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Responses to RAC Reviewer Comments

In response to RAC comments received on February 24, 2014, City of Hope's (COH) responses to RAC Reviewer Comments for the protocol noted below follow. RAC comments are noted in bold, followed by COH's Response.

NIH OBA Protocol No. 1401-1287: "Phase I Study of Cellular Immunotherapy Using T Cells Lentivirally Transduced to Express a CD123-Specific, Hinge-Optimized, CD28-Costimulatory Chimeric Antigen Receptor and a Truncated EGFR for Patients with Relapsed or Refractory CD123+ Acute Myeloid Leukemia"

Sponsor: COH

Principal Investigator: L. Elizabeth Budde, M.D., Ph.D.

Project Leader: Stephen Forman, M.D.

Clinical Site: COH

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RAC Reviewer: R. Dresser, J.D.

This phase I study will involve individuals with CD123+ relapsed or refractory Acute Myeloid Leukemia (AML) who have an available donor or stem cell source for allogeneic transplantation. The intervention will be autologous T cells genetically modified to express a CD123-specific chimeric antigen receptor (CAR). This will be the first time humans have been exposed to this CAR.

Consent Form

1. **The form refers to the study intervention as “treatment.” Patients reading this form could infer that the intervention has a good chance of benefitting them, which is unlikely. It would be better to use “study drug,” “investigational drug,” or “experimental product.”**

COH Response:

The informed consent has now been revised to remove such terms as ‘treatment’ when referring to the investigational drug.

2. **Some of the material in the form could be omitted to make it easier to navigate. For example, the information in the first two sentences at the top of page 2 is not essential for prospective subjects to know. Also, I am not sure that it is necessary to use the full scientific terms for the vector and T cells in the body of the form, as long as they are used in the title.**

COH Response:

The informed consent has now been revised to remove the first two sentences at the top of page 2, as well as simplify the names of the investigational drug and vector in the body of the informed consent text.

3. **The dosages in the table on page 5 will be meaningless to nonscientist readers.**

COH Response:

The informed consent has now been revised to remove the dosage table on page 5.

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4. **Page 7 – the information on withdrawal from the study should note that it is not possible to remove the infusion of genetically modified cells once they have been infused into the body. (Some prospective subjects may not realize this.) At the same time, you can tell them that it is possible to minimize the effects of the genetically modified cells through the use of cetuximab and other drugs.**

COH Response:

Information on page 7 of the informed consent regarding the withdrawal from study has now been revised to include the statement that ‘it is unknown whether or not it is possible to remove the investigational drug from you once it has been given’, and the statement ‘review **Possible Risks and Discomforts**’ has also been added.

Additionally, **Section V** of the informed consent ‘Possible Risks and Discomforts’, subsection ‘**Risks from Cetuximab**’ has been revised to include additional language stating that ‘Cetuximab has never been used in humans before to eliminate (remove) AML-specific immune cells. Therefore, it is possible that Cetuximab will not be able to remove the investigational drug once it has been given.

5. **Page 12 – explain what cytokine release syndrome involves.**

COH Response:

Section ‘Possible Risks and Discomforts’ of the informed consent has been revised to include a subsection of ‘**Likely and Serious Side Effects**’ which describes the risks associated with cytokine release syndrome.

6. **I think this form will be hard for prospective subjects to follow. I encourage you to simplify the language as much as possible. For example, the paragraph on page 3 describing leukapheresis will be very difficult for the ordinary reader to understand. To promote subjects’ understanding, experts recommend that forms be written at an eighth-grade reading level. Short sentences and paragraphs are easiest to read. Active voice is better than passive voice.**

COH Response:

The informed consent has been revised throughout to simplify terms used (such as the investigational drug), descriptions of procedures (such as leukapheresis), and sentence structure.

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RAC Reviewer: Kiem, M.D.,Ph.D.

This is a well-written protocol – the vector and its novel components are well described and vector-based risks and toxicities are also appropriately discussed and described for the most part.

COH Response:

COH appreciates the reviewer's recognition of our work.

There are few questions/comments for clarification:

- 1. Why do the investigators expect the CAR cells to work on CD123-expressing leukemia when 2 trials using an anti CD123 antibodies including one linked to diphtheria toxin did not show significant responses? There were also other toxicities including liver. Please explain why the investigators expect the CAR construct to work and whether they would expect the toxicity profile to be different.**

COH Response:

