A Phase II pilot study to evaluate the role of Siltuximab in treatment of Cytokine Release Syndrome (CRS) and Immune Effector Cell associated neurotoxicity (ICANS) related to Chimeric Antigen Receptor T-cell therapy (CAR-T) in hematological malignancies

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Study Product: Siltuximab

Support RECORDATI Rare Diseases (Funding and investigational agents)

Protocol Number: UAB2113

Summary of Changes Version 5 from prior version (Version 4)

Affected Section(s)	Summary of Revisions Made	Rationale
Title Page	Updated Principal Investigator, Sub-Investigator, and Support information.	Study staff changed.
	Removed Coordinating Center information.	This is a single-center trial, so a Coordinating Center is not applicable.
8.4.6.2 SAE Reporting to the FDA and IRB	Removed UAB CTNMO and replaced it with UAB CTO IIT Office.	UAB CTO IIT Office receives SAEs for this study.
8.5.2 Unanticipated Problem Reporting	Removed UAB CTNMO and replaced it with UAB CTO IIT Office.	UAB CTO IIT Office receives unanticipated problem reports for this study.
10.1.5 Key Roles and Study Governance	Removed UAB CTNMO and replaced it with UAB CTO IIT Office.	UAB CTO IIT Office provides oversight for this study.
10.1.7 Clinical Monitoring	Removed UAB CTNMO and replaced it with UAB CTO or UAB CTO IIT Office, where applicable.	Monitoring for this study will be performed by UAB CTO and UAB CTO IIT Office.
10.1.8 Quality Assurance and Quality Control	Removed UAB CTNMO and replaced it with UAB CTO.	UAB CTO provides quality assurance and quality control for this study.
	Updated Principal Investigator.	Study staff changed.

10.1.9 Data Handling and Record Keeping	Removed UAB CTNMO and replaced it with UAB CTO.	UAB CTO provides data handling and record keeping for this study.
10.1.10 Protocol Deviations	Removed UAB CTNMO and replaced it with UAB CTO IIT Office.	UAB CTO IIT Office receives protocol deviations for this study.
10.2 Abbreviations	Removed UAB CTNMO and replaced with UAB CTO IIT Office.	

Summary of Changes Version 4 from prior version (Version 3)

Affected Section(s)		**Summary of Revisions Made**	**Rationale**
1.1 *Protocol Synopsis*			
	Summary of Treatment Plan	Change made to measurement of vitals signs after first and second dose of siltuximab from hourly to every 4 hours for first 24 hours.	No infusion-related reactions were observed with siltuximab for the first 20 patients. Therefore, changed to the institutional standard of vital signs monitoring every 4 hours.
		Added special terms to consider Definition of resolution of CRS, Relapse of CRS, Resolution of ICANS, Relapse of ICANS.`	To improve clarity of the protocol and ensure uniformity in defining terms.
1.2 Schema		Changes made to footnote 1 of flowchart 1 and 2. Changes made to measurement of vitals signs after first and second dose of siltuximab from hourly to every 4 hours for first 24 hours.	No infusion-related reactions were observed with siltuximab for the first 20 patients. Therefore, changed to the institutional standard of vital signs monitoring every 4 hours.

1.3 Schedule of Activities			
	Visits	Changed window of Day 28 visit from Day +/- 2 to +/- 5 days	To allow adjustment of visits occurring on weekends/ Holidays
	Procedures	Changed superscript for cytokines from ee to e	To avoid two different schedules of blood collection and improve clarity of protocol
		Removal of procalcitonin	Procalcitonin did not add additional information for the first 20 patients, so it was removed to reduce the amount of blood collected from patients.
		Merging columns for PET or CT scan of Day 28 and Day 31-90	Multiple PET scans are often needed to assess best response starting after Day 28. Therefore, to capture the best response to CAR T-cell, the window for response assessment with PET / CT scan was widened.
		Footnote bb changed from every 1 hour to every 4 hours for 24 hours with a window of 2 hours	No infusion-related reactions were observed with siltuximab for the first 20 patients. Therefore, changed to the institutional standard of vital signs monitoring every 4 hours.
		Removed footnote ee	To avoid two different schedules of blood collection and improve clarity of protocol

		Footnote j changed to say Pk samples last to be collected at 48 hours post siltuximab.	To minimize blood collection from patient.
5.4 Screen Failures		Added "Patients who received CAR T-cell therapy but do not experience CRS/ ICANS and do not receive Siltuximab within 14 days after CAR T-cell infusion will be deemed screen failed."	The patients who did not get siltuximab cannot be assessed for primary endpoints therefore are screen failed / not enrolled on trial. The statement clarifies this and provides a window for assessing for CRS/ICANS and determining screen failure.
6.1.1 Study Intervention Description		Change made to measurement of vitals signs after first and second dose of siltuximab from hourly to every 4 hours for first 24 hours.	No infusion-related reactions were observed with siltuximab for the first 20 patients. Therefore, changed to the institutional standard of vital signs monitoring every 4 hours.
		Table 3. Steroid dosing frequency and guidelines. Added to grade 1 CRS "Unless persistent for 12 hours after dose of siltuximab. If persistent administer as Grade 2"	To clarify, if CRS is refractory at 12 hours after dose of siltuximab for grade 1 then corticosteroids can be administered. This was mentioned in footnote of schema but absent here.
8.1 Pre-Treatment Assessment		Removal of procalcitonin from pretreatment assessment.	Procalcitonin did not add additional information for the first 20 patients, so it was removed to reduce the amount of blood collected from patients.
		Added/ changed "Patients will be enrolled on the trial at the time of CRS or ICANS development after CAR T-cell	The patients who did not get siltuximab cannot be assessed for primary endpoints therefore are screen failed / not enrolled

	infusion. They will be called screen failed if they do not have CRS or ICANS after CAR T-cell infusion up to 14 days post CAR T-cell infusion. "	on trial. The statement clarifies this and provides a window for assessing for CRS/ICANS and determining screen failure.
8.2 Efficacy Assessment	Change made to measurement of vitals signs after first and second dose of siltuximab from hourly to every 4 hours for first 24 hours.	No infusion-related reactions were observed with siltuximab for the first 20 patients. Therefore, changed to the institutional standard of vital signs monitoring every 4 hours.

Summary of Changes Version 3 from prior version (Version 2)

Affected Section(s)	**Summary of Revisions Made**	**Rationale**
1.1 Protocol synopsis Study Design	Increased number of patient enrolled to 36 from 30. Trial will stop when 25 evaluable patients are enrolled.	After enrollment of 19 patients only 3 patients did not respond to siltuximab and had no adverse events related to siltuximab. This is still within the prior set rate of efficacy of 80% however, to further assess safety and efficacy of siltuximab we are increasing the sample size to 25 from 20.
	Added statement "If we reject the null hypothesis we will enroll additional 5 patients to have a total of 25 evaluable patients."	To better assess efficacy and safety of siltuximab we plan to have 25 evaluable patients after stage II is complete.
9.2 Sample Size determination	Increased number of patient enrolled to 36 from 30. Trial will stop when 25 evaluable patients are enrolled.	After enrollment of 19 patients only 3 patients did not respond to siltuximab and had no adverse events related to siltuximab. This is still within the

		prior set rate of efficacy of 80% however, to further assess safety and efficacy of siltuximab we are increasing the sample size to 25 from 20.
	Added statement "If we reject the null hypothesis we will enroll additional 5 patients to have a total of 25 evaluable patients."	To better assess efficacy and safety of siltuximab we plan to have 25 evaluable patients after stage II is complete.
9.4.5 Planned Interim Analysis	Added statement "If we reject the null hypothesis we will enroll additional 5 patients to have a total of 25 evaluable patients."	To better assess efficacy and safety of siltuximab we plan to have 25 evaluable patients after stage II is complete.

Summary of Changes Version 2 from prior version (Version 1)

Affected Section(s)	**Summary of Revisions Made**	**Rationale**
1.1 Protocol synopsis Summary of treatment plan	Added statement "screened after a decision to proceed with CAR T-cell has been made and be completed between day -60 to day -6"	To allow sufficient time for screening and avoid multiple patient visits to the hospital prior to CAR T-cell infusion.
	Added statement **"**If CAR T-cell infusion is delayed then screening procedures will have to be repeated".	Clarifying process in case CAR T-cell infusion is delayed
	Added statement **"**Note: If symptoms leading to Grade 1 CRS/ICANS resolve before 12 hours and remain absent for 24 hours then all future events should be treated as new events."	Clarification of time frame for administration of siltuximab.

	Modified statement " If only ICANS present or if any grade CRS with ICANS grade 3 or higher is present corticosteroids should be administered before first dose of siltuximab."	Clarification of when corticosteroids should be administered.
	Added statement in section similar grade of CRS and/or ICANs at 12 hours. "Add corticosteroids if not given previously. Dose as per table 3."	Clarification of when corticosteroids should be administered.
	Added statement in section similar grade of CRS and/or ICANs at 12 hours. "Any Grade."	Clarification of grade of CRS/ICANS at 48 hrs when to administered second dose of siltuximab.
	Added statement in section similar grade of CRS and/or ICANs after 2 doses of siltuximab. "If persistent Grade 2 CRS at 72 hours from the first dose of siltuximab or worsening of any grade CRS at any time point despite receiving two doses of siltuximab.."	Clarification of when to consider siltuximab failure.
1.2 Schema	Flowchart 1.In footnotes added statement "If Grade 1 CRS does not last 12 hours and symptoms leading to CRS grade 1 resolve for 24 hours then all future events should be treated as new events."	Clarification of time frame for administration of siltuximab.
	Flowchart 2 .In footnotes added statements -"If Grade 1 CRS does not last 12 hours and symptoms leading to CRS grade 1 resolve for 24 hours then all future events should be treated as new events." - "If Grade 1 ICANS does not last 12 hours and symptoms leading to ICANS grade 1	Clarification of time frame for administration of siltuximab.

	resolve for 24 hours then all future events should be treated as new events."	
	Added statement in the text below flowcharts "If the ICANS develops after two doses of siltuximab are administered for CRS then proceed as described in flowchart 2 without additional doses of siltuximab as described in "persistent ICANS only".	Clarification on how to proceed for persistent ICANS after two doses of siltuximab have been administered.
1.3 Schedule of activities Table	- Added Day -5 to day -1	To allow adequate time frame to conduct neurocognitive and frailty assessment testing without the need for multiple visits.
	Added " First dose of siltuximab (Window +/- 2 hours)"	To clarify time frame for labs and physical exam.
	Changed day 28 from day of siltuximab infusion to day 28 from CAR T-cell infusion"	To allow uniformity in scheduling clinic visits for all patients.
	Changed from day 30 to 90 after CAR T-cell infusion to day 31 to 90 after CAR T-cell infusion	To avoid overlap with day 28 evaluation as the window is +/2 days
	Added concomitant medication review at onset of CRS/ICANs and First dose of siltuximab	Clarification for data entry
	Added physical exam to first dose of siltuximab	To clarify time frame to assess patient at siltuximab infusion.
	Assessments at time of first dose of siltuximab "Vital signs, ICE scoring,	This was present before but clarified now by including a separate column.

	Hematology, serum chemistry, Liver function test, Lactate dehydrogenase, Phosphorous, Uric Acid, Cytokines, procalcitonin, CRP, ferritin and adverse event review."	
	Adverse event review added to D8 to D14 after CAR T-cell infusion	Clarification of time frame for assessment
	Pet/CT scan at Day 30 to 90.	To allow longer time frame for response assessment as responses to CAR T-cell deepen over time.
	Neurocognitive function testing and Fraility questionnaire rows separated	Prior assessment for fraility were missed. To clarify that these are separate tests.
	Added PK collection samples	As per suggestions from the FDA after initial IND application
Schedule of activities Footnotes	Added statement " All lab collections have window of 2 hours:"	To allow sufficient time for collection of labs.
	Added window for vital sign measurement of 10 minutes. "bb"	To allow sufficient time for vital measurement recording and input.
	Added window for lab collections of 2 hour. "b"	To allow sufficient time for collection of labs.
	Added statement for "e" . "Time resets when a dose of siltuximab is administered"	To clarify time frame when siltuximab is administered
	Added statement "ee". "at time zero and 8 hours after. Time resets when siltuximab is administered."	To clarify time frame when siltuximab is administered.

	Added "j" j – Pre-siltuximab infusion, Immediate post siltuximab infusion from site other than infusion site, 4 hours post siltuximab and 8 hours post siltuximab then every 8 hours for 48 hrs and then every day till discharge. If a second dose is administered the time resets.	PK lab collection as suggested during protocol development.
6.1.1 Study invervention and description	Added statement "screened when a decision to proceed with CAR T-cell is made and be completed between day -60 to day -6"	To allow sufficient time for screening and avoid multiple patient visits to the hospital prior to CAR T-cell infusion.
	Added statement **"**If there is a delay in infusion then screening tests should be repeated".	Clarifying process in case CAR T-cell infusion is delayed
	Added statement **"**Note: If symptoms leading to Grade 1 CRS/ICANS resolve before 12 hours and remain absent for 24 hours then all future events should be treated as new events."	Clarification of time frame for administration of siltuximab.
	Modified statement " If only ICANS present or if any grade CRS with ICANS grade 3 or higher is present corticosteroids should be administered before first dose of siltuximab."	Clarification of when corticosteroids should be administered.
	Added statement in section similar grade of CRS and/or ICANs at 12 hours. "Add corticosteroids if not given previously. Dose as per table 3."	Clarification of when corticosteroids should be administered.

	Added statement in section similar grade of CRS and/or ICANs at 12 hours. “Any Grade.”	Clarification of grade of CRS/ICANS at 48 hrs when to administered second dose of siltuximab.
	Added statement in section similar grade of CRS and/or ICANs after 2 doses of siltuximab. “If persistent Grade 2 CRS at 72 hours from the first dose of siltuximab or worsening of any grade CRS at any time point despite receiving two doses of siltuximab.”	Clarification of when to consider siltuximab failure.
5.4 Screen Failures	Definition of screen failures has been amended to the following. “*Screen failures are defined as participants who consent to participate in the clinical trial but do not enter in the study or if they are entered in the study they do not receive the study intervention.*	Clarification for patients that receive CAR t-cell therapy and do not experience ICANS or CRS to receive the study drug. This new definition allows defining them as screen failures.
7.2 Participant Discontinuation/Withdrawal From The Study	Added Statement “Patients who are replaced due to not receiving the study intervention will be followed up to day 28 after CAR T-cell infusion”	Clarification of duration of follow up for those patients that receive CAR t-cell therapy and do not experience ICANS or CRS to receive the study drug.
8.1 Pre-Treatment assessment	Added statemend “ This can be done up to day 0” for fraility and neurocognitive assessment	To allow sufficient time for testing without need for multiple clinic visits.
	Added statement “ Patient will sign consent after decision for CAR T-cells has been made”	To allow sufficient time for screening procedures.

8.2 Efficacy Assessment	Added statement " Time for labs will reset"	To clarify time frame for lab collection after first dose of siltuximab
	Added statement "time will reset with hourly vitals and every 8-hourly lab tests will be conducted for 24 hours after infusion of siltuximab "	To clarify time frame for labs and vitals after second dose of siltuximab.
8.4.2 Definition of Serious adverse Event	Modified statement, "requires at least a 24-hour in patient hospitalization or prolongation of existing hospitalization not related to CRS or ICANS from CAR T-cell therapy,	Patient on the trial are expected to have a prolonged hospitalization after they develop CRS / ICANS. Since this can develop at any time frame and is an expected event of CAR T-cell infusion, the definition for SAE is being changed.

Summary of Changes Version 1:

Affected Section(s)	**Summary of Revisions Made**	**Rationale**
Header	Deleted date May 19,2021	Version change
Table of contents	• Added Appendix K	Provided institutional guidelines for management of ICANS after two doses of ICANS.
	• Updated Table Numbers	To facilitate ease of navigation in the protocol

1.1 Protocol Synopsis - Summary of treatment plan	Screening period changed from day -30 to day -6 to day -60 to day -6	To avoid repeating multiple blood draws and/or imaging procedures due to change in clinical status of patient.
1.1 Protocol Synopsis - Summary of treatment plan	Clarified protocol schema with addition of statement "If only ICANS persists after two doses of siltuximab, this is not considered failure of siltuximab"	To clarify definition of failure of siltuximab.
1.1 Protocol Synopsis - Summary of treatment plan	In the section "Following special scenarios to consider" added reference to guidelines for management of ICANS	To provide easy access to suggested guidelines for ICANS management
1.2 Schema	The footnotes in schema "ICANS with or without CRS (Flow Chart 2) provided reference to guidelines for management of ICANS	To provide easy access to suggested guidelines for ICANS management
1.3 Schedule of activities	• Screening interval increased from day -30 to day -6 to day -60 to day -6 • Added window +/- 2 days for Day 14 after CAR T-cell and Day 28 after siltuximab evaluation. • Added statement " after last siltuximab infusion" to now reflect the following Day 28 after last siltuximab infusion visit(Window =/2 • Added evaluations of concomitant medication review, physical exam, vital signs,	• To avoid repeating multiple blood draws and/or imaging procedures due to change in clinical status of patient. • To allow flexibility if this assessment falls on a weekend. • Clarified that this visit is after last dose of siltuximab.

