Background IGM-7354 is an engineered, humanized high affinity, high avidity anti-PD-L1 pentameric IgM antibody with an IL-15Rα chain and IL-15 fused to the joining (J) chain. IGM-7354 was designed to deliver IL-15-mediated stimulation of NK and CD8+ T cells to PD-L1 expressing tumors and antigen-presenting cells, to enhance anti-tumor immune responses.

Methods IGM-7354 has 10 binding sites for human PD-L1 that cross-react with cynomolgus monkey (cyno) PD-L1, but not with rodent PD-L1. The IL-15 component of IGM-7354 binds to human and cyno β chain of the trimeric IL-15 receptor with similar affinities but has weaker affinity to rodent IL-15Rβ. In vitro activity of IGM-7354 on NK or CD8+ T cells was assessed using PBMCs from healthy donors. In vivo pharmacodynamic studies were conducted in cynos and humanized mice engrafted with human CD34+ cells from cord blood in the absence of tumor (BRGSF-HIS mice) or with human PBMC in MDA-MB-231 human tumor-bearing animals (MHC-/- NSG mice). Immune profiling was done by flow cytometry. Serum cytokines and chemokines were analyzed by ELISA or Luminex assays.

Results Using in vitro assays with human and cyno PBMCs, IGM-7354 dose-dependently enhanced the proliferation of NK and CD8+ T cells. These immune subsets were further phenotypically characterized in vivo in the humanized BRGSF mouse model. Increases in NKP30, Granzyme B, and the proliferation marker Ki67 in NK cells were observed in animals treated with IGM-7354 as low as 1 mg/kg. IGM-7354 also enhanced the proliferation of CD8+ T cells with an increase of serum soluble CD25, suggestive of T cell activation. In MDA-MB-231 tumor-bearing mice engrafted with human PBMCs, the frequencies of proliferating CD8+ T cells, effector memory and CD39+ TCF-1- CD8+ T cells were increased following IGM-7354 treatment. In cynos, intravenous infusion of IGM-7354 was well tolerated at dose levels up to 10 mg/kg, with increased proliferating NK and effector memory CD8+ T cells in blood and lymphoid tissues. Soluble CD25 was also elevated in the serum of treated monkeys.

Conclusions IGM-7354 administration in humanized mouse models and cynomolgus monkeys demonstrated potent activation and expansion of NK cells, effector memory CD8+ T cells, and increased levels of soluble CD25 in the serum. This approach may enhance targeted delivery of the immunostimulatory cytokine IL-15 through high affinity and high avidity binding to PD-L1 potentially improving anti-tumor responses and minimizing toxicity.

Ethics Approval The animal studies were approved by the Testing Facilities’ IACUC.