Background Epithelial OVCA remains a highly fatal disease. FSHR is a tissue specific antigen expressed in >55% of high-grade epithelial OVCA of different histological types. No significant FSHR expression is found in non-ovarian healthy tissues in women (figure 1). The treatment of OVCA patient derived xenografts with FSHCER T (FSH-Chimeric Endocrine Receptor + T-Cell (CER T)) cells (figure 2) in controlled, paired, mice was shown to effectively redirect the cytotoxic activity of T cells against patient-derived FSHR+ ovarian carcinomas (figure 3).\textsuperscript{1} We hypothesize targeting FSHR in women with FSHR+ OVCA will result in improved response rates due to engraftment, expansion, and survival of these adoptively transferred FSHCER T cells and will have acceptable toxicity.

Methods This is an open phase 1 dose-escalation study (NCT05316129) in high-grade epithelial OVCA to assess the safety of autologous T cells genetically modified to express CER targeting FSHR. Primary objective is to assess the safety of the intraperitoneal (IP) and intravenous (IV) infusions of FSHCER T cells with or without prior cyclophosphamide plus fludarabine. Secondary objectives include antitumor efficacy, persistence of transferred FSHR T cells, expansion of endogenous tumor-targeted cells, and to compare IP and IV routes of administration.

A screening part of the study will examine archived tissue from patients with recurrent platinum resistant or refractory OVCA following 2-8 prior lines of chemotherapy. Those who demonstrate positive or indeterminate FSHR Expression by an RNA Salah Targeted Expression Panel (STEP) will be eligible to screen for the treatment dose-escalation portion. Additional criteria include measurable or evaluative disease; performance status 0-2; adequate bone marrow, renal, and hepatic function; and eligibility for IP catheter placement. If a patient is unable to be treated in the IP arm, the patient may be treated in the IV arm in the lowest unfilled cohort for that arm. Cohorts of 3 to 6 patients will be infused with escalating doses of FSHCER T cells to establish the maximum tolerated dose (MTD) with 6 planned dose levels: 1 × 10\textsuperscript{5}, 3 × 10\textsuperscript{5}, 1 × 10\textsuperscript{6}, 3 × 10\textsuperscript{6}, and 1 × 10\textsuperscript{7} FSHCER T cells/kg. If the MTD is not established after 3 × 10\textsuperscript{6}, then next cohorts will receive conditioning cytoxan/fludarabine 5 days before starting T-cell infusion at dose levels 1 × 10\textsuperscript{6}, 3 × 10\textsuperscript{6} and 1 × 10\textsuperscript{7} FSHCER T cells/kg. Following determination of MTD, an expansion phase will be initiated.

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Trial Registration NCT05316129

REFERENCE

Ethics Approval This study was approved by Moffitt Scientific Review 
#21113 and Advarra Institutional Review Board 
#00000971. Patients give informed consent before participation.