IMNN-001, an IL-12 gene therapy added to Neo/Adjuvant chemotherapy safely turns the tumor microenvironment cold-to-hot in newly diagnosed epithelial ovarian cancer

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BACKGROUND

- **Epithelial Ovarian cancer (EOC) remains an unmet medical need,** with 80% of the cases diagnosed in advanced stage (III/IV). >60% of ovarian cancer patients die within 5 years [1].
- **EOC is an immunogenic tumor; however, effective immune therapies** (e.g., Immune checkpoint inhibitors) **remain elusive** due to EOC's marked immunosuppressive tumor microenvironment (TME)[2]. Neo/Adjuvant chemotherapy (N/ACT) and peri-debulking surgery are SoC treatment, followed by maintenance PARPi for non-progressing patients with homologous recombination deficiency (HRD)[3].
- **IL-12 is a pleiotropic immuno-stimulatory cytokine able to turn "cold" tumor microenvironments to "hot"** by activating both the innate and adaptive immune systems. However, systemic treatment with recombinant hIL-12 is too toxic for use in the clinic.
- **OVATION-2** randomized, controlled Phase I/II (NCT03393884) **study has shown that IMNN-001** (an IL-12 gene therapy[4]) **delivered IP in combination with N/ACT is safe and improves PFS and OS by 3 and 13 months, respectively,** as compared with the N/ACT alone control[3].
- Herein, we present OVATION-2 translational data on the changes induced by the local administration of IL-12 and its downstream effectors in the TME from paired samples (pre- and post-treatment) from patients treated with IMNN-001 and N/ACT.

METHODS

- **Immune markers expression in tumor:** pre- & post-treatment tissue samples were analyzed by cyclic immunofluorescence analysis (Phenocycler-fusion) for the expression of CD8, CD11c, CD44, CD4, HLA-DR, CD45, CD45RO, Ki67, CD14, CD3, CD20, CD56, HLA-A, CD68, CD163, CD11b, CD16, Pan CK, FOXP3, PD-L1, PD-1 and IDO-1.

REFERENCES

(1) Siegel et al., *Cancer Statistics*, 2023
(2) Blanc-Durand, *Front Immunol*, 2023
(3) Thaker et al., *Gynecol Oncol*, 2025
(4) Anwer et al., *Gene Ther*, 2009
(5) Preston et al., PLoS One 2013
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CONCLUSIONS

- IMNN-001 creates a "hot" anti-tumor microenvironment in EOC by i) increasing the recruitment of anti-tumor CD8+ and myeloid dendritic cells in 50-80% of the paired samples; and ii) decreasing immunosuppressive markers (IDO, PDL1, Treg) in 65-80% of the samples.
- These results, including induction of favorable ratios of CD8+/Tregs and CD8+/CD4+ cells, both associated with improved patient outcomes[5-6], are consistent with the results of the previous OVATION-1 study and with the efficacy seen in the clinic in the OVATION-2 study.
- This biomarker research confirms local immune activation at the tumor site by IMNN-001. Together with the excellent safety and activity observed in the clinic, these results warrant further investigation. A Phase III trial (OVATION-3, NCT06915025) is currently enrolling.

A: IMNN-001 Formulation and Delivery B: IL-12 MoA

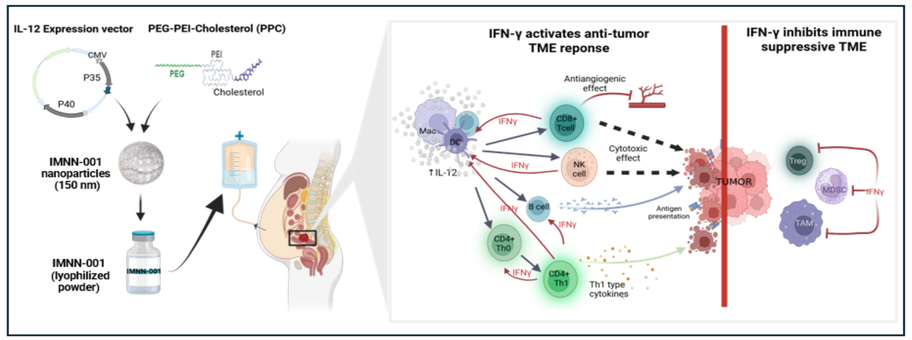
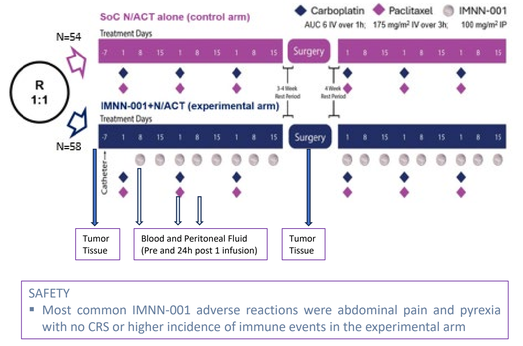


Figure 1 A-B. IMNN-001, comprised of a plasmid expressing the p35 and p45 subunits of hIL-12 encased in a synthetic lipopolymer delivery system composed of a polyethylenimine (PE) backbone covalently linked to polyethylene glycol (PEG) and cholesterol, is delivered intraperitoneally in the clinic. The expression of hIL-12 by cells in the tumor microenvironment (TME), through its downstream mediators (IFN-γ and other cytokines), activates the innate and adaptive immune systems and inhibits immune suppressive cells, turning the TME from cold to hot and providing anti-tumor activity.

