The Ohio State University Combined Consent to Participate in Research and HIPAA Research Authorization

Study Title: **Phase I study of cytokine release syndrome prophylaxis and treatment with Siltuximab**

Principal Investigator: Timothy Voorhees, MD, MSCR

Sponsor: The Ohio State University James Comprehensive Cancer Center
Funding Source: EUSA Pharma

- **This is a consent form for research participation.** It contains important information about this study and what to expect if you decide to participate. Please consider the information carefully. Feel free to discuss the study with your friends and family and to ask questions before making your decision whether or not to participate.
- **Your participation is voluntary.** You may refuse to participate in this study. If you decide to take part in the study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your usual benefits. Your decision will not affect your future relationship with The Ohio State University. If you are a student or employee at Ohio State, your decision will not affect your grades or employment status.
- **You may or may not benefit as a result of participating in this study.** Also, as explained below, your participation may result in unintended or harmful effects for you that may be minor or may be serious depending on the nature of the research.
- **You will be provided with any new information that develops during the study that may affect your decision whether or not to continue to participate.** If you decide to participate, you will be asked to sign this form and will receive a copy of the form. You are being asked to consider participating in this study for the reasons explained below.

Key Information About This Study

The following is a short summary to help you decide whether or not to be a part of this study. More detailed information is listed later in this form.

If you are a patient with CD19 positive non-Hodgkin lymphoma and you and your doctor plan to treat your disease with CD19 directed chimeric antigen receptor T-cell therapy (CD19.CAR-T), you may be eligible for this study. This study will try to determine if the drug siltuximab is safe to help prevent and treat certain side effects of CD19.CAR-T cell therapy.

Several of the major complications of CD19.CAR-T include cytokine release syndrome (CRS, a complication of a highly active immune system seen with some cancer treatments including CD19.CAR-T cell therapy) and immune effector cell therapy associated neurotoxicity (ICANS, neurologic complications related to an activated immune system seen with immunotherapy and CD19.CAR-T cell therapy).

The goal of this study is to determine if it is safe to administer siltuximab prophylaxis (an action taken to prevent future disease or medical complication) prior to CD19.CAR-T cell therapy and if it is safe to administer siltuximab treatment (an action to treat disease or medical complication) for CRS and/or ICANS if either of these complications develop after CD19.CAR-T cell therapy.

Treatment Plan:

If you enroll on this study, you will be treated with a 1-hour infusion of siltuximab given by infusion into your vein prior to CD19.CAR-T cell infusion (prophylaxis).

You will be monitored for CRS and/or ICANS complications of CD19.CAR-T (see Section 3). This monitoring will be the same as we recommend for all patients being treated with CD19.CAR-T cell therapy.

If you develop CRS and/or ICANS after CD19.CAR-T cell therapy, depending on the severity of your symptoms, you may be eligible for an infusion of siltuximab (treatment). If the CRS and/or ICANS remains the same, you may be eligible for a second infusion of siltuximab (treatment). Any worsening of CRS and/or ICANS will be considered siltuximab failure and you will receive standard of care tocilizumab and/or corticosteroids.

You will be asked to have a positron emission tomography (PET) scan or computed tomography (CT) scan within 28 days of the start of the study. This is typically standard of care prior to being treated with CD19.CAR-T cell therapy. You will be asked to have a PET or CT scan at Day 30 after CD19.CAR-T cell therapy. This is typically standard of care after CD19.CAR-T cell therapy. Any long term follow up imaging studies will be up to you and your doctor.

You will be asked to provide research blood samples at specified time-points which will allow the study team to better understand the changes occurring with your immune system during the study.

The most frequent side effects during treatment with siltuximab include upper respiratory tract infection, itchy skin, rash, joint stiffness, and diarrhea. The most serious side effect associated with the use of siltuximab is acute allergic reaction.

If you agree to take part in this study, there may or may not be a direct benefit to you. One possible benefit is prevention of developing CRS and/or ICANS. Additionally, if you do develop CRS and/or ICANS, symptoms may be less severe.

1. **Why is this study being done?**
   Cytokine release syndrome (CRS) and Immune effector cell therapy associated neurotoxicity (ICANS) can occur in the days to weeks following administration of certain types of immunotherapies including CD19.CAR-T cell therapy.

   Strategies are being studied to prevent these toxicities and increase the safety related to CD19.CAR-T cell therapy.

   Siltuximab is a chimeric (having parts of different origins) murine (from mice) antibody that binds directly to IL-6 (a cytokine/ body chemical causing toxicities described above) and allows for its clearance. IL-6 is known to increase in a patient's blood after CD19.CAR-T cell infusion and has been associated with development of CRS and ICANS.

