ANTI-CD161 ANTIBODY IMT-009 IS A NOVEL IMMUNOTHERAPEUTIC AGENT THAT REINVIGORATES T AND NK CELL FUNCTION AND ANTI-TUMOR EFFICACY THROUGH BLOCKING INTERACTION OF CD161 WITH ITS LIGAND CLEC2D

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Background The CLEC2D/CD161 axis is a novel ligand-receptor pathway for immunotherapeutic intervention. IMT-009 is a monoclonal, aglycosylated human IgG1 antibody directed against CD161, a C-type lectin-like receptor, which is broadly expressed on NK cells and subsets of both CD4+ and CD8+ T cells [Mathewson et al. 2021]. Its cognate ligand, CLEC2D (LLT1), is expressed on the surface of both malignant cells and immune cells, including activated B cells and myeloid cells.

Methods Functional inhibition of CD161 by IMT-009 was demonstrated by using several in vitro pharmacological and cellular assays which assessed NK cell degranulation, cytokine production and cellular cytotoxicity towards tumor targets, as well as T cell receptor signaling and polyfunctionality using primary antigen-specific human T cells. To prioritize indications that will likely benefit from CD161 blockade therapy, multiplexed immunofluorescence analysis of over 30 solid tumor types was performed.

Results IMT-009 binds CD161 with high affinity and selectivity, blocking its interaction with CLEC2D at an IC50 of 0.94 nM. In presence of CLEC2D-expressing target cells K562, NK cell degranulation, cytokine production and cellular cytotoxicity towards tumor targets is highly suppressed; IMT-009 can overcome this inhibition with an EC50 of 0.2 nM. Similarly, IMT-009 reversed CLEC2D-mediated inhibition and restored T cell receptor signaling and cytokine production in a Jurkat cell reporter system (EC50 = 3.5 nM), as well as enhanced polyfunctionality of primary antigen-specific human T cells, including secretion of TNF-α, IL2, and IFNγ (EC50 = 0.2 nM, 0.4 nM, and 1.4 nM, respectively), and direct T cell mediated cytotoxicity. IMT-009 also released CD161-mediated suppression on effector memory CD161+ CD4+ T cells, resulting in an increased frequency of IFN-γ+ cells and an increase in their proliferation indicative of a stronger recall response to antigen. Finally, multiplexed immunofluorescence data of over 30 solid tumor types showed the highest density of CLEC2D+ and CD161+ cells in the following indications: NSCLC-squamous cell carcinoma, NSCLC- adenocarcinoma, Head and Neck squamous cell carcinoma (HNSCC), Triple negative breast cancer (TNBC), Cutaneous squamous cell carcinoma and Colorectal carcinoma.

Conclusions These results support the development of IMT-009 as a novel cancer immunotherapy for application in several solid tumor indications.

REFERENCES