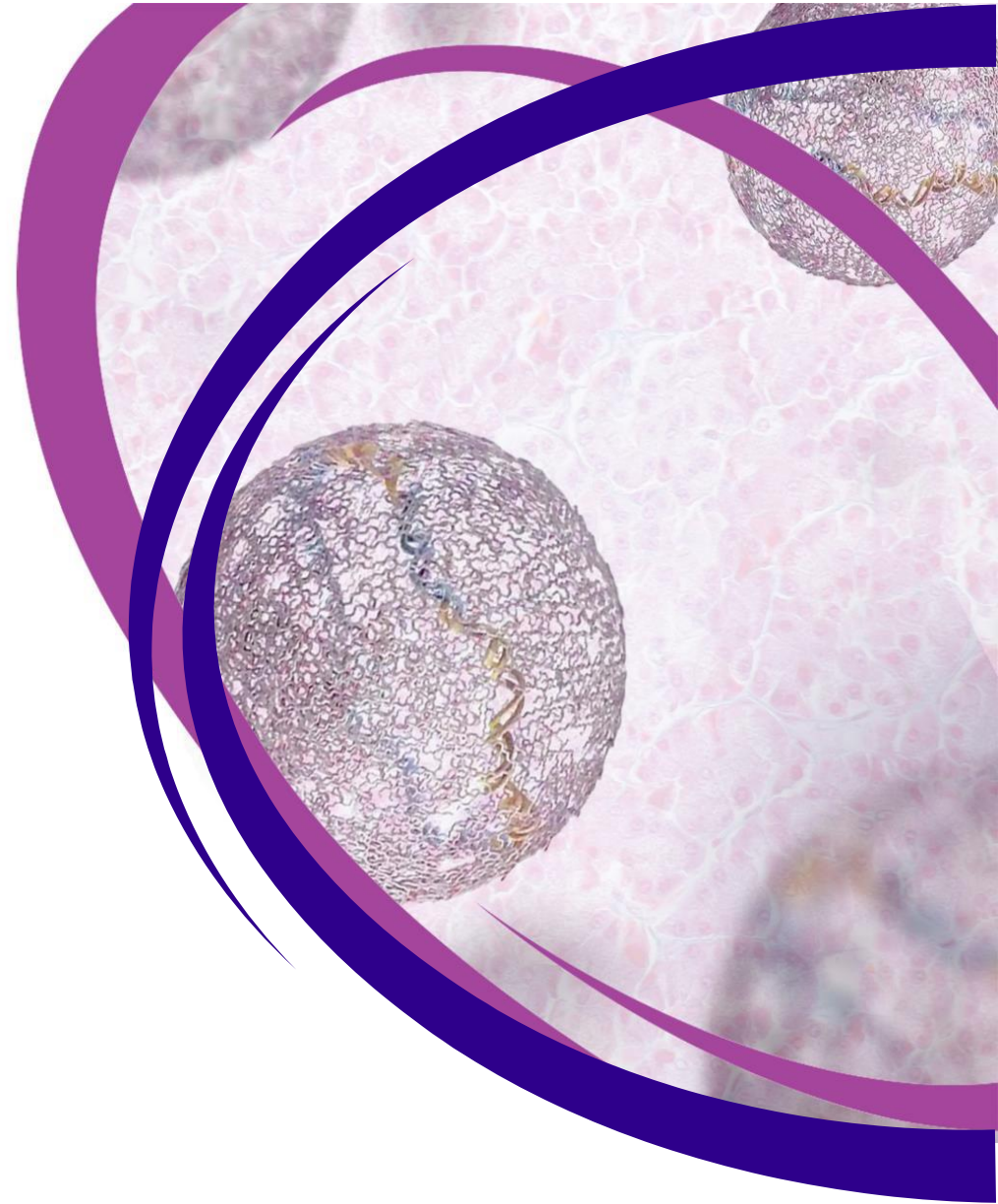


OVATION 2 Topline Results in Advanced Ovarian Cancer

Announced on July 30, 2024



Product Pipeline of DNA-based Transformative Medicines

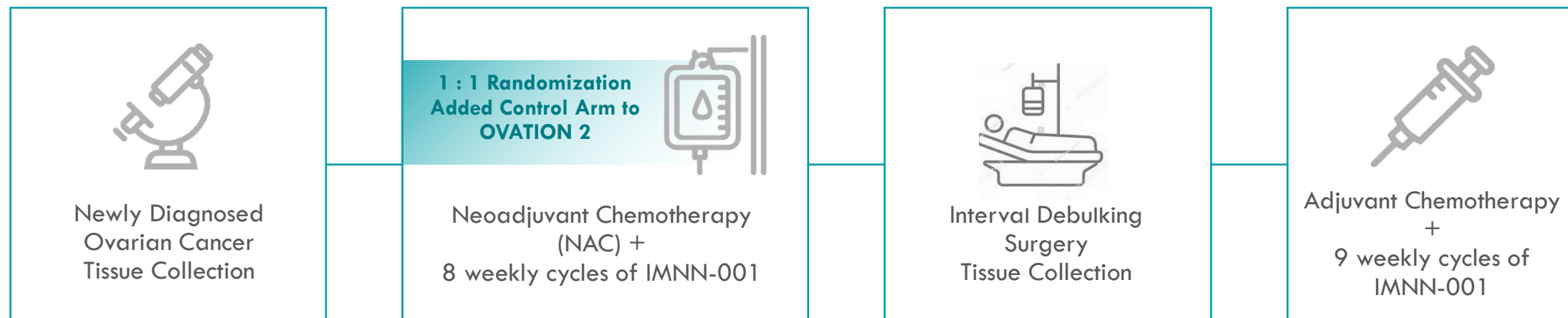
Platform	Program	Indication(s)	Discovery	IND enabling	Phase 1	Phase 2	Phase 3
TheraPlas	IL-12 (OVATION 1)	Newly Diagnosed Advanced Ovarian Cancer	IMNN-001 complete				
	IL-12 (OVATION 2)	Newly Diagnosed Advanced Ovarian Cancer	IMNN-001 top line readout July 2024				
	IL-12 IP in combination with Avastin*	Newly Diagnosed Advanced Ovarian Cancer	IMNN-001 enrolling				
	IL-12 (OVATION 3)	Newly Diagnosed Advanced Ovarian Cancer	IMNN-001 Expected to begin Q1 2025				
PlaCCine	SARS-CoV-2 Clinical Proof-of-Concept	COVID-19 Seasonal Vaccine	IMNN-101				

Partner



OVATION-2: A Phase I/II Study of the Safety and Efficacy of Intraperitoneal IMNN-001 in Combination with Neoadjuvant Chemotherapy (NACT) of Paclitaxel and Carboplatin in Patients Newly Diagnosed with Advanced Epithelial Ovarian Cancer (EOC)

To Determine Safety & Efficacy With NACT in Stage III/IV Patients



Ovarian Cancer Patients (FIGO IIIC & IV)

Up to 110 patients

14 patients in Phase I Run-in (100 mg/m²);

Up to 96 patients in Phase II

Randomized 1:1
NACT +/- IMNN-001

Primary Endpoint

- Safety
- Progression-free Survival (PFS)
 - After 80 PFS events or at least 16 months, whichever is longer

Secondary Endpoints

- Overall Survival
- Chemotherapy Response