   The study team believes that direct binding of IL-6 circulating in the blood will result in less CRS and/or ICANS after CD19.CAR-T. Based on this rationale, we propose a phase I study investigating the use of siltuximab for CRS and ICANS prophylaxis prior to CD19.CAR-T cell therapy and for treatment of CRS and/or ICANS if this does occur.

   Siltuximab is not approved for the clinical indications used in this study and, therefore, use of this drug is considered investigational.

2. **How many people will take part in this study?**
   12 people

3. **What will happen if I take part in this study?**
   If you are a patient with CD19 positive non-Hodgkin lymphoma who planned to undergo standard of care CD19.CAR-T cell therapy, you will be treated with siltuximab given by infusion into your vein over 1 hour prior to CD19.CAR-T infusion.

   You will be monitored for CRS and/or ICANS complications of CD19.CAR-T. Monitoring will be the same with respect to timing and frequency whether or not you

enroll on this trial**.** Depending on which CD19.CAR-T cell therapy you receive, monitoring will be either in the hospital daily for at least 7 days, or outside the hospital daily for at least 7 days. If no toxicity is observed in the first 7 days, you will be monitored outside the hospital at least once per week for up to 28 days.

If you develop CRS and/or ICANS after CD19.CAR-T cell therapy, depending on the severity of your symptoms, you may be eligible for a dose of siltuximab (treatment). If the CRS and/or ICANS remains the same, you may be eligible for a second (treatment) infusion of siltuximab. Any worsening of CRS and/or ICANS will be considered siltuximab failure and you will receive standard of care tocilizumab and/or corticosteroids.

This research study involves exposure to radiation from a CT chest - helical, CT abdomen/pelvis - axial, CT skull – axial. This radiation exposure is not necessary for your medical care and is for research purposes only. The total amount of radiation that you will receive in this study is about 65 mSv or 6500 mrem (this is equal to the amount of radiation exposure in about six X-rays). The Ohio State University Human Subjects Radiation Committee has reviewed the use of radiation in this research study and has approved this use as involving acceptable risk and necessary to obtain the research information desired. Please tell your doctor if you have taken part in other research studies or received any other medical care recently involving radiation. If you are pregnant or breast feeding, you SHOULD NOT participate in this research study.

Research Blood Studies:

The study team will collect a maximum of 50 milliliters (approximately 10 teaspoons) of blood from your veins to investigate and characterize changes which occur in the blood components through treatment.

Samples will be collected prior to receiving lymphodepleting chemotherapy (standard chemotherapy prior to CD19.CAR-T), at day 0 (prior to siltuximab and CD19.CAR-T infusion), and days 1, 2, 3, 4, 5, 6, 7, 14, 21, and 30 after siltuximab and CD19.CAR-T infusion. If you develop CRS or ICANS, additional samples will be collected at 12 hours, 24 hours, 48 hours, and at resolution of CRS and/or ICANS.

The study team will request and process any available diagnostic tissue (biopsy) that you may have had prior to CD19.CAR-T cell therapy to evaluate the immune cells present prior to CD19.CAR-T cells. If you did not have a biopsy or if diagnostic tissue is not available, you will not be required to have an additional biopsy.

The study team will request and process any residual blood samples which may have been collected and stored as part the blood cell collection process to make the CAR-T cells (apheresis). They will characterize and investigate the cytokines (body chemical) and immune cells in this blood sample.

4. How long will I be in the study?

You will be in the study for about a year.

5. Can I stop being in the study?

You may leave the study at any time. If you decide to stop participating in the study, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled. Your decision will not affect your future relationship with The Ohio State University.

6. What risks, side effects or discomforts can I expect from being in the study?

The most frequent discomfort during treatment with siltuximab include upper respiratory tract infection, itchy skin, joint stiffness and diarrhea. The most serious side effect with the use of siltuximab is serious allergic reaction.

There is also a potential risk of reduced efficacy of CAR-T cells by administering prophylactic siltuximab.

There is an alternative FDA approved drug (tocilizumab) for treatment of severe CRS, or steroids for ICANS. In this study, you will receive siltuximab (investigational drug) for treatment of CRS/ICANS. Standard treatment with tocilizumab may be delayed, which could cause the toxicity you experience.

