BMT378 RECIPIENT
STANFORD CONSENT FORM with HIPAA

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Are you participating in any other research studies? _____ Yes _____No

PURPOSE OF RESEARCH

You are invited to participate in a research study of B-cell Acute Lymphoblastic Leukemia (ALL). According to the Leukemia and Lymphoma Society, leukemia cells can be classified by the unique set of proteins found on their surface. These unique sets of proteins are known as "immunophenotypes."

Based on immunophenotyping of the leukemia cell, the World Health Organization (WHO) classifies ALL into two main subtypes. Your diagnosis of ALL is the B-cell subtype which is the most common ALL subtype.

If you are determined to be eligible for enrollment, you will receive a myeloablative (high-intensity) conditioning regimen which uses high doses of chemotherapy and may use radiation therapy to destroy your cancer cells. In the process, bone marrow/stem cells are also destroyed.

From an human leukocyte antigen (HLA) (a type of molecule found on the surface of most cells in the body that play an important part in the body's immune response to foreign substances) matched related donor, you will receive infusions of new stem cells to rebuild your blood and immune system.

The infusions from the HLA matched related donor will be the Orca-T graft and donor conventional CD19/CD22-CAR T cells.

The **Orca-T graft** will be manufactured by Orca Bio, Inc. contains the following parts:

The donor's blood cells will be collected through a process called "apheresis" and provided to the manufacturing company (Orca Bio, Inc.) to create the investigational product you will receive as part of the study treatment.

- purified hematopoietic stem and progenitor cells (HSPCs),
  - Healthy blood-forming "stem" cells. These will be isolated from the donor's blood cells. When infused, they will grow and make new healthy red blood cells, white blood cells, and platelets.

- regulatory T cells (T_{reg}),
  - A specific white blood cell population isolated from the donor's blood cells and when give to the transplant recipient (you), they are thought to prevent some of the known complications of blood cell transplants like graft-versus-host-disease – a potentially fatal condition that involves the immune attack on recipient tissues by donor cells.

- and conventional T cells (T_{con})
  - A specific white blood cell population isolated from the donor's blood cells that may help eradicate infection or cancer, but also may increase the risk of graft-versus-host-disease also known as GVHD.

Orca-T is being evaluated as a possible treatment of blood cancers and pre-cancerous blood conditions. Orca-T is an experimental therapy. It is not approved by the Food and Drug Administration (FDA).

The **donor conventional CD19/CD22-CAR T cells** will be manufactured by Stanford's Laboratory for Cell and Gene Medicine (LCGM) and will contain the following:

The donor's blood cells will be collected through a process called "apheresis" and provided to the manufacturing laboratory (LCGM) to create the investigational product you will receive as part of the study treatment.

- Genetically modified donor T cells
  - Donor immune cells (called T cells) will be genetically modified in the laboratory to recognize markers on your cancer cells. These markers are CD19 and CD22 and are commonly found on B cell cancers.

    We call these cells CD19/CD22-CAR T cells. Investigators want to test whether these genetically modified CD19/CD22-CAR T cells when re-introduced back into your body will be able to attack the cancer cells. The

CD19/CD22-CAR T cells attacked the cancer cells in mice studied in the laboratory. However, we do not know if these cells will have this effect when given to patients.

In this study, we will be using a CD19/CD22 gene and a type of virus (lentivirus) in making these cells (CD19/CD22-CAR T cells). The Chimeric Antigen Receptor (CAR) is a genetically-engineered receptor made so that immune cells can recognize and respond to a specific molecule, which in this study is the CD19/CD22 protein. This uses a portion of an antibody to CD19/CD22 and a part of a molecule that activates the immune cell.

We combine the CAR molecule with the donor T cells. When the lentiviral vectors enter a normal cell in the body, the deoxyribonucleic acid (DNA) of the vector inserts itself into the normal DNA in that cell This process is called DNA integration.

Together, the CAR will help these T cells find the cancer in your body; it will be the experimental intervention in this study. Your cancer cells must show the CD19 protein in order for these experimental cells to find them.

The CD19/CD22-CAR T cells are considered experimental as they are not approved by the US Food and Drug Administration (FDA). This type of experimental therapy is called "gene therapy" and is very closely monitored by the FDA and other regulatory agencies. The risks of gene therapy will be described later in this document.

We hope to learn whether or not the after receiving myeloablative conditioning, the infusion of Orca-T graft from a matched-related donor and the infusion of donor conventional CD19/CD22 T cells will increase the development of healthy blood cells versus your B-cell ALL without increasing acute graft versus host disease or graft failure. Graft failure is defined as the failure to achieve sustained engraftment (when the blood-forming cells you received on transplant day start to grow and make healthy blood cells) following your allogeneic stem cell transplantation.

This research study is the first in human research study since this infusion combination treatment has not been administered to human subjects previously.

You were selected as a possible participant in this study because you need an allogeneic transplant for B-cell ALL.

If you decide to terminate your participation in this study, you should notify Dr. Muffly at 650-721-2785.

This research study is looking for 12-18 participants with B-cell ALL. Enrollment will only occur at Stanford University, CA, United States. Stanford University expects to enroll 18 research study participants.