- Surgical Resection Scores (R0, R1, R2)
- Biological Response

Additional Treatment Regimen vs. OVATION I Trial Design

Continue IMNN-001 treatment following surgery (Maintenance Therapy)

OVATION 2 Summary

If results are replicated in Phase 3, we believe IMNN-001 will be approved as first-line treatment for ovarian cancer and will change the standard of care

- Ovation 2 is the only trial in Ovarian Cancer that has demonstrated a benefit in overall survival.
- An 11-month improvement in Overall Survival by IMNN-001 in intent-to-treat (ITT) population
 - A clinically meaningful improvement in a difficult to treat disease
- A 15.7-month improvement in OS by IMNN-001 in patients receiving at least 20% of protocol-specified treatments in both arms (91% ITT population)
 - Demonstrating greater benefit achieved with higher drug exposure
- The potential for an exceptionally remarkable improvement in the OS benefit by IMNN-001 in patients exposed to standard of care PARP inhibitor therapy (38% of ITT population)
- IMNN-001 treatment also improved progression-free survival (PFS) in intent to treat population (ITT)
 - Benefits in PFS are qualitatively consistent with the OS data
- Consistent with OS improvement, similar PFS improvement was seen in patients receiving at least 20% of protocol-specified treatments, along with Evidence of a PFS improvement in first line PARP inhibitor therapy (11.7-month improvement in Median PFS)

