

Preclinical characterization of IMGS-001, a dual-antagonist anti-PD-L1 and PD-L2 antibody with effector function, to treat patients resistant to immune checkpoint blockade

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Background

Antibody drugs that 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 preexisting immune infiltration and/or higher numbers of mutational neoantigens. To expand the percentage of cancer patients that benefit from immunotherapy, drugs are needed that can diminish multimodal immune suppression in immune-excluded tumors to the extent that T cells can accumulate and expand sufficiently to benefit from a PD-1 pathway blockade. Thus, in collaboration with MD Anderson Cancer Center, we characterized IMGS-001, a human monoclonal antibody against PD-L1 and PD-L2 with effector function. IMGS-001 is being tested in vitro and in vivo to support clinical development in patients resistant or naive 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 administered phosphate-buffered saline (PBS) or 2.5 to 20 mg/kg IMGS-001 twice per week for 3 weeks. In some studies, RMP1-14, an anti-mouse PD-1 antibody, was included for comparison.

IMGS-001-mediated antibody-dependent cellular cytotoxicity (ADCC) was assessed in 2 studies. Immune-competent mice were injected with CT26-PDL2 subsequent to natural killer (NK) cell depletion with an anti-asialo-GM1 antibody in half the groups. NK-cell-depleted and NK-cell-competent groups were then administered either PBS or IMGS-001 twice per week for 3 weeks. In a second ADCC experiment, immune-deficient mice lacking functional T cells (nu/nu) were injected with MDA-MB-231 and administered IMGS-001, avelumab, or PBS every 3 days for a total of 7 doses.

Results

CT26-PDL2

CT26 is a murine colon carcinoma cell line expressing PD-L1 on the cell surface. It is a hot tumor model, known to have immune cell infiltration and to be sensitive to anti-PD-1 treatment. CT26 was engineered to constitutively express murine PD-L2 (CT26-PDL2) for these studies.

IMGS-001 was able to inhibit the growth of CT26-PDL2 tumors when administered intraperitoneally at 10 mg/kg twice per week. At day 25, average tumor volume in the IMGS-001-treated group was 74% smaller than in the PBS group and 55% smaller than in the anti-PD-1 group. IMGS-001 treatment had a significant effect on survival, with 56% of mice alive at the end of the study versus no mice in the PBS group.

Results

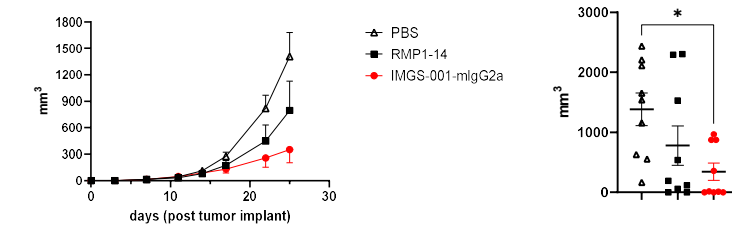


Figure 1. Left: Mean \pm SEM tumor volume (mm^3) is plotted on the y-axis against days post tumor inoculation on the x-axis. Right: Individual tumor volumes (mm^3) measured 25 days after tumor implantation are shown within each treatment group. Mean values are represented by solid black lines. One-way ANOVA with Dunnett's multiple comparison test was used to compare groups. * $P < 0.05$.

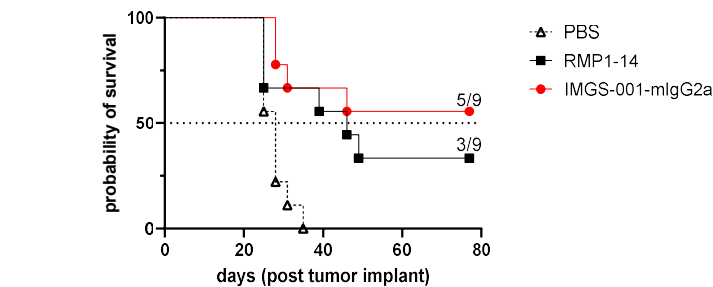


Figure 2. Kaplan-Meier plots of CT26-PDL2 tumor-bearing mice that received PBS, anti-PD-1, or IMGS-001. Mice were kept in the study for up to 77 days after tumor implant.