OVATION-2 trial and results of selected endpoints



SAFETY
- Most common IMNN-001 adverse reactions were abdominal pain and pyrexia with no CRS or higher incidence of immune events in the experimental arm

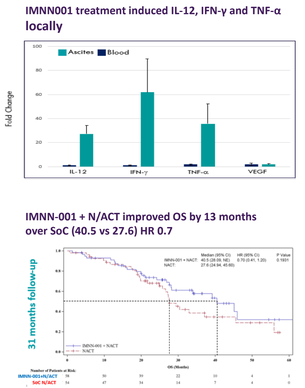
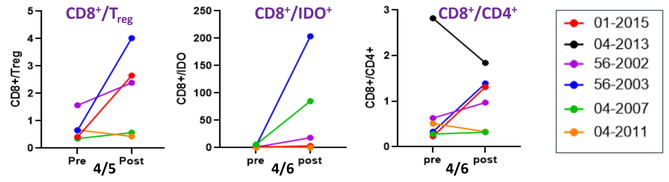


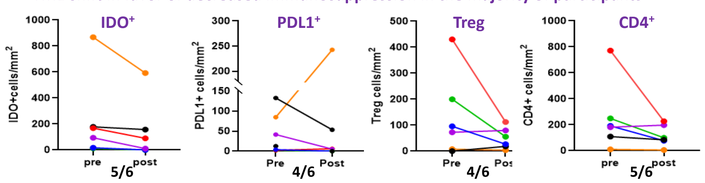
Figure 2. Left: OVATION-2 schema, biological sampling for translational research and relevant safety. Right Top: Mean + SE fold changes in cytokine/VEGF levels in ascites (n=10) and blood (n=15) collected at different time points from patients in the experimental arm. Right bottom: OS KM graph.

RESULTS

- **TME shift to favorable immune stimulatory T cell ratios in the majority of participants**



- **TME shift in favor of decreased immunosuppression in the majority of participants**



- **TME shift in favor of increased immunostimulatory cells in the majority of participants**

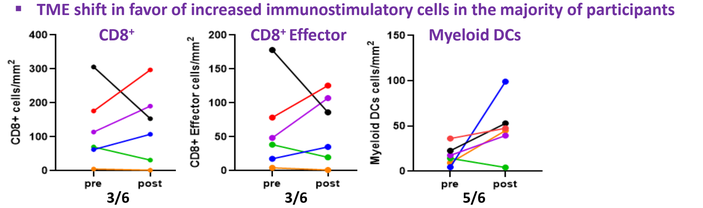


Figure 3. Changes on the density of immune cells in paired patient samples (n=5-6) obtained pre- and post-treatment with IMNN-001 and N/ACT. Numbers are normalized according to the total number of cells and area analyzed in each slide. $CD8^+$ cells ($CD3^+/CD4^-/CD8^+$); T_{reg} ($CD3^+/CD8^-/CD4^+FoxP3^+$); $CD4^+$ ($CD3^+/CD8^-/CD4^+$); CD8 Effector ($CD3^+/CD4^-/CD8^+/CD45RO^+$); Myeloid dendritic cells (DCs) ($CD3^-/CD16^-/D20^-/CD14^-/HLADR^+/CD11c^+$).

Figure 4. Images of FFPE tissue at screening (upper rows in each panel) and at the time of interval debulking surgery (lower rows) from 2 patients treated with IMNN-001 and N/ACT in OVATION-2. H&E staining is shown in the first column of each panel. The 2nd column shows multiplex-Phenocycler color assay for markers indicated in the legend to analyze changes in hematopoietic cell infiltration (CD45+ cells). Selected area (red square) from the tissue section at 20× magnification is shown in the last 3 columns with stains indicating lymphocyte infiltration (CD4+, CD8+, CD20+, 3rd column), expression of immunoregulatory cell markers (FoxP3+, IDO1+, PD-L1+, PD1+, 4th column) and macrophages, monocytes and dendritic cells markers (CD68+, CD163+, HLA-DR+, HLA-A+, last column), all with pan-cytokeratin staining (maroon) to identify tumor cells. Blue arrows in the H&E bottom panel indicate examples of tertiary lymphocyte structures appearing post-treatment.