Safety Summary of Adverse Events

IMNN-001 was Well-tolerated and Acceptable Toxicity Profile

Key observations:

- IMNN-001 was well tolerated, with a highly acceptable benefit/risk profile
- Cytokine Release Syndrome did not occur with IMNN-001 treatment
- Most common Adverse Events:
 - abdominal pain, nausea, vomiting
 - Significant improvement in control of abdominal pain when an instituted recommendation for a regimen of pain meds
- Adverse Event Sampling
 - Observed higher numbers of Hematological AE's due to higher sampling frequency in IMNN-001 arm
- Infections related to port mediated with subdural catheter

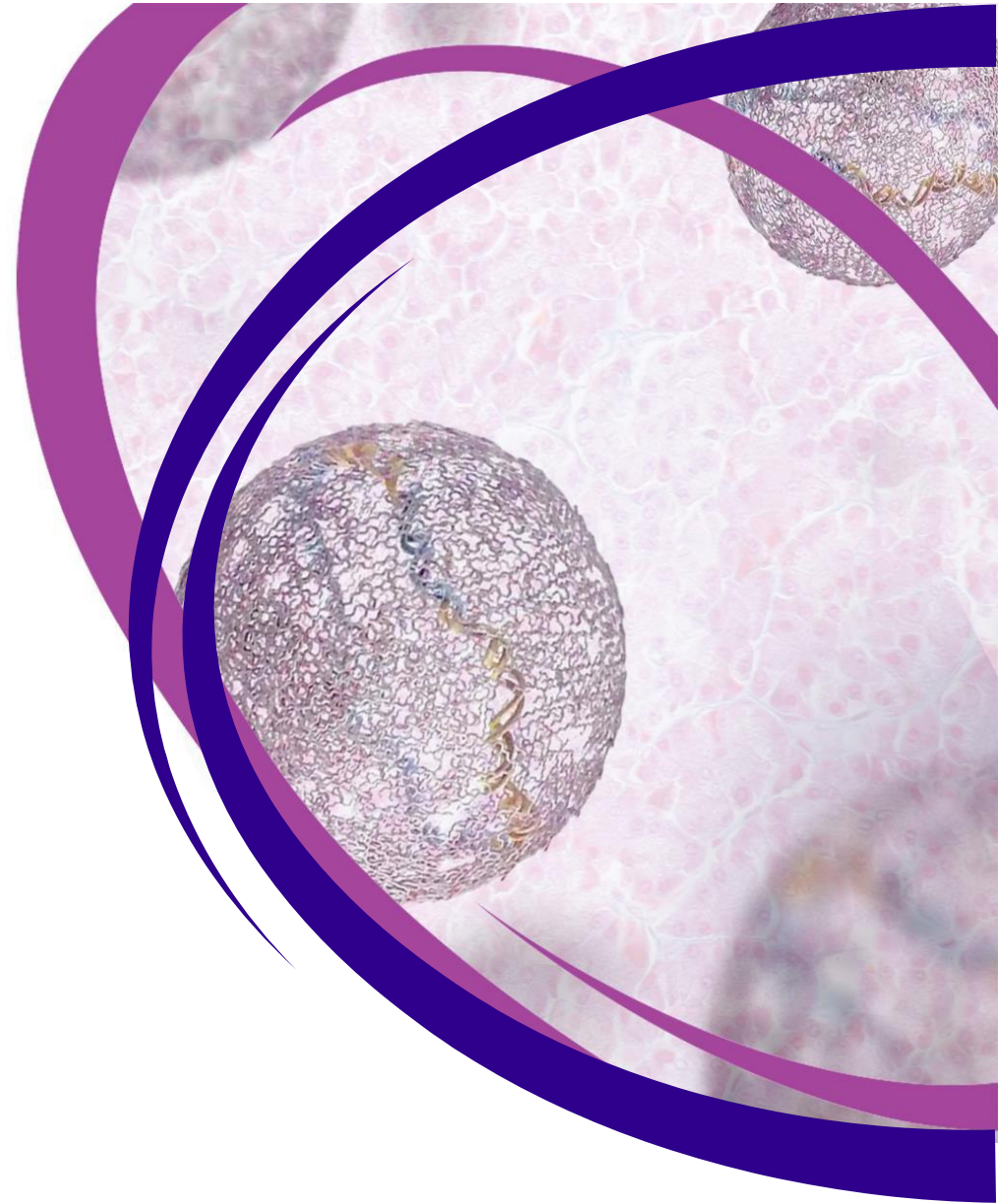
OVATION 2 Topline Data Readout

		Median time to event, Experimental vs Control (months)	Hazard Ratio, Experimental vs Control
