## 735 PERIPHERAL AND TISSUE PERSISTENCE OF AGENT-797, AN ALLOGENEIC INKT CELL-BASED CELL THERAPY FOR THE TREATMENT OF CANCER

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**Background** Invariant natural killer T cells (iNKTs) are unique innate-like tissue resident T cells, that mediate antitumor responses by direct and indirect mechanisms. iNKTs act as master regulators of immune responses, and interact extensively with the endogenous immune system to activate pro-inflammatory immunity in the tumor microenvironment, recruit endogenous cytotoxic lymphocytes (NK and T cells), and reverse exhaustion of endogenous T cells. agenT-797 is an allogeneic unmodified iNKT cell therapy and represents a novel, scalable, off-the-shelf approach against solid tumors. agenT-797 has demonstrated clinical activity both alone and in combination with standard of care agents across 34 solid tumor patients treated (NCT05108623).

**Methods** We developed multiple complementary approaches to detect and quantify agenT-797 in the periphery and in tissue in clinical samples from our ongoing clinical trial of agenT-797 in solid tumors. Clinical samples were taken up to 9 months post-infusion of agenT-797. Detection of agenT-797 was by single nucleotide polymorphisms (SNPs of donors) unique to the drug product in patient's PBMC (to measure peripheral persistence) or in serum-derived cell-free DNA (cfDNA; indicative of tissue-wide systemic persistence).

**Results** In this first report, we present our in-house developed highly sensitive approach for detecting agenT-797 in tissues using unique cfDNA markers, providing evidence of tissue persistence in patients without lymphodepletion. Initially, commercial assays were employed to detect agenT-797 in peripheral blood, revealing a dose-dependent spike at day 2 that gradually declined as the cells characteristically translocated to tissue. Notably, we observed consistent levels of peripheral agenT-797 up to 8 weeks post-infusion, suggesting potential recirculation from tissue and tumor reservoirs. Our in-house method significantly enhances sensitivity, enabling the detection of agenT-797 in tissues and highlighting its long-lasting presence in patients without lymphodepletion, marking a significant advancement in the pharmacokinetic profile of agenT-797.

**Conclusions** In this study we evaluate the persistence of agenT-797 and correlate persistence with clinical benefit and translational readouts. We demonstrate presence of agenT-797 in tissues and detect the cell therapy product in the periphery up to 8 weeks post infusion, representing unexpectedly prolonged persistence for an unmatched allogenic cell therapy. Such persistence and clinical activity were observed in the absence of traditional lymphodepletion regimens employed in nearly all other forms of immune cell therapy. The observed persistence of agenT-797 in the absence of lymphodepletion, therefore, uniquely allows it to unfold its maximal potential though directing integral endogenous immune responses, which otherwise would be severely compromised by lymphodepleting agents.

**Trial Registration** Trial registered at clinicaltrials.gov, registration number NCT05108623

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