TPS9603 **Poster Session**

Multicenter, randomized, double-blinded, placebo-controlled trial of IFx-Hu2.0 (IFx) as adjunctive therapy with pembrolizumab (pembro) in checkpoint inhibitor (CPI)-naïve patients with advanced or metastatic Merkel cell carcinoma (MCC).

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Background: CPIs have revolutionized the treatment of a wide variety of cancers. Despite their success, the majority of cancers do not respond primarily due to tumor-intrinsic mechanisms allowing immune evasion, and obviating activation of tumor specific cytotoxic T cells (cTc), which are required for CPIs to work. Activation of tumor-specific cTc is thus the goal for most therapies aiming to overcome primary resistance to CPIs. IFx is an innate immune agonist designed to overcome primary resistance to CPIs. It consists of a plasmid DNA, pAc/emm55, encoding for an immunogenic gram+ bacterial protein streptococcal Emm55, combined with a cationic polymer that facilitates cellular uptake of DNA. Intralesional injection of IFx results in Emm55 expression on the surface of tumor cells. Pathogen-associated molecular patterns on gram+ bacteria are recognized by toll-like receptors (TLRs) on innate immune cells. TLRs with CD14 as a co-receptor binds to these bacterial proteins, activating an innate immune response against the tumor cell and the expressed bacterial protein. This causes non-self tumor neo-antigen presentation to naïve B and T cells, resulting in activation of tumor specific cTc and antibodies. Unlike oncolytic viral approaches which rely on tumor lysis and distribution of tumor neoantigens into the tumor microenvironment, IFx causes phagocytosis of intact tumor cells and may provide more comprehensive and efficient antigen presentation, promoting inter-antigenic epitope spreading. In a Phase 1b trial among 23 patients with MCC or cutaneous squamous cell carcinoma (cSCC) that failed to respond to anti-PD(L)-1 therapy, intralesional IFx was well tolerated at weekly injections x3 dosing regimen. Post-protocol rechallenge with CPI resulted in 7 of 11 (63%) patients with MCC experiencing durable (median 19 mos.) complete or partial responses, despite prior failure of the same class of CPI. Based on these results, a randomized, double-blind, placebo-controlled trial to evaluate the potential for adjunctive IFx and pembro to improve response rates in the first-line treatment of CPI naïve patients with advanced or metastatic MCC is planned. **Methods:** 118 CPI naive adults with MCC will be assigned via 1:1 randomization to IFx (0.1mg) or placebo given weekly x3 concurrent with pembro 200 mg IV q3w for up to 2 years, or progression or toxicity. Responses assessed by blinded independent central review per RECIST v1.1 q12w during the first 24 months and q24w thereafter up to 5 years. Adverse events (AEs) will be assessed per CTCAE v5.0 up to 90 days after final treatment. Primary and key secondary endpoints include objective response rate and progression-free survival respectively. Other secondary endpoints are safety, duration of response, and overall survival. Clinical trial information: Pending as of submission deadline. Research Sponsor: TuHURA Biosciences, Inc.