Overall Survival (secondary endpoint)	ITT (n=112)	40.5 vs 29.4	0.74 (0.42; 1.30) p=NS
	≥20% of protocol-specified treatments in both arms (n=102)	45.1 vs 29.4	0.64 (0.35; 1.19) p=NS
	PARP-treated patients (n=43)	NE vs 37.1	0.41 (0.13; 1.28) p=NS
Progression- Free Survival (primary endpoint)	ITT (n=112)	14.9 vs 11.9	0.79 (0.51; 1.23) p=NS
	≥20% of protocol-specified treatments in both arms (n=102)	14.6 vs 11.9	0.76 (0.48; 1.22) p=NS
	PARP-treated patients (n=31)	33.8 vs 22.1	0.80 (0.31; 2.12) p=NS

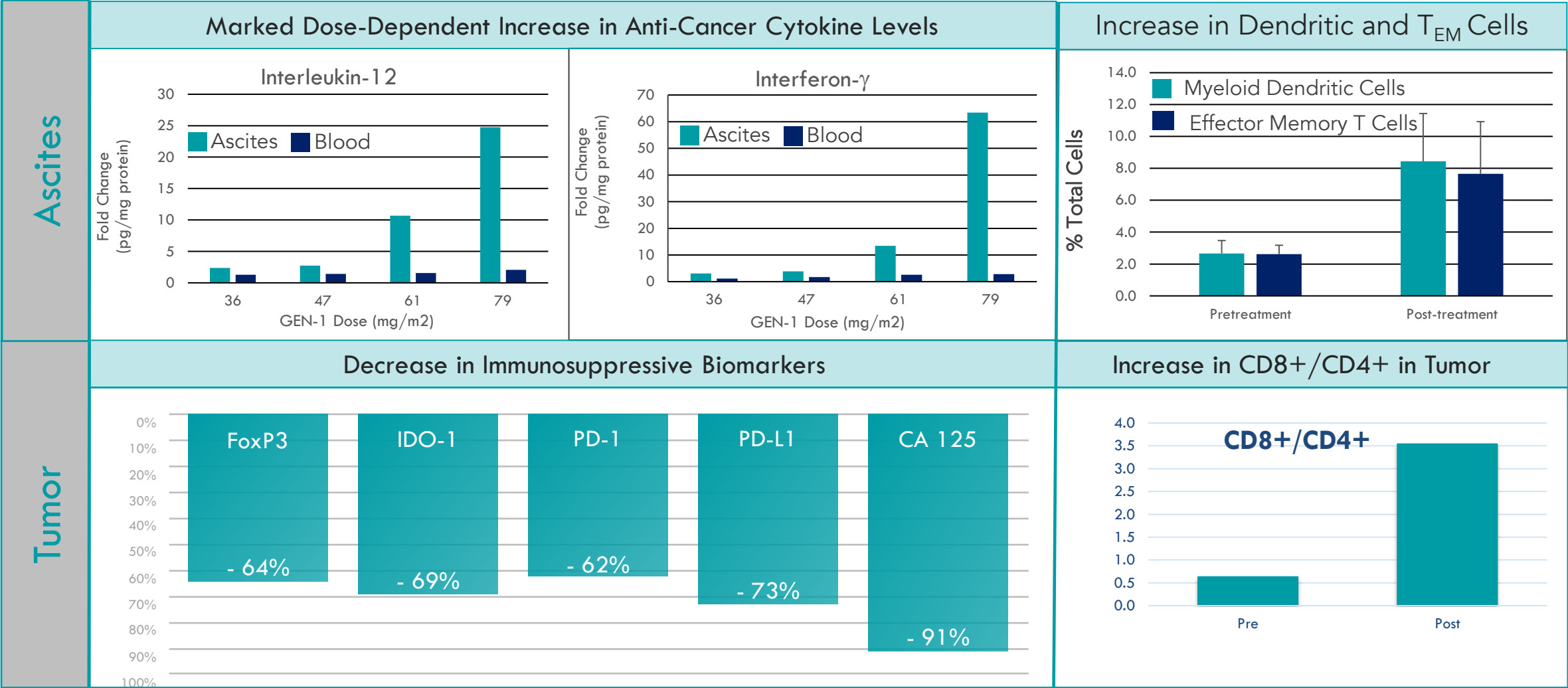
NACT neoadjuvant chemotherapy, **NE** not evaluable, **p=NS** p-value not significant
OVATION 2 treatment arms Experimental: IMNN-001 + NACT; Control: NACT

