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TITLE: TCR-engineered T cell immunotherapy for epithelial ovarian cancer enhanced by TGFbeta blockade and epigenetic modulation

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TCR-Engineered T-Cell Immunotherapy for Epithelial Ovarian Cancer Enhanced by TGFbeta Blockade and Epigenetic Modulation

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6. AUTHOR(S)

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Roswell Park Comprehensive
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13. SUPPLEMENTARY NOTES

14. ABSTRACT

This is a project to test the hypothesis that the combination of epigenetic modification (Decitabine) and adoptive cell therapy (ACT) of NY- ESO-1 TCR/ dnTGFβRII –engineered T cells will be safe and show improved clinical responses in women who have recurrent/persistent platinum-resistant ovarian cancers. We had successfully reached the milestones for the first year: We injected the highest dose of T cell (10e9 transgenic T cells) in the last cohort of our Phase I clinical trial with NY-ESO-1 TCR/dnTGFβRII engineered T cells for solid- tumors (including Ovarian Ca.) FDA approval (IND 17410), (clinicaltrials.gov reg. # NCT02650986). And we successfully got approval from IRB and FDA to add Decitabine to the clinical trial as proposed.

15. SUBJECT TERMS

Immunotherapy; T Cell Receptor; Adoptive T cell Transfer

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1. INTRODUCTION

This is a project to test the Hypothesis that the combination of epigenetic modification (Decitabine) and adoptive cell therapy (ACT) of NY-ESO-1 TCR/ dnTGFβRII –engineered T cells will be safe and show improved clinical responses in women who have recurrent/persistent platinum-resistant ovarian cancers. There are two aims: 1)To evaluate, in a phase I trial, the safety, persistence and clinical response of adoptive transfer of NY-ESO-1 TCR/dnTGFβRII engineered T cells + Decitabine in EOC patients. We will conduct a clinical trial infusing genetically engineered PBMC expressing a high affinity TCR specific for the HLA-A*0201-restricted NY-ESO-1 antigen together with the dnTGFβRII transgene to recurrent/persistent platinum-resistant EOC patients pre-treated with Decitabine. 2) To evaluate key immunological end-points that correlate with the degree of clinical responses. We will collect, at defined time points, and analyze blood (serum, PBMC), tumor infiltrating lymphocytes (TIL) from biopsies and ascites for number, immunophenotyping, and functional assays. Persistence of transgenic T cells will be monitored and quantified.

2. KEYWORDS

Immunotherapy
T Cell Receptor
Adoptive T cell Transfer

3. ACCOMPLISHMENTS

3.1. What were the major goals of the project?

Primary Objective: To evaluate the safety and feasibility of adoptive transfer of autologous NY-ESO-1 TCR/dn TGFβ-RII transgenic T-cells. Secondary Objectives: To evaluate correlative immunological and clinical responses following ACT with engineered TCR.
Milestones/target dates for important activities of the FIRST YEAR: Major Task 1: Assess maximum tolerated dose with NY-ESO-1 TCR/dn TGFβ-RII construct and new protocol approval. Subtask 1: Accrue 3 patients with advanced Ovarian Cancer to ongoing trial IRB 258514, a Phase 1 study of NY-ESO-1 TCR/dn TGFβRII transgenic T cells in patients with advanced solid tumors, at the maximum tolerated dose or Cohort 3. Screen patients for NYESO-1 + and HLA-A2+ . Subtask 2: a) Obtain IRB approval , b) IND meeting with FDA, c) Obtain FDA approval. Milestone: FDA, IND and IRB approval Subtask 3: Continue accrual of patients to Cohorts 3 or maximum tolerated dose.

Of important note: This DOD award was approved and meant to provide funds for an extension cohort (with Decitabine) to be added on top of the already ongoing clinical trial that had started years ago (# NCT02650986), as very clearly explained in the text of the awarded grant proposal. Therefore, <u>no funds from DOD assigned to human subjects were used before HRPO approval.</u> The Subtask 1 (which was completed) is related to the Non-DOD funded clinical trial, but that subtask is still important as requirement for Subtask 2 (which is related to the Regulatory Agencies' paperwork). The Subtask 2 was partially accomplished in 2019: the internal IRB was submitted and all the documents/materials related to DOD's HRPO approval were submitted to DOD, with various back-and-forth exchanges between DOD and Roswell Park.

