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IGM-7354 IS AN ANTI-PD-L1 IGM ANTIBODY AND IL-15 CYTOKINE FUSION THAT ENHANCES NK AND CD8+ T CELL PROLIFERATION AND TUMOR CYTOTOXICITY PLUS POTENTLY REVERSES T CELL EXHAUSTION

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Background While approved PD-1/PD-L1 inhibitory antibodies have demonstrated clinical efficacy in certain cancer patients, relapse following a primary response is often observed. Enhancing anti-tumor immune responses with an immunostimulatory cytokine, IL-15 is an attractive combination strategy to enhance anti-tumor NK and memory CD8+ T cell expansion and survival. We have developed IGM-7354, a high affinity, high avidity anti-PD-L1 pentameric IgM antibody with an IL-15R α chain and IL-15 fused to the joining (J) chain, designed to deliver IL-15 to PD-L1 expressing tumors for enhancing anti-tumor immune responses.

Methods IGM-7354 was generated by grafting heavy chain variable regions of a high affinity humanized anti-PD-L1 IgG onto the IgM heavy chain framework, co-expressed with the light chain and the J chain which included a single IL-15R α and IL-15 fusion. Binding ELISAs were performed using recombinant antigens. Human and cynomolgus monkey PBMCs were used for potency testing. Reversal of T cell exhaustion was tested using in vitro MLR. In vitro cytotoxicity assays were performed with luciferase-tagged MDA-MB-231 cells and PBMCs. In vivo pharmacodynamic studies were conducted in mice and cynomolgus monkeys.

Results IGM-7354 bound human and cynomolgus monkey PD-L1 with the same affinity but did not bind to rat or mouse PD-L1. In addition, the IL-15 component of IGM-7354 bound to human and cynomolgus β chain of the trimeric IL-15 receptor with similar affinities, but with weaker binding affinity to rodent IL-15R β . Using in vitro assays with PBMCs, IGM-7354 dose dependently enhanced the proliferation of human and cynomolgus monkey NK and CD8+ T cells. Furthermore, IGM-7354 was able to reverse T cell exhaustion in an in vitro MLR beyond that of an IL-15/IL15R α complex or anti-PD-L1 IgM or IgG alone, as demonstrated by an increase in activation and effector cytokine secretion. IGM-7354 also enhanced in vitro killing of PD-L1-expressing MDA-MB-231 breast cancer cells by human PBMCs. Pharmacodynamic studies in an MDA-MB-231 xenograft mouse model showed dose-dependent increases in circulating NK and CD8+ T cells and tumor infiltrating lymphocytes, which correlated with tumor regression. In cynomolgus monkeys, intravenous administration of IGM-7354 was well tolerated and dose dependently induced the proliferation of NK and CD8+ T cells.

Conclusions IGM-7354 stimulates NK and CD8+ T cell expansion in vitro and in vivo plus induces tumor regressions in mouse tumor models. This approach may enhance tumor localization of the immunostimulatory cytokine IL-15 through high affinity and high avidity binding to PD-L1 thereby improving anti-tumor responses and minimizing toxicity.

Ethics Approval All animal studies were conducted according to approved Institutional Animal Care and Use Committee (IACUC) protocols of the testing facilities.

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