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OVATION Study

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Immunological changes following intraperitoneal administration of a formulated IL-12 plasmid in combination with standard neoadjuvant chemotherapy in patients with newly diagnosed advanced stage ovarian cancer.

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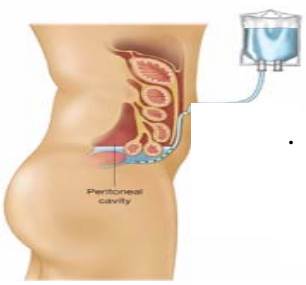
BACKGROUND

- In ovarian and other cancers, tumor growth is supported by a highly immunosuppressive and pro-angiogenic microenvironment. Angiogenic status is believed to be related to VEGF and other growth factors, while the immunosuppressive status is primarily governed by signals (PD-1, CTLA-4, FoxP3, IDO-1, PD-L1) that are suppressive to effector T cells, such as $CD8^+$ T cells.
- In ovarian cancer, the presence of intratumoral $CD3^+$ T cells was correlated with improved survival (1), while tumor infiltration of immunosuppressive T cells was associated with reduced survival (2). Sato et al. reported a positive survival correlation with high tumor $CD8^+$/Treg ratio suggesting that a positive balance favoring the cytotoxic $CD8^+$ T cells is predictive of improved clinical outcome (3).
- Ovarian cancer patients undergoing neoadjuvant chemotherapy (NACT) are ideally suited for immunological studies due to accessibility to pre and post treatment tissue. Recent studies demonstrate that NACT augments tumor infiltrating lymphocytes but fails to control overexpression of immunosuppressive signals including PD-1, PD-L1 and CTLA-4 (4, 5), suggesting that combination approaches could relieve suppressive signal and ensure durable responses.
- In this study, we examined immunological changes associated with NACT administered in combination with GEN-1, an IL-12 plasmid formulated with a lipopolymer PEG-PEI-Cholesterol (6, 7). Tumor tissue, peritoneal ascites and blood samples were collected before treatment, during treatment and at surgical debulking to examine changes of immune phenotype and cytokine production by the treatment. A systematic understanding of the various cellular and molecular components of the immune system before and after NACT + GEN-1 treatment could provide useful insight into GEN-1 mechanisms and rationalize future treatment strategies.

ADMINISTRATION – INTRAPERITONEAL CATHETER

- Silicone catheters were implanted laparoscopically to deliver GEN-1 to the peritoneal cavity.

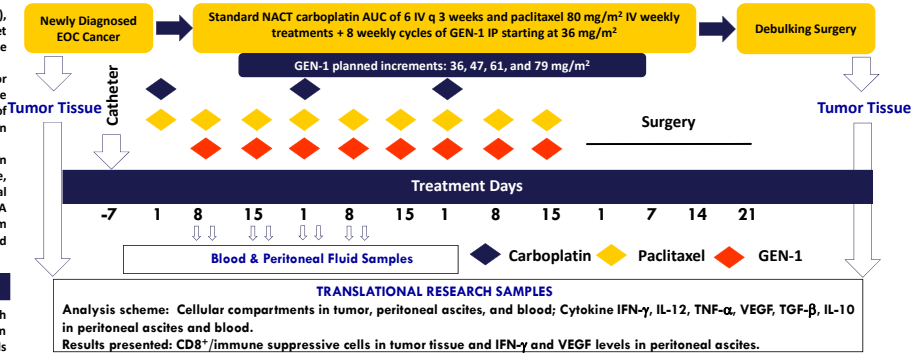


METHODS

- Standard 3+3 design was employed with approximately 30% dose increments between successive cohorts of patients. Four dose levels of GEN-1 (mg/m^2: 36, 47, 61, 79) were administered in conjunction with NACT carboplatin and paclitaxel. Carboplatin was administered every 21 days for three cycles, paclitaxel was administered weekly for nine cycles and GEN-1 was administered weekly for eight cycles before the debulking surgery, which was followed by continuation of carboplatin and paclitaxel per standard protocol. Tolerated dose is confirmed when 6 patients are treated at a dose level and <2 patients experience a dose-limiting toxicities (DLTs).
- Translational research: Tumor specimens were collected at laparoscopy and debulking surgery. The formalin-fixed and paraffin-embedded tumor specimens were sectioned and stained with specific antibodies to identify various immune cell types. Blood plasma and peritoneal ascites fluid/wash samples were collected just before and 24 hours after each of the four weekly GEN-1 treatments for cytokine ELISA and one week before the first GEN-1 treatment and 24 hours after the 4th weekly treatment for flow cytometry.

STUDY DESIGN & COLLECTION SCHEME FOR TRANSLATIONAL RESEARCH SAMPLES

- Standard 3+3 phase I design with approximate 30% dose increments between successive cohorts of patients. Dose levels of GEN-1 in combination with Taxane and Carboplatin.
- Tolerated dose is confirmed when 6 patients are treated at a dose level and <2 patients experience a dose-limiting toxicities (DLTs)

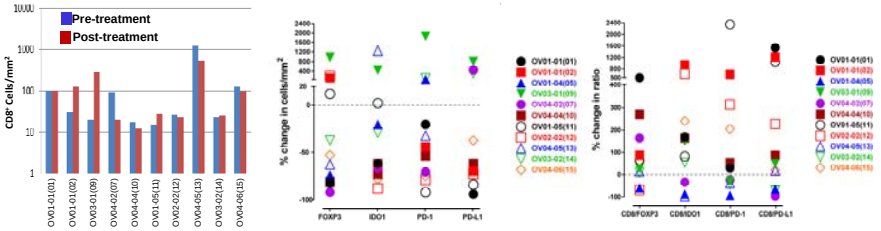


TRANSLATIONAL RESEARCH SAMPLES

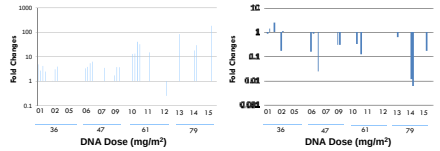
Analysis scheme: Cellular compartments in tumor, peritoneal ascites, and blood; Cytokine IFN-γ, IL-12, TNF-α, VEGF, TGF-β, IL-10 in peritoneal ascites and blood.

Results presented: $CD8^+$/immune suppressive cells in tumor tissue and IFN-γ and VEGF levels in peritoneal ascites.

% Change in Tumor Infiltrating Lymphocytes (pre-treatment vs post-treatment)



Treatment Related Changes in IFN-γ and VEGF Levels in Peritoneal Fluid



The fold changes represent the ratio of post-treatment to pre-treatment cytokine values. Pre-treatment samples were collected immediately before each of the four weekly treatments whereas post-treatment samples were collected 24 h thereafter. Samples could not be collected at several time points.

CONCLUSIONS

- Preliminary analyses of tissue specimens collected from the ongoing Ovation trial of GEN-1 + T/C combination NACT in epithelial ovarian cancer shows intriguing post-treatment immunological changes in tumor tissue and ascites.
- The GEN-1 + T/C treatment resulted in significant increases in IFN-γ levels and decreases in VEGF levels in peritoneal fluid. Immunohistochemical analysis of tumor tissue for various T-cell population showed reduction in immunosuppressive T-cell phenotype in several patients. The ratio of cytotoxic $CD8^+$ T cells to immunosuppressive FoxP3, IDO1 and PD-1 expressing cells was also increased in a majority of patients.
- The study is in progress and a complete analysis will be provided in the second half of 2017.

References

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