	Height, Weight, Performance status, Hematology, Serum chemistry, Liver function test, Lactate dehydrogenase, Phosphorus, uric acid, Cytokines, procalcitonin, CRP, Ferritin and adverse event review at Day 30 to Day 90 after CAR T-cell therapy infusion	• Prior iteration did not have post CAR T-cell evaluation if patients did not receive Siltuximab.
	• PET/CT scan changed to PET or CT scan	
	• Added "gg" suffix to day 30 to day 90 assessment for Response assessment	• Clarification that either PET or CT scan is acceptable. • To clarify that this assessment is not required for this trial if siltuximab is not given.
	• Footnote "e". Added statement – "at onset and every 8 hours for 24 hours. If siltuximab administered 12 hours after onset of grade 1 CRS/ICANS, then continue for up to 36 hours from onset of CRS /ICANS. Window for labs is within +/- 2 hours of the time frame."	• To clarify the timepoints for blood tests. Also provided a window for collection of blood tests.
	• Footnote "l" . Changed to PET or CT scan and added statement as per investigator discretion.	• To clarify that pretreatment scans is only if indicated as per the investigators discretion.
	• Removed day 30 to day 90 PET /CT scan assessment	• To avoid overlap between PET scan and response assessment for lymphomas.
6.1.1 Study intervention	• Change of screening interval to day -60 to day -6	• To avoid repeating multiple blood draws and/or imaging procedures due to change in clinical status of patient.
6.1.1 Study intervention	• Clarified protocol schema with addition of statement "If only ICANS persists after two doses of siltuximab, this is not considered failure of siltuximab"	• To clarify definition of failure of siltuximab.

6.1.1 Study intervention	• In the section "Following special scenarios to consider" added reference to guidelines for management of ICANS	• To provide easy access to suggested guidelines for ICANS management
Table 3	• Dexamethasone 10 mg IV one dose. Added statement to repeat every 24 hours if needed.	• To clarify that repeated doses of dexamethasone are permitted.
8.1 Pre-Treatment asssessment	• Baseline assessment for imaging changed to CT OR PET scan as per discretion of investigator	• To avoid multiple scans.
8.1 Pre-Treatment assessment	• Changed statement " Patient will sign consent after aphersis"	• Prior statement was inconsistent and incorrect.
8.2 Efficacy Assessment	• Added statement "For grade 1 CRS and/or ICANS that persist for 12 hours from onset and subsequently receive siltuximab, labs will be collected at onset and every 8 hours for up to 36 hours after onset of CRS/ICANS. Window for labs is within +/- 2 hours"	• To clarify the timepoints for blood tests. Also provided a window for collection of blood tests.
Appendix I	• Added new indication of Tecartus as per FDA label	• To specify which CAR T-cell is approved for precursor B-cell Acute lymphoblastic lymphoma
Appendix K	• New appendix with guidelines for ICANS management	• To provide easy access to suggested guidelines for ICANS management

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol no.	UAB2113
Study Title	A Phase II pilot study to evaluate the role of Siltuximab in treatment of Cytokine Release Syndrome (CRS) and Immune Effector Cell associated neurotoxicity (ICANS) related to Chimeric Antigen Receptor T-cell therapy (CAR-T) in hematological malignancies
Sponsor	University of Alabama at Birmingham
Study Sites & Enrollment	This study will be carried out at the University of Alabama at Birmingham, Birmingham, Alabama.
Study Rationale	Cancer immunotherapy seeks to harness the power of the immune system to eradicate malignant tissues. Autoimmunity related toxicity occurs not uncommonly after treatment with genetically engineered T-cells such as chimeric antigen receptor (CAR) T-cell. Cytokine-associated toxicity, also known as cytokine release syndrome (CRS), is one such non–antigen-specific toxicity that occurs because of increased immune activation and results in fatal toxicities. Emerging evidence implicates interleukin- 6 (IL-6) as a central mediator of toxicity in CRS (Lee et al Blood 2014). IL-6 is a pleiotropic cytokine with anti-inflammatory and pro-inflammatory properties. IL-6 receptor α (IL-6R) is located on macrophages, neutrophils, hepatocytes, and some T cells. IL-6-induced signaling is initiated by binding of IL-6 to the IL-6 receptor α. IL-6 receptor α exists in a soluble and a transmembrane form. Binding of IL-6 to membrane-bound IL-6 receptor α induces anti-inflammatory classical or cis- signaling, whereas binding of IL-6 to soluble IL-6 receptor α induces pro-inflammatory trans-signaling on cells that do not express IL-6 receptors (Reeh et al., Cell Communications and signaling 2019). The classical signaling predominates when IL-6 levels are low. However, when IL-6 levels are elevated, soluble IL-6R and IL-6R on the inflammatory cells can initiate trans-signaling, which occurs on a much wider array of cells. High levels of IL-6, present in the context of CRS, likely initiates a pro-inflammatory IL-6-mediated signaling cascade leading to the clinical manifestations of CRS.

	Currently, tocilizumab, an IL-6 receptor antagonist, is the only approved drug by the food and drug administration (FDA) for the treatment of CRS. This approval is based on a pooled retrospective analysis of 45 patients treated in clinical trials, with CAR T-cells, who received tocilizumab, once or twice with improvement in CRS within 14 days. However, despite widespread use of tocilizumab for CRS in patients receiving CAR T-cells, the incidence of severe grade 3 or higher CRS varies between 10-25% based on the CAR T-cell product and CRS grading criteria used. Siltuximab is monoclonal antibody that blocks IL-6 signaling by binding IL-6 itself and preventing it from activating immune effector cells through either the trans or cis mechanisms. Siltuximab has a higher affinity for IL-6 than tocilizumab has for the IL-6R making it an attractive tool in managing CRS. Currently, siltuximab is FDA approved for its use in multicentric castleman disease. With the increasing use of bispecific monoclonal antibodies and CAR T-cell therapy in clinical practice, there is an unmet need for better control of CRS. We hypothesize that by the direct binding of siltuximab with IL-6, the pro-inflammatory pathway will be disrupted leading to resolution of cytokine release syndrome. Therefore, we propose a prospective clinical trial for the use of siltuximab in patients receiving CAR T-cell therapy in hematological malignancies.
Study Objectives	**Primary objective** • To assess the efficacy of siltuximab in resolution of cytokine release syndrome (CRS) within 14 days after infusion of siltuximab. **Secondary objectives** • To assess the efficacy of siltuximab in resolution or stabilization of immune effector cell associated neurotoxicity (ICANS) within 28 days after infusion of siltuximab. • To determine the safety profile of siltuximab as characterized by adverse event (AE) type, severity, timing and relationship to study drug, as well as laboratory abnormalities within 28 days after siltuximab infusion. • To describe the influence of siltuximab on antitumor efficacy [Overall response rate (ORR), Complete response (CR), Partial response (PR)] of CAR T-cells between 28 to 90 days after infusion of CAR T-cells. **Exploratory objectives** • To assess the prognostic significance of pre-CAR T-cell therapy total metabolic tumor volume on the incidence and severity of CRS and ICANS.

	• To assess the prognostic significance of circulating CD19+ B-cell on the incidence and severity of CRS and ICANS. • To assess the effect of siltuximab on Th1,Th2,Th17 cytokines, MCP-1, procalcitonin, Angiopoeitin 1/2 CRP, LDH and ferritin after administration of siltuximab. • To assess the effect of siltuximab on HMGB1, a biomarker of neuroinflammation. • To measure the effect of siltuximab on frailty and neurocognitive function trajectories among patients treated with CAR-T therapy.
Inclusion Criteria	1. Patients who are planned to receive chimeric antigen receptor T-cell therapy as per the United States Food and Drug Agency (USFDA) approved indications for • Diffuse large B-cell lymphoma (DLBCL), • Mantle cell lymphoma (MCL), • Follicular lymphoma (FL), • Primary mediastinal large B-cell lymphoma (PMBCL), • High grade B-cell lymphoma, • DLBCL arising from follicular lymphoma. • Multiple myeloma • B-cell precursor acute lymphoblastic leukemia FDA approved indications for CAR T-cell therapy for different indications and products have been listed in Appendix I. The patient should also meet these indications for the study. 2. Patients with HCV can be included if they have completed therapy for hepatitis C with undetectable HCV RNA viral load. 3. Patients with Hepatitis B can be included if they are on suppressive therapy for hepatitis B infection and with no detectable viral load. 4. Adequate organ function as defined below unless attributed to disease involvement. Acceptable window for assessing adequate organ function is 7 days to 30 days before planned CAR T-cell infusion with day 0 as the planned day of CAR T-cell infusion.

	i. liver function (bilirubin ≤ 2mg/dL, AST and/or ALT ≤3 x ULN) ii. kidney function (crcl > 30ml/min using Cockroft-Gault, based on actual weight). iii. ANC ≥ 1,000/µL, Hgb > 8, Platelet Count ≥ 50,000/ µL. 5. Patients able to tolerate washout periods for therapies as defined below prior to CAR T-cell infusion. i. Systemic therapy: Washout period is 2 weeks prior to CAR T-cell infusion. ii. Radiation therapy : Washout period is 1 weeks prior to CAR T-cell infusion. iii. Corticosteroids : Washout period is 5 days prior to CAR T-cell infusion. 6. Age ≥ 18 years of age. 7. A negative urine pregnancy test is required within 1 week for all women of childbearing potential prior to enrolling on this trial. 8. For females of reproductive potential: use of highly effective contraception for at least 1 month prior to screening and agreement to use such a method during study participation and for an additional 4 months after infusion of siltuximab. 9. For males of reproductive potential: use of condoms or other methods to ensure effective contraception with partner 10. Willing and able to participate in all required evaluations and procedures in this study protocol including receiving intravenous administration of investigational product and being admitted, when required, for at least 24 hours during investigational product administration.
Exclusion Criteria	1. Subjects requiring ongoing daily corticosteroid therapy at a dose of > 10 mg of prednisone per day (or equivalent). Pulsed corticosteroid use for disease control is acceptable. 2. Active autoimmune disease requiring immunosuppressive therapy is excluded unless discussed with the principal investigator (PI) 3. Pregnant women are excluded from this study. 4. Evidence of ongoing systemic bacterial, or fungal or viral infection, except

	localized fungal infection of skin or nails. 5. Patients with ongoing or past HIV infection.
Primary endpoint	**<u>Complete response</u>** Complete response (CR) is defined as the complete resolution of CRS within 14 days from the last dose of siltuximab. **<u>Failure to respond</u>** Failure to respond (FR) is defined as occurrence of one of the following o Worsening of the CRS grade or persistence of grade 3 CRS, after 2 doses of siltuximab. o Need for rescue tocilizumab o Recurrence of CRS after achieving of a complete response and have had received two doses of siltuximab to attain the complete response
Secondary Endpoint - **Efficacy for ICANS**	**<u>Complete response</u>** Complete response (CR) is defined as the complete resolution of ICANS within 28 days from the last dose of siltuximab. **<u>Partial response</u>** Partial response (PR) is defined as improvement in the grade of ICANS from its maximum grade reached but persistence of ICANS within 28 days from the last dose of siltuximab. **<u>Stable disease</u>** Stable disease (SD) is defined as failure to achieve either CR or PR but does not fulfil criteria for failure to respond within 28 days from the last dose of siltuximab. **<u>Failure to respond</u>** Failure to respond (FR) is defined as occurrence of one of the following

	○ Worsening of the ICANS grade or persistence of grade 3 ICANS, after 2 doses of siltuximab. ○ Recurrence of ICANS after achieving of a complete response and have had received two doses of siltuximab to attain the complete response
Secondary Endpoint: **Influence on antitumor efficacy**	1. **Lymphoid malignancies, such as Diffuse Large B-cell lymphoma, Mantle cell lymphoma and follicular lymphoma.** Responses will be assessed based on Lugano Response Criteria for Malignant Lymphoma 2016 (Appendix B). 2. **Multiple Myeloma response assessment by the International Myeloma Working Group.** Responses will be assessed based on International Myeloma Working Group (IMWG) 2016 for response and minimal residual disease assessment in Multiple Myeloma (Appendix G). 3. **Acute Lymphoblastic leukemia response assessment** Responses will be assessed as per Acute lymphoblastic leukemia response criteria (Appendix H)
Safety Endpoints	All Adverse Events (AE's) will be reported and evaluated using National Cancer Institute's Common Terminology Criteria (CTCAE) v5.0.
Study Hypothesis	The primary hypothesis of the study is that siltuximab will mitigate the severity of CRS associated with CAR T-cell therapy. The secondary hypothesis of the study is that siltuximab will decrease the severity of ICANS associated with CAR T-cell therapy.
Study Design	Patient who have completed infusion of CAR T-cell therapy and are experiencing grade 1 or higher CRS and/or ICANS will receive siltuximab 11mg/kg infusion. Subsequent monitoring and follow up as per the study schema in *1.2*

	Simon's optimal two-stage design will be used for conducting the trial. Evaluable patients for the primary endpoint are defined as those patients who experience CRS and receive at least one dose of siltuximab. The trial will be carried out in two stages. In stage I, a total number of 7 evaluable patients will be accrued. If there are 3 or fewer responses among these 7 patients, the study will be early stopped. Otherwise, additional 13 evaluable patients will be accrued in stage II, resulting in a total number of evaluable patients of 20. If there are 12 or more responses among these 20 evaluable patients, we reject the null hypothesis and claim that the treatment is promising. The design controls the type I error rate at 0.05 and yields the power of 0.8. If we reject the null hypothesis we will enroll additional 5 patients to have a total of 25 evaluable patients. Only patients who experience CRS and receive siltuximab will be included in the intent to treat population. The incidence of CRS amongst various CAR T-cell therapies vary between 60 to 90%. Therefore, assuming a CRS event rate of 70%, we plan to enroll 36 patients. However, the trial will stop when 25 patients who are evaluable for primary endpoint are accrued.
Study Drugs	Siltuximab
Phase of study	Phase II Pilot study
Study Duration	36 months
Participant duration	90 days from the time of Siltuximab infusion.
Summary of Treatment Plan	The study intervention is the use of siltuximab. The schema to refer is in Section *1.2* The treatment plan is as follows. Patients who meet the eligibility criteria should be screened after a decision to proceed with CAR T-cell has been made and can be completed between day -60 to day -6 of planned CAR T-cell infusion. If CAR T-cell infusion is delayed then screening

procedures will have to be repeated. The patient will then be enrolled on the day of CAR T-cell therapy infusion (i.e Day 0).

The patients should be assessed as per the schedule of activities in Section *1.3*. Once patient meets the following criteria's, siltuximab will be administered.

- Grade 1 CRS lasting for more than 12 hours.
- Grade 1 ICANS lasting for more than 12 hours.
- Any Grade 2 or higher CRS/ICANS.

Note: If symptoms leading to Grade 1 CRS/ICANS resolve before 12 hours and remain absent for 24 hours then all future events should be treated as new events.

Administer siltuximab at the dose of 11mg/kg via intravenous infusion over 1 hour. After siltuximab is administered heart rate, blood pressure, oxygen saturations and respiratory rate should be monitored every 4 hours for the first 24 hours. If only ICANS present or if any grade CRS with ICANS grade 3 or higher is present corticosteroids should be administered before first dose of siltuximab. Dose and type of corticosteroids to be administered is described below in table 3.

Following scenarios are expected to occur

A. <u>Resolution of CRS / ICANS symptoms:</u>
   Resolution is defined as absence of symptoms leading to the diagnosis of CRS / ICANS for a period of 24 hours.

B. <u>Similar grade of CRS and/or ICANS at 12 hours :</u>
   i. If Yes : Then proceed with the second dose of siltuximab. Add corticosteroids if not given previously. Dose as per table 3.
   ii. If No: Then continue to reassess. If at 48 hours from the first dose of Siltuximab, CRS/ ICANS persists (Any grade), then administer second dose of siltuximab.

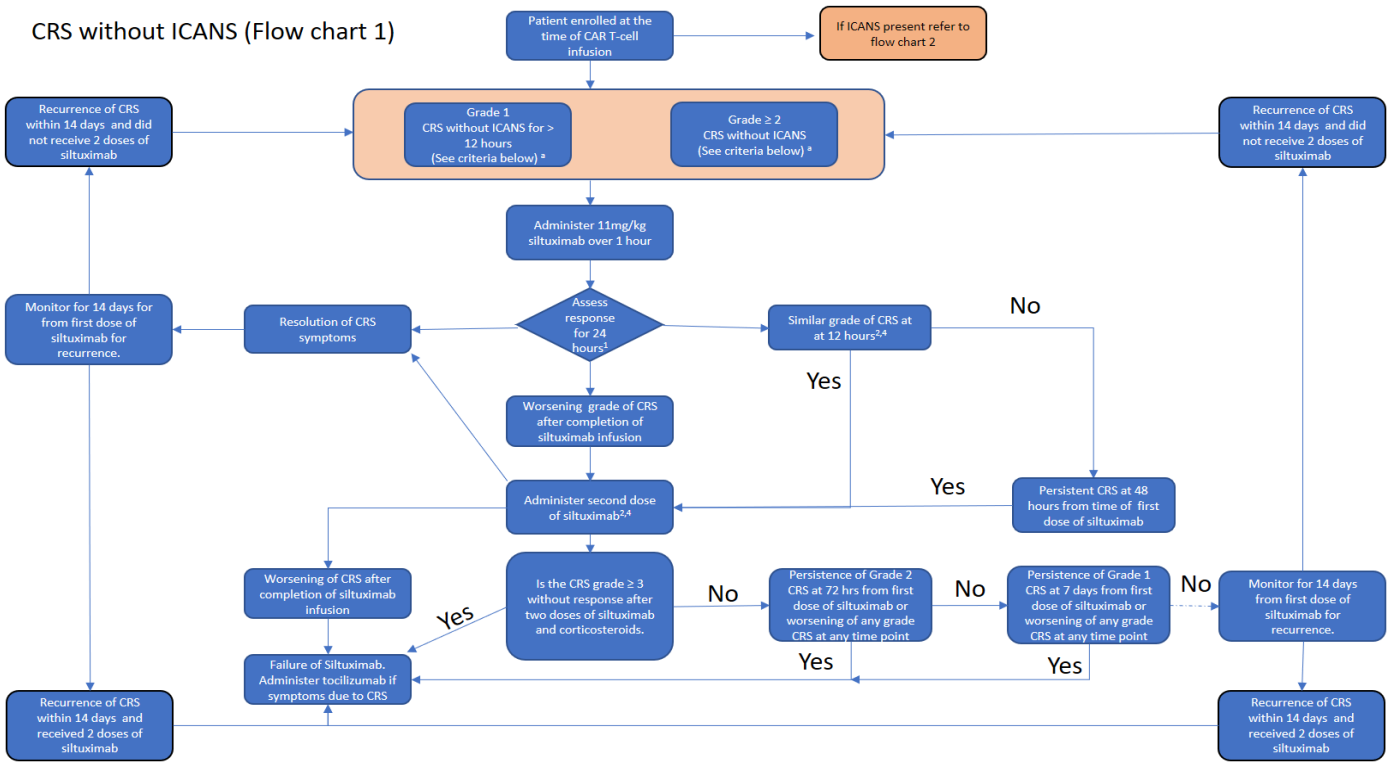
C. <u>Worsening grade of CRS and/or ICANS after completion of first dose of siltuximab :</u>
   Administer second dose of siltuximab.

