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

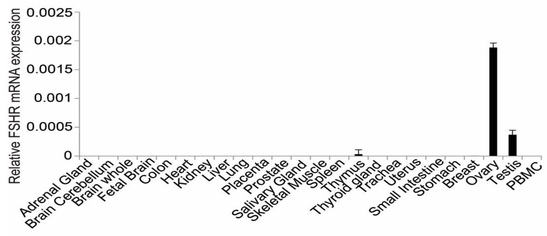
This is an open phase 1 dose-escalation study in high-grade epithelial OVCA to assess the safety of autologous T cells genetically modified to express CER targeting FSHR.

Patients with recurrent platinum resistant or refractory OVCA following 2-8 prior lines of chemotherapy who are successfully screened undergo plasmapheresis, intraperitoneal (IP) port placement, and subsequent cohort defined cell administration. Those unable to receive IP may be placed in the open cohort in the intravenous (IV) arm. Will examine archived tissue from patients. Patients' tumors will be examined for FSHR Expression by an RNA Salah Targeted Expression Panel (STEP). 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.

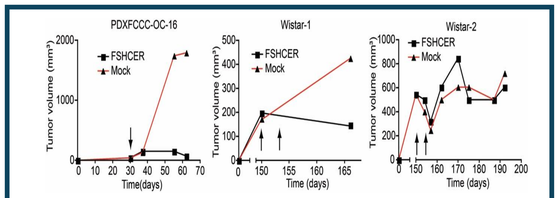


Normal ovarian tissue was obtained from the tumor-free contralateral ovary of an ovarian cancer patient and PBMCs were obtained from the aphaeresis of a healthy donor. Quantification of human FSHR was performed on the 7500 Fast Real-Time PCR system (Applied Biosystem) using Taqman assay. Expression was normalized by GAPDH levels (Assay ID: Hs99999905).

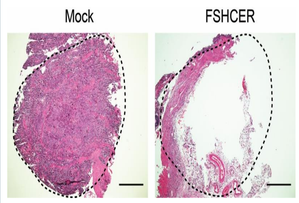
Figure 2. FSHCER construct for expression in T cells

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):

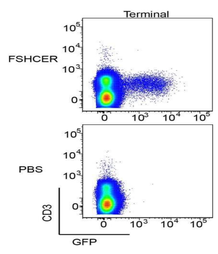
Figure 3. Patient-derived xenografts could be effectively targeted with FSH-expressing chimeric receptors.



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 orthotopic 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

Patients

- Adults with platinum-refractory or resistant, recurrent borderline*, low*, or high grade epithelial; or sex-chord stromal* ovarian cancer (OC) *new amendment for cohort 4
- 2 to 8 prior lines of chemotherapy
- Measurable disease or Detectable disease with
- Presence of CA-125 2x Upper limit of Normal
- FFPE available for FSHR RNA Saleh assay
- 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.
- Must have received disease type appropriate therapies (for example, PARP inhibitors for BRCA-mutated high grade cancers, FRa antibody drug conjugate for FRa qualifying high grade cancers, one hormonal therapy for granulosa cell tumors.
- No prior checkpoint inhibitors in 3-months prior

Cohorts

Table 1. Dose-escalation scheme.

Cohort	Dose Level	Cyclophosphamide 500 mg/m² and fludarabine (30 mg/m²) × 3 days	FSHCER T-cell Dose	Number of Patients
-1	-1	No	3×10^4 cells/kg	3-6 patients
1	1	No	1×10^5 cells/kg	3-6 patients
2	2	No	3×10^5 cells/kg	3-6 patients
3	3	No	1×10^6 cells/kg	3-6 patients
4	4	No	3×10^6 cells/kg	3-6 patients
5	5	Yes	1×10^7 cells/kg	3-6 patients
6	6	Yes	1×10^8 cells/kg	3-6 patients
7*	7	Yes	1×10^9cells/kg	3-6 patients

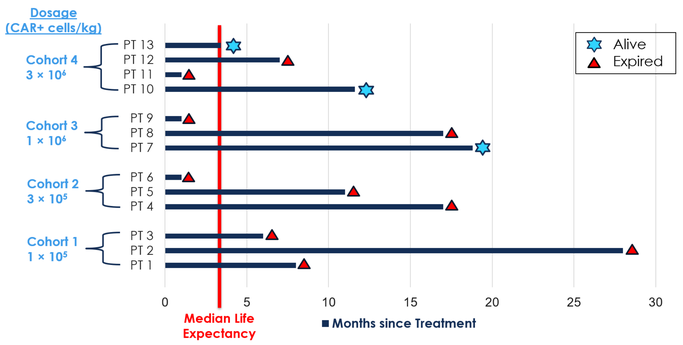
Parallel cohorts with enrollment to IP first for each patient, but those who can't have port placed or have infusion access problems, a parallel intravenous IV cohort will be filled.
Following determination of MTD, an expansion phase is planned.
* Higher dose levels allowed pending data review if no MTD reached.

Demographics

Cohort	Sequence No.	Race	Ethnicity	Age yr	FSHR Gene Expression[1,2]	No. of Prior Treatments
1	1	White	Non-hispanic	59	YES	5
	2	White	Hispanic or Latino	59	YES	6
	3	White	Non-hispanic	61	YES	5
2	4	White	Non-hispanic	55	NO	5
	5	White	Hispanic or Latino	63	NO	10
	6	White	Non-hispanic	53	NO	8
3	7	White	Hispanic or Latino	62	NO	6
	8	White	Hispanic or Latino	37	NO	5
	9	White	Non-hispanic	41	Not done	7
4	10	White	Non-hispanic	69	YES	8
	11	White	Non-hispanic	68	NO	3
	12	White	Non-hispanic	60	YES	8
	13(R)	White	Non-hispanic	51	NO	3

[1] The initial protocol required positive FSHR expression for enrollment, however, due to slow enrollment, the protocol was amended to do the analysis retrospectively and not require positive expression for enrollment
[2] Assessed with a clinically validated 204 gene panel; nCounter, Bruker, Inc

Patient Status



Conclusions

- Phase 1 study testing CAR-T in ovarian cancer with a novel target of a very specific protein expressed by ovarian cells in a majority of ovarian cancers.
- No DLTs have been encountered in first 4 Dose Cohorts. All doses have been administered successfully by intraperitoneal (IP) route.
- There have been 13 SAEs unrelated to CAR-T and no ICANS or CRS.
- 33% of enrolled patients had positive FSHR gene expression
- One patient from cohort 1, who came off study after after immune (i) RECIST[2] confirmed progression of disease (icPD), remained off therapy for over a year without further progression. She received a second dose under single patient IND/protocol MCC#23373. Study amended to allow for new cohorts on master protocol.

Acknowledgements:

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

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).

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