COH acknowledges that the efficacy of CD123 T cells in the clinical setting is unknown. However, based on the potent anti-leukemic activity we observed with the CAR123 T cells, the impressive 70 to 90% complete response (CR) rate seen in recent clinical trials using CD19CAR T cells that contain the same CD28 costimulatory domain in treating acute lymphoblastic leukemia (ALL) (NCI and MSKCC experience) and cumulative studies that demonstrate CD123 is a well characterized leukemia-associated antigen, we believe that CD123-specific CAR T cell adoptive immunotherapy is a promising approach in treating acute myeloid leukemia (AML) and warrants clinical testing. There are mechanistic differences between cell-based therapy and antibody or receptor-drug conjugate mediated therapy. The two published clinical trials mentioned above testing CSL360 (a neutralizing antiCD123 antibody) and SL401 (a diphtheria toxin and human IL-3 conjugate) are both phase 1 studies. Therefore, efficacy was not the primary objective. Currently CSL362, an improved version of CSL360 with enhanced antibody-dependent cell-mediated cytotoxicity (ADCC) activity is being studied in a multicenter clinical trial. SL401 was tested in a phase Ib clinical trial treating patients with CD123+ blastic plasmacytoid dendritic cell neoplasm. The SL401 dosing schedule was based on the dose-finding results from the previous phase 1 clinical trial. Five of seven evaluable patients achieved CR, confirming that potent clinical anti-tumor activity can be achieved by targeting CD123 (personal communication with Dr. Arthur Frankel, University of Texas Southwestern Medical Center).

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COH expects that the CAR T cell therapy would have an overlapping but different toxicity profile. As previously stated, there are mechanistic differences between cell-based therapy and antibody or receptor-drug conjugate mediated therapy. The expected adverse events (AEs) are outlined in **Section 8.1** of the proposed clinical protocol. We expect to see similar on-target toxicities including possible reduced hematopoiesis, reduced numbers of basophils, monocytes, plasmacytoid dendritic cells and natural killer (NK) cells; similar off target toxicities such as infusion reactions. We also expect to see toxicities that are unique to T cell therapy: cytokine release syndrome and macrophage activation syndrome. The abnormal liver function seen in patients treated with SL401 is likely due to nonspecific liver uptake and damage by the drug. There is no CD123 expression on Kuffer cells or hepatocytes (Urieto et al. Protein Exp Purif. 2004; 33(1):123-133).

- 2. CD123 is expressed on other tissues – please provide information which in vivo studies were performed to evaluate the potential for on-target off tumor effects – ie toxicities from the CAR cells binding to non-AML tissue.**

COH Response:

This is an excellent comment. Low level expression of CD123 is found on a subset of CD34+CD38-hematopoietic stem/progenitor cells (HSPC). It is also expressed at high levels on plasmacytoid dendritic cells and basophils and at low levels on monocytes, eosinophils, myeloid dendritic cells.

Pizzitola et al. (Leukemia 2014, Feb 7. Epub) recently showed, treatment of human cord blood or bone marrow derived CD34+ cells reconstituted NSG mice with anti-CD123 CAR CIK (CD3+CD56+ cytokine induced killer) cells, resulted in a mild, but non-statistically significant reduction in the number of the human Lin⁻CD34⁺CD38⁻ and Lin⁻CD34⁺ HSPC compartments. This indicates that CD123 CAR treatment has limited capacity in killing normal HSPCs *in vivo* in this model. In line with this finding, reduced but full recovery of normal hematopoiesis was seen in all three responders in the SL-401 clinical trial. Our proposed clinical protocol provides an excellent opportunity for us to evaluate the impact of our CD123 CAR T cells on hematopoiesis in the actual clinical setting. Only patients with an identified donor stem cell source are eligible to enroll on this proposed study. Therefore, in the event of prolonged severe cytopenia, an allogeneic stem cell transplantation (alloSCT) will restore a patient's hematopoiesis.

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- 3. The investigators discuss optional cetuximab administration. Please clarify when this treatment will be employed ie criteria and whether patients will be able to move to allo transplant without CAR depletion? What would be the impact on the allotransplant if CAR CD123 cells still persist at significant levels? Please clarify in the consent form why the patient would want to wish the T cell ablation – discuss the rationale and risks is there a particular CAR level that is acceptable before allo transplant – when would they use a second cetuximab infusion. What is the experience with CAR depletion with Cetuximab?**

COH Response:

Section 8.1.2 of the proposed clinical protocol describes when Cetuximab will be used for CAR+ T cell ablation which includes prolonged neutropenia, and optional ablation prior to start of conditioning for alloSCT. Cetuximab will be offered to research participants prior to alloSCT, but will not be required for 2 reasons: (1) The study team recognizes that administration of Cetuximab introduces the potential for additional side effects while the ability to ablate CAR+ T cells with Cetuximab in humans is still theoretical, and (2) since the manufacturing platform utilized in this proposed clinical protocol has not endowed the CAR+ T cells with any survival advantages we have every reason to believe the CAR+ T cells will follow the same fate as unmanipulated T cell through myeloablative conditioning.

Furthermore, patients who were treated with autologous CD19 CAR T cells prior to alloSCT had normal donor B cell reconstitution, indicating that autologous CD19CAR T cells pose no impact on donor B cell engraftment (Brentjens et al. Science Translational Medicine 2013, 15(177): 177). Therefore, any level of CAR+ T cells detected prior to alloSCT is acceptable, and all participants regardless of % detectable CAR+ T cells or Cetuximab ablation will move on to alloSCT per standard of care. This protocol provides an opportunity to assess the clinical efficacy of Cetuximab in ablating the CAR T cells. This is one of the exploratory objectives.

