COMBINATION INTRAPERITONEAL CHEMOIMMUNOTHERAPY TRIGGERS A T-CELL CHEMOTACTIC LOCOREGIONAL RESPONSE IN PATIENTS WITH RECURRENT PLATINUM-SENSITIVE OVARIAN CANCER

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Background The increased prevalence of CD8+ tumor-infiltrating lymphocytes (TIL) in the tumor microenvironment (TME) correlates with improved outcomes in patients with epithelial ovarian cancer (EOC). We hypothesize that a combination of intraperitoneal (IP) chemotherapy (via immunogenic cell death-inducing cisplatin) with dual agent immunotherapy using IV pembrolizumab (anti-PD1) and IP rintatolimod (dsRNA and TLR-3 agonist) promotes increased T cell chemotaxis and cytolytic function, for improved clinical outcomes.

Methods We have performed translational studies focused on the immune TME, using a longitudinal collection of biospecimens, including plasma, PBMC, IP washes and tumor tissue. The samples were obtained from patients treated in a phase II, investigator- initiated trial (NCT03734692) that tests the efficacy/safety of IP cisplatin/IP rintatolimod/IV pembrolizumab administered in 6 cycles, three weeks apart. Serial collection of biologic samples includes aspiration of peritoneal resident cells (IP washes) before and after each treatment, at each of the 6 cycles. RNA sequencing of IP wash cells was performed using the Novogene platform. Additionally, the MesoScale Delivery (MSD) platform was used to profile 20 biomarkers in the peritoneal samples throughout treatment.

Results Sequential sampling of the intraperitoneal cavity showed an increase in cellularity immediately after treatment consistent with an ‘acute’ pro-inflammatory reaction. RNA sequencing data showed a significant upregulation acutely in genes associated with anti-tumor immunity (STAT1/STAT2 and downstream targets), T lymphotactic chemokines (CXCL9, 10, and 11), and TH1 type response (IFN gamma, Tbet) (<0.05) all of which are important for T lymphotaxis and function via TCR engagement with cognate tumor antigens. Gene Set Enrichment Analysis demonstrates an acute enrichment in Interferon alpha response as well as the Interferon gamma response (figure 1). MSD measurements in IP washes demonstrated an acute increase in granzyme B, perforin, TNF alpha, CXCL9, 10 and 11, IFN gamma, and IL-15 after treatment (p<0.05) (figure 2). Longitudinal data revealed a progressive increase in CXCL9, 10 and 11, as well as perforin, IFN gamma and TNF alpha from baseline levels at cycle 1 to cycle 6, suggestive of a sustained, chronic response during treatment.

Conclusions Analysis of the locoregional immune environment taken from patients receiving this novel, triple drug combination has demonstrated an acute and persistent increase in biomarkers associated with T cell chemotaxis and T cell function. Ongoing chip cytometry profiling of both IP wash cells and tumor samples will further elucidate the treatment induced changes in various innate and adaptive immune cell types in the TME.

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Trial Registration NCT03734692

Abstract 799 Figure 1 Gene Set Enrichment Analysis shows a significant enrichment in the Interferon gamma and Interferon alpha response
Abstract 799 Figure 2  Intra-cycle increase from day 1 to day 3 of cycles 1, 4 and 6 (p<0.05, Student t test).

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