In a dose-ranging study, IMGS-001 administered at 2.5, 5, 10, and 20 mg/kg inhibited CT26-PDL2 tumor growth in mice. The 2 highest doses showed significant inhibition of tumor growth, but there was no difference between treatment at 10 or 20 mg/kg.

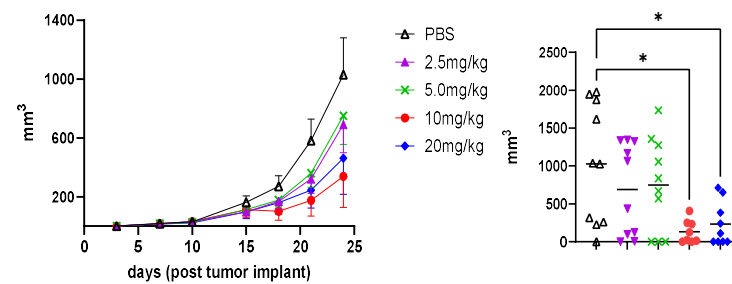


Figure 3. Left: Mean \pm SEM tumor volume (mm^3) is plotted on the y-axis against days post tumor inoculation on the x-axis. Right: Tumor volumes (mm^3) of individuals within each treatment group are shown. Mean values are represented by black lines. Robust regression and outlier removal (ROUT) was applied to remove outliers. One-way ANOVA with Tukey's multiple comparisons test was used to compare the treatment groups. * $P < 0.05$.

MC38

MC38 is a murine colon carcinoma cell line. It is a hot tumor model, known to have immune cell infiltration and to be sensitive to checkpoint inhibitors. MC38 expresses PD-L1, but not PD-L2, on the surface.

At all doses administered, IMGS-001 was able to significantly inhibit tumor growth compared to PBS, and the highest doses (10 mg/kg and 20 mg/kg) had a significant effect on overall survival. There was no statistical difference between treatment at 10 mg/kg and treatment at 20 mg/kg.

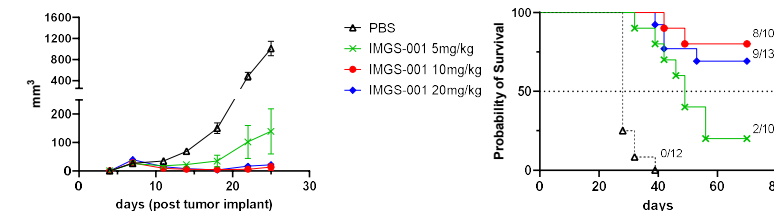


Figure 4. Left: Mean \pm SEM tumor volume (mm^3) is plotted on the y-axis against days post tumor inoculation on the x-axis. Right: Kaplan-Meier plots of MC38 tumor-bearing mice that received PBS, anti-PD-1, or 5 to 20 mg/kg IMGS-001.

B16F10-PDL2

B16F10 is a murine melanoma tumor cell line that grows aggressively in C57BL/6 mice. It is known to have poor immune cell infiltration and is therefore used as a model of cold tumors. B16F10 is not sensitive to anti-PD-1 or anti-PD-L1 treatment. This cell line expresses PD-L1 and for this study was engineered to express mouse PD-L2.

IMGS-001 significantly inhibited the growth of B16F10-PDL2 tumors when administered intraperitoneally at 10 or 20 mg/kg twice per week. IMGS-001 treatment had a significant effect on survival, with 35% of mice alive at the end of the study (50% in the 20 mg/kg group and 20% in the 10 mg/kg group) versus no mice in the PBS group.

