Preliminary results of an in progress, first-in-human Phase 1 study of Decoy20, an intravenous, killed, multiple immune receptor agonist bacterial product in patients with advanced solid tumors

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Background Systemic activation of multiple immune receptors, such as Toll-like (TLR), Nucleotide oligomerization domain (NOD)-like, and Stimulator of interferon genes (STING) may be required for efficient anti-tumor immune responses. Decoy10 and Decoy20 are attenuated and killed, non-pathogenic, bacterial products with ~90% reduction of lipopolysaccharide (LPS)-endotoxin activity to enhance intravenous (IV) safety, and retention of endogenous TLR1,2,6,8,9, NOD2 and STING agonist activity. Decoy products produced pre-clinical single-agent and combination-mediated anti-tumor activity (breast, colorectal, hepatocellular, non-Hodgkins lymphoma, pancreatic), including innate/adaptive immune-mediated eradication of established tumors, involving combination with anti-PD-1, indomethacin, cyclophosphamide and/or rituximab [1]. We hypothesized that, due to clearance of systemic bacteria by the liver and spleen within minutes to a few hours, Decoy products might produce transient immune activation, suitable as monotherapy or combination with approved agents (pulse-prime hypothesis).

Methods INDP-D101 is a first-in-human, open label, single dose escalation and multi-dose expansion, multicenter Phase 1 trial of Decoy20 in patients with advanced/metastatic solid tumors with an initial DLT period of 28 days. Primary objectives: safety/tolerability. Secondary objectives: anti-drug immunogenicity, pharmacokinetics (PK) and preliminary anti-tumor activity. Exploratory objective: systemic immune activation via immune biomarkers.

Results As of August 2023, 4 patients (ages 45-71) with adenoid cystic, piriform sinus, appendiceal, or colon cancer received a single dose of $7x10^7$ killed Decoy20 bacteria via 1-hour IV infusion and were evaluable for safety and efficacy. One dose limiting toxicity of Grade (G) 3 bradycardia occurred and resolved in <30 minutes following bolus normal saline, acetaminophen, meperidine, and oxygen; G3 malaise in the same patient resolved within 2 days. Two patients experienced G3 AST increase, improving to G1 within 1-2 days. Overall, G1 chills, fatigue, fever, G2 vomiting, hypotension, G1-2 ALT increase resolved within 1-2 days and G4 lymphopenia resolved within 2-3 days, all expected following exposure to LPS (TLR4 agonist), an active ingredient of Decoy20. Biomarker and PK analysis (two patients) demonstrated immune activation, based on transient ≥4-133-fold induction of plasma analytes, including CD40L, G-CSF, IFN-γ, soluble IL-2 receptor, IL-2,6,8,9,10,12p70, IP-10, MCP-1, MIG, MIP-1α/β, TNF-α and TRAIL. Decoy20 was detected in blood and was then unmeasurable 30-120 minutes after infusion. Post-dose tumor re-staging demonstrated all 4 patients with RECIST 1.1 stable disease, 3 previously progressing, after a single dose of Decoy20.

Conclusions Decoy20 generated transient adverse events largely expected for LPS exposure, transient systemic immune activation beyond expectation for LPS alone, and preliminary evidence of stable disease. These observations and PK data support our pulse-prime hypothesis.

References

1. Newman M. A systemically administered killed bacteria-based multiple immune receptor agonist for pulsed anti-tumor immunotherapy. [abstract]. In: Proceedings of the American Association for Cancer Research Annual Meeting 2023; Part 1 (Regular and Invited Abstracts); 2023 Apr 14-19; Orlando, FL. Philadelphia (PA): AACR; Cancer Res 2023;83(7_Suppl):Abstract nr 4165.

Ethics Approval This study was approved by the following institutions' Ethics Boards: WIRB/Copernicus covering Atlantic and Karmanos with approval number 20223025; USC approval number HS-22-00497.

Trial Registration NCT05651022