VOLUNTARY PARTICIPATION

Your participation in this study is entirely voluntary. Your decision not to participate will not have any negative effect on you or your medical care. You can decide to participate now, but withdraw your consent later and stop being in the study without any loss of benefits or medical care to which you are entitled.

DURATION OF STUDY INVOLVEMENT

This research study is expected to take approximately 2 years for the active participation of participants. A total of 15 years of long-term follow-up from the time of cell infusion for the last participant. The extended long-term follow-up period is due to this study involving "gene therapy" and the current regulations for this type of research.

PROCEDURES

If you choose to participate, the Protocol Director and her research study staff will perform the following procedures.

The study is comprised of the following time periods:

- Pre-Transplant Monitoring Period
  - Screening
  - Myeloablative conditioning (MAC)
- Cell Infusions
  - $CD34^+$ HSPC T_{reg} (Orca-T) infusion
  - T_{con} infusion and Donor CD19/CD22 CAR-T cell infusion
- Post-Transplant Assessment Period

- Supportive Care/Continuation of Inpatient Monitoring
- Long-Term Follow-Up

If you are coming in-person to research visits, you are required to be fully vaccinated—2 doses (1 for Johnson and Johnson), 2 weeks out and to provide proof of your vaccination (e.g., CDC COVID-19 Vaccination Card, e-Health record, etc.) to the researcher prior to study participation. Alternately, you can provide a negative COVID test within 72 hours of your visit.
In order to help you understand the timeframes for the study procedures, we have provided a schedule of events table on the following pages for you to review and reference in the future.

Schedule of Events for Recipient Participants

	Pre-Transplant Monitoring Period		Cell Infusions			Post-Transplant Assessment Period						Long Term Follow-Up		
Procedure	**Screening**	**MAC**	**CD34+ HSPC T_{reg} (Orca-T) Infusion**	**Prior to cell infusions (< 24 h)**	**T_{con} Infusion & Donor CD19/CD22 CAR T cell Infusion**	**Supportive Care/Continuation of Inpatient Monitoring**								
Study Day (vs. 1st allo-HCT infusion)	**Must be completed within 60 days of conditioning regimen**	**Days -8 to -2 or Days -6 to -2**	**Day 0**	**Day 1**	**Day 2**	**Daily, Day 1 to Day 21**	**Twice weekly, Day 22 to Day 29**	**Day 30**	**Day 42**	**Day 60**	**Month 3, 6, 12**	**Every 6 Months 1 to 5 Years**	**Annually, Year 6 to 15**	**At Disease Relapse**
Window						**± 2 d**	**± 4 d**	**± 4 d**		**± 1 week**	**±2 weeks**	**±2 mo.**	**±3 mo.**	
Medical and Disease History	X													
Prior Therapies	X													
Physical Exam	X		X	X	X	X		X		X	X	X		

	Pre-Transplant Monitoring Period		Cell Infusions			Post-Transplant Assessment Period						Long Term Follow-Up		
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Window						**± 2 d**	**± 4 d**	**± 4 d**		**± 1 week**	**±2 weeks**	**±2 mo.**	**±3 mo.**	
Vital signs	X	X	X	X	X	X	X	X		X	X	X		
Neurologic exam	X			X		X		X		X	X	X		
Height (screening only) and weight	X	X	X	X						X	X			

	Pre-Transplant Monitoring Period		**Cell Infusions**			**Post-Transplant Assessment Period**						**Long Term Follow-Up**		
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Karnofsky Score or ECOG	X		X					X		X	X	X		

	Pre-Transplant Monitoring Period		Cell Infusions			Post-Transplant Assessment Period						Long Term Follow-Up		
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Evaluation for COVID-19 Risk[1]	X													

	Pre-Transplant Monitoring Period		Cell Infusions			Post-Transplant Assessment Period						Long Term Follow-Up		
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	Labs													
• Coagulation	X			X	X	X	X	X		X				
• CBC with diff	X	X	X	X		X	X	X		X	X	X		

	Pre-Transplant Monitoring Period		Cell Infusions			Post-Transplant Assessment Period						Long Term Follow-Up		
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Window						**± 2 d**	**± 4 d**	**± 4 d**		**± 1 week**	**±2 weeks**	**±2 mo.**	**±3 mo.**	
• Chemistries	X	X	X	X		X	X	X		X	X			
• Phosphorus	X		X					X						
• Magnesium	X	X	X	X		X		X						

	Pre-Transplant Monitoring Period		Cell Infusions			Post-Transplant Assessment Period						Long Term Follow-Up		
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Window						**± 2 d**	**± 4 d**	**± 4 d**		**± 1 week**	**±2 weeks**	**±2 mo.**	**±3 mo.**	
• CRP	X	X	X	X		X	X	X		X				
• Ferritin	X	X				X	X							
• LDH		X			X	X	X							

	Pre-Transplant Monitoring Period		Cell Infusions			Post-Transplant Assessment Period						Long Term Follow-Up		
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Window						**± 2 d**	**± 4 d**	**± 4 d**		**± 1 week**	**±2 weeks**	**±2 mo.**	**±3 mo.**	
• Uric acid	X	X	X											
• TSH	X				X			X			X			
• Chimerism								X		X	X			

