Summary of Protocol Changes

CTO-IUSCCC-ICG122-101

Date: 09/26/2024

Amendment Rationale: The main purpose of this amendment is to make updates to align with the other CD4CAR trials, including update the infusion process to gravity feed, clarify DLT and stopping language, add windows for follow-up visits and revising language to better align with our IU DSMP.

Protocol version: 09/24/2024

Previous version: 01/22/2024

***Bolded Language under sections indicates changed language**

Protocol Changes
1. Minor administrative clarifications throughout including but not limited to: • Updating the version date • Formatting adjustments
2. Removing Dr. Assi and Dr. Becker as they are no longer collaborating
• **Schedule of Events – pg 14-18** • Updated the timeframes for second screening (~Day -7 **to -5**), Conditioning chemo (~Day -4 **to -2**), and third screening (**~Day -1**) to align with the other CD4CAR trials • Added an Echo AN to second screening timepoint • Removed additional procedures from Leukapheresis timepoint and moved them back to Screening with the footnote that those procedures must be completed prior to leukapheresis • Removed ECOG from Day 4 as this is no longer needed during inpatient stay • Added a clinical flow on Day 0 • Moved the following procedures from screening to prior to start of pre-conditioning chemo: o Research flow cytometry o Transgene copy number o HAMA o Replication competent lentivirus o Optional blood samples • Removed Research flow from Day 0 and Day 1 to align with other CD4CAR trials • Removed transgene copy number from Day 0 and Day 1 to align with other CD4CAR trials • Removed HAMA from Day 0 to align with other CD4CAR trials • Updated the following footnotes: o ** footnote updated to remove research flow o Footnote 4: **To be obtained the day before or within** 12 hours prior to CD4CAR infusion: CBC with diff, assessment of CD3, CD4, and CD8 counts, **and** serum potassium and uric acid o Footnote 5: To include vital signs (**including temperature, respiratory rate, pulse and blood pressure**) and pulse oximetry prior to infusion, at the end of infusion, and every 15 minutes for 1 hour post infusion. If vital signs and/or pulse oximetry values are abnormal, continue to monitor every 15 minutes until stable **(may be up to 6 hours post-infusion).** o Footnote 6: To be drawn **Day -4 prior to start of conditioning chemotherapy**

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○ Footnote 8: Optional blood samples: to be obtained at **Day -4 prior to start of conditioning chemotherapy,** and again approximately on Day 7, Day 14 (+/-3 days) and Day 28 (+/-3 days), day 60 (+/- **7** days), 3 (+/- 7 days) months, 6 months (+/- 30 days) and 2 years (+/- 30 days) post CD4CAR infusion . The timing of this test should be decided in consultation with the principal investigator. Refer to ICF to verify participant's agreement before obtaining the sample. ○ Footnote 9: Bone marrow biopsy/aspirate will only be done if clinically indicated (i.e. depending on the participant's diagnosis). Screening bone marrow biopsy/aspirates must occur **no later than** 30 days prior initiation of conditioning chemotherapy. **Indolent skin lymphomas and other CD4 positive T cell hematological malignancies with very low incidence of marrow involvement may be excluded from screening bone marrow biopsy/aspirate requirement at the discretion of the treating physician.** ○ Footnote 10: The following tests do not need to be repeated if completed within 28 days of Day -6: disease assessments, clinical flow, CMP, CBC, echocardiogram, PFT, Syphilis, Ig (IgA, IgM, IgG, IgD, IgE), ABO & Rh screen, **or** RBC antibody screen. ○ Footnote A sub footnotes-added windows for visits to align with other CD4CAR trials ○ Footnote H: RCL to be performed at **Day -4 prior to start of conditioning chemotherapy**, month 3, 6 and 12 months after CD4CAR infusion. ○ Footnote L: The nursing staff will conduct focused neurologic examinations **approx.** every 8 hours for at least 7 days (or earlier if the patient is deemed stable for discharge prior to 7 days post-infusion) post CAR T cell infusion for ICANS using the American Society for Transplantation and Cellular Therapy's Immune Effector Cell-Associated Encephalopathy (ICE) score grading scale. ○ Footnote Q: R.Q. Clinical Flow Cytometry will include lymphocyte subset quantitation, including CD4, CD8, and CD3 cell determination (t-cell subsets). A leukemia/lymphoma assay may be used as a substitution for t-cell subsets, per PI discretion. Collection of the clinical flow will coincide with disease assessment collection timepoints (see footnote 3), **as well as a mandatory collection within 12 hours of CD4CAR infusion (see section 10.1)**; with the exception of: if a subject has circulating tumor cells. If this occurs, the clinical flow will be collected on Day-1 **(no collection on day 0 if day-1 sample is collected)**, and on Day 28. The clinical flow may be repeated more frequently as necessary at investigator discretion ○ Footnote R: removed RPR and STS reference as only syphilis test is needed ○ Footnote U: New footnote- **EKG to be performed on day -1 or more as clinically indicated.**
3. Section 1.2 Updated manufacturing schema to reflect the current process of manufacturing across all 3 CD4CAR trials.
4. Section 4.4 Dose Limiting Toxicity (DLT) **1.** Updated criteria 5 to: Any Grade 4 hematologic toxicity that does not resolve to Grade ≤ 2 within 28 days (4 weeks) from CD4CAR infusion **except for the following:** **a. Lymphopenia, the complication of which rather than the lymphocyte count in itself is to define a DLT if this complication is a grade 3 or 4 and does not resolve within the washout period. These complications include fungal infections, disseminated viral infections, or organ failure that is attributed to the infectious agent itself.**

