TUMOR GROWTH INHIBITION MEDIATED BY A SINGLE DOSE OF INTRATUMORAL TRANSCON™ TLR7/8 AGONIST WAS ASSOCIATED WITH ACTIVATED CIRCULATING T AND B CELLS AND SUSTAINED LOW LEVELS OF SYSTEMIC CYTOKINES

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Background TLR agonists can elicit anti-tumor activity by activating innate immune cells and promoting a proinflammatory microenvironment. Local delivery of TLR agonists has shown encouraging preclinical and clinical anti-tumor activity. However, intratumoral (IT) delivery of naked TLR agonists such as resiquimod, a TLR7/8 agonist, can lead to rapid efflux from the tumor, resulting in acute high systemic drug exposure and transient but high level of peripheral proinflammatory cytokines, thus limiting anti-tumor benefit and increasing risk of cytokine-driven adverse effects.

Methods TransCon™ TLR7/8 Agonist was designed to elicit a sustained and local release of resiquimod following IT administration of a hydrogel depot. In the syngeneic murine CT26 tumor model, a single IT injection of TransCon TLR7/8 Agonist monotherapy was sufficient to induce potent tumor growth inhibition. Following treatment, the induction of key cytokines and chemokines associated with innate immunity was determined.

Results Proinflammatory cytokines (IL-1b, IL-6, and TNFα) were induced following IT TransCon TLR7/8 Agonist treatment, but in contrast to free resiquimod, peak levels were more than 10-fold lower than those observed with an equimolar dose of free resiquimod. The circulating levels of these cytokines were sustained above control alone through Day 21. TH1-associated IFNγ was induced with levels increased at Day 1 and maintained at Day 7. Additionally, expression of myeloid-associated chemokines (KC/GROα/CXCL1, MCP-1/CCL2, IP-10/CXCL10, and MIP-1α/CCL3) were induced and sustained in a largely dose-dependent manner through Day 21. The sustained increase in cytokines was consistent with an increase in circulating innate immune cells, such as NK and myeloid cells. Furthermore, evidence of adaptive immune cell activation was observed as indicated by expression of Ly6C, ICOS and Ki67, which were increased on CD8+ T cells, CD4+ T cells (Ki67, ICOS), and B cells (Ly6C).

Conclusions These data show that a single IT injection of TransCon TLR7/8 Agonist can elicit sustained expression of key cytokines and chemokines, promote innate immune cell mobilization, activate adaptive immune cells, and mediate robust anti-tumor activity. The levels of the cytokines remained relatively low through the observation period of 21 days, suggesting a low risk of systemic cytokine-associated adverse events. The increase in activated B, T, and NK cells in blood was associated with induction of a potent anti-tumor response, further supporting TransCon TLR7/8 Agonist as a novel and potentially efficacious PRRA therapy. A clinical trial to evaluate its safety and efficacy in cancer patients is currently underway (transcendIT-101; NCT04799054).

Ethics Approval The animal studies described were performed in accordance with the 'Guide for the Care and Use of Laboratory Animals: Eighth Edition' and approved by the institutional animal care and use committee (IACUC).

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