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"RE-STIMULATED" TUMOR-INFILTRATING LYMPHOCYTES AND LOW-DOSE INTERLEUKIN-2 THERAPY IN PATIENTS WITH PLATINUM RESISTANT HIGH GRADE SEROUS OVARIAN, FALLOPIAN TUBE, OR PRIMARY PERITONEAL CANCER (NCT01883297)

There is increasing evidence that epithelial ovarian carcinoma is immunogenic and may respond to immunotherapy. Adoptive cell therapy with autologous tumor-infiltrating lymphocytes (TILs) has shown remarkable clinical activity in early phase trials in the setting of metastatic melanoma. We have developed a clinical trial based on the adoptive transfer of TILs for ovarian cancer. Our preclinical work focused on evaluating TIL expansion from ovarian tumors, and also on developing a novel *in vitro* method of enhancing TIL function prior to adoptive transfer. In this method, expanded TILs are re-stimulated *in vitro* for one day with anti-CD3 mAb, IL-2 and autologous dendritic cells matured with TNF, IL-1β and IL-6. The "Re-stimulated TILs" are then harvested for infusion.

The clinical trial is a first-in-human, phase I, single centre study with the primary endpoints of feasibility and safety. Secondary endpoints are clinical and immunological responses. The trial design is a standard 3+3 dose escalation, with the following three dose levels: $3x10^7$, $1x10^8$ then $3x10^8$ Re-stimulated TILs. The investigational treatment involves preparative lymphodepletion with cyclophosphamide (30mg/kg/day x 2 days), followed by intravenous infusion of Re-stimulated TILs. Interleukin-2 therapy commences thereafter (125,000 IU/kg/day subcutaneous injection for ≤10 doses). With the aim of reducing acute IL-2-related toxicities, our protocol uses a lower dose regimen of IL-2 therapy compared to that used in the landmark TIL protocol developed at the National Cancer Institute. Eligible patients must have measurable platinum-resistant disease, ECOG ≤1 and adequate organ function. Radiological response by RECIST v1.1 and immune-related Response Criteria is performed 4 weeks post TIL infusion and 3 monthly thereafter. Initial immune monitoring will focus on tracking the phenotype and persistence of TILs after transfer.