OVATION-1

Study Results



OVATION I Study Translational Data Sampling



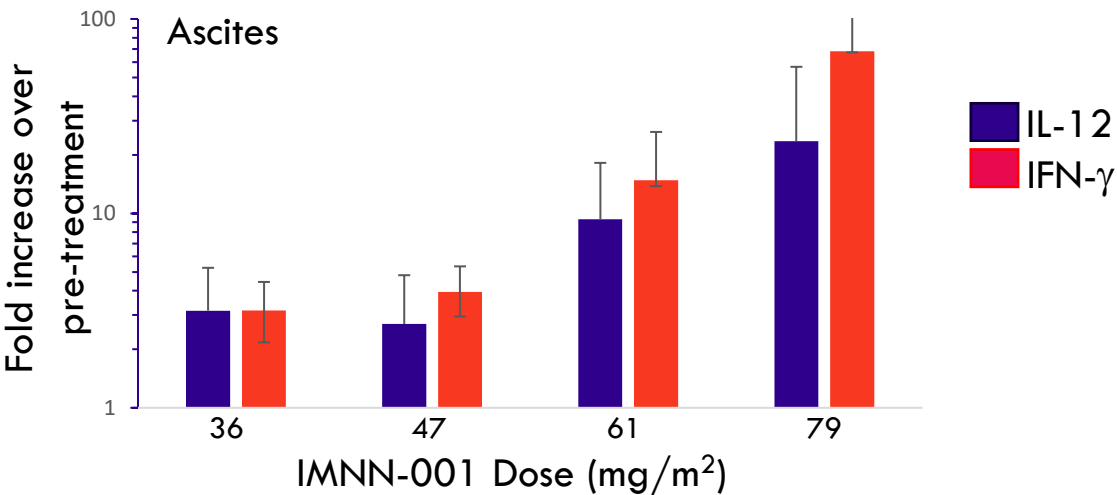
- Increases in cytokine levels shows GEN-1’s activity; Low cytokine blood levels underpin the safety profile of GEN-1
- Increase in anti-cancer dendritic cells & effector memory T-cells demonstrate activation of the cellular immune system
- Overall shift in tumor microenvironment to immunostimulatory

OVATION 1 Study in Neoadjuvant Ovarian Cancer

Dose Dependent Biological (IL-12 & IFN- γ) and Clinical Responses Demonstrate POC

Tumor response, surgical outcome, pathologic response, and chemotherapy response score with NACT/IMNN-001 escalating doses