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Window						**± 2 d**	**± 4 d**	**± 4 d**		**± 1 week**	**±2 weeks**	**±2 mo.**	**±3 mo.**	
• Recipient Infectious Disease Markers	X													
• PCR-based testing for SARS-CoV-2	X													

	Pre-Transplant Monitoring Period		Cell Infusions			Post-Transplant Assessment Period						Long Term Follow-Up		
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Window						**± 2 d**	**± 4 d**	**± 4 d**		**± 1 week**	**±2 weeks**	**±2 mo.**	**±3 mo.**	
• Serum Ig Levels (IgM, IgA, IgG)	X		X					X		X				X
• Urine analysis	X			X										

	Pre-Transplant Monitoring Period		Cell Infusions			Post-Transplant Assessment Period						Long Term Follow-Up		
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• Serum or urine β-HCG (if WOCBP)	X													
• ABO and Rh Typing	X													

	Pre-Transplant Monitoring Period		Cell Infusions			Post-Transplant Assessment Period						Long Term Follow-Up		
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Window						**± 2 d**	**± 4 d**	**± 4 d**		**± 1 week**	**±2 weeks**	**±2 mo.**	**±3 mo.**	
• HLA Typing and anti-donor HLA antibody testing[2]	X													

	Pre-Transplant Monitoring Period		Cell Infusions			Post-Transplant Assessment Period						Long Term Follow-Up		
Procedure	**Screening**	**MAC**	**CD34+ HSPC T_{reg} (Orca-T) Infusion**	**Prior to cell infusions (< 24 h)**	**T_{con} Infusion & Donor CD19/CD22 CAR T cell Infusion**	**Supportive Care/Continuation of Inpatient Monitoring**								
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Window						**± 2 d**	**± 4 d**	**± 4 d**		**± 1 week**	**±2 weeks**	**±2 mo.**	**±3 mo.**	
• RCL blood sample				X							X			
Electrocardiogram, 12-lead	X													

	Pre-Transplant Monitoring Period		Cell Infusions			Post-Transplant Assessment Period						Long Term Follow-Up		
Procedure	**Screening**	**MAC**	**CD34+ HSPC T_{reg} (Orca-T) Infusion**	**Prior to cell infusions (< 24 h)**	**T_{con} Infusion & Donor CD19/CD22 CAR T cell Infusion**	**Supportive Care/Continuation of Inpatient Monitoring**								
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Window						**± 2 d**	**± 4 d**	**± 4 d**		**± 1 week**	**±2 weeks**	**±2 mo.**	**±3 mo.**	
ECHO, MUGA or cardiac MRI	X													
DLCO Pulmonary Function Test	X													

	Pre-Transplant Monitoring Period		**Cell Infusions**			**Post-Transplant Assessment Period**						**Long Term Follow-Up**		
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Window						**± 2 d**	**± 4 d**	**± 4 d**		**± 1 week**	**±2 weeks**	**±2 mo.**	**±3 mo.**	
EBV/CMV NAT						Weekly from Day 7 through Day 60[7]					X	X		
Correlative Research Studies		Correlative samples outlined in Section 8												
	Disease Evaluation													

Participant ID:

STUDY

	Pre-Transplant Monitoring Period		Cell Infusions			Post-Transplant Assessment Period						Long Term Follow-Up		
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Window						**± 2 d**	**± 4 d**	**± 4 d**		**± 1 week**	**±2 weeks**	**±2 mo.**	**±3 mo.**	
• Brain MRI (or other appropriate imaging only, if necessary, based	X			X				X		X[3]	X			

	Pre-Transplant Monitoring Period		Cell Infusions			Post-Transplant Assessment Period						Long Term Follow-Up		
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Window						**± 2 d**	**± 4 d**	**± 4 d**		**± 1 week**	**±2 weeks**	**±2 mo.**	**±3 mo.**	
on the site of disease)[3]														

	Pre-Transplant Monitoring Period		Cell Infusions			Post-Transplant Assessment Period						Long Term Follow-Up		
Procedure	**Screening**	**MAC**	**CD34+ HSPC T_{reg} (Orca-T) Infusion**	**Prior to cell infusions (< 24 h)**	**T_{con} Infusion & Donor CD19/CD22 CAR T cell Infusion**	**Supportive Care/Continuation of Inpatient Monitoring**								
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Window						**± 2 d**	**± 4 d**	**± 4 d**		**± 1 week**	**±2 weeks**	**±2 mo.**	**±3 mo.**	
• Lumbar puncture[4]	X							X		X[4]	X[4]			

	Pre-Transplant Monitoring Period		Cell Infusions			Post-Transplant Assessment Period						Long Term Follow-Up		
Procedure	**Screening**	**MAC**	**CD34+ HSPC T_{reg} (Orca-T) Infusion**	**Prior to cell infusions (< 24 h)**	**T_{con} Infusion & Donor CD19/CD22 CAR T cell Infusion**	**Supportive Care/Continuation of Inpatient Monitoring**								
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• Bone marrow aspirate with MRD[5]	X								X	X[5]	X			