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b. <u>Pre-existing Cytopenia</u>, if a subject has the equivalent to a grade 3 or 4 cytopenia at study entry, then this will not constitute a DLT on day 28. All other subjects a DLT may be reached unless the new onset cytopenia is deemed to be due to underlying disease. **c. Hematologic toxicities occurring or persisting after HSCT, or additional treatment do not constitute a DLT** **2.** Revised criteria #6: Any Grade 5 toxicity **related to the study treatment**. *Rationale: Updated to align with other CD4CAR trials and provide clearer clarification on what constitutes a DLT on this trial.*
5. Section 5.1 Inclusion Criteria • Removed criteria #4 and 5 (examples of CD4+ Leukemias and Lymphomas) as these list were not inclusive of all potentially eligible subjects. Updated criteria #3 to "Subjects with **any** documented CD4+ **T cell** hematologic malignancies. Male and female subjects with CD4+ T-cell hematologic malignancies with either relapsed or refractory disease (including those patients who have undergone a prior transplant **(if allogeneic, subjects are eligible if there are no remaining donor cells)** and patients with an inadequate response after 4-6 cycles of standard chemotherapy) **are eligible. Response criteria for each disease subset will be evaluated based on Standard of Care Guidelines.**
6. Section 5.3 Eligibility for Conditioning Chemotherapy • Moved "Planned infusion dose was successfully manufactured and met release criteria." From Eligibility for CD4CAR Infusion and the release criteria is a requirement for admission.
7. Section 7.2.1 Baseline assessment • Removed "RPR" from Syphilis RPR. • Moved verbiage "RCL testing, baseline human anti-murine antibody (HAMA) and optional blood samples for future unspecified research may also be collected during the screening period" to Section 7.3.2 **Conditioning Chemotherapy for CD4CAR.** • Updated bullet point "flow cytometry lymphocyte subset quantitation…" with "Clinical flow cytometry lymphocyte subset quantitation…"
8. Section 7.3.2 Conditioning Chemotherapy for CD4CAR Infusion Updated the following sentence from "Chemotherapy is started approximately 6 days before infusion so that CD4CAR cells may be given 3-4 days after completion of the chemotherapy" to "**Chemotherapy is started approximately 4 days before infusion so that CD4CAR cells may be given 2 days after completion of the chemotherapy.**"
9. Section 8.3.3 CD4CAR Infusion • Added new note, "Note: Hematologic toxicities are an expected outcome from the preconditioning chemotherapy and therefore are excluded and will not delay receipt of T cell infusion."
10. Section 8.4 Assessment of engraftment and persistence • Updated the following sentences "CD4CAR Transgene Copy Number (PCR) and flow cytometry in order to evaluate the presence of CD4CAR cells on day 0, 1, 3, 5, 7, 14, and 28 post infusion, or more often as clinically indicated. Subjects will undergo approx. once a week thereafter until Day 28 the following:…," with "…**CD4CAR Transgene Copy Number (PCR) and research flow cytometry in order to evaluate the presence of CD4CAR cells on day 0 (cytokines only), 1 (cytokines only), 3, 5, 7, 14, and 28 post**