After second dose of siltuximab is administered heart rate, blood pressure, oxygen saturations and respiratory rate should be monitored every 4 hours for the first 24 hours after the second dose. If two doses of siltuximab have already been received before this step then consider failure of siltuximab and proceed with tocilizumab. If only ICANS persists after two doses of siltuximab, this is not considered failure of siltuximab.

	Following scenarios are expected to occur 1. <u>Resolution of CRS / ICANS symptoms:</u> Resolution is defined as absence of symptoms leading to the diagnosis of CRS / ICANS for a period of 24 hours. 2. <u>Worsening grade of CRS and/or ICANS after completion of siltuximab :</u> Consider failure of siltuximab and administer rescue tocilizumab. 3. <u>Similar grade CRS/ICANS</u> If CRS and ICANS continue to be similar grade after completing the second dose of siltuximab and assessed one hour after completion then the severity of the current grade has to be determined. i. If grade ≥ 3 or higher CRS with or without ICANS, without response after two doses of siltuximab:- Then consider failure of siltuximab and administer rescue tocilizumab. ii. If persistent Grade 2 CRS at 72 hours from the first dose of siltuximab or worsening of any grade CRS at any time point despite receiving two doses of siltuximab. Consider failure of siltuximab and administer tocilizumab.. If persistence of CRS Grade 1 at 7 days from the time from first dose of siltuximab, consider failure of siltuximab and administer rescue tocilizumab. iii. If there is worsening of CRS grade at any time point after two doses of siltuximab, consider failure of siltuximab and administer rescue tocilizumab. iv. If persistence of ICANS only after two doses of siltuximab, treat as per guidelines for ICANS managements as in Appendix. Continue to monitor for 28 days for response assessment from first dose of siltuximab. **Following special scenarios to consider** A. Recurrence of CRS episode with or without ICANS after resolution of the first episode within 14 days of first dose of siltuximab • Restart and follow the algorithm as a new episode of CRS with or without ICANS only if less than 2 doses of siltuximab have been received. If 2 doses have already been received by the patient then consider failure of siltuximab and administer tocilizumab. B. Resolution of CRS only episode but new episode of ICANS only within 14 days of first dose of siltuximab

	• Restart and follow the algorithm as a new episode of ICANS only. Do not administer additional doses of siltuximab if the patient has already received two doses of siltuximab. If only ICANS is present, refer to the guidelines for management of ICANS after the patient has received a maximum of two doses of siltuximab (Appendix K). **<u>Special terms to consider</u>** • Resolution of CRS: Defined as the absence of symptoms / signs leading to the onset of CRS for a period of 24 hours measured from the first incidence of resolution. • Relapse of CRS : Recurrence of CRS after resolution of CRS. • Resolution of ICANS: Defined as the absence of symptoms leading to the onset of ICANS or ICE score of 10/10 for a period of 24 hours measured from the first incidence of resolution. • Relapse of ICANS : Recurrence of ICANS after resolution of ICANS.

1.2 SCHEMA



a - Should meet criteria as below:7

Grade 1 CRS lasting for more than 12 hours. If Grade 1 CRS does not last 12 hours and symptoms leading to CRS grade 1 resolve for 24 hours then all future events should be treated as new events.

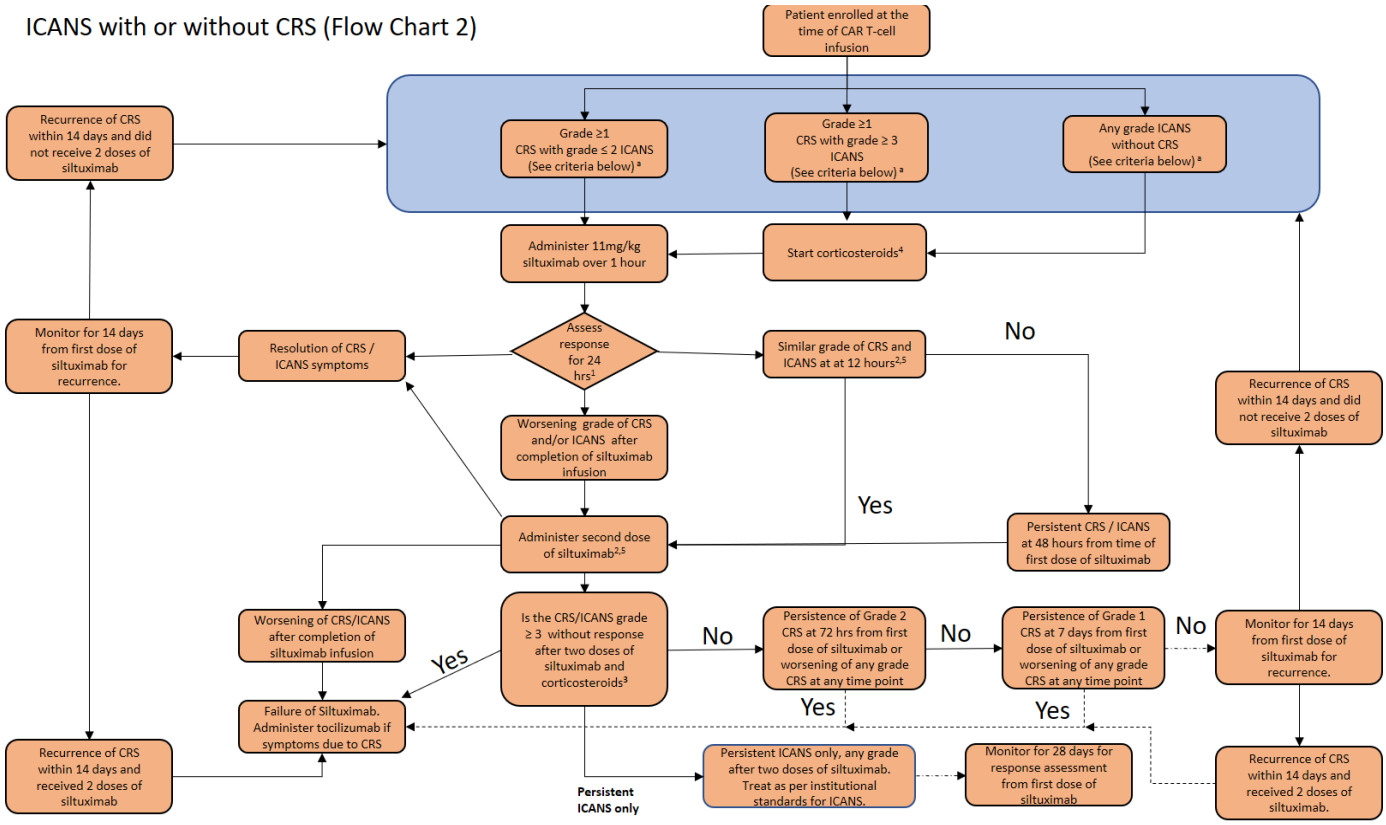
Any Grade 2 or higher CRS/ICANS.

1 - Response to be assessed every 4 hours with HR, blood pressure, SpO2 and respiratory rate for the first 24 hours.

2- For Grade 2 or higher CRS after first dose of siltuximab at 12-24 hours. Add corticosteroids as table 3 in section 6.1.1 and proceed with second dose of siltuximab.

3 – For Persistent Grade 2 CRS at 48 hours. Add corticosteroids. Refer to Table 3 in section 6.1.1

4 – If already received 2 doses of siltuximab, Consider failure of siltuximab and administer tocilizumab



a - Should meet criteria as below:

Grade 1 CRS lasting for more than 12 hours. If Grade 1 CRS does not last 12 hours and symptoms leading to CRS grade 1 resolve for 24 hours then all future events should be treated as new events.

Grade 1 ICANS lasting for more than 12 hours. If Grade 1 ICANS does not last 12 hours and symptoms leading to ICANS grade 1 resolve for 24 hours then all future events should be treated as new events.

Any Grade 2 or higher CRS/ICANS.

1- Response to be assessed every 4 hours with HR, blood pressure, SpO2 and respiratory rate for the first 24 hours.

2- If Grade ≥ 2 CRS and/or Grade ≥ 2 ICANS after first dose of siltuximab at 12 hours. Start corticosteroids if not given previously and proceed with second dose of siltuximab.

3- If only ICANS is grade 3, proceed with managing as per institutional guidelines for ICANS management (Appendix K).

4- Corticosteroids Refer to Table 3 in section 6.1.1.

5- If already received 2 doses of siltuximab, Consider failure of siltuximab and administer tocilizumab

- If patient develops CRS first and then followed by ICANS refer to Flowchart 2 (ICANS with or without CRS). If the ICANS develops after two doses of siltuximab are administered for CRS then proceed as described in flowchart 2 without additional doses of siltuximab as described in "persistent ICANS only".
- For multiple episodes per patient, consider each episode as independent if the prior episode completely resolves.
- Resolution of CRS is defined as absence of symptoms leading to diagnosis of CRS for 24 hours.

1.3 SCHEDULE OF ACTIVITIES (SOA)

			Time since CAR T-cell infusion														
Procedures	Screening (Day -60 to Day -6)[aa]	Day -5 to Day -1	Day 0	D1	D2	D3	D4	D5	D6	D7	Onset of CRS and/or ICANS	First Dose of siltuximab (Window +/- 2 hours)	Second dose of Siltuximab	D8 to D 14 (if still hospitalized)	Day 14 after CAR T-cell infusion (window :+/- 2 days)	Day 28 after CAR T-cell infusion (Window +/- 5 days)	Day 31 to 90 after CAR T-cell infusion
Informed consent	X																
Demographics	X																
Medical history	X																
Administer study intervention											X		X[a]				
Concomitant medication review	X										X	X	X		X[gg]	X[gg]	X
Physical exam	X										X	X	X	X[g]	X[gg]	X[gg]	X
Vital signs	X		X	X	X	X	X	X	X	X	X[bb]	X[bb]	X[bb]	X[g]	X[gg]	X[gg]	X

Procedures	Screening (Day -60 to Day -6) [aa]	Day -5 to Day -1	Time since CAR T-cell infusion								Onset of CRS and/or ICANS	First Dose of siltuximab (Window +/- 2 hours)	Second dose of Siltuximab	D8 to D 14 (if still hospitalized)	Day 14 after CAR T-cell infusion (window :+/- 2 days)	Day 28 after CAR T-cell infusion (Window +/- 5 days)	Day 31 to 90 after CAR T-cell infusion
			Day 0	D1	D2	D3	D4	D5	D6	D7							
ICE Scoring[c]			X	X	X	X	X	X	X	X	X[b]	X[b]	X[b]	X[g]	X[gg]	X[gg]	
Height	X														X[gg]	X[gg]	X
Weight	X														X[gg]	X[gg]	X
Performance status	X														X[gg]	X[gg]	X
Hematology	X		X	X	X	X	X	X	X	X	X	X	X	X[g]	X[gg]	X[gg]	X
Serum chemistry	X		X	X	X	X	X	X	X	X	X	X	X	X[g]	X[gg]	X[gg]	X
Liver Function Test	X		X	X	X	X	X	X	X	X	X	X	X	X[g]	X[gg]	X[gg]	X
Lactate Dehydrogenase	X		X	X	X	X	X	X	X	X	X	X	X	X[g]	X[gg]	X[gg]	X
Phosphorus and Uric Acid	X		X	X	X	X	X	X	X	X	X	X	X	X[g]	X[gg]	X[gg]	X
Cytokines	X				X						X[e]	X[e]	X[e]		X[gg]	X[gg]	X
CRP and Ferritin	X		X	X	X	X	X	X	X	X	X[e]	X[e]	X[e]	X[g]	X[gg]	X[gg]	X
Pregnancy test for female patients	X																

Procedures	Screening (Day -60 to Day -6) [aa]	Day -5 to Day -1	Time since CAR T-cell infusion								Onset of CRS and/or ICANS	First Dose of siltuximab (Window +/- 2 hours)	Second dose of Siltuximab	D8 to D 14 (if still hospitalized)	Day 14 after CAR T-cell infusion (window :+/- 2 days)	Day 28 after CAR T-cell infusion (Window +/- 5 days)	Day 31 to 90 after CAR T-cell infusion
			Day 0	D1	D2	D3	D4	D5	D6	D7							
EKG	X																
Adverse event review and evaluation[f]	X											X	X	X	X[gg]	X[gg]	X
PET or CT scan[i]	X															X	
Response Assessment																	X[, h]
Complete Case Report Forms (CRFs)	X										X		X		X[gg]	X[gg]	
Frailty Questionnaire	X															X	X
Neurocognitive Function Testing	X															X	X
PK collection												X[j]	X[j]		X	X	

Day 0 is the day of CAR T-cell infusion
Hematology: Include complete blood count with differentials
Chemistry: Includes electrolytes, BUN, creatinine, Glucose, magnesium and calcium
Liver Function test: Includes AST, ALT and Bilirubin.
PET/CT scan as per standard of care.
All lab collections have a window of 2 hours
a - Only if needed as per study schema
aa – To be done before lymphodepleting chemotherapy. Between day -60 until day -6 of CAR T-cell infusion. Ensure adequate washout for systemic therapy is evaluated before enrollment on the trial.
b - Every 8 hours for 24 hours. Window is 2 hours
bb - Every 4 hours for the first 24 hours. Window is 2 hours.

c - once per day.
e – at onset and every 8 hours for 24 hours.. Window for labs is within +/- 2 hours of the time frame. Time resets when a dose of siltuximab is administered.
f – Adverse event review to determine relationship to siltuximab to begin after first dose of siltuximab
g- not required for the study if siltuximab was not given. Also not required if the patient is discharged from the hospital
gg – If the patient is discharged from the hospital, a clinic visit for assessments is needed. If siltuximab is not given then the assessment is not needed for this trial.
h – Response assessment as per the disease specific criteria for which the CAR T-cell therapy was approved as per investigator discretion.
i – PET or CT scan if appropriate for the underlying disease for which CAR T-cell is being considered as per investigator discretion
j – Pre-siltuximab infusion, Immediate post siltuximab infusion from site other than infusion site, 4 hours post siltuximab and 8 hours post siltuximab then every 8 hours for 48 hrs. If a second dose is administered the time resets.

2 INTRODUCTION

2.1 STUDY RATIONALE

Tocilizumab, an interleukin-6 (IL-6) receptor antagonist, is the only FDA approved drug for the treatment of cytokine release syndrome. This approval is based on a pooled retrospective analysis of 45 patients treated in clinical trials, with CAR T-cells, who received tocilizumab, once or twice with improvement in CRS within 14 days [1]. However, despite widespread use of tocilizumab for CRS in patients receiving CAR T-cells, the incidence of severe grade 3 or higher CRS varies between 10-25% based on the CAR T-cell product and CRS grading criteria used [2].

This study is a prospective study evaluating the efficacy of siltuximab, an IL-6 antagonist, in patients who develop cytokine release syndrome (CRS) and/or immune effector cell associated neurotoxicity syndrome (ICANS).

2.2 BACKGROUND

2.2.1 CHIMERIC ANTIGEN RECEPTOR T-CELL THERAPY

Cancer immunotherapy seeks to harness the power of the immune system to eradicate malignant tissues. Significant advances have been made in last couple of decades in the development of cancer immunotherapy. None have been as promising and exciting as chimeric antigen T-cell (CAR T-cell) therapy. CAR T-cell therapy is a paradigm shifting approach to treating cancer. Using genetically modified cytotoxic immune T cells to target tumor-specific antigens, this immunotherapy platform has resulted in durable remissions in relapsed and/or refractory B-cell non-Hodgkin lymphoma (NHL) and B-cell acute lymphoblastic leukemia (ALL) and is showing promising early results in multiple myeloma [2]. Currently, there are two FDA-approved products for the treatment of relapsed/refractory B-cell NHL, namely tisagenlecluce l and axicabtagene ciloleucel. Recently, Ide-cel was FDA approved for the treatment of relapsed/refractory multiple myeloma.

Recent clinical successes have helped to thrust CART cells towards wider applicability, including clinical trials for other hematologic malignancies and even solid tumors. Moreover, there is an expectation to expand use of CART beyond specialized academic centers into the wider community practice at large. Use of CART cells has brought a unique set of toxicities such as cytokine release syndrome (CRS) and Immune Effector Cells Associated Neurotoxicity Syndrome (ICANS).

2.2.2 CYTOKINE RELEASE SYNDROME

Autoimmunity related toxicity occurs not uncommonly after treatment with genetically engineered T-cells such as chimeric antigen receptor (CAR) T-cell. Cytokine-associated toxicity, also known as cytokine release syndrome (CRS), is one such non–antigen-specific toxicity that occurs because of increased immune activation and results in fatal toxicities. It is a cytokine-mediated systemic inflammatory response

which occurs in concert with in vivo CART activation and expansion. The exact mechanism of CRS remains to be better understood. Cytokines are released when interaction between tumor and immune effector cell occurs; and it can originate not only from the CART cell but also from host immune cells such as macrophages, which respond in part to CART activation. The hyperactive immune system leads to the release of pro-inflammatory cytokines such as interleukin-6 (IL-6), IL-10, interferon-γ and granulocyte-macrophage stimulating factor[3]. Clinically, CRS manifests as fever, fatigue, malaise, nausea, tachycardia, hypotension, capillary leak syndrome, and end-organ damage. The severity of CRS was graded based on various criteria in the past, but now, American Society for Transplantation and Cellular Therapy (ASTCT) recommends the use of ASTCT consensus criteria for grading of CRS [4]. Most patients with grade 1 CRS are managed with supportive care, whereas higher grades of CRS require the administration of interleukin-6 antagonist, tocilizumab.

