PRECLINICAL CHARACTERIZATION OF IMGS-001, A DUAL ANTAGONIST ANTI-PD-L1, ANTI-PD-L2 ANTIBODY WITH EFFECTOR FUNCTION, TO TREAT PATIENTS RESISTANT TO IMMUNE CHECKPOINT BLOCKADE

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Background Antibody drugs which block engagement of the T cell co-inhibitory receptor programmed cell death-1 (PD-1) or its cognate ligand programmed death-1 ligand-1 (PD-L1) are a key pillar of modern oncology. While the impact of these drugs has been profound, their efficacy remains limited to cancers with pre-existing immune infiltration and/or higher numbers of mutational neoantigens. To expand the percentage of cancer patients that benefit from immunotherapy, drugs are needed which can diminish multi-modal immune suppression in immune excluded tumors to the extent that T cells can accumulate and expand sufficiently to benefit from PD-1 pathway blockade. Thus, we characterized IMGS-001, a human monoclonal antibody against PD-L1 and PD-L2 with effector functions, developed in collaboration with MD Anderson. IMGS-001 is being tested in vitro and in vivo to support clinical development in patients resistant or naïve to immuno-oncology (IO) treatment.

Methods In vivo dose-regimen anti-tumor activity was analyzed using syngeneic mouse models of colon cancer (CT26-expressing mouse PD-L2, MC38) and melanoma (B16F10 expressing mouse PD-L2). Tumor-bearing mice were treated with IMGS-001 at 5-10-20 mg/kg twice a week for 3 weeks. In addition, IMGS-001 mediated antibody dependent cellular cytotoxicity (ADCC) was assessed in immune-competent and immune-deficient mice (nu/nu) injected with CT26-PD-L2 and MDA-MB-231, respectively. In both studies, mice were treated with IMGS-001 twice a week for 3 weeks while a second group (only CT-26-PD-L2 model) was first depleted of natural killer (NK) cells.

Results IMGS-001 significantly inhibited CT26-PD-L2 tumor growth compared to PBS treatment (p=0.0239) and extended survival (p=0.0007) with an optimal dose of 10 mg/kg. Against MC38, 70% of animals treated with ≥10mg/kg IMGS-001 were alive with no evidence of tumor 70 days post-inoculation. IMGS-001 (10mg/kg) showed 90% inhibition of B16F10-PD-L2 tumor volume compared to the control (p<0.0001). In mice lacking T cells, IMGS-001 significantly inhibited MDA-MB-231 tumor growth at 10 mg/kg, indicating a mechanism of action driven by ADCC. Moreover, in NK-depleted immune-competent mice, IMGS-001 lost activity against CT26-PD-L2 (p=0.0403).

Conclusions These data suggest 10 mg/kg of IMGS-001 being the optimal dose to induce a strong anti-tumor activity in vivo. Moreover, IMGS-001 displayed a mechanism of action driven by the cytoreduction of immune suppressive stroma in vivo via ADCC. These results, with a favorable PK, the absence of off-target activity and a clean toxicology profile, support the clinical development of IMGS-001. IMG-S001 would increase the benefit of IO therapy for patients with immune-infiltrated tumors and could mediate significant clinical responses against immune-excluded cancers.