Background Toll Like Receptor 7/8 (TLR7/8) agonists like resiquimod trigger innate immune activation by enhancing antigen presentation and cytokine/chemokine production, resulting in activation and recruitment of immune effector cells to tumors. However, systemic resiquimod administration may lead to unacceptable toxicities. TransCon TLR7/8 Agonist is a first-in-class investigational prodrug designed for intratumoral administration and local resiquimod release for at least 3 weeks leading to sustained immune activation and thereby potentially producing a potent anti-tumoral response while minimizing systemic adverse events. TransCon TLR7/8 Agonist is currently in clinical phase 1/2 testing in patients with locally advanced or metastatic solid tumors (NCT04799054).

Methods During dose-escalation, 23 patients were enrolled. Nine patients received intratumoral TransCon TLR7/8 Agonist (0.3 or 0.5 mg/lesion) as monotherapy every 3 weeks while the remaining 14 patients received combination therapy with staggered dosing of pembrolizumab in cycle 1 (administered 7 days after TransCon TLR7/8 Agonist) and same day dosing every 3 weeks at subsequent cycles. Longitudinal blood and tumor tissue samples from injected and non-injected lesions were evaluated, as available, for pharmacodynamic effects. Comprehensive immune gene expression profiling of tumor tissue samples from injected and non-injected lesions were evaluated, as available, for pharmacodynamic effects.

Results Comprehensive immune gene expression profiling of injected tumor lesions demonstrated upregulation of TLR7/8 and Type I Interferon Pathway genes after 1 week, also after repeated dosing. HLA-A, HLA-B and HLA-C genes encoding antigen presenting MHC-I proteins were also upregulated. Increased tumor infiltration of CD68+ macrophages, CD8+ T cells and NK cells was observed 1 week after dosing, while the fraction of regulatory T cells remained largely unchanged (table 1). Importantly, the presence of CD8+ T cells and NK cells was maintained or increased in biopsies collected at later timepoints. Increased infiltration of cytotoxic lymphocytes and macrophages was observed in non-injected paired tumor biopsies from one patient, suggesting systemic immune activation and distant anti-tumor effects. In addition, plasma CXCL10 and MCP-1 chemokine levels increased significantly 24–72 hours post-dosing and subsequently decreased but remained elevated for 1–2 weeks. TNF-alpha levels were low but detectable 24–72 hours after dosing and stayed elevated for at least 2 weeks, pointing to sustained immune activation.

Conclusions TransCon TLR7/8 Agonist mediates sustained immune activation with increased intratumoral infiltration of antigen presenting macrophages and cytotoxic lymphocytes as well as elevated chemokine plasma levels which may further support immune cell recruitment to the tumors. Increased numbers of immune cells in a non-injected lesion indicate distant anti-tumor immune effects. Currently patient enrollment continues into dose-optimization and indication-specific cohorts.

Ethics Approval The study protocol was approved by the institutional review board at each participating center. All the patients provided written informed consent.