2.2.3 IMMUNE EFFECTOR CELLS ASSOCIATED NEUROTOXICITY SYNDROME

Neurotoxicity is the second most common adverse event with CAR T-cell therapy, which is now termed as immune effector cells-associated neurotoxicity syndrome (ICANS). The pathophysiology of ICANS is not well understood. It manifests clinically as toxic encephalopathy with confusion, word-finding difficulty, and aphasia, but it can seldom progress to more severe forms with coma, seizures, motor weakness, and cerebral edema[5]. Like CRS, cytokines, chemokines, and degree of CAR T-cell expansion have been associated with severity of neurotoxicity. In addition, CAR T cells are frequently found in cerebrospinal fluid of patients with neurotoxicity. However, it is unclear why CAR T cells traffic to central nervous system (CNS) in the absence of disease. Because of the limited understanding on the pathophysiology, ICANS is primarily managed with supportive care for low-grade toxicity, and corticosteroids are frequently used for more severe grades. Like CRS, ICANS is also completely reversible in most patients and tends to have a self-limited course.

2.2.4 SILTUXIMAB AND ITS RATIONALE FOR USE IN CRS *AND/OR ICANS*

Siltuximab is a chimeric (murine-human) monoclonal antibody (mAb) that has shown high affinity for interleukin-6 (IL-6) in both nonclinical and clinical studies. It blocks IL-6 signaling by binding IL-6 itself and preventing it from activating immune effector cells through either the trans or cis mechanisms. Siltuximab has a higher affinity for IL-6 than tocilizumab has for the IL-6R making it an attractive tool in managing CRS and/or ICANS. Siltuximab has been approved by the USFDA for its use in multicentric Castleman disease (MCD) who are human immunodeficiency virus (HIV) negative and human herpesvirus-8 (HHV-8) negative[6].

2.2.5 PRECLINICAL DEVELOPMENT OF SILTUXIMAB

Siltuximab is a mouse-human chimeric mAb to IL-6. It is also referred to as mouse-human chimeric neutralizing anti-IL-6 (cCLB8) in these studies and the cell line that produces siltuximab is referred to as C175A. The murine version of siltuximab (ie, mCNTO 328) was also used in tumor growth inhibition studies.

These studies demonstrate the high affinity of siltuximab for IL-6, as well as the inhibition of IL-6 biologic activity by siltuximab. Results of in vitro and in vivo studies have demonstrated the ability of siltuximab to reduce tumor growth and tumor cell survival, and to enhance the anti-tumor effects of other agents in combination therapy. Taken together, these nonclinical studies demonstrate the multiple roles played by IL-6 in cancer growth, progression, angiogenesis, cachexia and other morbidities, and highlight the ability of an IL-6-neutralizing antibody to reduce and/or eliminate the IL-6-induced effects.

2.2.6 CLINICAL TRIAL EXPERIENCE WITH SILTUXIMAB

The first study (NCT01400503) of siltuximab in MCD, was an international, multicenter, randomized Phase 2 study of every 3 week infusions comparing siltuximab and best supportive care (BSC) to placebo and BSC. There were 53 patients randomized to the siltuximab arm at a dosage of 11 mg/kg and 26 patients randomized to the placebo arm. Of the 26 placebo-treated patients, 13 patients subsequently crossed-over to receive siltuximab. The median age was 48 years (range 20 to 78), 66% male, 48% Asian, 39% White, 4% Black or African American, 7% other. The patients randomized to siltuximab received a median of 19 infusions (range 1 to 50) compared to patients randomized to placebo who received a median of 8 infusions (range 2 to 32). The adverse events observed in this study are described in the section *2.3.1*.

In a second study (NCT01400503) was an open label, long term extension study of patients with MCD treated on prior trials. The median duration of siltuximab treatment was 5.52 years (range:0.8 to 10.8 years); more than 50% of patients received siltuximab treatment for ≥5 years. The rate of serious or Grade ≥3 adverse events did not increase over time as a function of cumulative exposure. This is the first study to explore efficacy of siltuximab in CRS and ICANS.

2.2.7 RATIONALE FOR DOSING OF SILTUXIMAB

In an open-label, dose-finding, 7 cohort, phase I study, patients with NHL, multiple myeloma, or symptomatic Castleman disease received siltuximab 3, 6, 9, or 12 mg/kg weekly, every 2 weeks, or every 3 weeks (Kuzrock et al 2013). No dose-related or cumulative toxicity was apparent across all disease indications. A dose of 12 mg/kg every 3 weeks was recommended based on the high response rates in Castleman disease and the sustained CRP suppression. Phase 2 study of every 3 week infusions comparing siltuximab and best supportive care (BSC) to placebo and BSC, the dose of siltuximab used was 11mg/kg. Siltuximab was approved by the FDA at this dose for its use in MCD. Therefore, we will use drug label approved dosing for our study.

2.2.8 RATIONALE FOR SCHEDULE OF SILTUXIMAB

Siltuximab is an antagonist of IL-6. Currently FDA approved drug for the management of CRS is tocilizumab which is an IL-6R antagonist. With early administration of siltuximab at CRS Grade 1, the hypothesis is to neutralize IL-6 produced and minimize the interaction of IL-6 with its receptor. Since CRS is a time-limited phenomenon with temporal relationship to the infusion of CAR T-cells, every 3 weekly infusions of siltuximab is not required. The protocol allows the use of second dose of siltuximab in order neutralize the surplus IL-6 produced after the first dose of siltuximab.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

2.3.1.1 Infusion related reactions and hypersensitivity

Siltuximab may cause infusion related reactions and anaphylaxis. Approximately 945 patients have been treated with siltuximab in clinical trials. Of these, one patient experienced an anaphylactic reaction. Data from 254 patients treated with siltuximab monotherapy forms the basis of the safety evaluation of infusion related reactions. Infusion related reactions were reported in 5.1% of these patients. Two (0.8%) were Grade 3 or higher, and 1 (0.4%) was serious; none were fatal. Symptoms of infusion reactions consisted of back pain, chest pain or discomfort, nausea and vomiting, flushing, erythema, and palpitation.

In long-term treatment of iMCD patients with siltuximab at the recommended dosage of 11 mg/kg every 3 weeks, infusion related reactions or hypersensitivity reactions occurred at a frequency of 6.3% (1.3% for severe reactions).

2.3.1.2 Gastrointestinal Perforation

Gastrointestinal (GI) perforation has been reported in clinical trials although not in iMCD trials. Use with caution in patients who may be at increased risk for GI perforation. Promptly evaluate patients presenting with symptoms that may be associated or suggestive of GI perforation.

2.3.1.3 Concurrent Active Severe Infections

Siltuximab may mask signs and symptoms of acute inflammation including suppression of fever and of acute Phase reactants such as C-reactive protein (CRP). Monitor patients receiving siltuximab closely for infections. Institute prompt anti-infective therapy and continue to monitor for worsening of infection.

2.3.1.4 Other known Common Adverse Reactions observed in clinical trials

The most common adverse reactions (> 10% compared to placebo) during treatment with siltuximab in the iMCD clinical trial were rash, pruritus, upper respiratory tract infection, increased weight, and hyperuricemia. Table 1 below described the per patient incidence of common adverse reactions during study 1 (as described above) during initial 8 infusion.

Other important adverse reactions reported in MCD clinical studies, all of which were very common, were:

- Infections and infestations: nasopharyngitis, urinary tract infection
- Blood and lymphatic system disorders: neutropenia
- Nervous system disorders: dizziness
- Vascular disorders: hypertension
- Gastrointestinal disorders: nausea, abdominal pain, vomiting, diarrhea, gastroesophageal reflux disease, mouth ulceration.

Table 1: Per Patient Incidence of Common Adverse Reactions in Study 1 During Initial 8 Infusions

Body System/Adverse Reactions	SYLVANT+BSC[a] n=53		Placebo+BSC n=26	
	All Grades	Grades 3-4	All Grades	Grades 3-4
Skin disorders				
Rash (rash, rash generalized, rash maculopapular, rash popular and rash pruritic)	15 (28%)	1 (2%)	3 (12%)	0
Pruritus	15 (28%)	0	2 (8%)	0
Skin hyperpigmentation	2 (4%)	0	0	0
Eczema	2 (4%)	0	0	0
Psoriasis	2 (4%)	0	0	0
Dry Skin	2 (4%)	0	0	0
Infections				
Lower respiratory tract	4 (8%)	2 (4%)	1 (4%)	1 (4%)
Upper respiratory tract	14 (26%)	1 (2%)	4 (15%)	1 (4%)
Blood and lymphatic system disorders				
Thrombocytopenia	5 (9%)	2 (4%)	1 (4%)	1 (4%)
General disorders				
Edema (general and localized)	14 (26%)	4 (8%)	7 (27%)	0
Gastrointestinal disorders				
Constipation	4 (8%)	0	1 (4%)	0
Metabolism				
Hypertriglyceridemia	4 (8%)	0	0	0
Hypercholesterolemia	2 (4%)	0	0	0
Hyperuricemia	6 (11%)	1 (2%)	0	0
Respiratory, thoracic and mediastinal disorders				
Oropharyngeal pain	4 (8%)	0	1 (4%)	0
Renal and urinary disorders				
Renal impairment	4 (8%)	0	0	0
Nervous system disorders				
Headache	4 (8%)	0	1 (4%)	0
Investigations				
Weight increased	10 (19%)	1 (2%)	0	0
Vascular disorders				
Hypotension	2 (4%)	1 (2%)[b]	0	0

[a] Best Supportive Care
[b] Anaphylactic reaction

2.3.2 KNOWN POTENTIAL BENEFITS

Siltuximab is a human-mouse chimeric monoclonal antibody that binds human interleukin-6 (IL-6) and is produced by Chinese hamster ovary cells. Siltuximab binds human IL-6 and prevents the binding of IL-6 to both soluble and membrane-bound IL-6 receptors. IL-6 has been shown to be involved in diverse normal physiologic processes such as induction of immunoglobulin secretion. Overproduction of IL-6 has been linked to CRS and ICANS.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

CRS and ICANS occurring after CAR T-cell therapy are life threatening conditions that require management under close supervision with frequent monitoring of vital signs. Currently tocilizumab has been approved by the FDA for its use in the management of CRS. Tocilizumab binds to IL-6R but does not neutralize the excess circulating IL-6 produces during CRS. Siltuximab, by binding to circulating IL-6 has the potential to mitigate the deleterious effects seen in CRS and/or ICANS. With a fewer than 10% experiencing any grade 3 or higher adverse events in clinical trials, the benefits of studying the use of siltuximab outweigh the harm.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To assess the efficacy of siltuximab in resolution of cytokine release syndrome (CRS) within 14 days after infusion of siltuximab.	Complete response rate. Complete response (CR) is defined as the complete resolution of CRS within 14 days from the last dose of siltuximab.	Observed response rate in the FDA approved similar class of drug (tocilizumab) was measured at 14 days.
Secondary		
To assess the efficacy of siltuximab in resolution or stabilization of immune effector cell associated neurotoxicity (ICANS) within 28 days after infusion of siltuximab.	Overall response rate. [CR+PR+SD]	Median onset for ICANS is 5 - 7 days with persistence up to 6 weeks after infusion of CAR T-cells.
To determine the safety profile of siltuximab as characterized by adverse event (AE) type, severity, timing and relationship to study drug, as well as laboratory abnormalities within 28 days after siltuximab infusion.	All Adverse Events (AE's) will be reported and evaluated using National Cancer Institute's Common Terminology Criteria (CTCAE) v5.0.	To evaluate the toxicity profile of siltuximab.
To describe the influence of siltuximab on antitumor efficacy of	Responses based on disease specific criteria. (Appendix B, G & H)	To evaluate the influence of siltuximab

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
CAR T-cells between 28 to 90 days after infusion of CAR T-cells.		on efficacy of CAR T-cells
Tertiary/Exploratory		
To assess the prognostic significance of pre-CAR T-cell therapy total metabolic tumor volume on the incidence and severity of CRS and ICANS.	Total metabolic tumor volume (TMTV)	Higher tumor burden is associated with higher incidence of CRS and ICANS.
To assess the prognostic significance of circulating CD19+ B-cell on the incidence and severity of CRS and ICANS.	Cells/ml of circulating CD19+ B cells	Higher microscopic antigen burden is associated with higher incidence of CRS
To assess the effect of siltuximab on Th1,Th2,Th17, MCP-1, Procalcitonin, Angiopoeitin 1/2 CRP, LDH and ferritin after administration of siltuximab.	Quantitative measurement before and after siltuximab infusion.	Biomarkers of inflammation
To assess the effect of siltuximab and CAR T-cells on HMGB1.	Quantitative measurement before and after siltuximab infusion.	Biomarker for neuro-inflammation
To measure the effect of siltuximab on frailty and neurocognitive function trajectories among patients treated with CAR-T therapy.	Frailty and Neurocognitive assessment before, at day 30 and day 90 post-CAR-T	Measure the impact of siltuximab on frailty and neurocognitive function decline post CAR-T.

4 STUDY DESIGN

4.1 OVERALL DESIGN

Primary Hypothesis

The primary hypothesis of the study is that siltuximab will mitigate the severity of CRS associated with CAR T-cell therapy.

Secondary Hypothesis

The secondary hypothesis of the study is that siltuximab will decrease the severity of ICANS associated with CAR T-cell therapy

Phase of the trial

Phase 2 pilot study

A description of the type/design of trial to be conducted

This is an open label, single-arm, pilot study.

Name of study intervention(s)

Siltuximab at a dose of 11mg/kg.

Planned Interim Analysis

Refer to details in Section 9.4.6,

Study schema and schedule of activities

Refer to details in section 1.2 and 1.3

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This is a single arm study with siltuximab as the intervention given as per the study schema. The rationale for the study design is to intervene with siltuximab early after the onset of CRS and/or ICANS. By early administration of siltuximab, the surplus IL-6 produced by CAR T-cells will be neutralized, mitigating the severity of CRS and/or ICANS. The study design also determines early futility, to allow the use of rescue medications with the current accepted standard of care.

4.3 JUSTIFICATION FOR DOSE

The dose for siltuximab used is 11mg/kg as per the FDA label for its use in iMCD.

In non-clinical toxicology studies, in the 3-month and 6-month IV toxicology studies of siltuximab (9.2 mg/kg or 46 mg/kg once weekly) conducted in cynomolgus monkeys, higher doses of siltuximab showed no signs indicative of toxicity. Therefore, a repeat dose of siltuximab at the dose of 11mg/kg will be given as per the study schema.

4.4 END OF STUDY DEFINITION

The end of the study is defined as completion of the last visit or procedure shown in the Schedule of activities (SoA) in the trial.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

1. Patients who are planned to receive chimeric antigen receptor T-cell therapy as per the United States Food and Drug Agency (USFDA) approved indications for

   - Diffuse large B-cell lymphoma (DLBCL),
   - Mantle cell lymphoma (MCL),
   - Follicular lymphoma (FL),
   - Primary mediastinal large B-cell lymphoma (PMBCL),
   - High grade B-cell lymphoma,
   - DLBCL arising from follicular lymphoma.
   - Multiple myeloma
   - B-cell precursor acute lymphoblastic leukemia

   FDA approved indications for CAR T-cell therapy for different indications and products have been listed in Appendix I. The patient should also meet these indications for the study.

2. Patients with HCV can be included if they have completed therapy for hepatitis C with undetectable HCV RNA viral load.

3. Patients with Hepatitis B can be included if they are on suppressive therapy for hepatitis B infection and with no detectable viral load.

4. Adequate organ function as defined below unless attributed to disease involvement. Acceptable window for assessing adequate organ function is 7 days to 30 days before planned CAR T-cell infusion with day 0 as the planned day of CAR T-cell infusion.

   i. liver function (bilirubin $\leq$ 2mg/dL, AST and/or ALT $\leq$3 x ULN)

   ii. kidney function (crcl > 30ml/min using Cockroft-Gault, based on actual weight).

   iii. ANC ≥ 1,000/µL, Hgb > 8, Platelet Count ≥ 50,000/ µL.

5. Patients able to tolerate washout periods for therapies as defined below prior to CAR T-cell infusion.

   i. Systemic therapy: Washout period is 2 weeks prior to CAR T-cell infusion.
   ii. Radiation therapy : Washout period is 1 week prior to CAR T-cell infusion.

   iii. Corticosteroids : Washout period is 5 days prior to CAR T-cell infusion.

6. Age ≥ 18 years of age.
7. A negative urine pregnancy test is required within 1 week for all women of childbearing potential prior to enrolling on this trial.
8. For females of reproductive potential: use of highly effective contraception for at least 1 month prior to screening and agreement to use such a method during study participation and for an additional 4 months after infusion of siltuximab.
9. For males of reproductive potential: use of condoms or other methods to ensure effective contraception with partner
10. Willing and able to participate in all required evaluations and procedures in this study protocol including receiving intravenous administration of investigational product and being admitted, when required, for at least 24 hours during investigational product administration.

5.2 EXCLUSION CRITERIA

1. Subjects requiring ongoing daily corticosteroid therapy at a dose of > 10 mg of prednisone per day (or equivalent). Pulsed corticosteroid use for disease control is acceptable.
2. Active autoimmune disease requiring immunosuppressive therapy is excluded unless discussed with the principal investigator (PI)
3. Pregnant women are excluded from this study.
4. Evidence of ongoing systemic bacterial, or fungal or viral infection, except localized fungal infection of skin or nails.
5. Patients with ongoing or past HIV infections.

