A Phase I Clinical Trial of an Infusion of Autologous T cells Genetically Engineered with a Chimeric Receptor to Target the Follicle-Stimulating Hormone Receptor in Patients with Recurrent Ovarian Cancer

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Background

Epithelial OVCA remains a highly fatal disease. FSHR is a tissue specific antigen expressed in >55% of high-grade epithelial OVCAs of different histological types. No significant FSHR expression is found in non-ovarian healthy tissues in women (Fig.1). The treatment of OVCA patient derived xenografts with FSHCER T (FSH-Chimeric Endocrine Receptor + T-Cell (CER T)) cells (Fig.2) in controlled, paired, mice was shown to effectively redirect the cytotoxic activity of T cells against patient-derived FSHR+ ovarian carcinomas (Fig. 3)[1]. We hypothesize targeting FSHR in women with FSHR+ OVCA will have acceptable toxicity and may have objective responses due to selective targeting by the adoptively transferred cells.

Methods

This is an open phase 1 dose-escalation study in high-grade epithelial OVCA to assess the safety of autologous T cells genetically modified to express CER targeting FSHR.

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. CTCAE v5.0 will be used for toxicity evaluation and antitumor efficacy will be defined according to the iRECIST criteria as previously described.[2]

Objectives

- Primary: assess the safety of Intraperitoneal (IP) and Intravenous (IV) infusion of FSHCER T cells with or without lymphodepleting chemotherapy with cyclophosphamide plus fludarabine.
- Secondary: assess: (1) the antitumor efficacy of adoptively transferred FSHCER T cells, (2) the *in vivo* persistence of adoptively transferred FSHCER T cells, (3) whether infusion of FSHCER T cells enhances the expansion of endogenous tumor-targeted T cells, and (4) to compare IP and IV routes of administration for tolerability, toxicity, and efficacy.

Figure 1. Q–PCR of FSHR expression in human healthy tissues.

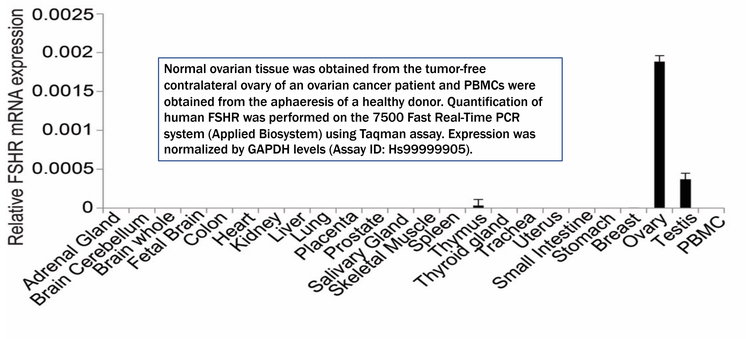
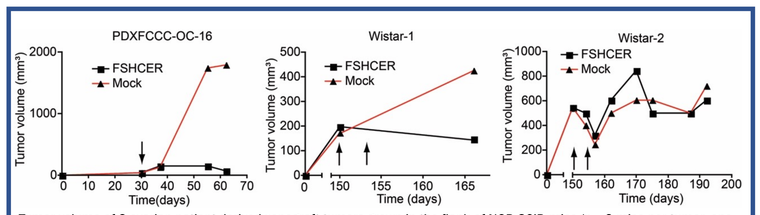


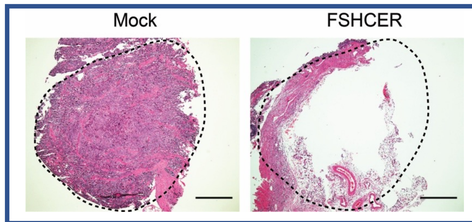
Figure 2. FSHCER construct for expression in T cells

The codon-optimized sequence of the insert and its translation are: (Signal Peptide (FSH β); hFSHβ; Spacer; hFSHα; Hinge (from human CD8); TM domain (from human CD8); human 4-1BB (intracellular); human CD3z domain):

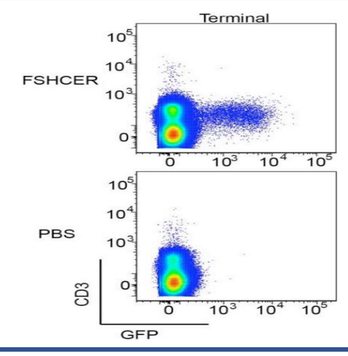
Figure 3. Patient-derived xenografts could be effectively targeted with FSH-expressing chimeric receptors.



