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

Alexandria Fusco, Elizabeth Scanlon, Franco Irvine, Flavian Brown, Jeffrey Colbert, Andy Tu, Stephanie Gaerlan, Kelly Nichols, Teresse de Rham, Matthew Huggins, Kendall Dionne, Ming Tang, Heather Flick, Alison Tisdale, Seng-Lai Tan, Shrut Malu*. Immunitas Therapeutics, Waltham, MA, USA

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