5.3 LIFESTYLE CONSIDERATIONS

Not-applicable.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but do not enter in the study or if they are entered in the study they do not receive the study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing

requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Patients who received CAR T-cell therapy but do not experience CRS/ ICANS and do not receive Siltuximab within 14 days after CAR T-cell infusion will be deemed screen failed.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

- Target study sample size: 30 patients.
- Anticipated accrual rate: 10/year
- Anticipated number of sites: One site
- Source of participants: Patients referred to the participating site for FDA approved indications for chimeric antigen T-cell therapy.
- Recruitment venues: Outpatient clinics.
- How potential participants will be identified and approached: All patients who are eligible to receive on-label CAR T-cells therapy for FDA approved indications will be approached for enrollment in the clinical trial.
- Types of recruitment strategies planned: Description of trial on clinicaltrial.gov and description of study to patients eligible to participate.
- Participants will not be compensated or provided any incentives (e.g. vouchers, gift cards,) for study participation
- Vulnerable participants and recruitment strategy. Vulnerable participants include, but not limited to pregnant women, those who lack consent capacity, including the mentally ill, prisoners, cognitively impaired participants, children, and employee volunteers will not be recruited to the study as they will not meet the eligibility criteria.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

The study intervention is the use of siltuximab.

The schema to refer is in Section *1.2*

The treatment plan is as follows.

Patients who meet the eligibility criteria should be screened when decision to proceed with CAR T-cell is made and completed between day -60 to day -6 of planned CAR T-cell infusion. If there is a delay in infusion the screening tests should be repeated. The patient will then be enrolled on the day of CAR T-cell therapy infusion (i.e Day 0).

The patients should be assessed as per the schedule of activities in Section *1.3*. Once patient meets the following criteria's, siltuximab will be administered.

- Grade 1 CRS lasting for more than 12 hours.
- Grade 1 ICANS lasting for more than 12 hours.
- Any Grade 2 or higher CRS/ICANS.

Note: If symptoms leading to Grade 1 CRS/ICANS resolve before 12 hours and remain absent for 24 hours then all future events should be treated as new events.

Administer siltuximab at the dose of 11mg/kg via intravenous infusion over 1 hour. After siltuximab is administered heart rate, blood pressure, oxygen saturations and respiratory rate should be monitored every 4 hours for the first 24 hours. If only ICANS present or if any grade CRS with ICANS grade 3 or higher is present corticosteroids should be administered before first dose of siltuximab. Dose and type of corticosteroids to be administered is described below in table 3. If two doses of siltuximab have already been received before this step then consider failure of siltuximab and proceed with tocilizumab. If only ICANS persists after two doses of siltuximab, this is not considered failure of siltuximab.

Following scenarios are expected to occur

I. Resolution of CRS / ICANS symptoms:
Resolution is defined as absence of symptoms leading to the diagnosis of CRS / ICANS for a period of 24 hours.

II. Similar grade of CRS and/or ICANS at 12 hours :

i. If Yes : Then proceed with the second dose of siltuximab. Add corticosteroids if not given previously. Dose as per table 3.
ii. If No: Then continue to reassess. If at 48 hours from the first dose of Siltuximab, CRS/ ICANS persists (any grade), then administer second dose of siltuximab.

III. Worsening grade of CRS and/or ICANS after completion of first dose of siltuximab :
Administer second dose of siltuximab.

After second dose of siltuximab is administered heart rate, blood pressure, oxygen saturations and respiratory rate should be monitored every 4 hours for the first 24 hours after the second dose.

Following scenarios are expected to occur

1. Resolution of CRS / ICANS symptoms:
Resolution is defined as absence of symptoms leading to the diagnosis of CRS / ICANS for a period of 24 hours.

2. Worsening grade of CRS and/or ICANS after completion of siltuximab :
Consider failure of siltuximab and administer rescue tocilizumab.

3. Similar grade CRS/ICANS
If CRS and ICANS continue to be similar grade after completing the second dose of siltuximab and assessed one hour after completion then the severity of the current grade has to be determined.
   i. If grade ≥ 3 or higher CRS with or without ICANS, without response after two doses of siltuximab:- Then consider failure of siltuximab and administer rescue tocilizumab.
   ii. If persistent Grade 2 CRS at 72 hours from the first dose of siltuximab or worsening of any grade CRS at any time point despite receiving two doses of siltuximab. Consider failure of siltuximab and administer tocilizumab.. If persistence of CRS Grade 1 at 7 days from the time from first dose of siltuximab, consider failure of siltuximab and administer rescue tocilizumab.
   iii. If there is worsening of CRS grade at any time point after two doses of siltuximab, consider failure of siltuximab and administer rescue tocilizumab.
   iv. If persistence of ICANS only after two doses of siltuximab, treat as per institutional guidelines for ICANS managements (Appendix K). Continue to monitor for 28 days for response assessment from first dose of siltuximab.

Following special scenarios to consider

A. Recurrence of CRS episode with or without ICANS after resolution of the first episode within 14 days of first dose of siltuximab
   - Restart and follow the algorithm as a new episode of CRS with or without ICANS only if less than 2 doses of siltuximab have been received. If 2 doses have already been received by the patient then consider failure of siltuximab and administer tocilizumab.

B. Resolution of CRS only episode but new episode of ICANS only within 14 days of first dose of siltuximab
   - Restart and follow the algorithm as a new episode of ICANS only. Do not administer additional doses of siltuximab if the patient has already received two doses of siltuximab. If only ICANS is present, follow institutional guidelines for management of ICANS after the patient has received a maximum of two doses of siltuximab (Appendix K).

Table 3: Dosing and frequency guidelines for corticosteroid administration

	Grade	**Dexamethasone**	**Methylprednisone**
CRS	1	None (Unless persistent for 12 hours after dose of siltuximab. If persistent administer as Grade 2)	None (Unless persistent for 12 hours after dose of siltuximab. If persistent administer as grade 2)
	2	10mg IV one dose. Repeat every 24hrs if needed.	50mg IV one dose. Repeat every 24hrs if needed.
	3	20 mg IV every 6 hours	100mg IV every 6 hours
	4	None	1000 mg IV / day for 3 days followed by rapid taper
ICANS	1	10 mg IV one dose. Repeat every 24hrs if needed	50 mg IV one dose. Repeat every 24 hours if needed
	2	10 mg IV every 12 hours	50 mg IV every 12 hours
	3	10 mg IV every 6 hours 20 mg IV every 6 hours if seizures present	50 mg IV every 6 hours

			100 mg IV every 6 hours if seizures present
	3 or 4 with cerebral edema	None	1000 mg IV / day for 3 days followed by rapid taper

6.1.2 DOSING AND ADMINISTRATION

Siltuximab is for intravenous infusion only. It is to be administered as an 11 mg/kg dose given over 1 hour by intravenous infusion through a peripheral or central venous catheter.

Dose changes are not required for this study.

6.1.3 PRE-MEDICATIONS

Premedication with acetaminophen (650 mg orally) and diphenhydramine (50 to 100 mg IV or orally) before infusion of siltuximab, may attenuate infusion reactions and can be considered.

6.1.4 INFUSION RELATED REACTIONS

Medications, including epinephrine for SC injections, corticosteroids, and diphenhydramine hydrochloride for IV injection, and resuscitation equipment should be available for immediate use. Guidelines for management of infusion-related symptoms are provided in Table 4.

Table 4: Management of Infusion related reactions.

Infusion-Related Symptoms	Guidance
Grade 1-2	• Slow infusion rate to 50% of the current rate. • Give supportive treatment. [a] • Upon symptom resolution, may resume prior infusion-rate at the investigator's discretion.

	• For Grade 2 wheezing or urticaria, patient must be premedicated for any subsequent doses. • If symptoms recur, stop the infusion immediately and permanently discontinue study drug.
Grade 3	• Hold infusion. • Give supportive treatment. [a] • Upon symptom resolution, resume at infusion-rate with 50% reduction as per the investigator's discretion. [b] • Note: If the same adverse event recurs with same severity, treatment must be permanently discontinued. • Note: For Grade 3 hypotension or fever that is attributed to the IRR, patient must be pre-medicated before re-treatment. If symptoms recur, then study drug must be permanently discontinued. • Note: If patient has Grade 3 wheezing, bronchospasm, or generalized urticaria at first occurrence which is attributed to IRR, permanently discontinue study drug.
Grade 4	• Discontinue infusion immediately, treat symptoms aggressively, and permanently discontinue study drug.

IV = intravenous; NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0.

IRR = Infusion related reactions.

Refer to the NCI-CTCAE v5.0 for the grading of symptoms. Management of IgE-mediated allergic reactions should be as directed in the text following this table.

a Supportive treatment: Patients should be treated with acetaminophen/paracetamol 650mg, an antihistamine such as diphenhydramine (Diphenhydramine 50 or 100 mg IV) and famotidine 20mg IV, if they have not been received in the previous 4 hours. IV saline may be indicated. . If rigors are present then may require meperidine 25mg IV.

For bronchospasm, urticaria, or dyspnea which is attributed to IRR and not the underlying CRS, patients may require antihistamines, oxygen, corticosteroids (e.g., 100 mg IV prednisolone or equivalent), and/or bronchodilators.

b Infusion-rate escalation after re-initiation: Upon complete resolution of symptoms, the infusion may be resumed at 50% of the rate achieved prior to interruption. In the absence of infusion-related symptoms, the rate of infusion may be escalated in increments of 50 ml/hr every 30 minutes.

In the event of a life-threatening IRR (which may include pulmonary or cardiac events) or IgE-mediated anaphylactic reaction, study treatment should be discontinued. Patients who experience any of these reactions should receive aggressive symptomatic treatment and will be discontinued from study treatment. See Appendix J for recommended management of anaphylaxis.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

Siltuximab is *the study* agent provided by *EUSA pharmaceuticals.*

Siltuximab (SYLVANT) for injection is supplied as a sterile, white, preservative free, lyophilized powder in single-dose vials.

Each siltuximab vial is individually packaged in a carton:

NDC: 73090-420-01 contains one 100 mg vial

NDC: 73090-421-01 contains one 400 mg vial.

Vials should be procured and stored in the institutions pharmacy repository before a patient receives CAR T-cell infusion. All unused or expired vials should be disposed or returned.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

SYLVANT (siltuximab) for injection is available as:

- 100 mg of lyophilized powder in a single-dose vial for intravenous infusion.
- 400 mg of lyophilized powder in a single-dose vial for intravenous infusion.

6.2.3 PRODUCT STORAGE AND STABILITY

SYLVANT must be refrigerated at 2ºC to 8ºC (36ºF to 46ºF) in the original carton to protect from light. Do not freeze. Do not use SYLVANT beyond the expiration date (EXP) located on the carton and the vial.

6.2.4 PREPARATION

Use aseptic technique for reconstitution and preparation of dosing solution.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit

1. Calculate the dose (mg), total volume (mL) of reconstituted siltuximab solution required and the number of vials needed. A 21-gauge 1½ inch needle is recommended for preparation. Infusion bags (250 mL) must contain Dextrose 5% in Water and must be made of polyvinyl chloride (PVC), or polyolefin (PO), or polypropylene (PP), or polyethylene (PE). Alternatively, PE bottles may be used.

2. Allow the vial(s) of siltuximab to come to room temperature over approximately 30 minutes. Siltuximab should remain at room temperature for the duration of the preparation.

Table 5: Reconstitution Instructions

Strength	**Amount of Sterile Water for Injection, USP required for reconstitution**	**Post-reconstitution concentration**
100 mg vial	5.2 mL	20 mg/mL
400 mg vial	20 mL	20 mg/mL

3. Gently swirl the reconstituted vials to aid the dissolution of the lyophilized powder. DO NOT SHAKE or SWIRL VIGOROUSLY. Do not remove the contents until all the solids have been completely dissolved. The lyophilized powder should dissolve in less than 60 minutes.

Once reconstituted, and prior to further dilution, inspect the vials for particulates and discoloration. Do not use if particles or solution discoloration are present or if visibly opaque. The reconstituted product should be kept for no more than two hours prior to addition into the infusion bag.

4. Dilute the reconstituted siltuximab solution dose to 250 mL with sterile Dextrose 5% in Water by withdrawing a volume equal to the total calculated volume of reconstituted siltuximab from the Dextrose 5% in Water, 250 mL bag. Slowly add the total calculated volume (mL) of reconstituted siltuximab solution to the Dextrose 5% in Water infusion bag. Gently invert the bag to mix the solution.

5. Administer the diluted siltuximab solution in 5% Dextrose in Water 250 mL by intravenous infusion over a period of 1 hour using administration sets lined with PVC, or polyurethane (PU), or PE, containing a 0.2-micron inline polyether sulfone (PES) filter. The infusion should be completed within 4 hours of the dilution of the reconstituted solution to the infusion bag.

6. Do not infuse siltuximab concomitantly in the same intravenous line with other agents.

7. Siltuximab does not contain preservatives. Do not store any unused portion of the reconstituted product or of the infusion solution. Waste material should be disposed of in accordance with local requirements.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

This is a single arm, open label study. Randomization and blinding will not be done.

6.4 STUDY INTERVENTION COMPLIANCE

A study initiation visit, will be performed to review investigator responsibilities and protocol requirements. During the initiation, the electronic case report forms (eCRFs) and other pertinent study materials will be reviewed with the research staff. During the study, the principal investigator will conduct necessary reviews to determine protocol compliance, examine eCRFs, and individual patient medical records, and ensure that the study is being conducted according to the protocol and pertinent regulatory requirements. Selected eCRF entries will be verified with source documentation. The review of medical records will be done in a manner to assure that patient confidentiality is maintained.

Monitoring shall be conducted to ensure the human patient protection, study procedures, laboratory, study intervention administration, and data collection processes are of high quality and meet the GCP/ICH and, when appropriate, regulatory guidelines.

6.5 CONCOMITANT THERAPY

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the Case Report Form (CRF) are concomitant prescription medications, over-the-counter medications and supplements.

6.5.1 DRUG INTERACTIONS WITH CYTOCHROME P450 SUBSTRATES

Cytochrome P450s in the liver are down regulated by infection and inflammation stimuli including cytokines such as IL-6. Inhibition of IL-6 signaling in patients treated with siltuximab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates compared to metabolism prior to treatment with siltuximab.

Upon initiation or discontinuation of siltuximab, in patients being treated with CYP450 substrates with a narrow therapeutic index, perform therapeutic monitoring of effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) as needed and adjust dose. The effect of siltuximab on CYP450 enzyme activity can persist for several weeks after stopping therapy. Exercise caution when siltuximab is co-

administered with CYP3A4 substrate drugs where a decrease in effectiveness would be undesirable (e.g., oral contraceptives, lovastatin, atorvastatin).

6.5.2 RESCUE MEDICINE

The study site should procure enough supply of rescue medication that will be obtained locally. The following rescue medications may be used: Tocilizumab.

The use of rescue medications should be delayed, if possible, till failure of siltuximab has been defined as per the study schema, following the administration of siltuximab. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

The patient will receive rescue medication with tocilizumab after the failure of situximab as described in the study schema. Failure of siltuximab does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the following:

- Outcome of CRS and/or ICANS with the administration of rescue medication of tocilizumab

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Failure of siltuximab in resolving or stabilizing CRS or/and ICANS after two doses administered.
- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression as determined by the treating physician which requires discontinuation of the study intervention.
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who sign the informed consent form, receive CAR T-cell infusion but do not receive the study intervention may be replaced. Patients who are replaced due to not receiving the study intervention will be followed up to day 28 after CAR T-cell infusion. Subjects who sign the informed

consent form and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for end of study visit visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 PRE-TREATMENT ASSESSMENT

Pre-treatment evaluation should be done at screening. Screening window is day -60 to day -6 of anticipated CAR T-cell infusion. Day 0 is the anticipated day of CAR T-cell infusion.

- History and physical examination, including vital signs, height, weight and performance status by ECOG scale.
- Baseline assessment of disease with CT scan or PET scan as per disease specific criteria as per the discretion of the investigator. If presence of multiple myeloma or Acute lymphoblastic leukemia, CT scan or PET-CT is not required per the protocol but can be performed at the treating physicians' discretion.
- CBC with differential
- Serum chemistry: BUN, creatinine, electrolytes, Calcium, Magnesium, glucose,
- Liver function test with AST, ALT and Bilirubin.
- Phosphorus, Uric acid.
- CRP and Ferritin .
- Cytokines . Separate lab manual for collection, processing and shipping will be provided.
- Urine pregnancy test within one week for women of childbearing potential.
- For women of childbearing age effective measures of contraception without interruption. Contraception methods must include 1 highly effective and 1 additional effective (barrier) method of contraception used simultaneously from screening and during the treatment period of 30 days after receiving CAR-T cell infusion.
- 12-lead EKG of study entry.
- Frailty using CARE Questionnaire and Neurocognitive function assessment using NIH toolbox. This can be done up to Day 0.
- Signed informed consent.

Patients will sign consent after decision for CAR T-cells has been made.

Patients will be enrolled on the trial at the time of CRS or ICANS development after CAR T-cell infusion. They will be called screen failed if they do not have CRS or ICANS after CAR T-cell infusion up to 14 days post CAR T-cell infusion.

8.2 EFFICACY ASSESSMENTS

The study intervention (Siltuximab) will be given when the patient first experiences a clinical syndrome consistent with CRS and/or ICANS. The definition and grading of CRS and/or ICANS will be done as per ASTCT consensus grading by Lee et al 2019. (Appendix 1).

The inpatient treating physician (if patient is admitted) or outpatient treating physician will determine if the patient meets the criteria for CRS and/or ICANS.

After siltuximab is administered, the patient will be assessed as per the study schema with every 4 hours vitals and lab tests every 8 hours for the first 24 hours. For grade 1 CRS and/or ICANS that persist for 12 hours from onset and subsequently receive siltuximab, the time for labs will reset and be collected at onset and every 8 hours for up to 24 hours after infusion of siltuximab. Window for labs is within +/- 2 hours.

If patient meets criteria for a second dose of siltuximab, time will reset with every 4 hours vitals and every 8-hourly lab tests will be conducted for 24 hours

Assessment of efficacy of siltuximab for resolution of CRS should be performed at 14 days by the primary treating physician as per response criteria described below:

- **Complete response**

  Complete response (CR) is defined as the complete resolution of CRS within 14 days from the last dose of siltuximab.