	Pre-Transplant Monitoring Period		Cell Infusions			Post-Transplant Assessment Period						Long Term Follow-Up		
Procedure	**Screening**	**MAC**	**CD34+ HSPC T_{reg} (Orca-T) Infusion**	**Prior to cell infusions (< 24 h)**	**T_{con} Infusion & Donor CD19/CD22 CAR T cell Infusion**	**Supportive Care/Continuation of Inpatient Monitoring**								
Study Day (vs. 1st allo-HCT infusion)	**Must be completed within 60 days of conditioning regimen**	**Days -8 to -2 or Days -6 to -2**	**Day 0**	**Day 1**	**Day 2**	**Daily, Day 1 to Day 21**	**Twice weekly, Day 22 to Day 29**	**Day 30**	**Day 42**	**Day 60**	**Month 3, 6, 12**	**Every 6 Months 1 to 5 Years**	**Annually, Year 6 to 15**	**At Disease Relapse**
Window						**± 2 d**	**± 4 d**	**± 4 d**		**± 1 week**	**±2 weeks**	**±2 mo.**	**±3 mo.**	
• Engraftment assessment									X					
• MRD blood sample	X							X		X	X	X		
	Treatment Regimen													

	Pre-Transplant Monitoring Period		Cell Infusions			Post-Transplant Assessment Period						Long Term Follow-Up		
Procedure	**Screening**	**MAC**	**CD34+ HSPC T_{reg} (Orca-T) Infusion**	**Prior to cell infusions (< 24 h)**	**T_{con} Infusion & Donor CD19/CD22 CAR T cell Infusion**	**Supportive Care/Continuation of Inpatient Monitoring**								
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Window						**± 2 d**	**± 4 d**	**± 4 d**		**± 1 week**	**±2 weeks**	**±2 mo.**	**±3 mo.**	
• Continuing Regimen[6]		X												
• Tacrolimus						X	X	X		X				

	Pre-Transplant Monitoring Period		**Cell Infusions**			**Post-Transplant Assessment Period**						**Long Term Follow-Up**		
Procedure	**Screening**	**MAC**	**CD34+ HSPC T_{reg} (Orca-T) Infusion**	**Prior to cell infusions (< 24 h)**	**T_{con} Infusion & Donor CD19/CD22 CAR T cell Infusion**	**Supportive Care/Continuation of Inpatient Monitoring**								
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Window						**± 2 d**	**± 4 d**	**± 4 d**		**± 1 week**	**±2 weeks**	**±2 mo.**	**±3 mo.**	
• Levetiracetam (Keppra)				X	X	X	X							
• Letermovir				All CMV-seropositive recipients should receive letermovir prophylaxis beginning between day 0 and day +28; therapy should continue through day +100. Other patients may receive letermovir per institutional practice.										

	Pre-Transplant Monitoring Period		**Cell Infusions**			**Post-Transplant Assessment Period**						**Long Term Follow-Up**		
Procedure	**Screening**	**MAC**	**CD34+ HSPC T_{reg} (Orca-T) Infusion**	**Prior to cell infusions (< 24 h)**	**T_{con} Infusion & Donor CD19/CD22 CAR T cell Infusion**	**Supportive Care/Continuation of Inpatient Monitoring**								
Study Day (vs. 1st allo-HCT infusion)	**Must be completed within 60 days of conditioning regimen**	**Days -8 to -2 or Days -6 to -2**	**Day 0**	**Day 1**	**Day 2**	**Daily, Day 1 to Day 21**	**Twice weekly, Day 22 to Day 29**	**Day 30**	**Day 42**	**Day 60**	**Month 3, 6, 12**	**Every 6 Months 1 to 5 Years**	**Annually, Year 6 to 15**	**At Disease Relapse**
Window						**± 2 d**	**± 4 d**	**± 4 d**		**± 1 week**	**±2 weeks**	**±2 mo.**	**±3 mo.**	
• CD34+ HSPC T_{reg} (Orca-T) Infusion			X											
• Donor CD19/CD22-CAR T cell Infusion					X									

	Pre-Transplant Monitoring Period		Cell Infusions			Post-Transplant Assessment Period						Long Term Follow-Up		
Procedure	**Screening**	**MAC**	**CD34+ HSPC T_{reg} (Orca-T) Infusion**	**Prior to cell infusions (< 24 h)**	**T_{con} Infusion & Donor CD19/CD22 CAR T cell Infusion**	**Supportive Care/Continuation of Inpatient Monitoring**								
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Window						**± 2 d**	**± 4 d**	**± 4 d**		**± 1 week**	**±2 weeks**	**±2 mo.**	**±3 mo.**	
• T_{con} Infusion					X									
Response Evaluation								X		X	X	X	X	X
GVHD Assessment						X	X	X		X	X*			

