FIRST-IN-HUMAN PHASE I CLINICAL TRIAL EVALUATING INTRAPERITONEAL ADMINISTRATION OF MOV19-BBZ CAR T CELLS IN PATIENTS WITH ALPHA FOLATE RECEPTOR-EXPRESSING RECURRENT HIGH GRADE SEROUS OVARIAN CANCER

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Background Most women with epithelial ovarian cancer develop uniformly incurable disease recurrence. Chimeric antigen receptor (CAR) T cells pair the MHC-independent tumor-recognition capabilities of monoclonal antibodies with the cytotoxicity of effector T cells. The success of CAR T cell therapy in solid tumors has been hindered by (1) difficulty identifying highly expressed, tumor-specific, cell surface target antigens; (2) limited trafficking and infiltration; and (3) suboptimal cytotoxic activity. Alpha folate receptor (FR α) is a transmembrane protein involved in cellular folate transport; expression has been reported in 80% of ovarian cancer, with limited physiologic expression on epithelial cells including bronchial, renal, and intestinal tissue. We hypothesize that intraperitoneal administration of alpha folate receptor (FR α) directed CAR T cells with dual 4-1BB and TCRzeta signaling domains will circumvent the above challenges and be safe, feasible, and elicit anti-tumor responses.

Methods We initiated a first-in-human phase I clinical trial to evaluate the feasibility, safety and preliminary efficacy of intraperitoneal administration of FR α directed CAR T cells with and without antecedent lymphodepleting chemotherapy (LDC) in women with recurrent high grade serous ovarian cancer. The lentivirally-transduced CAR is composed of a MOv19 anti-FR α -specific single chain variable fragment fused to 4-1BB and TCRzeta signaling domains. Eligible patients have persistent or recurrent high grade serous epithelial ovarian, fallopian tube, or primary peritoneal carcinoma that is not platinum refractory and expresses $\geq 2+$ FR α staining in $\geq 70\%$ of tumor cells. Subjects must have an ECOG performance status 0–1, measurable disease, adequate hematologic and organ function, and must have progressed on at least two prior chemotherapy regimens for advanced disease. Patients undergo biopsy pre-infusion and Day +14 after infusion. After same-day placement of an intraperitoneal catheter by Interventional Radiology, CAR T cells are administered via a single infusion on three dose cohorts: Cohort 1 (starting cohort), $1-3 \times 10^7/\text{m}^2$ cells without LDC; Cohort 2, $1-3 \times 10^7/\text{m}^2$ CAR T cells after LDC; Cohort 3, $1-3 \times 10^8/\text{m}^2$ cells after LDC. Catheter is removed after infusion. A 3+3 dose escalation design to determine maximum tolerated dose (MTD) yields approximately 9 to 18 subjects. The primary objective is safety and feasibility, and secondary objectives are anti-tumor response (endpoints: overall response rate based on RECIST v 1.1 and irRECIST when feasible, progression-free survival and overall survival). Correlative endpoints include CAR T cell engraftment and persistence in peripheral blood and body fluids examined via quantitative PCR of CAR T DNA, and bioactivity of CAR T cells. Enrollment is ongoing.

Trial Registration This trial is registered at ClinicalTrials.gov (NCT03585764).

Ethics Approval This study was approved by the Institutional Review Board at the University of Pennsylvania (IRB 830111). All subjects provided written informed consent prior to any study-related procedures.

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