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infusion, or more often as clinically indicated. Subjects will undergo approx. once a week (+/-3 days) thereafter until Day 28 the following…"
11. Section 8.5 Post discharge evaluations for 6 months post infusion • Added "(+/-7 days)" to the following sentence: "Stable subjects will return on a monthly basis during months 2 to 6 (+/- 7 days) post CD4CAR cell infusion."
12. Section 8.6 Quarterly evaluations for up to 2 Years Post Infusion • Added "+/-30 days" to the following sentence: "Subjects will be evaluated on at least a quarterly basis (+/-30 days) until 2 years post infusion."
13. Section 8.7 Annual evaluations for up to 15 Years Post Infusion (optional in person visits) • Added "+/-30 days" to the following sentence: "Following this evaluation at 2 years, subjects will be followed up to twice a year (+/-30 days) by phone…"
14. Section 9.3.1.2 Apheresis • Removed following sentence "Optional blood samples for future unspecified research may also be collected at this time if not collected prior."
15. Section 9.3.1.3 Cryopreservation • Added the following sentence: "If a back-up bag cannot be made from the original manufacturing run, a back-up product will be created from an additional manufacturing run."
16. Section 10.1 Pre-Infusion Premedication and lab tests • Removed the following sentence "Within 24 hours before infusion, serum baseline human anti-mouse antibodies (HAMA)" • Removed the following sentence "Within 12 hours before the first infusion, a blood sample for determination of baseline/ control CD4CAR level by both CD4CAR flow cytometry and transgene copy number will be obtained."
17. Section 10.2 Procedure to be followed for cell infusion • Added the following sentence: "Below is an example on how the process could be performed."
18. Section 10.2.1 Day of infusion • Replaced "One-liter bags" with One liter bag" • Removed "One-BD Alaris Pump Infusion Burette Set" with "One BD SmartSite Gravity" • Relaced the following sentence "One secondary Admin Set with Bag Hanger" with "**One secondary admin set with bag hanger (Note: secondary admin set is not applicable if gravity set has dual spikes)**" • Removed "10mL syringes" • Removed "20mL syringes" • Removed "alcohol swabs"
19. Section 10.2.2 Prior to infusion • Replaced the following sentence "Prime BD Alaris Pump Infusion Burette Set (or equivalent) with sufficient amount of Plasma-Lyte A" with "**Prime one spike and line of tubing with approx. 500ml of Plasmalyte A. This will connect to central line on subject. Clamp after primed**." • Replaced the following sentence "Spike bag of Plasmalyte with secondary infusion set, prime and attach to luer port of Buretrol" with "**Spike CAR T- cell bag with the non-primed side of tubing and prime with CART-T cells to drip chamber. Remainder of tubing should already be primed with Plasmalyte A**." • Removed the following sentence "Take care to prime the tubing only, and fill Buretrol with Plasma-Lyte A enough to not allow air into the tube. • Removed the following sentence: "Load into Alaris pump."

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• Added the following sentences "**Infuse the entire contents of the CAR-T cell bag by gravity. Gently agitate the CAR-T cell bag during infusion to prevent cell clumping**. **Continued Section 10.2.2 Prior to infusion** • Removed "CAR-T Cells will be thawed in a sterile bag at the bedside prior to infusion in 37C water bath by a designated staff member." • Removed "The RN will spike CAR T cell bag with the BD Alaris Pump Infusion Burette Set (or equivalent) and add CAR T cell content to Buretrol cylinder. Clamp tubing from CAR T cell bag to cylinder once contents are infused." • Removed "Add Quantity Sufficient (QS) of Plasmalyte A to Buretrol cylinder (approx. 15cc) to achieve the total volume to administer according the Principal Investigator/Cell Therapy Lab (or site equivalent). Program the Alaris pump to volume, rate and time of infusion needed." • Removed "Prior to starting infusion, program patient monitor to automatically record vital signs Q15minutes." • Removed "Once baseline vitals are completed, start infusion pump at previously calculated rate." • Replaced "After infusion the line should be backflushed/rinsed with an adequate volume of PlasmaLyte A to ensure product bag and line are clear of remaining cells (approximately 2 minutes, but may be longer depending on volume of product)" with "**Following infusion, repeat backflush process by adding 20 mL of Plasmalyte A into the the IP bag. Leave the bag inverted and seal above the bag so that the bag can be aseptically removed.**" *Rationale: PI is removing post infusion culture as this is no longer required and this aligns all the CD4CAR trials.*
20. Section 15.0 CRITERIA FOR STOPPING / PAUSING THE STUDY • Updated the following sentence "Enrollment of subjects and treatment of consented participants on the study will be put on hold" to "**Enrollment of subjects and treatment of consented participants on the study will be put on hold if any of the following events occur provided if deemed as study procedure related**:" • Added the following paragraph: "**For any event outlined above, this will trigger a pause in enrollment while the toxicity is assessed by the PI, study team, and the DSMC. The DSMC will examine all relevant data, including global assessment of the safety data to determine if patient enrollment should resume. If the sponsor terminates the study for safety reasons, the Sponsor will notify the investigators and the relevant regulatory authorities**."
21. Section 16.2 Data Safety Monitoring Plan • Updated the following sentence "In addition, conference calls with investigators and staff at participating sites will be scheduled at least monthly" to "**In addition, conference calls with investigators and staff at participating sites will be scheduled at least weekly**." • Updated the following sentence "If there are no patients on treatment or in follow-up," to "If **the study is not open to accrua**l, there are no patients on treatment or in **safety** follow-up,"
22. Section 16.2.4 Data Management/Oncore Reporting Requirements • Updated the following sentence "Study data must be entered within Oncore promptly, no later than one week" to "**Study data must be entered within Oncore promptly, no later than 15 business days…**"