NCT03734692: Systemic Immune Checkpoint Blockade and Intraperitoneal Chemo-Immunotherapy in Recurrent Ovarian Cancer

Primary Endpoint Report

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This serves as a summary report on a phase II clinical trial investigating a novel combination treatment for recurrent platinum-sensitive epithelial ovarian cancer (EOC) involving intraperitoneal (IP) chemotherapy with cisplatin, dual agent immunotherapy with IP Rintatolimod (a TLR3 agonist), and systemic anti-PD1 therapy (Pembrolizumab). The study aims to improve clinical outcomes by overcoming the immunosuppressive tumor microenvironment (TME) characteristic of ovarian cancer through locoregional and systemic immune activation strategies.

Introduction

EOC is the most common ovarian cancer type and a leading cause of gynecologic cancer mortality in the U.S., with over 70% diagnosed at late stages and high recurrence rates. Five-year survival remains low, necessitating improved early detection and therapies. Although ovarian tumors often have tumor-infiltrating lymphocytes (TILs), single-agent immunotherapies have shown limited success due to complex immune suppression in the TME. The trial tests a combination approach using IP cisplatin to induce immunogenic cell death, IP Rintatolimod to enhance immune modulation via TLR3 activation favoring cytotoxic T lymphocytes (CTLs), and systemic Pembrolizumab to block PD-1 immune checkpoints, hypothesized to synergistically enhance anti-tumor immunity and clinical benefit.

Clinical Trial Design and Methods

This investigator-initiated, single-arm phase II trial (NCT03734692) was conducted from 2017 to 2025, enrolling patients with first or second recurrence of platinum-sensitive ovarian or fallopian tube cancer who had measurable peritoneal or retroperitoneal lesions. Patients received six 3-week cycles of IP cisplatin (50 mg/m^2), followed by IV Pembrolizumab (200 mg) and IP Rintatolimod (200 mg) administered sequentially. Treatment continued until progression, toxicity, or patient/provider decision. The primary endpoint was objective response rate (ORR) by RECIST 1.1 at 13 weeks. Secondary endpoints included changes in tumor-infiltrating CD8+ T cells, safety, and adverse events. Extensive biospecimens including blood, ascites, IP washes, and tissues were collected longitudinally for translational studies.

Clinical Results

Among 27 enrolled patients, 24 were evaluable for response. Median age was 68, with most having high-grade serous histology. The regimen was generally well tolerated; no grade 4 or 5 toxicities occurred. Common adverse events included fatigue, anemia, abdominal pain, and nausea. Three patients experienced immune-related adverse events (irAEs) leading to trial discontinuation; notably, two of these patients remain disease-free for over 70 months. The ORR was 50%, with 21% complete responses and 29% partial responses. The clinical benefit rate (CR+PR+SD) was 79%. Median progression-free survival was 8.3 months, and median overall survival was 32.5 months. Half of the patients were deceased at publication time, with the remainder either disease-free or receiving further treatment.

Patient Demographics

- Median age 68 (range 51-79)
- No grade 4/5 toxicities
- 89% high-grade serous histology
- 64% first recurrence

Adverse Events

- Fatigue 100%
- Anemia 79%
- Abdominal pain 67%
- Nausea 83%
- Immune-mediated reactions in 3 patients
- 44% completed all 6 cycles

Translational Findings

The trial collected over 1400 biospecimens for detailed immune profiling. Sequential IP wash sampling revealed an acute increase in cellularity post-treatment indicative of a pro-inflammatory response that normalized between cycles. Immunophenotyping showed dynamic changes in immune cell populations, with a notable expansion of pro-inflammatory macrophages expressing activation markers CD80, CD86, and STAT1, and a reduction in immunosuppressive pathways. RNA sequencing demonstrated acute upregulation of genes and chemokines associated with Th1-type, anti-tumor immunity including CXCL9, CXCL10, CXCL11, IFN-γ, and T-bet. Protein analyses confirmed increased cytotoxic effectors such as granzyme B, perforin, and TNF-α in IP washes shortly after treatment. Over time, a durable increase in T cell chemotactic ligands and cytolytic markers was observed, alongside upregulation of both activating and inhibitory checkpoint molecules, suggesting sustained immune activation with regulatory feedback. Spatial profiling of tumor tissues from responders revealed higher infiltration of CD8+ cytotoxic T cells, granzyme B+ cells, memory T cells (CD45RO+), and total T cells (CD3+) within tumor areas compared to non-responders, indicating enhanced effector immune presence correlating with clinical benefit.

Discussion

The combination of IP cisplatin, IP Rintatolimod, and systemic Pembrolizumab was clinically feasible and showed promising efficacy in recurrent platinum-sensitive ovarian cancer, with a 50% ORR and manageable toxicity. Immune-related adverse events, though present, were associated with durable responses in some patients. Translational data support the mechanistic rationale that this regimen induces immunogenic cell death and robust locoregional immune activation, including expansion of pro-inflammatory macrophages and sustained type 1 immune responses. The observed inversion of platinum-free interval in 21% of patients compared to historical 3% suggests enhanced treatment efficacy. The study highlights the potential of combining locoregional chemotherapy with dual immunotherapy to overcome immune suppression in ovarian cancer and improve outcomes.