  Complete resolution is defined as absence of symptoms leading to the diagnosis of CRS for 24 hours.

- **Partial response**

  Partial response (PR) is defined as improvement in the grade of CRS from its maximum grade reached but persistence of CRS within 14 days from the last dose of siltuximab.

- **Stable disease**

  Stable disease (SD) is defined as failure to achieve either CR or PR but does not fulfil criteria for failure to respond within 14 days from the last dose of siltuximab.

- **Failure to respond**

  Failure to respond (FR) is defined as occurrence of one of the following

  - Worsening of the CRS grade or persistence of grade 3 CRS, after 2 doses of siltuximab.
  - Need for rescue tocilizumab
  - Recurrence of CRS after achieving of a complete response and have had received two doses of siltuximab to attain the complete response

Assessment of efficacy of siltuximab for resolution of ICANS should be performed at 28 days by the primary treating physician. The responses will be assessed as following.

- **Complete response**

  Complete response (CR) is defined as the complete resolution of ICANS within 28 days from the last dose of siltuximab.

  Complete resolution is defined as absence of symptoms leading to the diagnosis of ICANS for 24 hours.

- **Partial response**

  Partial response (PR) is defined as improvement in the grade of ICANS from its maximum grade reached but persistence of ICANS within 28 days from the last dose of siltuximab.

- **Stable disease**

  Stable disease (SD) is defined as failure to achieve either CR or PR but does not fulfil criteria for failure to respond within 28 days from the last dose of siltuximab.

- **Failure to respond**

  Failure to respond (FR) is defined as occurrence of one of the following

  - Worsening of the ICANS grade or persistence of grade 3 ICANS, after 2 doses of siltuximab.
  - Recurrence of ICANS after achieving of a complete response and have had received two doses of siltuximab to attain the complete response

Anti-tumor efficacy assessment will be performed between days 28 to day 90 at a time frame determined appropriate by the treating physician. The responses will be assessed for the indication for which CAR T-cell was administered.

1. **Lymphoid malignancies, such as Diffuse Large B-cell lymphoma, Mantle cell lymphoma, follicular lymphoma and marginal zone lymphoma.**

   Responses will be assessed based on Lugano Response Criteria for Malignant Lymphoma 2016 (Appendix B).

2. **Multiple Myeloma response assessment by the International Myeloma Working Group.**

   Responses will be assessed based on International Myeloma Working Group (IMWG) 2016 for response and minimal residual disease assessment in Multiple Myeloma (Appendix G).

3. **Acute Lymphoblastic leukemia response assessment**

   Responses will be assessed as per Acute lymphoblastic leukemia response criteria (Appendix H)

8.3 SAFETY AND OTHER ASSESSMENTS

Safety evaluations will be based on the incidence, intensity, and type of adverse events, as well as on clinically significant changes in the patient's physical examination, vital signs, and clinical laboratory results. Exposure to study treatment and reasons for discontinuation of study treatment should also be tabulated.

All adverse events resulting in discontinuation from the study should be followed until resolution or stabilization or until the patient is lost to follow up. Patients should be followed for AEs for 30 calendar days after discontinuation or completion of protocol-specific. All new AEs occurring during this period must be reported and followed until resolution unless, in the opinion of the investigator, these values are not likely to improve because of the underlying disease or until the patient is lost to follow up. In this case, the investigators must record his or her reasoning for this decision in the patient's medical record and as a comment on the eCRF. After 30 days, only AEs, SAEs, or deaths assessed by the investigator as treatment related are to be reported.

Patients medical chart or results of diagnostic tests performed as part of an individual's regular medical care should also be used for screening or as a part of collection of trial data. Confidentiality of patient's personal data should be protected in accordance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA), and national data protection laws.

On receiving the study intervention, the patient should be monitored as detailed in the schedule of activities and study schema. The safety assessments will continue up to 28 days after the administration of siltuximab and will be recorded on appropriate case record forms.

8.4 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.4.1 DEFINITION OF ADVERSE EVENTS (AE)

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation patient who is administered a pharmaceutical product. An AE does not necessarily have to have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporarily associated with the use of a medicinal product, whether or not considered related to the medicinal product. This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition.

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site. http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

'**Expectedness':** AEs can be 'Unexpected' or 'Expected' for expedited reporting purposes only. Expected AEs are defined as those described in the Reference Safety Information (RSI) from the Investigator Brochure. Please refer to RSI for a listing of expected AEs.

8.4.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

The definitions of serious adverse events (SAEs) are given below. The investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

An SAE or reaction is defined as any untoward medical occurrence that:

- results in death,
- is immediately life-threatening,
- requires at least a 24-hour in patient hospitalization or prolongation of existing hospitalization not related to CRS or ICANS from CAR T-cell therapy,
- results in persistent or significant disability/incapacity, and/or
- causes a congenital anomaly/birth defect.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the previous definition. These should also

usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per IWG Cheson et al. 2014, should not be reported as a serious adverse event.

A suspected unexpected serious adverse reaction (SUSAR) is defined as an SAE that is suspected to be at least possibly related to study medication(s) and is an unexpected event. SUSAR reporting is encompassed within SAE reporting guidelines as defined in this section.

Treatment within or admission to the following facilities is not considered to meet the criteria of "in-patient hospitalization" (although if any other SAE criteria are met, the event must still be treated as an SAE and immediately reported):

- Emergency Department or Emergency Room
- Outpatient or same-day surgery units
- Observation or short-stay unit
- Rehabilitation facility
- Hospice or skilled nursing facility
- Nursing homes, Custodial care or Respite care facility

Hospitalization during the study for a pre-planned surgical or medical procedure (one which was planned prior to entry in the study), does not require reporting as a serious adverse event to the Sponsor.

8.4.3 CLASSIFICATION OF AN ADVERSE EVENT

8.4.3.1 Severity of Event

For clinical syndrome, consistent with CRS and/or ICANS the treating physician will use the ASTCT consensus criteria (Appendix 1) for grading and assessment of response of siltuximab.

All adverse events will also be assessed by the treating physician and/or the study nurse by using the NCI CTCAE v5.0

For adverse events not covered by the NCI-CTCAE Version 5.0 grading system, the following definitions will be used:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

- Grade 2: Moderate; minimal, local or non-invasive intervention indicated.
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

8.4.3.2 Relationship to Study INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

8.4.3.3 Expectedness

The treating physician will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention and is not a part of the RSI.

8.4.4 RECORDING OF ADVERSE EVENTS

All adverse events of any patient during the course of the study will be reported on the case report form, and the investigator will give his or her opinion as to the relationship of the adverse event to study drug treatment (i.e., whether the event is related or unrelated to study drug administration - Siltuximab). If the adverse event is serious, it should be reported as soon as possible and no greater than 24 hours to the sponsor or designee. Other untoward events occurring in the framework of a clinical study are also to be recorded as AEs (i.e., AEs that occur prior to assignment of study treatment that are related to a protocol-mandated intervention, including invasive procedures such as biopsies, medication washout, or no treatment run-in).

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits, interviews and physical exam of a study participant while receiving medical care, review of the patient's laboratory and/or vitals , or upon review by the principal investigator.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

8.4.4.1 Abnormal Laboratory Values and Vital Signs

The reporting of abnormalities of vital signs in isolation, as adverse events should be avoided. Abnormalities of vital signs should not be reported unless any criterion for an SAE or CRS/ICANS is fulfilled, the vital signs abnormalities cause the patient to discontinue study treatment, or the investigator insists that the abnormality should be reported as an AE. Abnormal laboratory results should be noted in the eCRF as an adverse event if they are associated with an overdose, require or prolong inpatient hospitalization, or are otherwise considered clinically significant by the investigator. If an abnormal laboratory value or vital sign is associated with clinical signs and/or symptoms, the sign or symptom should be reported as an AE, and the associated laboratory value or vital sign should be considered additional information that must be collected in the relevant eCRF. If the laboratory abnormality is a sign of a disease or syndrome, only the diagnosis needs to be recorded on the SAE Report Form or AE eCRF.

Clinical Laboratory Results will be summarized. Summary statistics for actual values and for changes from baseline will be tabulated for laboratory results by scheduled visit. Patients with laboratory values outside of the normal reference range at any post-baseline assessment will be summarized, and graded per NCI CTCAE Version 5.0 when applicable. Patient incidence of abnormal laboratory results will be summarized by maximum grade for each abnormal laboratory finding.

8.4.5 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The study personnel and/or the treating physician will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the

occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization or until the patient is lost to follow up.

8.4.6 ADVERSE EVENT REPORTING

8.4.6.1 SAE Reporting to EUSA Pharma

SAEs require expeditious handling and reporting to EUSA Pharma in order to comply with regulatory requirements. All SAEs (regardless of causality assessment) occurring on study or within 30 days of last study treatment should be immediately reported to EUSA Pharma according to the timelines and methods specified in the safety data exchange agreement between Sponsor and EUSA Pharma.

8.4.6.2 SAE Reporting to the FDA and IRB

The investigator is responsible for reporting relevant SAEs. The investigator is responsible for reporting unexpected fatal or life-threatening events associated with the use of the study drugs to UAB CTO IIT Office within 7 calendar days after being notified of the event. The investigator will report all related but unexpected SAEs including non-death/non-life-threatening related but unexpected SAEs (SUSAR) associated with the use of the study medications to UAB CTO IIT Office by a written safety report within 15 calendar days of notification. Both these events should be reported on MedWatch 3500A form with support documents submitted to UAB CTO IIT Office within the above mentioned timelines. Investigators must report SUSARs and follow-up information to their responsible Institutional Review Board (IRBs)/Independent Ethics Committee according to the policies of the responsible IRB (Research Ethics Committee).

8.4.7 SERIOUS ADVERSE EVENT REPORTING

The study clinician will immediately report to the sponsor any serious adverse event, whether or not considered study intervention related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. Adverse events classified by the treating investigator as serious require expeditious handling and reporting to the Sponsor in order to comply with regulatory requirements. Serious adverse events may occur at any time from the signing of the informed consent form through the 30-day follow-up period after the last study treatment. Sponsor or designee should be notified of all SAEs, regardless of causality, within 24 hours of the first knowledge of the event by the treating physician or research personnel

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable, or until the patient is lost to follow up. Other supporting documentation of the event may be requested by the Data Coordinating Center (DCC)/study sponsor and should be provided as soon as possible.

Sponsor is responsible for reporting relevant SAEs to the competent authority, other applicable regulatory authorities, and participating investigators, in accordance with ICH guidelines, FDA regulations, and/or local regulatory requirements.

Sponsor is responsible for reporting unexpected fatal or life-threatening events associated with the use of the study drugs to the regulatory agencies and competent authorities within 7 calendar days after being notified of the event. The Sponsor will report all related but unexpected SAEs including non-death/non-life-threatening related but unexpected SAEs (SUSAR) associated with the use of the study medications to the regulatory agencies and competent authorities by a written safety report within 15 calendar days of notification. Following the submission to the regulatory agencies and competent authorities, Investigators and trial sites will be notified of the SUSAR. Investigators must report SUSARs and follow-up information to their responsible Institutional Review Board (IRBs)/Independent Ethics Committee according to the policies of the responsible IRB (Research Ethics Committee).

8.4.8 REPORTING OF PREGNANCY, ABORTION, BIRTH DEFECTS/CONGENITAL ANOMALIES

During the course of the study, all female patients of childbearing potential (see Appendix F - Contraception Guidelines and Pregnancy) must contact the treating investigator immediately if they suspect that they may be pregnant (a missed or late menstrual period should be reported to the treating investigator).

If an investigator suspects that a patient may be pregnant prior to administration of study drug(s), the study drug(s) must be withheld until the result of the pregnancy test is confirmed. If a pregnancy is confirmed, the patient must not receive any study drug(s). The patient may be allowed to be on study for follow up and study related activity as deemed safe by the investigator.

If an investigator suspects that a patient may be pregnant after the patient has been receiving study drug(s), the study drug(s) must immediately be withheld until the result of the pregnancy test is confirmed. If a pregnancy is confirmed, the study drug(s) must be immediately and permanently stopped, the patient must be discontinued from the study, and the investigator must submit a Pregnancy Report Form to EUSA Pharma according to the timelines and methods specified in the safety data exchange agreement between Sponsor and EUSA Pharma.

The pregnancy should be followed up to 6 months after the end of the pregnancy, which can include birth, spontaneous abortion or voluntary termination, to collect the outcome with details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications, as applicable. Proper follow-up to a pregnancy includes an assessment of the causal relationship to the study drug and reporting by the Investigator to EUSA Pharmaceuticals on a Pregnancy Report Form following the same process described for reporting SAEs. Pregnancy outcomes must also be reported on the Pregnancy Report Form to EUSA Pharma for the female partners of any males who took study drug. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

Abortions (spontaneous, accidental, or therapeutic) must also be reported to EUSA Pharma using the Pregnancy Report Form within 24 hours of the first knowledge of the event by the treating physician or research personnel following the same process as described above for reporting SAEs and pregnancies to EUSA Pharmaceuticals.

Any SAE experienced during pregnancy and congenital anomalies/birth defects always meet SAE criteria, and must be expeditiously reported as an SAE to EUSA Pharma according to the timelines and methods specified in the safety data exchange agreement between Sponsor and EUSA Pharma.

8.5 UNANTICIPATED PROBLEMS

8.5.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems (UP) involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

If an UP problem occurs, the following corrective action plan or changes will be considered in response to an UP include:

- Modification of inclusion or exclusion criteria to mitigate the newly identified risks
- Implementation of additional safety monitoring procedures
- Suspension of enrollment of new participants or halting of study procedures for enrolled participants
- Modification of informed consent documents to include a description of newly recognized risks

- Provision of additional information about newly recognized risks to previously enrolled participants.

8.5.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the local Institutional Review Board (IRB) and to the Data Coordinating Center (DCC)/lead principal investigator (PI). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are life threatening or fatal will be reported to the local IRB, the FDA, and the UAB CTO IIT Office within **7 days** of the investigator becoming aware of the event.
- Any other (non-fatal/non-life threatening) serious events that are study related (Ups) will be reported to the local IRB, the FDA, and to the UAB CTO IIT Office within **15 days** of the investigator becoming aware of the problem.
- All UPs will be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within **15 days** of the IRB's receipt of the report of the problem from the investigator.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

This is a Phase II open label, single arm clinical trial. The primary of objective is to determine the complete response rate of siltuximab in the treatment of CRS associated with CAR T-cell therapy. The complete response rate will be assessed at day 14 from the time of siltuximab infusion. The statistical hypothesis is that siltuximab will result in a complete response rate of 70 %.

The secondary endpoints are to assess the overall response rate of siltuximab in the treatment of ICANS, safety profile of siltuximab and explore the influence of siltuximab on overall response rate with CAR T-cell therapy.

9.2 SAMPLE SIZE DETERMINATION

Simon's optimal two-stage design will be used for conducting the trial.

Evaluable patients for the primary endpoint are defined as those patients who experience CRS and receive at least one dose of siltuximab.

The primary endpoint of complete response rate will be used to determine sample size.

The null hypothesis is that the response rate is 40% and assumes that siltuximab has no impact on the resolution of CRS .The alternative hypothesis is that the response rate is 70%. For a response rate of 70%, the exact binomial 95% two-sided confidence interval is (0.457, 0.881).

Simon's optimal two-stage design will be used for conducting the trial.

Evaluable patients for the primary endpoint are defined as those patients who experience CRS and receive at least one dose of siltuximab.

The trial will be carried out in two stages. In stage I, a total number of 7 evaluable patients will be accrued. If there are 3 or fewer responses among these 7 patients, the study will be early stopped. Otherwise, additional 13 evaluable patients will be accrued in stage II, resulting in a total number of evaluable patients of 20.

If there are 12 or more responses among these 20 evaluable patients, we reject the null hypothesis and claim that the treatment is promising. The design controls the type I error rate at 0.05 and yields the power of 0.8. The probability of early termination is 0.710. This sample size calculation was performed using PASS software.

If we reject the null hypothesis we will enroll additional 5 patients to have a total of 25 evaluable patients

Only patients who experience CRS and receive siltuximab will be included in the intent to treat population. The incidence of CRS amongst various CAR T-cell therapies vary between 60 to 90%. Therefore, assuming a CRS event rate of 70%, we plan to enroll 36 patients. However, the trial will stop when 25 patients who are evaluable for primary endpoint are accrued.

9.3 POPULATIONS FOR ANALYSES

Efficacy Analysis Dataset: All patients who received at least one dose of siltuximab will be included in the efficacy analysis dataset. Analysis will be performed for each event.

Safety analysis: *All* patients who received at least one dose of siltuximab will be included in the safety analysis dataset.

9.4 STATISTICAL ANALYSES

9.4.1 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The primary endpoint of complete response rate will be estimated with binomial distribution along with 2-sided 95% exact confidence intervals. The response rate is assumed to have a binomial-distributed distribution and 95% confidence interval will be calculated by approximating the distribution of error.

9.4.2 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Similar to the primary endpoint, the secondary endpoint of overall response rate will be estimated with binomial distribution along with 2-sided 95% exact confidence intervals.

The secondary endpoint of ORR of CAR T-cell will be presented as a percentage and frequency estimated with binomial distribution along with 2-sided 95% exact confidence intervals

9.4.3 SAFETY ANALYSES

Analysis of safety data will be descriptive. Descriptive statistics will be calculated for quantitative safety data and frequency counts will be compiled for classification of qualitative safety data. Adverse event and serious adverse event (AE/SAE) reporting during the study will be summarized by relationship to study drug and intensity by dose cohorts. Number and proportion of adverse event, serious adverse event and grade 3 or 4 lab toxicity will be reported by body system. Patient's baseline lab data and its change during treatment at each visit will be presented. Graphic statistics tool such as box plot will be used when it is appropriate.

The safety analysis plan to evaluate the safety profile of the drug is also described in detail in section *8.4*.

9.4.4 BASELINE DESCRIPTIVE STATISTICS

Baseline demographic, laboratory measurements and disease characteristics will be descriptive and descriptive statistics will be calculated for these variables.