More common

- Black, tarry stools
- bleeding gums
- bloating or swelling of the face, arms, hands, lower legs, or feet
- bloody urine
- blurred vision
- body aches or pain
- chills
- confusion
- cough
- decreased frequency or amount of urine
- difficulty with breathing
- dizziness, faintness, or lightheadedness when getting up suddenly from a lying or sitting position

- ear congestion
- fever
- full or bloated feeling
- headache
- increased thirst
- loss of appetite
- loss of voice
- lower back or side pain
- nasal congestion
- nausea
- pinpoint red spots on the skin
- pressure in the stomach
- rapid weight gain
- runny nose
- sneezing
- sore throat
- stomach pain
- sweating
- swelling of the abdominal or stomach area
- tingling of the hands or feet
- unusual bleeding or bruising
- unusual tiredness or weakness
- unusual weight gain or loss
- vomiting

Less common

- Back pain
- chest pain or discomfort
- dizziness
- dry mouth
- fainting
- fast, irregular, pounding, or racing heartbeat or pulse
- feeling of warmth
- flushing or redness of the skin

- lightheadedness
- rapid breathing
- redness of the face, neck, arms, and occasionally, upper chest
- sunken eyes
- unusually warm skin
- wrinkled skin

Rare

- Difficulty with swallowing
- hives, itching, or skin rash
- puffiness or swelling of the eyelids or around the eyes, face, lips, or tongue
- tightness in the chest

Pregnancy

It is not known whether siltuximab can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. If you are a female of childbearing potential, you must be willing to abstain from heterosexual activity or use 2 forms of effective methods of contraception from the time of informed consent until 12 months after treatment the last dose of siltuximab. The two contraception methods can be comprised of two barrier methods, or a barrier method plus a hormonal method or an intrauterine device that meets < 1% failure rate for protection from pregnancy in the product label.

7. What benefits can I expect from being in the study?

Possible benefits to you:

If you agree to take part in this study, there may or may not be a direct benefit to you. One possible benefit is either prevention of CRS and/or ICANS or a less severe CRS and/or ICANS after CD19.CAR-T cell therapy. However, you may not receive any benefit from taking part and it may make your health worse.

Possible benefits to others or society:

This study will help the researchers learn more about the safety of siltuximab when given prior to CD19.CAR-T cells for prevention of CRS and/or ICANS toxicity.

8. What other choices do I have if I do not take part in the study?

You may choose not to participate without penalty. Your relationship with The Ohio State University and with your physician will not be affected by your participation on this study.

In some scenarios, you may be eligible for corticosteroids for prevention of CRS and/or ICANS prior to CD19.CAR-T cell therapy.

There is an alternative FDA approved drug (tocilizumab) for treatment of severe CRS, or steroids for ICANS.

9. What are the costs of taking part in this study?

The study drug, Siltuximab, will be provided to you and will not be billed to you or your insurance company. You and/or your insurance company will not be billed for the cost of any tests or procedures that are required as part of this research study and are outside the standard of care for your condition.

You and/or your insurance company will still be responsible for the cost of routine medications, tests and procedures that you would receive even if you were not in this research study. You and/or your insurance company will be billed for the costs of these routine tests and procedures in the usual manner. You will be responsible for any co-payments, co-insurance and deductibles that are standard for your insurance coverage. You will be responsible for any charges not reimbursed by your insurance company.

Some insurance companies will not pay for routine costs for people taking part in research studies. Before deciding to be in this research study, you should check with your insurance company to find out what they will pay for. Participating in this research study may lead to additional costs to you. In some cases, it is possible that your insurance company will not pay for these costs because you are taking part in a research study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

10. Will I be paid for taking part in this study?

You will not be paid for taking part in this study.

11. What happens if I am injured because I took part in this study?

If you suffer an injury from participating in this study, you should notify the researcher or study doctor immediately, who will determine if you should obtain medical treatment at The Ohio State University Wexner Medical Center.

The cost for this treatment will be billed to you or your medical or hospital insurance. The Ohio State University has no funds set aside for the payment of health care expenses for this study.

12. What are my rights if I take part in this study?

If you choose to participate in the study, you may discontinue participation at any time without penalty or loss of benefits. By signing this form, you do not give up any personal legal rights you may have as a participant in this study.

You will be provided with any new information that develops during the course of the research that may affect your decision whether or not to continue participation in the study.

You may refuse to participate in this study without penalty or loss of benefits to which you are otherwise entitled.

An Institutional Review Board responsible for human subject's research at The Ohio State University reviewed this research project and found it to be acceptable, according to applicable state and federal regulations and University policies designed to protect the rights and welfare of research participants.

13. Will my de-identified information and bio-specimens be used or shared for future research?

No

14. Will my study-related information be kept confidential?

Efforts will be made to keep your study-related information confidential. However, there may be circumstances where this information must be released. For example, personal information regarding your participation in this study may be disclosed if required by state law.

Also, your records may be reviewed by the following groups (as applicable to the research):

- Office for Human Research Protections or other federal, state, or international regulatory agencies;
- U.S. Food and Drug Administration;
- The Ohio State University Institutional Review Board or Office of Responsible Research Practices;
- The sponsor supporting the study, their agents or study monitors; and
- Your insurance company (if charges are billed to insurance).

