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PHARMACODYNAMICS OF JNJ-70218902, A TMEFF2 × CD3 BISPECIFIC ANTIBODY, IN CYNOMOLGUS MONKEY

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Background TMEFF2 is a transmembrane protein with epidermal growth factor-like and 2 follistatin-like domains. The enriched expression of TMEFF2 in prostate cancer and its restricted expression in healthy brain and prostate make it an attractive candidate for targeted prostate cancer therapy. JNJ-70218902 (JNJ-902) is a bispecific TMEFF2 × CD3 antibody that binds to human TMEFF2 on prostate cancer cells and to human CD3 on T cells to promote T cell-mediated killing of tumor cells. Given the 100% sequence homology and analogous biodistribution of TMEFF2 in humans and monkey, the pharmacodynamics of JNJ-902 was studied in cynomolgus monkeys.

Methods Two dosing regimens of JNJ-902 were evaluated in cynomolgus monkeys: single, fixed dosing (0.075 mg/kg) and step-up dosing (0.075 mg/kg followed by 0.3 mg/kg 1 week later). Blood, serum, and prostate tissue were collected for flow cytometry to assess number of T cell infiltrates and myeloid cells, and surface markers of T cell function (activation, proliferation, and suppression).

Results An approximately dose proportional increase in JNJ-902 exposure was observed in this study. Both dosing regimens increased CD4+ and CD8+ T cell infiltration in the prostate, including activation and proliferation of CD4+ and CD8+ T cells (measured by granzyme B, CD25, CD69, and Ki-67), and in the periphery, minimal suppressive biomarkers (CD4+CD25hi Foxp3+) were observed. Interestingly, greater infiltration of CD8+ T cells was observed with step-up dosing. Both dosing regimens led to an influx of pro-inflammatory cells (dendritic cells, myeloid cells, macrophages, and B cells) into the prostate.

Conclusions Redirecting T cell activity to TMEFF2-expressing tumors by JNJ-902 is a promising immunotherapy for prostate cancers. In cynomolgus monkeys, treatment with JNJ-902 induced the infiltration of activated and proliferating T cells and inflammatory cells into the prostate, suggesting the potential to mediate an effective immune response. The clinical evaluation of JNJ-902 is currently underway in a phase 1 dose escalation trial in patients with metastatic castration-resistant prostate cancer (NCT04397276).

Ethics Approval The procedures involving the care and use of animals in this study were reviewed and approved by CR-MWN Institutional Animal Care and Use Committee before conduct (Testing Facility Study Number 886-526). During the study, the care and use of animals were conducted with guidance from the guidelines of the USA National Research Council.

<http://dx.doi.org/10.1136/jitc-2022-SITC2022.1360>