9.4.5 PLANNED INTERIM ANALYSES

The trial will be carried out in two stages. An interim analysis will be carried out after 7 evaluable patients have been enrolled. At this interim analysis, the data safety monitoring committee will assess the response rate and conduct a safety review. If there are 3 or fewer responses among these 7 evaluable patients, the study will be early stopped. Otherwise, additional 13 evaluable patients will be accrued in stage II, resulting in a total number of 20 evaluable patients.

If we reject the null hypothesis we will enroll additional 5 patients to have a total of 25 evaluable patients

9.4.6 SUB-GROUP ANALYSES

Sub-group analysis for the primary endpoint will be conducted based on age, race, sex, stage of disease, type of hematological malignancy, type of CAR T-cell product, performance status, bone marrow involvement, pre-treatment circulating CD19+ B-cell (for lymphoid malignancies) and pre-treatment TMTV (for lymphoid malignancies).

Sub-group analysis for the secondary efficacy endpoint for ICANS and CAR T-cell will be conducted based on age, race, sex, stage of disease, type of hematological malignancy, type of CAR T-cell product, CNS involvement, performance status, bone marrow involvement, pre-treatment circulating CD19+ B-cell (for lymphoid malignancies), pre-treatment HMGB1, and pre-treatment TMTV (for lymphoid malignancies).

9.4.7 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual patient data will be tabulated by type of CAR T-cell product used, presence of CRS and/ or ICANS, time to CRS/ICANS, highest grade of CRS/ICANS, response to siltuximab, time to response to siltuximab, failure to siltuximab, response to CAR T-cell therapy.

9.4.8 EXPLORATORY ANALYSES

1. To assess the prognostic significance of pre-CAR T-cell therapy total metabolic tumor volume(TMTV) on the incidence and severity of CRS and ICANS.

The total metabolic tumor volume (TMTV) will be calculated using a fixed SUVmax threshold of 41% and measured as cubic centimeter.

Total lesion glycolysis (TLG) is a measure of the level of glucose accumulation within all regions of interest on a 18-FDG PET scan. TLG is calculated as TLG = MTV × mean SUV within the lesion. TLG will be reported as a continuous variable.

The strength of association of TMTV and TLG with the patient's incidence and severity of CRS/ICANS and responsiveness to siltuximab will be calculated using multiple linear regression models.
We will report the summary statistics for TMTV and TLG.

2. To assess the effect of siltuximab on Th1, Th2, Th17, MCP-1, Angiopoietin 1/2 CRP, LDH and ferritin before and after administration of siltuximab.

   The biomarkers will be assessed at screening, immediately after CAR T-cell infusion and every 8 hours during CRS/ICANS for a maximum of 8 measurements per patients. The values will be compared using Wilcoxon signed rank test.

   We will report the summary statistics (mean, median, standard deviation and interquartile range) for the changes in the biomarkers. This will be reported for all patients who received siltuximab for whom such measurements of biomarkers were possible. Since the expected values at the time of CRS will be very high compared to the post-infusion measurements, we will split the measurements into three subsets: pre-infusion, post-infusion, and at the time of the event (CRS). If the patient did not have CRS, there will be no measurement at the time of event. If the patient does encounter CRS, we will determine the average of the measurements (up to 8) at the time of the event, and use this value for comparison with the prior subsets.

3. To assess the prognostic significance of circulating CD19+ B-cell on the incidence and severity of CRS and ICANS.

   The pre-treatment circulating CD19+ B-cells will be measured on flow cytometry and reported as cells/microliter.

   The strength of association of CD19+ B-cell with the patient's incidence and severity of CRS/ICANS and responsiveness to siltuximab will be calculated using linear and multiple regression models.
   We will report the summary statistics for circulating CD19+ B-cells.

4. To assess the effect of siltuximab and CAR T-cells on HMGB1

   HMGB1 will be assessed at screening, immediately after CAR T-cell infusion and every 8 hours during CRS/ICANS for a maximum of 8 measurements per patients. The values will be compared using Wilcoxon signed rank test.

We will report the summary statistics (mean, median, standard deviation and interquartile range) for the changes in HMGB1. This will be reported for all patients who received siltuximab for whom such measurements of HMGB1 was possible. Since the expected values at the time of CRS will be very high compared to the post-infusion measurements, we will split the measurements into three subsets: pre-infusion, post-infusion, and at the time of the event (CRS). If the patient did not have CRS, there will be no measurement at the time of event. If the patient does encounter CRS, we will determine the average of the measurements (up to 8) at the time of the event, and use this value for comparison with the prior subsets.

5. To measure the effect of siltuximab on frailty and neurocognitive function trajectories among patients treated with CAR-T therapy.

   Frailty will be measured using the UAB CARE questionnaire and quantified in terms of CARE Frailty Index. Neurocognitive function will be conducted by trained research staff under the supervision of neuropsychologist (Dr. Donnna Murdaugh PhD) at screening (pre-CART) and at 30 and 90 days post CAR-T infusion.

   All participants will complete the interview based Blessed Orientation Memory Concentration Test (BOMC) as well as a formal neuropsychological testing using the NIH toolbox which is a computerized measure designed to assess attention, memory, language and executive function. This test has been well validated to measure cognition in patients with cancer and, on average, takes about 20 minutes to complete. The results will be measured in terms of T scores normalized to the control population. The BOMC takes about 5 minutes to complete. No PHI will be included on the iPAD; only a study ID will be used. Data from these tests will be entered into a RedCap, a secure database maintained by the Department of Medicine.

   Descriptive analysis will be used to measure the proportion of patients with decline in frailty and neurocognitive function and compared to historical controls.

NIH Toolbox[7]	Computerized measure of cognitive functioning (attention, memory, language, executive function)	20 min	Adult

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 Consent/assent and Other Informational Documents Provided to participants

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to administering study intervention. The informed consent forms (ICF) are submitted with this protocol.

10.1.1.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the study participants, investigator, funding agency, the Investigational New Drug (IND) and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).]

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the **University of Alabama at Birmingham**. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by the **university of Alabama at Birmingham** research staff will be

secured and password protected. At the end of the study, all study databases will be de-identified and archived at the University of Alabama at Birmingham.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at the **University of Alabama at Birmingham**. After the study is completed, the de-identified, archived data will be transmitted to and stored at the **University of Alabama at Birmingham Cancer Center**, for use by other researchers including those outside of the study. Permission to transmit data to the **data repository at the University of Alabama at Birmingham** will be included in the informed consent.

With the participant's approval and as approved by local Institutional Review Boards (IRBs), de-identified biological samples will be stored at the **biosample repository at the University of Alabama at Birmingham Cancer Center** with the same goal as the sharing of data with the **data repository at the University of Alabama at Birmingham**. These samples could be used to research the causes of CRS and ICANS , its complications and other conditions for which individuals with hematological malignancies who are receiving CAR T-cell therapy, are at increased risk, and to improve treatment. The **data repository at the University of Alabama at Birmingham** will also be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the blinding of the identity of the participant.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage may not be possible after the study is completed.

When the study is completed, access to study data and/or samples will be provided through the **data repository at the University of Alabama at Birmingham**.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	**UAB CTO IIT Office**
Amitkumar Mehta, MD	
University of Alabama at Birmingham	University of Alabama at Birmingham
1802 6th Avenue South; NP 2556; Birmingham, AL 35294	
205-996-8400	
amitkumarmehta@uabmc.edu	*iit-ctooffice@uabmc.edu*

10.1.6 SAFETY OVERSIGHT

The protocol will adhere to the Data Safety and Monitoring Plan (DSMP) of the O'Neal Comprehensive Cancer Center. Under the DSMP risk-based monitoring approach, the Data Safety and Monitoring Committee (DSMC) will be responsible for direct oversight and monitoring of this trial. Based on the risk assigned by the Protocol Review and Monitoring Committee (PRMC), the DSMC will conduct monitoring of this trial every 6 months or annually. The DSMC will review trial progress, participant safety, data integrity, and adverse event reporting and their findings will be shared with PRMC, UAB Institutional Review Board (IRB), and the Associate Director of Clinical Research of the O'Neal Comprehensive Cancer Center. The findings of the DSMC may prompt PRMC or the IRB to take action on this study.

10.1.7 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

- Monitoring for this study will be performed by UAB CTO.
- The each patient at each participating center will have their eligibility criteria reviewed prior to enrollment by the UAB CTO IIT Office. During the course of the study, each site will be selected for an audit by the UAB Quality Assurance Committee approximately once a year. Audit will include 10% of the subjects enrolled at the site. In addition to the once yearly QA audit, monitoring for each patient entered into this trial will be 100%. Sites are to send source information on each patient to the UAB CTO IIT Office where a shadow chart will be maintained on each subject for this trial. Source will be verified to data entered into the OnCore database. Details of clinical site monitoring are documented in a Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

The data will be initially reviewed for quality assurance purposes to identify any discrepancies or missing data. The staff of the UAB CTO will notify the participating site of any data queries and manage the overall data quality of the study. If data received relates to a serious adverse event or protocol deviation, the information will be processed for report to the UAB CCC DSMB for review. The sponsor- investigator, Amitkumar Mehta, MD and the assigned statistician, will also have access to study data for quality assurance and analysis purposes. During the course of the study, data quality will be monitored by random inspection of the completed forms by a designated monitor. Any problems detected will be discussed with the PI. If necessary, re-training of data collectors will be conducted.

All data should be substantiated by clinical source documents organized within a patient research record. ICH Good Clinical Practices are to be followed. The study will be subject to a yearly internal audit via the

UAB CCC Quality Assurance Committee at a minimum and audits may occur more frequently at the request of the QA Committee.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Data collection will be managed by the UAB CTO staff via the study database which is housed and maintained at UAB Cancer Center. Time sensitive information such as patient registration, serious adverse events reporting, and protocol deviation reporting will be collected via completed hard copy form. These forms are available from the UAB CTO. Information collected will be reviewed and processed by the UAB CTO.

10.1.9.2 Study Records Retention

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harminosation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3

- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 30 working days of identification of the protocol deviation, or within 30 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to the UAB CTO IIT Office. The UAB CTO IIT Office will report the event report to the UAB CCC DSMB so that the information can be reviewed at the next available DSMB meeting. During the DSMB review, the DSMB can make recommendations for any further study action.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers x years after the completion of the primary endpoint by contacting <specify person or awardee institution, or name of data repository>.

In addition, this study will comply with the NIH Genomic Data Sharing Policy, which applies to all NIH-funded research that generates large-scale human or non-human genomic data, as well as the use of these data for subsequent research. Large-scale data include genome-wide association studies (GWAS), single nucleotide polymorphisms (SNP) arrays, and genome sequence, transcriptomic, epigenomic, and gene expression data.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the **University of Alabama at Birmingham** has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ABBREVIATIONS

The list below includes abbreviations utilized in this template. However, this list should be customized for each protocol (i.e., abbreviations not used should be removed and new abbreviations used should be added to this list).

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CRS	Cytokine release syndrome
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee

eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICANS	Immune Effector Cell Associated Neurotoxicity Syndrome
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization

ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure

UAB CTO IIT Office	University of Alabama at Birmingham, Clinical Trials Office, Investigator Initiated Trials Office
UP	Unanticipated Problem
US	United States

10.3 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	**Date**	**Description of Change**	**Brief Rationale**
1	05/19/2021	Added windows for trial procedures and other changes to language and text of protocol.	Clarification of protocol
2	08/09/2022	Changes to language and text of protocol	Clarification of protocol
3	12/04/2023	Increase in sample size	Sample size increased from 20 to 25
4	05/13/2024	Increased window of vital signs to 4 hours from every hour and removed procalcitonin blood collection	Clarification of protocol to align with institutional practices.
5	05/20/2025	Change of Principal Investigator	

11 APPENDIX A : CRS AND ICANS GRADING

11.1 TABLE 1 GRADING FOR CYTOKINE RELEASE SYNDROME (CRS)

CRS parameter	GRADE 1	GRADE 2	GRADE 3	GRADE 4
Fever*	Temperature ≥38°c	Temperature ≥38°c	Temperature ≥38°c	Temperature ≥38°c
		WITH		
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		AND/OR†		
Hypoxia	None	Requiring low-flow nasal cannula‡ or blow-by	Requiring high-flow nasal cannula‡, facemask, nonrebreather mask, or venturi mask	Requiring positive pressure (eg, cpap, bipap, intubation and mechanical ventilation)

Organ toxicities associated with CRS may be graded per CTCAE v5.0 but they do not influence CRS grading

*** Fever is defined as temperature ≥38°C not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.**

† CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

‡ Low-flow nasal cannula is defined as oxygen delivered at ≤6L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6L/minute.

11.2 TABLE 1 GRADING FOR IMMUNE CELL EFFECTOR ASSOCIATED NEUROTOXICITY (ICANS)

NEUROTOXICITY DOMAIN	GRADE 1	GRADE 2	GRADE 3	GRADE 4
ICE score * (See scoring below)	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ice)
Depressed level of consciousness †	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or repetitive clinical or electrical seizures without return to baseline in between
Motor findings‡	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis

Elevated ICP/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging§	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve vi palsy; or papilledema; or cushing's triad

ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause; for example, a patient with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS.

N/A indicates not applicable.

⁕ A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.

† Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).

‡ Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.

§ Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

IMMUNE EFFECTOR CELL-ASSOCIATED ENCEPHALOPATHY SCORE (ICE) SCORE	
Orientation	Orientation to year, month, city, hospital: **4 points**
Naming	Ability to name 3 objects (eg, point to clock, pen, button): **3 points**
Following commands	Ability to follow simple commands (eg, “show me 2 fingers” or “close your eyes and stick out your tongue”): **1 point**

Writing	Ability to write a standard sentence (eg, "our national bird is the bald eagle"): **1 point**
Attention	Ability to count backwards from 100 by 10: **1 point**

12 APPENDIX B: RESPONSE ASSESSMENT FOR LYMPHOMA AND ANN ARBOR STAGING OF LYMPHOMA[8]

Response and Site	PET-CT–Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS†	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi
	It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm
		For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions

(continued on following page)

Response and Site	PET-CT–Based Response	CT-Based Response
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.

*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

†PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

ANN ARBOR STAGING FOR LYMPHOMA

Stage	Involvement	Extranodal (E) Status
Limited		
I	One node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
II bulky*	II as above with "bulky" disease	Not applicable
Advanced		
III	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement	Not applicable
IV	Additional noncontiguous extralymphatic involvement	Not applicable

NOTE. Extent of disease is determined by positron emission tomography–computed tomography for avid lymphomas and computed tomography for nonavid histologies. Tonsils, Waldeyer's ring, and spleen are considered nodal tissue.

*Whether stage II bulky disease is treated as limited or advanced disease may be determined by histology and a number of prognostic factors.

13 APPENDIX C: CTCAE V5 FOR GRADING OF TOXICITIES

REFER TO

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf

14 APPENDIX D: INTERPRETATION OF HEPATITIS B SEROLOGY

Interpretation of Hepatitis B Serologic Test Results

Hepatitis B serologic testing involves measurement of several hepatitis B virus (HBV)-specific antigens and antibodies. Different serologic "markers" or combinations of markers are used to identify different phases of HBV infection and to determine whether a patient has acute or chronic HBV infection, is immune to HBV as a result of prior infection or vaccination, or is susceptible to infection.

HBsAg **anti-HBc** **anti-HBs**	negative negative negative	Susceptible
HBsAg **anti-HBc** **anti-HBs**	negative positive positive	Immune due to natural infection
HBsAg **anti-HBc** **anti-HBs**	negative negative positive	Immune due to hepatitis B vaccination
HBsAg **anti-HBc** **IgM anti-HBc** **anti-HBs**	positive positive positive negative	Acutely infected
HBsAg **anti-HBc** **IgM anti-HBc** **anti-HBs**	positive positive negative negative	Chronically infected
HBsAg **anti-HBc** **anti-HBs**	negative positive negative	Interpretation unclear; four possibilities: 1. Resolved infection (most common) 2. False-positive anti-HBc, thus susceptible 3. "Low level" chronic infection 4. Resolving acute infection

Adapted from: A Comprehensive Immunization Strategy to Eliminate Transmission of Hepatitis B Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices. Part I: Immunization of Infants, Children, and Adolescents. MMWR 2005;54(No. RR-16).

- **Hepatitis B surface antigen (HBsAg):** A protein on the surface of hepatitis B virus; it can be detected in high levels in serum during acute or chronic hepatitis B virus infection. The presence of HBsAg indicates that the person is infectious. The body normally produces antibodies to HBsAg as part of the normal immune response to infection. HBsAg is the antigen used to make hepatitis B vaccine.
- **Hepatitis B surface antibody (anti-HBs):** The presence of anti-HBs is generally interpreted as indicating recovery and immunity from hepatitis B virus infection. Anti-HBs also develops in a person who has been successfully vaccinated against hepatitis B.
- **Total hepatitis B core antibody (anti-HBc):** Appears at the onset of symptoms in acute hepatitis B and persists for life. The presence of anti-HBc indicates previous or ongoing infection with hepatitis B virus in an undefined time frame.
- **IgM antibody to hepatitis B core antigen (IgM anti-HBc):** Positivity indicates recent infection with hepatitis B virus (≤6 mos). Its presence indicates acute infection.

DEPARTMENT OF HEALTH & HUMAN SERVICES
Centers for Disease Control and Prevention
Division of Viral Hepatitis

www.cdc.gov/hepatitis

15 APPENDIX E: ECOG PERFORMANCE STATUS

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

*Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649-655.

16 APPENDIX F : CONTRACEPTION GUIDELINES AND PREGNANCY

Females Not of Childbearing Potential are Defined as Follows:

Females are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or six months of spontaneous amenorrhea with serum FSH levels > 40 mIU/mL and estradiol < 20 pg/mL] or have had surgical bilateral oophorectomy (with or without hysterectomy) at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

Contraceptive Guidelines for Females of Child-Bearing Potential:

Females of child-bearing potential, defined as all females physiologically capable of becoming pregnant, must use effective contraception for at least 1 month prior to screening, during the study and for 4 months after the last dose of either study treatment. Effective contraception is defined as either:

1. True abstinence: When this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

2. Sterilization: have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.

3. Male partner sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). For female patients on the study, the vasectomised male partner should be the sole partner for that patient.

