A POTENT STING AGONIST IN COMBINATION WITH A NOVEL ANTI-PD-L1/PD-L2 ANTIBODY LEADS TO SIGNIFICANT TUMOR RESPONSES IN CHECKPOINT-REFRACTORY CANCERS

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Background Activation of stimulator of interferon genes (STING) has shown great potential to enhance antitumor immunity. Several synthetic STING agonists have been tested preclinically and in the clinic. However, these molecules are susceptible to enzymatic degradation leading to low bioavailability in target tissues, unwanted toxicities, and narrow therapeutic windows. We have previously reported a novel STING agonist, ISAC-8803, with marked anti-cancer activity in mouse tumor models and in canine companion animals with glioblastoma. Here, we tested ISAC-8803 in combination with an antibody against both PD-L1 and PD-L2 with effector function (IMGS-27907), developed to diminish the immune suppression in immune excluded tumors.

Methods ISAC-8803 was analyzed in vitro for potency in activating the human (THP-1 reporter cells) and mouse (293 reporter cells) STING pathways. ISAC-8803 was tested in vivo, alone and in combination with IMGS-27907, against mouse models of melanoma (B16F10 expressing mouse PD-L2) and mammary adenocarcinoma (TS/A). Mice with established tumors were treated with ISAC-8803 intratumorally at 10 µg/dose twice (days 11 and 14 for B16F10-PDL2 and days 23 and 26 for TS/A) and with IMGS-27907 at 10 mg/kg twice a week for 3 weeks, starting with the first ISAC-8803 treatment. TS/A tumors were removed 32 days post-tumor challenge and analyzed via H&E, IHC and FACS to assess overall necrosis, T cell infiltration, and macrophage content.

Results ISAC-8803 more potently activated human and mouse STING relative to clinical benchmarks. Its EC50 of 0.1µg/ml and 0.28µg/ml in mouse and human cell lines, respectively, was 12–175X lower than the other compounds. In vivo, the combination of ISAC-8803 with IMGS-27907 resulted in 70% overall survival in B16F10-PDL2, compared to ≤10% in monotherapy and control groups, and significant extension of survival in the TS/A model that shows <10% PD-L1 and no PD-L2 expression. In the TS/A model, the combination therapy resulted in a large necrotic area compared to the respective control and individual treatments. CD3+ and CD8+ cells were more numerous in the tumors treated with the combination, while F4–80+ cells showed a decrease in comparison with the controls.

Conclusions We demonstrated that ISAC-8803 is a potent STING agonist that when used in conjunction with a novel anti-PD-L1/PD-L2 monoclonal antibody induces curative responses in checkpoint-refractory tumor models. The increased survival is associated with an increase of T cells and potential decrease of M2 macrophages at the tumor site suggesting that delivery of STING intratumorally can potentiate the systemic activity of a novel checkpoint inhibitor.

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