Radiographic Response		Total (n)	Cohort 1 36 mg/m ²	Cohort 2 47 mg/m ²	Cohort 3 61 mg/m ²	Cohort 4 79 mg/m ²
Tumor Response	CR	2	1	0	0	1
	PR	10	0	3	3	4
	SD	2	2	0	0	0
Objective Response Rate			67%		100%	
Surgical Resection	R0	9	2	0	2	5
	R1	3	1	2	0	0
	R2	2	0	1	1	0
R0 Resection Rate			33%		88%	
Pathologic Response	cPR	1	1	0	0	0
	Micro	8	1	2	1	4
	Macro	5	1	1	2	1
cPR/micro rate			60%		63%	
Chemotherapy Response Score	CRS 3	5	1	0	2	2
	CRS 2	5	2	1	0	2
	CRS 2	4	0	2	1	1
CRS 3 rate			17%		50%	



Efficacy of IMNN-001, an Interleukin-12 Immune Gene Therapy, at Different Dose Frequencies

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Abstract

The purpose of this study was to investigate the effect of dosing frequency on the antitumor activity of intraperitoneal IMNN-001, an interleukin-12 (IL-12) immune gene therapy in a mouse model of peritoneally disseminated ovarian cancer. IMNN-001 expressing murine IL-12 was designed for this study, mIMNN-001. Three dosing regimens were examined for efficacy in ID8 tumor-bearing mice either weekly, every 2 weeks or every 3 weeks (Table 1). Six animals from each group B, C, and D were harvested for translational research (TR) after 5 weekly (3 every 2-week and 2 every 3-week) treatments, respectively. The remaining 4 animals in each group were followed for weight change (tumor burden) and survival. Additionally, TR evaluated change in ascites T cell populations. There was a gradual rise in tumor burden and mortality in all treatment groups with comparable rate between once every week and once every 2-week regimens. Once every 3-week regimen had relatively higher mortality rate and higher tumor burden. There were similar or higher increases in T-cell and B cells with reduced treatment frequency with lesser increases in myeloid cell density with reduced treatment frequency. Once every 2-week dosing of IMNN-001 in human studies is warranted.

Introduction

Epithelial ovarian cancer (EOC) is the fifth deadliest malignancy among women in the United States (1). There are approximately 22,000 new cases of ovarian cancer every year and the majority, approximately 70% of cases, are diagnosed in advanced stages III and IV. EOC is characterized by dissemination of tumor in the peritoneal cavity with a high risk of recurrence (75%, stage III and IV) after seemingly successful surgery and chemotherapy (2). Immunotherapy interventions are considered promising candidates for the treatment of ovarian cancer considering the immunogenic nature of the malignancy (3). The evidence of immune activation in ovarian cancer has been demonstrated in the production of antibodies or antitumor T-cell lymphocytes in primary tumor, ascites, and blood (4-6). Presence of tumor-infiltrating cytotoxic T-cell lymphocytes has been linked to better prognosis while presence of immunosuppressive regulatory T cells (Tregs) has been associated with poor prognosis in ovarian cancer (7-9). The peritoneal cavity of patients with advanced ovarian cancer contains the primary tumor environment and is an attractive target for a regional approach to immune modulation.

Interleukin 12 (IL-12) is a pluripotent cytokine associated with stimulation of innate and adaptive immune response against cancer. Clinical responses to recombinant IL-12 have been observed in multiple cancers (10-12). IMNN-001 is a gene therapy that produces safe and durable local levels of IL-12 to stimulate innate and adaptive components of the immune system. The IMNN-001 nanoparticle comprises a DNA plasmid encoding IL-12 gene and a synthetic polymer facilitating plasmid delivery (13).

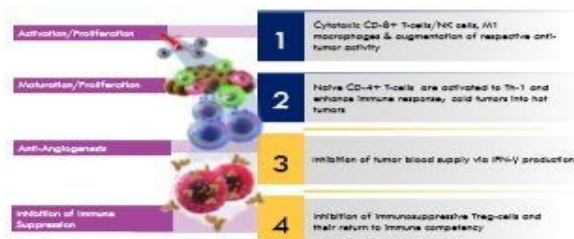


Figure 1. Mechanism of Action of IL-12

Methods

The preclinical study was conducted to compare once every week dosing with once every two weeks or once every three weeks dosing. 2.5×10^6 ID8 cells were injected intraperitoneal (IP) into 8-10 weeks C57BL/6 mice. ID8 is an aggressive tumor model with short life span therefore the time-dependence of the model was taken into account in the study design. Treatment with mouse IL-12 was initiated at day 14. 250 mg DNA was delivered IP once every week, once every two weeks, or once every three weeks. Tumor burden (animal weight) was followed along with survival. Ascites was assessed by flow cytometry for immune infiltrating cells: CD4⁺, CD8⁺, FoxP3⁺, CD8⁺/CD4⁺, CD8⁺/FoxP3.



