DEVELOPMENT OF IMGS-001, A NOVEL ANTI-PD-L1/PD-L2 DUAL SPECIFIC, MULTI-FUNCTIONAL ANTIBODY, TO TREAT IMMUNE EXCLUDED TUMORS

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Background Interruption of the programmed cell death-1 (PD-1) inhibitory pathway by binding PD-1 or its ligand PD-L1 is an effective treatment for various cancers, 1 although resistance is common. 2 PD-1 has a second ligand, PD-L2, that can be expressed by a variety of immunosuppressive stromal cells, endothelial cells, and tumor cells. 3 IMGS-001 is a dual specific monoclonal antibody designed to bind PD-L1 and PD-L2 and block their engagement with PD-1. The Fc region is engineered to induce robust cell-mediated cytotoxicity, enabling depletion of PD-L1+ and PD-L2+ immunosuppressive cells throughout the tumor microenvironment. Here we describe the development of IMGS-001, including potency, specificity, cytokine release potential, pharmacokinetics (PK), and repeat-dose toxicity.

Methods Affinities were measured with the Octet system. Reporter cell assays assessed PD-1 pathway blockade, antibody-dependent cellular cytotoxicity (ADCC), and antibody-dependent cellular phagocytosis (ADCP). Specificity was evaluated by Retrogenix microarray technology. Potential for spontaneous cytokine release was measured by co-culturing with healthy donor peripheral blood mononuclear cells. PK was measured in mice and in cynomolgus monkeys. In a GLP toxicity study, IMGS-001 was dosed weekly over 4 weeks at 10, 50, or 100mg/kg with a 4-week recovery.

Results The affinity of IMGS-001 to monomeric PD-L1 and PD-L2 is 7.62nM and 1.90nM, respectively. Dimer affinities are 1.28nM and 600pM. It has an EC50 of 0.3-1.1nM in a PD-1 blockade assay, the same range as pembrolizumab and avelumab. IMGS-001 has an EC50 of <0.5nM in ADCC and ADCP assays. Specificity screening showed no relevant off-target binding and there was no evidence of specific cytokine release. Mouse PK showed drug exposure of ~1.0x10^4 μg-hr/ml at the efficacious dose. Half-life was 3.2 days in mice, and 3.7 days in cynos. Repeat-dose toxicity showed mild to moderate hematological and pathological changes, all of which had evidence of reversal within the recovery period. IMGS-001 was manufactured with a titer of 5.95g/L, 98.9% monomer, and 98% purity in the first GMP batch.

Conclusions These data indicate that IMGS-001 binds PD-L1 and PD-L2 and functions per its design. It shows no biologically relevant off target effects, was administered up 100 mg/kg without toxicity, and has a viable PK profile for human administration. Its mechanisms of elimination of immunosuppressive cells with PD-1 pathway blockade could benefit patients that are resistant to existing PD-(L)1 drugs by restoring immune driven anti-tumor activity. IMGS-001 is poised to enter clinical trial in immune excluded tumors by the end of 2022.

REFERENCES