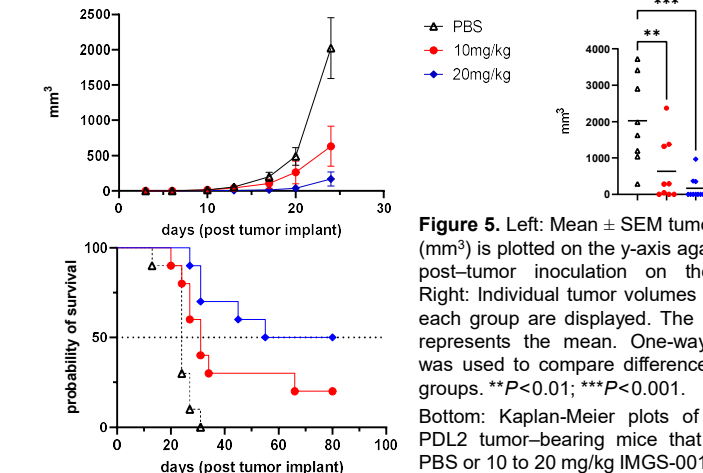


Figure 5. Left: Mean \pm SEM tumor volume (mm^3) is plotted on the y-axis against days post-tumor inoculation on the x-axis. Right: Individual tumor volumes (mm^3) for each group are displayed. The black line represents the mean. One-way ANOVA was used to compare differences among groups. ** $P < 0.01$; *** $P < 0.001$. Bottom: Kaplan-Meier plots of B16F10-PDL2 tumor-bearing mice that received PBS or 10 to 20 mg/kg IMGS-001.

MDA-MB-231

The MDA-MB-231 cell line is a human epithelial, highly aggressive, invasive, and poorly differentiated TNBC cell line that expresses both PD-L1 and PD-L2 as a result of a super-enhancer located in the 9p24.1 region. When injected into the mammary fat pad of nu/nu mice, MDA-MB-231 grows and induces myeloid-derived suppressor cell expansion in the spleen and bone marrow. IMGS-001 was able to significantly inhibit the growth of MDA-MB-231 tumors in immunocompromised mice that lack T cells, suggesting a mechanism of action mainly driven by ADCC.

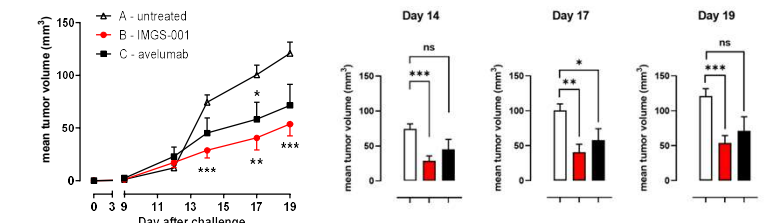


Figure 6. Left: Mean \pm SEM tumor volume (mm^3) is plotted on the y-axis against days post-tumor challenge on the x-axis. Right: Mean tumor volumes on days 14, 17, and 19. Unpaired t-tests were used to compare groups. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

CT26-PDL2 + NK Cell Depletion

NK cells were depleted in vivo by administration of anti-asialo-GM1 antibody. CT26-PDL2 tumor-bearing mice received IMGS-001 or PBS with and without NK cell depletion.

Depletion of NK cells lessens the inhibitory effect of IMGS-001 on tumor growth. These data confirm the contribution of ADCC toward the mechanism of action of IMGS-001.

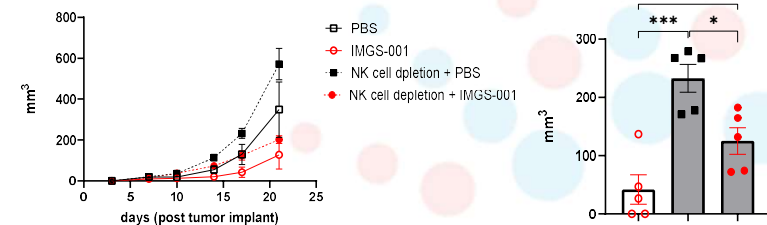


Figure 7. Left: Mean \pm SEM ($n=5$) tumor volume (mm^3) is displayed on the y-axis. Red lines indicate groups that were treated with IMGS-001, and black lines indicate groups that received PBS. Right: Mean \pm SEM and individual tumor volumes for CT26-PDL2 tumor-bearing animals treated with IMGS-001 with or without asialo GM1 to deplete NK cells. Unpaired t-tests were used to compare groups. * $P < 0.05$; *** $P < 0.0006$.

Conclusions

These data suggest that 10 to 20 mg/kg of IMGS-001 is the optimal dose range to induce a strong anti-tumor activity in vivo. Moreover, IMGS-001 displayed a mechanism of action driven by the cyto-reduction 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. IMGS-001 could benefit cancer patients who are refractory or resistant to current IO therapy.