EVALUATION OF CHECKPOINT INHIBITOR EFFICACY IN THE ABSENCE OF MURINE FC GAMMA RECEPTORS IN A HUMANIZED IMMUNE SYSTEM MOUSE MODEL

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Background: Humanized immune system (HIS) mice are critical immuno-oncology tools for evaluating antibody-based therapeutic target engagement and efficacy in a human-like context. Most therapeutics have an IgG backbone and thus engage Fc gamma receptors. Traditional HIS mice retain murine immune cells such as neutrophils and macrophages which can interact with human IgG-based therapeutics and confound preclinical results. To determine whether knockout of murine Fc gamma receptors (FcγRs) in a super-immunodeficient mouse model would alter anti-PD1 efficacy compared to the parent strain in a lung adenocarcinoma model, we studied tumor growth kinetics, human reconstitution, and tumor infiltrating leukocytes (TILs) in each strain engrafted with HCC872 tumor cells treated with Pembrolizumab or Vehicle.

Methods: HIS NOG (huNOG) or HIS FcγR knockout NOG mice (available as the FcResolv™ huNOG mouse) were created using identical protocols with CD34+ cells from three human donors shared across both strains. Baseline reconstitution was evaluated in naïve animals via flow cytometry. HCC827 cells were inoculated in remaining animals. Animals were randomized on day 7 post-tumor implantation into 12 groups. Body weight, clinical observations, and tumor growth were measured. Mice received treatment from D7, dosed twice weekly for four weeks, and were then euthanized for FACS analysis, collecting blood, spleen, and tumor samples.

Results: For a given donor, no significant differences were seen in human immune reconstitution and kinetics between strains. Pembrolizumab treatment showed significant tumor growth inhibition in one donor in FcResolv huNOG, but not in donor-matched huNOG mice. Evaluation of human TILs in pembrolizumab-treated animals showed significant differences between the strains across all donors, with FcResolv huNOG mice showing increased CD8+ T cells and decreased tumor-associated macrophages compared to vehicle-treated mice, and no significant differences in huNOG. Evaluation of murine TILs revealed differences in murine macrophage populations, regardless of treatment, with LyC<sub>lo</sub> dominant in FcResolv huNOG and LyC<sub>hi</sub> dominant in huNOG. In the presence of Pembrolizumab, the murine myeloid and granulocyte population within the tumor was significantly decreased in FcResolv huNOG mice whereas no change was seen in huNOG.

Conclusions: Our study demonstrates when treated with anti-PD1, FcResolv huNOG mice show expected pharmacodynamic changes and donor-dependent efficacy whereas, despite identical donors and creation protocols, Pembrolizumab-treated huNOG mice showed neither. These differences are due to the presence or absence of murine FcγRs and their impact on antibody IgG-based therapeutics.

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