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search the website at any time.

15. HIPAA AUTHORIZATION TO USE AND DISCLOSE INFORMATION FOR RESEARCH PURPOSES

I. What information may be used and given to others?

- Past and present medical records;
- Research records;
- Records about phone calls made as part of this research;
- Records about your study visits;
- Information that includes personal identifiers, such as your name, or a number associated with you as an individual;
- Information gathered for this research about:
  HIV / AIDS
  Hepatitis infection
  Physical exams
  Pregnancy test
  Laboratory, x-ray, and other test results
  Diaries and questionnaires
- Records about any study drug you received;
- Records about the study device; and

II. Who may use and give out information about you?

Researchers and study staff.

III. Who might get this information?

- The sponsor of this research. "Sponsor" means any persons or companies that are:
  - working for or with the sponsor; or
  - owned by the sponsor.
- Authorized Ohio State University staff not involved in the study may be aware that you are participating in a research study and have access to your information;
- If this study is related to your medical care, your study-related information may be placed in your permanent hospital, clinic, or physician's office record;
- Others: EUSA PHARMA

IV. Your information <u>may</u> be given to:

- The U.S. Food and Drug Administration (FDA), Department of Health and Human Services (DHHS) agencies, and other federal and state entities;
- Governmental agencies in other countries;
- Governmental agencies to whom certain diseases (reportable diseases) must be reported; and

- The Ohio State University units involved in managing and approving the research study including the Office of Research and the Office of Responsible Research Practices.

V. Why will this information be used and/or given to others?

- To do the research;
- To study the results; and
- To make sure that the research was done right.

VI. When will my permission end?

There is no date at which your permission ends. Your information will be used indefinitely. This is because the information used and created during the study may be analyzed for many years, and it is not possible to know when this will be complete.

VII. May I withdraw or revoke (cancel) my permission?

Yes. Your authorization will be good for the time period indicated above unless you change your mind and revoke it in writing. You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the researchers. If you withdraw your permission, you will not be able to stay in this study. When you withdraw your permission, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others.

VIII. What if I decide not to give permission to use and give out my health information?

Then you will not be able to be in this research study and receive research-related treatment. However, if you are being treated as a patient here, you will still be able to receive care.

IX. Is my health information protected after it has been given to others?

There is a risk that your information will be given to others without your permission. Any information that is shared may no longer be protected by federal privacy rules.

X. May I review or copy my information?

Signing this authorization also means that you may not be able to see or copy your study-related information until the study is completed.

16. Who can answer my questions about the study?

For study questions, concerns, or complaints, to withdraw consent and HIPAA authorization, or if you feel you have been harmed as a result of study participation, you may contact:

Timothy Voorhees, MD, MSCR
OSU James Comprehensive Cancer Center
1800 Cannon Drive
Columbus, OH 43210
614-293-6943 (office hours)
614-293-8000 (24 hours)

For questions related to your privacy rights under HIPAA or related to this research authorization, please contact:
Medical Center Office of Compliance & IntegrityPhone: 614-293-4477
Email: compliance@osumc.edu
Address: 1590 N. High Street, Suite 500, Columbus, OH 43201

For questions about your rights as a participant in this study or to discuss other study-related concerns or complaints with someone who is not part of the research team, you may contact **Office of Responsible Research Practices at 1-800-678-6251.**

If you are injured as a result of participating in this study or for questions about a study-related injury, you may contact:

Timothy Voorhees, MD, MSCR
OSU James Comprehensive Cancer Center
1800 Cannon Drive
Columbus, OH 43210
614-293-6943 (office hours)
614-293-8000 (24 hour**s)**

Signing the consent form

I have read (or someone has read to me) this form and I am aware that I am being asked to participate in a research study. I have had the opportunity to ask questions and have had them answered to my satisfaction. I voluntarily agree to participate in this study.

I am not giving up any legal rights by signing this form. I will be given a copy of this combined consent and HIPAA research authorization form**.**

Printed name of participant	**Signature of participant**
	AM/PM
	Date and time
Printed name of person authorized to consent for participant (when applicable)	**Signature of person authorized to consent for participant (when applicable)**
	AM/PM
Relationship to the participant	**Date and time**

Investigator/Research Staff

I have explained the research to the participant or his/her representative before requesting the signature(s) above. There are no blanks in this document. A copy of this form has been given to the participant or his/her representative.

Printed name of person obtaining consent	**Signature of person obtaining consent**
	AM/PM
	Date and time

Witness(es) - *May be left blank if not required by the IRB*

Printed name of witness	**Signature of witness**
	AM/PM

Date and time

Printed name of witness

Signature of witness

AM/PM

Date and time