	Pre-Transplant Monitoring Period		Cell Infusions			Post-Transplant Assessment Period						Long Term Follow-Up		
Procedure	**Screening**	**MAC**	**CD34+ HSPC T_{reg} (Orca-T) Infusion**	**Prior to cell infusions (< 24 h)**	**T_{con} Infusion & Donor CD19/CD22 CAR T cell Infusion**	**Supportive Care/Continuation of Inpatient Monitoring**								
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Window						**± 2 d**	**± 4 d**	**± 4 d**		**± 1 week**	**±2 weeks**	**±2 mo.**	**±3 mo.**	
Adverse Events		X	X	X	X	X	X	X		X	X			X
Concomitant Medications	X	X	X	X	X	X	X	X		X	X			X

Footnotes:

1) Evaluation of COVID-19 risk will be performed according to the most current version of the BMT-CT COVID SOP
2) HLA typing can occur prior to the 60-day screening window and will be accepted for eligibility and enrollment procedures.
3) Only if abnormal at Day 30.
4) Only if abnormal at Day 30 or if prior CNS involvement of ALL.
5) Only if MRD positive at Day 30.
6) During the TBI regimen, in the outpatient setting, daily labs and vitals will not be collected. Labs and vitals will be collected at least 2x per week.
7) CMV/EBV monitoring will start on Day 7 and proceed weekly until Day 60

Pre-Transplant Monitoring Period

Screening

During **screening**, you will undergo several tests, assessments and/or procedures to determine if you are eligible to participate in this study. The following exams and tests will be reviewed if previously done within the screening period window or repeated:

- A medical history, including prior treatments for your disease
- Physical examination, neurologic examination, including vital signs
- Performance status, a measure of how well you feel and move
- Blood tests, including blood count, chemistries (electrolytes, kidney and liver function), coagulation tests, tests for various infectious diseases, your blood type and other compatibility tests for matching to a related donor.
- A pregnancy test (blood or urine), for women of childbearing potential.
- A test for the coronavirus, SARS-CoV-2, that causes COVID-19. This may consist of a nasal swab, a test of your saliva, or another test. Your research team will know how this test is collected at your treatment site.
- An electrocardiogram (ECG) - this is a test that measures the electrical activity and health of the heart.
- An echocardiogram (ECHO) which is an ultrasound study of your heart to check its functionality. You doctor may instead alternatively suggest that you undergo a multigated acquisition (MUGA) scan. This is another noninvasive test of heart function, but differs from an echocardiogram in that a small amount of radioactive tracer is injected into a vein, and a special camera is used to detect the radiation released by the tracer to assess heart function. Or cardiac MRI, a test that checks the function of your heart.
- A pulmonary function test which measures how well your lungs work. For this test, you will be asked to breathe in (inhale) air containing a very small amount of carbon monoxide and a trace gas, such as helium or methane; hold your breath, and then rapidly breathe out (exhale), using an instrument that measures your breath.
- Brain MRI or other appropriate imaging, if necessary, based on where your disease is located in your body
- Lumbar puncture ("spinal tap") to collect spinal fluid

- Disease evaluation, including a bone marrow aspirate and/or biopsy which involves taking small pieces of tissue from inside one of your bones. This is like the biopsy you likely had that helped diagnose your disease.
- Documentation of concomitant medications (medications you are taking while participating in the research study)

These procedures are considered standard of care procedures.

Myeloablative conditioning (MAC)
After successful screening procedures, and if your match related donor is also willing and eligible to participate, you will begin a conditioning regimen to prepare your body to receive the Orca-T graft and the donor conventional CD19/CD22 CAR-T cell infusion.

The conditioning procedure is considered part of the standard of care procedure to prepare your body for the treatment. Conditioning regimens consist of combinations of chemotherapies and sometimes radiation. You will receive one of the study regimens listed below:

- Total Body Irradiation, Cyclophosphamide (TBI/Cy)
- Busulfan, Fludarabine, and Thiotepa (Bu/Flu/TT)

These conditioning regimens are typically administered over the course of 6-8 days, but your specific schedule may vary slightly.

You will be monitored for adverse events during this time period. Adverse events are defined as any unfavorable and unintended sign or symptom, including abnormal laboratory findings, or disease, that is temporally associated with the use of a drug, and does not imply any judgment about causality – whether or not it is connected to the drug.

Cell Infusions

$CD34^+$ HSPC T_{reg} (Orca-T) infusion

Orca-T Treatment (Day 0 and Day +2)

You receive components of Orca-T (day 0 and day +2). On day 0, the day of transplant, the following procedures will happen:

- Physical exam, including weight
- Vital signs
- Performance score
- Blood tests
- All cytomegalovirus-seropositive recipients should receive letermovir prophylaxis beginning between day 0 and day +28; therapy should continue through day +100. Other subjects may receive letermovir per institutional practice.
- A combination of stem cells and T_{reg}. These cells are infused through your central venous catheter.

Two days later, the T_{con} cells will be infused through your central venous catheter prior to your CD19/CD22 CAR-T cell infusion.

You will be monitored for adverse events during this time period.