Section V of the informed consent, subsection '**Risks from Cetuximab**' has now been revised to include reasons why CAR+ T cells may be ablated.

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- 4. It seems still unclear to what extent the normal hematopoiesis will be affected –how will this be analyzed and studied and how will it be part of the dose escalation and de-escalation scheme especially in light of the cyclophosphamide conditioning which can also lead to myelosuppression especially after reinduction chemotherapy or salvage chemotherapy.**

COH Response:

COH agrees with the reviewer that it is not clear and that it is hard to predict to what extent normal hematopoiesis will be affected by our CD123CAR T cells. Therefore, we have added exploratory objectives which include impact on hematopoiesis (1.0 Goals and Objectives in the proposed clinical protocol). A few preclinical studies and two phase I clinical trials indicate that normal hematopoiesis might be mildly affected when targeting CD123. We propose to analyze the hematopoietic stem/progenitor cell compartments using flow cytometric analysis and immunohistochemistry of bone marrow samples, follow numbers of subsets of blood cells in the peripheral blood at various time points after T cell infusion. As all patients are expected to move on to receive alloSCT with available stem cell source, we do not include hematopoiesis capacity as one of the determining factors in the dose finding Design.

The cyclophosphamide dose as a lymphodepletion regimen is modest at 1.5 gm/m². It is not myelosuppressive at this dose level. We agree that in our treatment population, cyclophosphamide treatment might transiently worsen the extent of myelosuppression caused by prior systemic chemotherapies. Therefore, we require collection of research bone and blood samples prior to cyclophosphamide administration to document the hematopoietic function at baseline. We will also assess hematopoietic function at day 28 post T cell infusion. If there is worsening hematopoiesis 28 days post T cell infusion, it is most likely due to effects from CAR T cells rather than from cyclophosphamide.

- 5. Please clarify how soon after reinduction cyclophosphamide will be given.**

COH Response:

For patients who receive salvage chemotherapy, cyclophosphamide will be given only after a response assessment is completed and treatment related toxicities are adequately assessed. This has been added to Section 5.1.1.4 in the proposed clinical protocol.

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- 6. Please clarify whether allo transplant be done before 60 days – why did you pick 60 days, what happens if patients progress beyond the second dose – will alternative therapy be discussed before a second dose is offered in case of progression.**

COH Response:

COH has revised the language in the proposed clinical protocol to allow initiation of allogeneic transplant workup any time 28 days post T cell infusion.

The second T cell infusion is optional and exploratory in nature. The study team will definitely discuss with the patient other alternative treatment options prior to the second dose of T cell infusion. This is reflected in the revised informed consent.

- 7. Please clarify the eligibility criteria for moving forward with an allotransplant if they respond and if yes at what point after the 60 days. Currently the protocol says “Decisions regarding a participant’s eligibility to receive alloSCT will be made by the participant and their treating physician. The study team strongly recommends that any patient who achieves CR, CRi or partial response to CD123 CAR T cell therapy proceed to an alloSCT” This should be discussed further – if it is up to the patient and the patient elects not to proceed there is likely increased risks for relapse and thus impact on survival since without transplant with any traditional therapy after recurrent disease outcome would be extremely poor and patients would in most cases proceed to transplant**

COH Response:

Patients can proceed to alloSCT 28 days after T cell infusion. Their eligibility will be determined per standard of care and by their treating physician.

COH has modified the proposed clinical protocol as follows, Section 5.1.1.8: “The study team strongly recommends that any patient who achieves CR, CRi or partial response to CD123 CAR T cell therapy proceed to an alloSCT as the proposed T cell treatment is experimental and is designed to bridge patients to alloSCT and not to replace alloSCT”. This has also been reflected in the revised informed consent.

Additionally, the **Section III** of the informed consent ‘What Will Be Done’, subsection ‘**Option to Ablate the T cells and undergo alloSCT**’ has been revised for clarity. The subsection has been retitled to ‘**Preparation for AlloSCT**’, and reorganized to first discuss with the patient what will happen when they are ready for standard of care alloSCT, and then to understand their option to receive Cetuximab for the experimental use of potentially eliminating the investigational

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drug, AML-specific immune cells. A clean and redline copy of the revised informed consent has been provided with this response.

8. Please clarify how and when will the Treg cells will be depleted and what is the experience.

COH Response:

For clarification, regulatory T (Treg) will only be depleted *in vivo* through lymphodepletion as stated in Section 2.1.2.2 of the proposed clinical protocol, and will NOT be depleted from the cellular product. However, the study team acknowledges that there was a typographical error in the clinical protocol which may have misinformed the reviewers suggesting that CD25+ Tregs would be depleted from the cellular product in Section 2.1.3.2. The study will use bulk T cells collected from patient without subset selection. The typographical error has been corrected in the attached revised copy of the proposed clinical protocol.