4. Oral contraception, injected or implanted hormonal methods.

5. Use of a combination of any two of the following (a+b):

a. Placement of an intrauterine device (IUD) or intrauterine system (IUS).

b. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.

The following are unacceptable forms of contraception for females of childbearing potential:

· Female condom

· Natural family planning (rhythm method) or breastfeeding

· Fertility awareness

· Withdrawal

· Cervical shield

Females of child-bearing potential must have a negative serum pregnancy test within 1 week prior to initiating treatment.

Fertile Males

Fertile males, defined as all males physiologically capable of conceiving offspring must use condom during treatment and for 4 months after the last dose of either study treatment. They should also not father a child during this period.

Pregnancies

To ensure patient safety, each pregnancy in a patient on study treatment must be reported to the sponsor within 24 hours of learning of its occurrence as outlined in the Safety Reporting section of this protocol. The pregnancy should be followed up for 3 months after the termination of the pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

17 APPENDIX G : RESPONSE CRITERIA FOR MULTIPLE MYELOMA[9]

IMWG MRD criteria (requires a complete response as defined below)	
Sustained MRD-negative	MRD negativity in the marrow (NGF or NGS, or both) and by imaging as defined below, confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (eg, MRD-negative at 5 years)[†]
Flow MRD-negative	Absence of phenotypically aberrant clonal plasma cells by NGF[‡] on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher
Sequencing MRD-negative	Absence of clonal plasma cells by NGS on bone marrow aspirate in which presence of a clone is defined as less than two identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using the LymphoSIGHT platform (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells[§] or higher

Imaging plus MRD-negative	MRD negativity as defined by NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT or decrease to less mediastinal blood pool SUV or decrease to less than that of surrounding normal tissue[¶]
Standard IMWG response criteria[‖]	
Stringent complete response	Complete response as defined below plus normal FLC ratio[**] and absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 plasma cells)[††]
Complete response	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow aspirates
Very good partial response	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum M-protein plus urine M-protein level <100 mg per 24 h
Partial response	≥50% reduction of serum M-protein plus reduction in 24 h urinary M-protein by ≥90% or to <200 mg per 24 h;
	If the serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria;
	If serum and urine M-protein are unmeasurable, and serum-free light assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma-cell percentage was ≥30%. In addition to these criteria, if present at baseline, a ≥50% reduction in the size (SPD)[§§] of soft tissue plasmacytomas is also required
Minimal response	≥25% but ≤49% reduction of serum M-protein and reduction in 24-h urine M-protein by 50–89%. In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size (SPD)[§§] of soft tissue plasmacytomas is also required
Stable disease	Not recommended for use as an indicator of response; stability of disease is best described by providing the time-to-progression estimates. Not meeting criteria for complete response, very good partial response, partial response, minimal response, or progressive disease
Progressive disease [¶¶],[‖‖]	Any one or more of the following criteria:
	Increase of 25% from lowest confirmed response value in one or more of the following criteria:
	Serum M-protein (absolute increase must be ≥0·5 g/dL);
	Serum M-protein increase ≥1 g/dL, if the lowest M component was ≥5 g/dL;
	Urine M-protein (absolute increase must be ≥200 mg/24 h);

	In patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL); In patients without measurable serum and urine M-protein levels and without measurable involved FLC levels, bone marrow plasma-cell percentage irrespective of baseline status (absolute increase must be ≥10%);
	Appearance of a new lesion(s), ≥50% increase from nadir in SPD[§§] of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis;
	≥50% increase in circulating plasma cells (minimum of 200 cells per µL) if this is the only measure of disease
Clinical relapse	Clinical relapse requires one or more of the following criteria:
	Direct indicators of increasing disease and/or end organ dysfunction (CRAB features) related to the underlying clonal plasma-cell proliferative disorder. It is not used in calculation of time to progression or progression-free survival but is listed as something that can be reported optionally or for use in clinical practice;
	Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression);
	Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and ≥1 cm) increase as measured serially by the SPD[§§] of the measurable lesion;
	Hypercalcaemia (>11 mg/dL);
	Decrease in haemoglobin of ≥2 g/dL not related to therapy or other non-myeloma-related conditions;
	Rise in serum creatinine by 2 mg/dL or more from the start of the therapy and attributable to myeloma;
	Hyperviscosity related to serum paraprotein
Relapse from complete response (to be used only if the end point is disease-free survival)	Any one or more of the following criteria:
	Reappearance of serum or urine M-protein by immunofixation or electrophoresis;
	Development of ≥5% plasma cells in the bone marrow;
	Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcaemia see above)
Relapse from MRD negative (to be used	Any one or more of the following criteria:

only if the end point is disease-free survival)	
	Loss of MRD negative state (evidence of clonal plasma cells on NGF or NGS, or positive imaging study for recurrence of myeloma);
	Reappearance of serum or urine M-protein by immunofixation or electrophoresis;
	Development of ≥5% clonal plasma cells in the bone marrow;
	Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcaemia)

For MRD assessment, the first bone marrow aspirate should be sent to MRD (not for morphology) and this sample should be taken in one draw with a volume of minimally 2 mL (to obtain sufficient cells), but maximally 4–5 mL to avoid haemodilution. IMWG=International Myeloma Working Group. MRD=minimal residual disease. NGF=next-generation flow. NGS=next-generation sequencing. FLC=free light chain. M-protein=myeloma protein. SPD=sum of the products of the maximal perpendicular diameters of measured lesions. CRAB features=calcium elevation, renal failure, anaemia, lytic bone lesions. FCM=flow cytometry. SUVmax=maximum standardised uptake value. MFC=multiparameter flow cytometry. 18F-FDG PET=18F-fluorodeoxyglucose PET. ASCT=autologous stem cell transplantation.

* All response categories require two consecutive assessments made any time before starting any new therapy; for MRD there is no need for two consecutive assessments, but information on MRD after each treatment stage is recommended (eg, after induction, high-dose therapy/ASCT, consolidation, maintenance). MRD tests should be initiated only at the time of suspected complete response. All categories of response and MRD require no known evidence of progressive or new bone lesions if radiographic studies were performed. However, radiographic studies are not required to satisfy these response requirements except for the requirement of FDG PET if imaging MRD-negative status is reported.

† Sustained MRD negativity when reported should also annotate the method used (eg, sustained flow MRD-negative, sustained sequencing MRD-negative).

‡ Bone marrow MFC should follow NGF guidelines.30 The reference NGF method is an eight-colour two-tube approach, which has been extensively validated. The two-tube approach improves reliability, consistency, and sensitivity because of the acquisition of a greater number of cells. The eight-colour technology is widely available globally and the NGF method has already been adopted in many flow laboratories worldwide. The complete eight-colour method is most efficient using a lyophilised mixture of antibodies which reduces errors, time, and costs. 5 million cells should be assessed. The FCM method employed should have a sensitivity of detection of at least 1 in 105 plasma cells.

§ DNA sequencing assay on bone marrow aspirate should use a validated assay such as LymphoSIGHT (Sequenta).

¶ Criteria used by Zamagni and colleagues,85 and expert panel (IMPetUs; Italian Myeloma criteria for PET Use).81, 97 Baseline positive lesions were identified by presence of focal areas of increased uptake within bones, with or without any underlying lesion identified by CT and present on at least two consecutive slices. Alternatively, an SUVmax=2·5 within osteolytic CT areas >1 cm in size, or SUVmax=1·5 within osteolytic CT areas ≤1 cm in size were considered positive. Imaging should be performed once MRD negativity is determined by MFC or NGS.

‖ Derived from international uniform response criteria for multiple myeloma.11 Minor response definition and clarifications derived from Rajkumar and colleagues.14 When the only method to measure disease is by serum FLC levels: complete response can be defined as a normal FLC ratio of 0·26 to 1·65 in addition to the complete response criteria listed previously. Very good partial response in such patients requires a ≥90% decrease in the difference between involved and uninvolved FLC levels. All response categories require two consecutive assessments made at any time before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions or extramedullary plasmacytomas if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments do not need to be confirmed. Each category, except for stable disease, will be considered unconfirmed until the

confirmatory test is performed. The date of the initial test is considered as the date of response for evaluation of time dependent outcomes such as duration of response.

** All recommendations regarding clinical uses relating to serum FLC levels or FLC ratio are based on results obtained with the validated Freelite test (Binding Site, Birmingham, UK).

†† Presence/absence of clonal cells on immunohistochemistry is based upon the κ/λ/L ratio. An abnormal κ/λ ratio by immunohistochemistry requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is κ/λ of >4:1 or <1:2.

‡‡ Special attention should be given to the emergence of a different monoclonal protein following treatment, especially in the setting of patients having achieved a conventional complete response, often related to oligoclonal reconstitution of the immune system. These bands typically disappear over time and in some studies have been associated with a better outcome. Also, appearance of monoclonal IgG κ in patients receiving monoclonal antibodies should be differentiated from the therapeutic antibody.

§§ Plasmacytoma measurements should be taken from the CT portion of the PET/CT, or MRI scans, or dedicated CT scans where applicable. For patients with only skin involvement, skin lesions should be measured with a ruler. Measurement of tumour size will be determined by the SPD.

¶¶ Positive immunofixation alone in a patient previously classified as achieving a complete response will not be considered progression. For purposes of calculating time to progression and progression-free survival, patients who have achieved a complete response and are MRD-negative should be evaluated using criteria listed for progressive disease. Criteria for relapse from a complete response or relapse from MRD should be used only when calculating disease-free survival.

|||| In the case where a value is felt to be a spurious result per physician discretion (eg, a possible laboratory error), that value will not be considered when determining the lowest value.

18 APPENDIX H : RESPONSE CRITERIA FOR ACUTE LYMPHOBLASTIC LEUKEMIA

Term	Definition
CNS-1	No lymphoblasts in the CSF regardless of WBC count.
CNS-2	WBC count <5 leukocytes/µl in the CSF with the presence of blasts.
CNS-3[a]	WBC count of ≥5 leukocytes/µl with the presence of blasts.
CNS disease remission	No lymphoblasts in CSF regardless of WBC count in a patient with CNS-2 or CNS-3 at diagnosis.
CNS relapse	Development of CNS-3 status or development of clinical signs of CNS leukemia (eg, facial nerve palsy, brain/eye involvement, hypothalamic syndrome).
CR	Complete remission; meeting all the following for at least 4 weeks (ie, no recurrence): - No circulating blasts and <5% blasts in the BM. - Normal maturation of all cellular components in the BM. - No extramedullary disease (CNS involvement, lymphadenopathy, splenomegaly, skin/gum infiltration, testicular mass). - Adequate bone marrow cellularity (≥ 20 %) with trilineage hematopoiesis - ANC >1000/µl (or >1.0 × 10^9/L). - Platelets >100,000/µl (or >100 × 10^9/L).
CRi	Either of the following two: -Meets all criteria for CR except platelet count and/or ANC. -Meets all criteria for CR but bone marrow cellularity <20%
CRh	Same as CR except unsupported platelets > 50,000/µL, hemoglobin > 7 g/dL, and absolute neutrophil count > 500/µL.
PR	A PR requires all of the CR criteria except that marrow may still contain 5-25% leukemia blast cells. An absolute neutrophil count (segs and bands) > 1000/µL, no circulating blasts, and platelets > 100,000/µL are required as for a CR.
MRD negativity (for patients with CR/CRh/CRi)	For Philadelphia chromosome positive B-cell ALL: ≤0.01% BCR-ABL1/ABL1, or undetectable BCR-ABL1 transcripts in cDNA with ≥10,000 ABL1 transcripts. Also referred to as MR4. For Philadelphia chromosome negative B-cell ALL: Bone marrow lymphoblast percent < 0.01% (<10^{-4})
PD	Increase of at least 25% in the absolute number of

	circulating or BM blasts or development of extramedullary disease.
Refractory disease	Failure to achieve a CR or PR with persistence of leukemia cells
Relapse	The reappearance of unequivocal leukemia blast cells in the blood or the bone marrow (>5%) or in any other extramedullary site after a CR; or progression to >25% leukemia blast cells in the marrow after a PR. In the case of isolated CNS relapse (positive cytospin examination of CSF), please consult with the Study Chair.

Abbreviations: ANC, absolute neutrophil count; BCR-ABL, breakpoint cluster region-Abelson; BM, bone marrow; CNS, central nervous system; CSF, cerebrospinal fluid; CR, complete remission; CRi, incomplete blood count recovery; CSF, cerebrospinal fluid; MR4, molecular response 4-log reduction (BCR-ABL1/ABL1 ≤0.01%); MRD, minimal residual disease; PD, progressive disease; Ph+ ALL, Philadelphia chromosome–positive acute lymphoblastic leukemia; WBC, white blood cell.

[a]If the patient has leukemic cells in the peripheral blood and the lumbar puncture is traumatic and WBC ≥5/µL in CSF with blasts, then compare the CSF WBC/RBC ratio to the blood WBC/RBC ratio. If the CSF ratio is at least 2-fold greater than the blood ratio, then the classification is CNS-3; if not, then it is CNS-2.

19 APPENDIX I FDA APPROVED INDICATIONS FOR CAR T-CELL THERAPY

Yescarta (Axicabtagene Ciloleucel)

1. Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including
    - Diffuse Large B- cell lymphoma
    - Diffuse large B-cell lymphoma (DLBCL) not otherwise specified
    - Primary mediastinal large B-cell lymphoma
    - High grade B-cell lymphoma
    - DLBCL arising from follicular lymphoma
2. Adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy

Breyanzi (Lisocabtagene Maraleucel)

1. Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including
    - Diffuse Large B- cell lymphoma
    - Diffuse large B-cell lymphoma (DLBCL) not otherwise specified
    - Primary mediastinal large B-cell lymphoma
    - Follicular lymphoma Grade 3B
    - DLBCL arising from indolent lymphoma

Kymriah (Tisagenlecleucel)

1. Patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse.

2. Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including
    - Diffuse Large B- cell lymphoma
    - Diffuse large B-cell lymphoma (DLBCL) not otherwise specified
    - High grade B-cell lymphoma
    - DLBCL arising from follicular lymphoma

Tecartus (Brexucabtagene autoleucel)

Treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL).

Treatment of adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).

Abecma (Idecabtagene vicleucel)

Treatment of adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody

20 APPENDIX J : RECOMMENDED ANAPHYLAXIS GUIDELINES

Recommended Anaphylaxis Management

The following equipment is needed in the event of a suspected anaphylactic reaction during study drug administration:

- Appropriate monitors (electrocardiogram, blood pressure, pulse oximetry)
- Oxygen and masks for oxygen delivery
- Airway management devices per SOC
- Epinephrine for intravenous, intramuscular, and/or endotracheal administration in accordance with institutional guidelines
- Salbutamol (or albuterol or equivalent)
- Antihistamines (H1 and H2 blockers)
- Corticosteroids
- IV infusion solutions, tubing, catheters, and tape

The following are the procedures to follow in the event of a suspected anaphylactic reaction during study drug administration:

- Stop the study drug administration.
- Call for additional assistance.
- Maintain an adequate airway.
- Provide oxygen.
- Ensure that appropriate monitoring is in place, with continuous electrocardiogram and pulse oximetry monitoring, if possible.
- Administer epinephrine first, followed by antihistamines, albuterol, or other medications as required by patient status and directed by the physician in charge.
- Continue to observe the patient and document observations.

21 APPENDIX K : INSTITUTIONAL GUIDELINES FOR ICANS MANAGEMENT

ICANS Grade	Sign or symptom	Management
Grade 1	Encephalopathy and/or depressed level of consciousness	Dexamethasone 10 mg IV for 1 dose (or methylprednisolone equivalent) and reassess in 6 hours or earlier if clinically indicated
Grade 2	Encephalopathy and/or depressed level of consciousness	Dexamethasone 10 mg IV every 12 hours (or methylprednisolone equivalent) - If associated with concurrent CRS, add anti IL-6 therapy Once ICANS improves to Grade 1 or less, taper and/or stop corticosteroids depending on clinical situation.
Grade 3	Encephalopathy and/or depressed level of consciousness	Dexamethasone 10 mg IV every 6 hours (or methylprednisolone equivalent) - If associated with concurrent CRS, add anti IL-6 therapy If Grade 3 encephalopathy is persistent for > 24 hours, increase dexamethasone to 20 mg IV every 6 hours (or methylprednisolone equivalent) Once ICANS improves to Grade 1 or less, taper and/or stop corticosteroids depending on clinical situation
	Seizure	Dexamethasone 10 mg IV every 6 hours (or methylprednisolone equivalent) - If associated with concurrent CRS, add anti IL-6 therapy
	Focal cerebral edema	If focal edema is in brain stem or thalamus, methylprednisolone 1,000 mg/day in divided doses IV for 3 days followed by taper depending on clinical situation - If associated with concurrent CRS, add anti IL-6 therapy If focal edema is in other areas of brain, methylprednisolone 1,000 mg/day in divided doses IV for 1 day; assess daily and continue or taper depending on clinical situation - If associated with concurrent CRS, add anti IL-6 therapy

Grade 4		Methylprednisolone 1,000 mg/day in divided doses IV for 3 days followed by taper as clinically indicated; - if associated with concurrent CRS, add anti IL-6 therapy Continue corticosteroids until improvement to less than or equal to Grade 1 ICANS and then taper and stop corticosteroids depending on clinical situation If Grade 4 ICANS is refractory for > 24 hours or if patient is deteriorating rapidly, consider additional therapies (see below)

Drug	**Dose**
Anakinra	100mg subcutaneously daily for 7 days
Cyclophosphamide	1,500 mg/m2 IV for one dose with mesna 1500 mg/m2 IV over 24 hours
Anti-thymocyte globulin (rabbit)	1-2mg/kg IV daily for 3 days. Infuse over 6 hours.

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