Day +1

One Day +1, the day between infusions, the following procedures will happen:

- Premedications
    - Keppra, an antiseizure medication
    - Participants at high-risk for tumor lysis syndrome (TLS), per the Protocol Director's or Sub-Investigator's discretion, will receive allopurinol (uric acid reducer) orally once daily
        - TLS is a condition that occurs when a large number of cancer cells dies within a short period, releasing their contents into the bloodstream. Your levels of uric acid, potassium, and phosphorus rise faster than the kidneys can remove them.
- Physical exam, including weight
- Vital signs
- Neurologic examination
- Blood tests and laboratory tests
- Brain MRI or other appropriate imaging, if necessary, based on where your disease is located in your body

You will be monitored for adverse events during this time period.

T_{con} Infusion and Donor CD19/CD22 CAR-T cell infusion (Day +2)
On Day +2, the following procedures will happen:

- Premedications
  - Keppra, an antiseizure medication
- Physical exam, including weight
- Vital signs
- Blood tests
- The Orca-T T_{con} cells will be infused through your central venous catheter prior to your CD19/CD22 CAR-T cell infusion
- The CD19/CD22-CAR T cells will be given intravenously over 10- 30 minutes. The doctors and nurses will watch you closely (taking your temperature, blood pressure, heart rate and breathing rate) during and after the infusion and will treat you immediately if you have any side effects.

You will be monitored for adverse events during this time period.

Post-Transplant Assessment Period

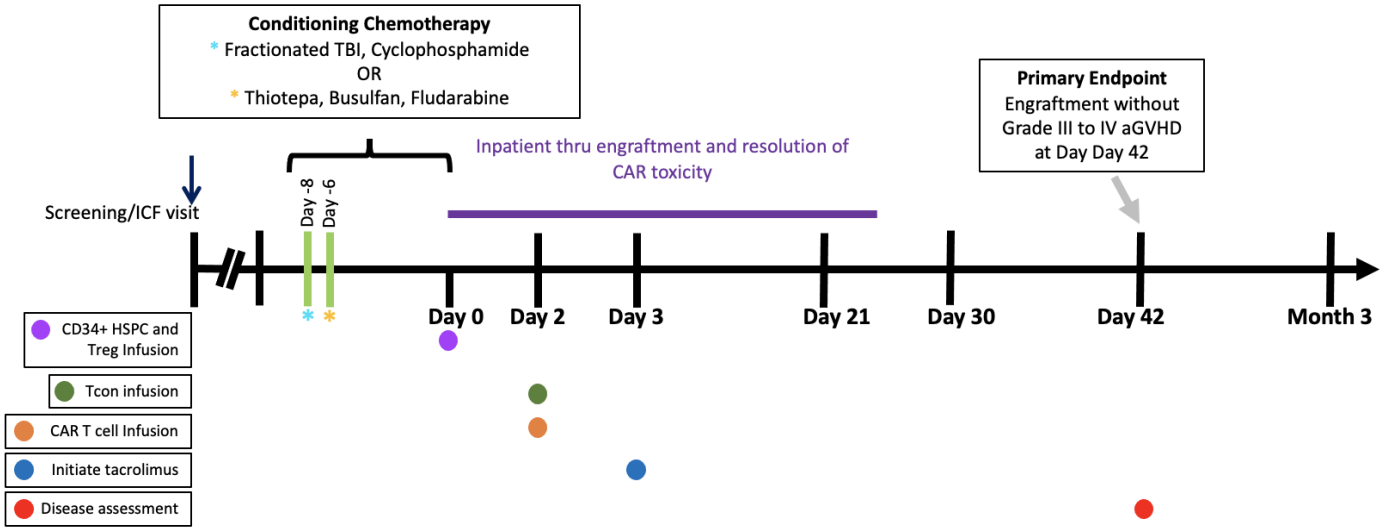
Supportive Care/Continuation of Inpatient Monitoring

After cell infusion, you will be required to stay in the hospital for about 7 days; however, you may remain in the hospital for longer than 7 days until your healthcare team determines that you are well enough to go home. We will ask you to stay close to Stanford after you are discharged until 28 days after CD19/CD22-CAR T cell therapy administration so the doctors and nurses can care for you.

You will have daily safety tests from Day 0 to Day 21, then twice per week until Day 30. These assessments may be part of your inpatient stay or return clinic visits. The following assessments and procedures will be performed:

- Ask how you are feeling and review medications you are taking

- Brief Physical exam
- Neurological exam
- Vital signs and a questionnaire designed to test your mental status and ability to complete tasks (ICE assessment), performed every 12 hours while you are in the hospital and then during clinic visits until Day 21
- After you receive Orca-T you will begin to take a medication (tacrolimus) to prevent the development of GVHD, starting on Day +3. It will typically be given IV first, but may later be changed to an oral route when you are able to tolerate food. You will continue to take this medication until at least Day +60 after transplant, at which time the dose may be slowly tapered under your doctor's guidance.
- GVHD assessment
- Viral testing to see if you may have active Epstein-Barr Virus (EBV) and/or cytomegalovirus (CMV) infections.
- Keppra, an antiseizure medication
- All cytomegalovirus-seropositive recipients should receive letermovir prophylaxis beginning between day 0 and day +28; therapy should continue through day +100. Other subjects may receive letermovir per institutional practice.
- Blood sample collection for routine and research testing.