3.2.What was accomplished under these goals?
We successfully reached the highest dose of T cell (10e9 transgenic T cells) in the last cohort of our Phase I clinical trial with NY-ESO-1 TCR/dnTGFβRII engineered T cells for solid-tumors (including Ovarian Ca.) FDA approval (IND 17410), (clinicaltrials.gov reg. # NCT02650986). This clinical trial precedes the DOD Award and it is funded from other sources (Non-DOD). The # NCT02650986 clinical trial is an open label Phase I/IIa clinical trial. Patients with NY-ESO-1-positive advanced malignancies who are HLA-A*0201-positive, and HIV, hepatitis B and C seronegative are enrolled in the study providing they meet the remaining eligibility criteria. Upon enrollment, patients underwent leukapheresis on day -6 for T cell collection and their cells were genetically engineered and expanded ex-vivo. 5 days prior to ACT, patients received a conditioning regimen consisting of 45 mg/kg IV cyclophosphamide for two days as an outpatient or inpatient, according to the investigator's discretion to create space for the transgenic cells. The cell product was infused fresh after lot release on day 0 as an inpatient. This is a 3 + (3) design dose escalation study with the first cohort receiving 10e7, second cohort 10e8 and the third cohort 10e9 NY-ESO-1 TCR/dnTGFb-RII transgenic cells as a single dose, calculated based on the transduction efficiency by tetramer assay. With no dose-limiting toxicity in the highest dose so far, we applied for an amendment to the clinical protocol to add Decitabine as epigenetic modulator, as proposed for this DOD project (internal IRB submission). We successfully obtained approval from IRB to go forward with the addition of decitabine, so that we can continue accrual within the Newly added cohort 4 (the DOD funded portion), pending HRPO approval. The cohort 4 will have patients with treatment refractory or recurrent epithelial ovarian, primary peritoneal or fallopian tube carcinoma patients to receive the MTD of NY-ESO-1 TCR/dnTGFb-RII transgenic cells in combination with Decitabine, following the 3 + (3) rule accrual and phase I trial design.

3.3.What opportunities for training and professional development has the project provided?
The project was not intended to provide training and professional development.

3.4. How were the results disseminated to communities of interest?
Nothing to report yet.

3.5. What do you plan to do during the next reporting period to accomplish the goals?
Continue with primary objective as described above for Subtask 4 : Accrue patients to Cohorts 4 (3 (+6) subjects). Screen patients for NYESO-1 + and HLA-A2+. Dose predicted: Decitabine followed by 1 x 10e9 TCR/dnTGFbRII iv. Safety analysis of enrolled patients.

4. IMPACT

Since this is the FIRST YEAR report and we had successfully reached IRB milestones as stated in the SOW, we are waiting for HRPO approval, with all the documents already submitted to DOD. After HRPO approval, we will start accrual of patients for the cohort 4, so the IMPACT will be seen in the next year and after when we collect/summarize data from the clinical trial. As policy of our Cancer Center, only mature and confirmed results from a clinical trial are publishable.

What was the impact on the development of the principal discipline(s) of the project? Nothing to Report.
What was the impact on other disciplines? Nothing to Report.
What was the impact on technology transfer? Nothing to Report.
What was the impact on society beyond science and technology? Nothing to Report.

5. CHANGES/PROBLEMS

Nothing to Report.

6. PRODUCTS

Nothing to Report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?
1) NAME: Richard Koya; ROLE: PI; NEAREST PERSON MONTH WORKED: 1.2 calendar months; CONTRIBUTION TO PROJECT: As PI , Dr Koya supervised all aspects of the clinical trial, worked in the regulatory agencies' required applications, documents and reports.
2) NAME: Thinle Chodon; ROLE: co-investigator; NEAREST PERSON MONTH WORKED: 0.6 calendar months; CONTRIBUTION TO PROJECT: supported the PI in the regulatory agencies' required applications, documents, reports and manufacture of the T cell products. FUNDING SUPPORT: additional internal institutional support from the Cancer Center.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period? Nothing to Report.

What other organizations were involved as partners? Nothing to Report.

8. SPECIAL REPORTING REQUIREMENTS

Not applicable.

9. APPENDICES

Not applicable.