Tumor volume of 3 ovarian patient-derived xenograft tumors grown in the flank of NOD-SCID mice (n = 2 mice per tumor, one case-one control, single experiment) injected intra-tumorally with 10 million total FSHCER or mock-transduced T-cells (arrows mark time of T-cell injection).



Hematoxilin-Eosin staining of ovarian PDX tumor grown in NOD-SCID mice ovary treated with either FSHCER ("case" mouse) or mock ("control" mouse) transduced autologous HUMAN FSHCER T cells (10^6 total; >70%GFP+).



CONGENIC FSHCER T cells persist in the peritoneal cavity of oprthotopic ovarian cancer-bearing mice. Immunocompetent CD45.1+ mice bearing ID8-Defb29/Vegfa/FSHR orthotopic tumors (n=5 mice/group; 2 independent experiments), were intraperitoneally injected with 106 (total) congenic CD45.1+ MOUSE FSHFSHCER T cells (>70% GFP+ cells; pBMN retroviruses) or vehicle (PBS), at days 7 and 14 after tumor challenge (after 250 rads), and terminal ascites (~ day 65) was analyzed for the presence of CD3+GFP+CD45.1+ cells. PMID: 27435394

Study Population:	• Adults with recurrent high grade epithelial ovarian cancer (EOC) • 2 to 8 prior lines of chemotherapy with measurable disease • Performance status 0-2; adequate bone marrow, renal, and hepatic function; and eligibility for IP catheter placement. • Patients with other active malignancies, a life expectancy of < 3 months, or an ECOG score > 2 at the time of planned treatment of the FSHCER T cells will be ineligible.

Cohorts

Table 1: Planned Dose-Escalation Scheme for the Clinical Trial

Cohort	Dose Level	Cyclophosphamide dose	FSHCER T-cell Dose	Number of Patients
-1	-1	None	3×10^4 cells/kg	3-6 patients
1	1	None	1×10^5 cells/kg	3-6 patients
2	2	None	3×10^5 cells/kg	3-6 patients
3	3	None	1×10^6 cells/kg	3-6 patients
4	4	None	3×10^6 cells/kg	3-6 patients
6	5	None	1×10^7 cells/kg	3-6 patients
5	3	cyclophosphamide 500 mg/m² and fludarabine (30 mg/m²) × 3 days	1×10^6 cells/kg	3-6 patients
5b	4	cyclophosphamide 500 mg/m² and fludarabine (30 mg/m²) × 3 days	3×10^6 cells/kg	3-6 patients
5c	5	cyclophosphamide 500 mg/m² and fludarabine (30 mg/m²) × 3 days	1×10^7 cells/kg	3-6 patients

Parallel cohorts with enrollment to IP first for each patient, but those who can't have port placed or have infusion access problems, a parallel intravenous IV cohort will be filled.

Following determination of MTD, an expansion phase will be initiated.

Conclusion

This is a recently opened and ongoing phase 1 study that has begun enrollment during 2022 and aims to test CAR-T in ovarian cancer with a novel target of a very specific protein expressed by ovarian cells and a majority of ovarian cancers.

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- Trial Registration: (NCT05316129)
- Ethics Approval. This study was approved by Moffitt Scientific Review #21113 and Advarra Institutional Review Board #00000971.

1. Perales-Puchalt, A., et al.. Follicle-Stimulating Hormone Receptor Is Expressed by Most Ovarian Cancer Subtypes and Is a Safe and Effective Immunotherapeutic Target. Clin Cancer Res, 2017; 23(2), 441-453. doi:10.1158/1078-0432.CCR-16-0492
2. Seymour, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics Lancet Oncol., 18(3) 2017).