Long-Term Follow-Up

Long-term Follow-Up for Gene Therapy Safety

Long-term Follow-Up involves clinic visits every 3 months through Month 12, then every 6-12 months through Year 5, then annually from Year 6-15. After Year 5, contact may be by phone, email or mail rather than an in person clinic visit.

We will collect samples of your blood over the next several years. This testing will determine if the cells have grown or changed in your body.

During these long-term follow-up visits, the following assessments and procedures will be performed:

- Physical exam with performance status and vital signs
- Disease evaluation (bone marrow aspiration and/or lumbar puncture to assess the extent and location of your cancer)
- Brain MRI or other appropriate imaging, if necessary
- Possible bone marrow or tissue biopsy for research purposes.

- Possible apheresis to collect your white blood cells for research purposes at Month 6, 9 and 12.
- Standard laboratory tests and research blood tests.
- All cytomegalovirus-seropositive recipients should receive letermovir prophylaxis beginning between day 0 and day +28; therapy should continue through day +100. Other subjects may receive letermovir per institutional practice.
- Collect adverse events and medications you are taking for 12 months after the Orca-T and CD19/CD22-CAR T cell infusions

According to FDA requirements, we need you to return annually to Stanford for a physical examination for five years after you receive the cells. After that time, we will be sending you a questionnaire to get information regarding your health for the next ten years, for a total follow up time period of 15 years. For this reason, we ask that you continue to provide us with a current address and telephone number, even after you complete this research study. If you should die, no matter the cause, we may request permission for an autopsy in order to obtain vital information concerning the safety of this experimental therapy approach.

Future Use of Private Information and/or Specimens

Research using private information and/or specimens is an important way to try to understand human disease. You are being given this information because the investigators want to save private information and/or specimens for future research.

Identifiers might be removed from identifiable private information and/or identifiable specimens and, after such removal, the information and/or specimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from you.

The process of determining all or nearly all of your DNA sequence is called whole genome sequencing. It is different from genetic testing that does not involve whole genome sequencing because it provides a much more detailed snapshot of your genome. THIS RESEARCH WILL NOT INCLUDE WHOLE GENOME SEQUENCING.

At the time of consent, each subject is assigned a unique, study number (with no identifiers) used by the BMT-CT Biobank and correlative science unit team to identify the subject while protecting personal health information (PHI) and privacy.

PHI is removed from the labels on the original research kit and collection tubes and destroyed appropriately. After processing the sample, via appropriate approved protocols, each derivative aliquot is inputted, assigned a unique, barcode label and tracked in OpenSpecimen (LIMS Database).

Each parent sample and derivative aliquots are accounted for, and its storage location and distribution are tracked in the OpenSpecimen database. Sample storage locations have keycard-controlled building access and are temperature monitored 24 hours a day, seven days a week, 365 days a year, with emergency backup power.

Your specimens will be sent outside of Stanford for analysis.

Any of your specimens which are used in research may result in new products, tests or discoveries. In some instances, these may have potential commercial value and may be developed and owned by the Investigators, Stanford University and/or others. However, donors of specimens do not retain any property rights to the materials. Therefore, you would not share in any financial benefits from these products, tests or discoveries.

Reportable Communicable Diseases (e.g., COVID-19, HIV)

You will be tested for communicable diseases, such as COVID, HIV, Hepatitis B and C, as part of this research study. If your test results are positive, the results will be reported to health authorities as required by law.

If you test positive for HIV, counseling will be provided.

Gene Transfer Studies

If you participate in this study, the research doctor may ask your family for permission to perform an autopsy if you pass away while the study is still in follow up. An autopsy may help researchers learn more about the safety and effectiveness of gene transfer. Because the decision about performing an autopsy would be up to your family, we

encourage you to advise them of your wishes. Your family would not be responsible for the costs of the autopsy.

PARTICIPANT RESPONSIBILITIES

As a participant, your responsibilities include:

- Follow the instructions of the Protocol Director and study staff.
- Keep your study appointments. If it is necessary to miss an appointment, please contact the Protocol Director or research study staff to reschedule as soon as you know you will miss the appointment.
- Tell the Protocol Director or research study staff about any side effects, doctor visits, or hospitalizations that you may have.
- Tell the Protocol Director or research staff if you believe you might be pregnant or gotten your partner pregnant.
- Complete your questionnaires as instructed.
- Ask questions as you think of them.
- Tell the Protocol Director or research staff if you change your mind about staying in the study.

WITHDRAWAL FROM STUDY

If you first agree to participate and then you change your mind, you are free to withdraw your consent and discontinue your participation at any time. Your decision will not affect your ability to receive medical care for your disease and you will not lose any benefits to which you would otherwise be entitled.

If you decide to withdraw your consent to participate in this study, you should notify Dr. Muffly at 650-721-2785.

If you withdraw from the study, or the study medication is stopped for any reason, it will be confirmed and documented if you will consent to continue to be followed per protocol, if applicable.

If you are removed from study due to unacceptable adverse event(s) or toxicity, you will be followed and safety data collected for at least **30** days or until resolution or stabilization of the adverse event, whichever is longest, to the extent possible.