Figure 2. IMNN-001 Formulation. IMNN-001 is formulated with a three-component delivery system of polyethylene glycol (PEG) polyethylenimine (PEI) cholesterol combined with IL-12 DNA plasmid

Table 1.

Group	N	Route	ID8	
A	10 ²	IP	2.5X10 ⁶ ID8/mIMNN-001	Weekly (6 Rx)
B	10 ²	IP	2.5X10 ⁶ ID8/mIMNN-001	Every 2 weeks (3 Rx)
C	10 ²	IP	2.5X10 ⁶ ID8/mIMNN-001	Every 3 weeks (2 Rx)
D	15*	IP	2.5X10 ⁶ ID8	No mIMNN-001 Rx

*Extra animals for untreated controls as they may start to die earlier

† If the animals survive longer than 6 weeks (12/09/2021) the IMNN-001 treatment frequency will continue per design and the harvest will be done in two stages- First harvest on 12/09/2021, and second harvest thereafter per survival status.

Results

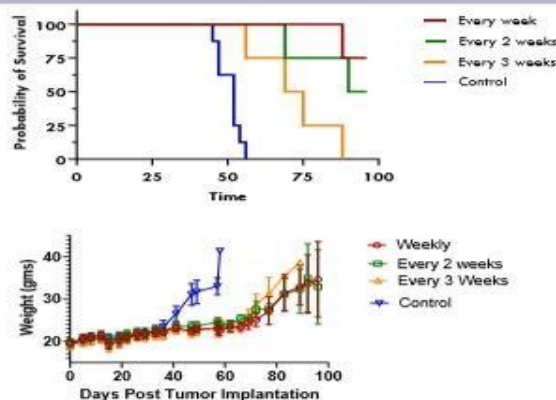


Figure 3. Survival and Tumor Growth. Mice were challenged with 2.5×10^6 ID8 Cells. Following establishment of tumor, mice were treated weekly, every two weeks or every three weeks with mIMNN-001.

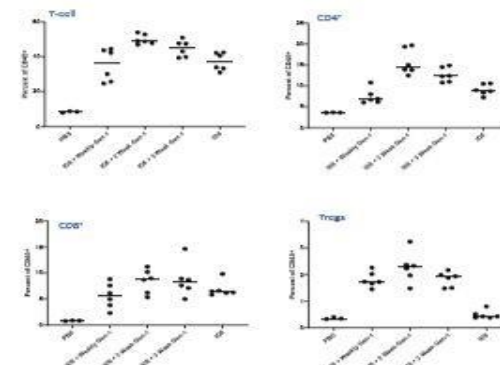


Figure 4. Day 49: Increases in T-cell Populations in Ascites after mIMNN-001 Treatment Every 2-week and every 3-week treatments yield similar or higher T-cell response

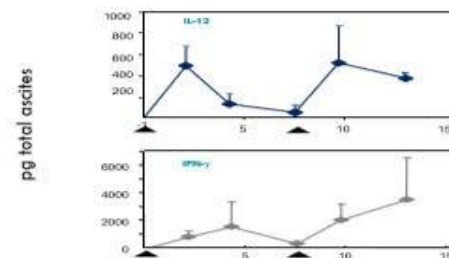


Figure 5. IL-12 and IFN- γ levels in ascites following two weekly IP infusions (at arrows) of mIMNN-001 in peritoneal disseminated ID-8 ovarian tumor bearing mice (Fewell, 2009)

Conclusion

mIMNN-001 demonstrated stimulation of the immune response in the ID8 ovarian tumor model. Of the 3 dosing regimens tested, the once every 2-week regimen demonstrated comparability to the weekly regimen while showing superiority to the once every 3-week regimen, particularly with respect to mortality and tumor burden (Figure 3). Thus, exploring once every 2-week dosing of IMNN-001 in human studies is warranted.

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