the TIGIT pathway, stimulation of CD226 dimerization/activation, and depletion of TIGIT+ immune subsets by Fc-mediated effector function
- M6223 has shown dose-dependent anti-tumor efficacy in multiple preclinical tumor models
- Bintrafusp alfa is a first-in-class bifunctional fusion protein designed to target transforming growth factor β (TGF-β) and programmed death ligand 1 (PD-L1), two key immunosuppressive pathways in the tumor microenvironment[2]

METHODS

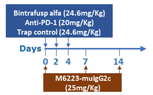
- To attenuate the tumor immunosuppressive microenvironment, the anti-tumor immunity and efficacy of combining M6223 with bintrafusp alfa were investigated in syngeneic models in humanized mice with huTIGIT knock-in sequences

RESULTS

- M6223 combined with bintrafusp alfa significantly enhanced anti-tumor efficacy and extended survival compared with either monotherapies or the combination of M6223 with anti–PD-L1 (**Figure 1**)
- M6223 combined with bintrafusp alfa stimulated higher CD8+ T cells and natural killer cells infiltration, proliferation and cytotoxicity in the tumor microenvironment in comparison to the combination of M6223 with anti–PD-L1 (**Figures 2 and 3**)
- The ratio of CD8+ T cells to regulatory T cells and the ratio of CD226 to TIGIT were significantly increased, indicating the conversion of the tumor microenvironment from an immuno-suppressive phenotype to a more immune-permissive phenotype (**Figure 4**)
- With the combination therapy, bintrafusp alfa was the main driver promoting CD8+ T cell proliferation, infiltration, and cytotoxicity (**Figure 3**)
- Alternatively, adding M6223 to bintrafusp alfa may decrease the risk of immune resistance caused by elevated TIGIT expression triggered by bintrafusp alfa (**Figure 4**)

RESULTS

Treatment schedule Figure 1



Treatment schedule Figure 2–5

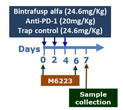


Figure legend (All figures)

- Anti-HEL mulgG2c + anti-PD-L1 isotype
- Anti-HEL mulgG2c + Trap control
- M6223-mulgG2c + anti-PD-L1 isotype
- Anti-HEL mulgG2c + anti-PD-L1
- Anti-HEL mulgG2c + bintrafusp alfa
- M6223-mulgG2c + Trap control
- M6223-mulgG2c + anti-PD-L1
- M6223-mulgG2c + bintrafusp alfa

P value definition (all figures)

ns, non-significant
* p<0.05
** p<0.01
*** p<0.001
**** p<0.0001

Figure 1. Combination treatment with M6223-muIgG2c and bintrafusp alfa enhanced anti-tumor efficacy in MC38 model in huTIGIT knock-in (KI) mice

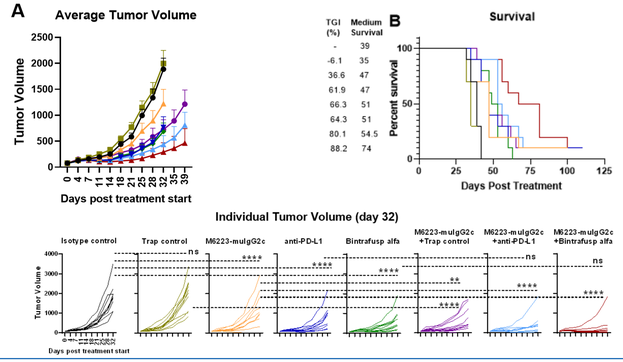
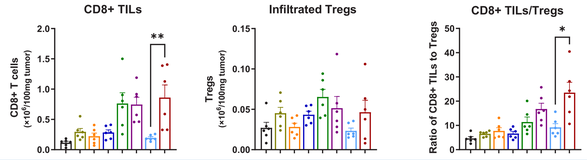


Figure 2. M6223-muIgG2c and bintrafusp alfa combination significantly increased the ratio of CD8/Tregs in MC38 tumor in huTIGIT KI mice



RESULTS

Figure 3. M6223-muIgG2c and bintrafusp alfa combination treatment significantly changed immune phenotype signature in MC38 tumor in huTIGIT KI mice

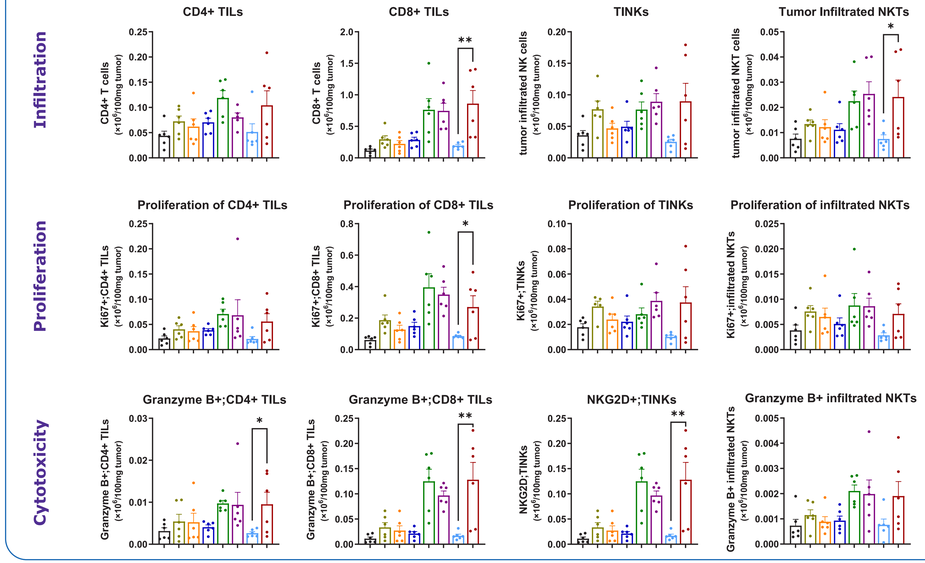
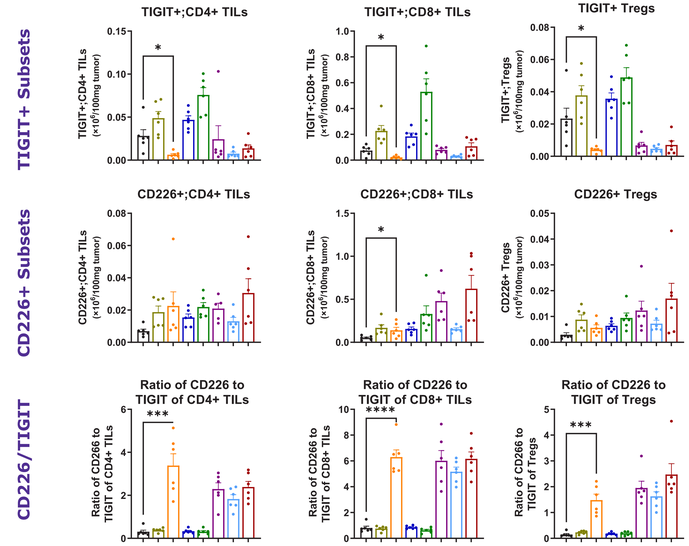


Figure 4. M6223-muIgG2c treatment significantly increased the ratio of CD226/TIGIT in MC38 tumor in huTIGIT KI mice



1. Harjunpää H and Guillerey C. Clin Exp Immunol. 2019;200:108–119. doi: 10.1111/cei.13407; 2. Lan Y, et al. Sci Transl Med. 2018;10:eaan5488. doi: 10.1126/scitranslmed.aan5488.

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