Participants that personally withdraw will be requested to attend a 30-day follow-up visit (or longer), or otherwise receive a follow-up contact, unless specifically countermanded by you.

The Protocol Director may also withdraw you from the study and the study treatment may be stopped, without your consent for one or more of the following reasons:

- Failure to follow the instructions of the Protocol Director and study staff.
- The Protocol Director decides that continuing your participation could be harmful to you.
- Pregnancy
- You need treatment not allowed in the study.
- The study is cancelled.
- Other administrative reasons.
- Unanticipated circumstances.

POSSIBLE RISKS, DISCOMFORTS, AND INCONVENIENCES

There are risks, discomforts, and inconveniences associated with any research study. These deserve careful thought. You should talk with the Protocol Director if you have any questions.

Toxicities Of Conditioning Regimens And Supportive Agents

Fludarabine

Likely

- Exacerbation of nausea, vomiting, mouth sores, and diarrhea, which are primarily due to the cyclophosphamide.
- Immune suppression

Less likely

- Jaundice and elevations of liver enzymes

Rare but serious

- Effects on the nervous system are rare, but if they occur could include confusion, coma, weakness or numbness, loss of balance, difficulty walking, or loss of vision and could be very serious or lethal.

Thiotepa

Likely

- Myelosuppression is the major dose-limiting toxicity, occurring regularly at doses >405mg/m2. Other non-fatal toxicities have been observed almost exclusively after administration of thiotepa at doses greater than 1000mg/m2.
- Increased risk of infection.
- Cutaneous erythema and bronzing are seen in most patients given 900mg/m2. Erythema develops 4-14 days after the first dose and may last up to 3weeks. Bronzing may persist for months.

Less likely

- Nausea, vomiting, diarrhea - occasional, rarely severe

Rare but Serious

- CNS toxicity manifested by mild cognitive dysfunction, disorientation, confusion, irritability, bizarre behavior, is usually not observed at doses <1000mg/m2.
- Interstitial pneumonia
- Renal failure
- Transient hepatic transaminase elevations are occasionally seen, but rarely severe.

Busulfan

Busulfan is a chemotherapy drug that has the following side effects nausea, vomiting, diarrhea, sores in the mouth and throat, darkening of the skin, seizures and low blood counts. In rare circumstances, busulfan may result in permanent hair thinning or loss.

Busulfan can cause liver damage which may be fatal. There is also a risk of the development of a second cancer.

Total Body Irradiation (TBI)

Likely

- Nausea and vomiting: Virtually all patients will experience nausea and vomiting after irradiation. This can be diminished somewhat with mild anti-emetics. Strong sedatives or phenothiazine derivatives should be avoided just before radiation treatment, as they frequently cause excessive drowsiness and/or symptomatic orthostasis, which prevent delivery of TBI done in the standing position. We will limit the use of dexamethasone for nausea unless discussed with the study PI.
- Myelosuppression is the major dose-limiting toxicity.
- Hyperpigmentation: Most patients will get some degree of hyperpigmentation within 2-3 weeks of transplantation.
- Increased risk of infection
- Mucositis: Most patients will develop moderate to severe mucositis of the oral and GI tracts, which will be managed with aggressive nursing mouth care, analgesics and prophylactic antifungal and antiviral agents. We will limit the use of dexamethasone for mucositis unless discussed with the study PI.
- Late effects: There is the possibility of cataract formation. Although mild cataracts may occur in up to 70% of cases with single dose TBI, we have seen cataracts in < 30% of patients treated with hyperfractionated TBI.
- Sterility is extremely common following total body irradiation and administration of alkylating chemotherapy; the risk increases with the number of years since puberty.
- Diarrhea: Most patients develop some diarrhea in the first week post irradiation. This can be treated symptomatically.

Less likely

- Parotitis: Some patients will experience symptomatic parotitis within the first 24 hours post radiation. This resolves spontaneously over several days.
- Fever: Low-grade fever [greater than 38°C] may occur for 24-hour post irradiation. This can be treated symptomatically.
- Erythema: This may occur in patients within 24 hours and resolves in 2-3 days.

- Hypothyroidism has been reported in small numbers of adult patients following TBI plus alkylating chemotherapy, and this will be routinely monitored post-transplant with hormonal replacement as indicated.

Rare but serious

- High doses of radiation in combination with high dose chemotherapy may contribute to damage to vital organs such as the kidneys, lung or the liver.
- There is a possibility that secondary malignancies may develop, particularly due to the combined effects of radiation and an alkylating agent [cyclophosphamide]. The age-adjusted incidence of secondary cancer in transplant patients after radiation and chemotherapy has recently been estimated to be 6.7 times higher than that of first cancers in the general population; and most of these were non-Hodgkin's lymphomas.

Cyclophosphamide

Cyclophosphamide is a chemotherapy drug that has the following side effects nausea, vomiting, diarrhea, sores in the mouth and throat, skin changes, loss of appetite, irritation and bleeding of the bladder lining and lowered blood counts. Cyclophosphamide may also damage the heart which in some cases can be fatal. There is also a risk of the development of a second cancer.

Tacrolimus

The use of a single medication (i.e., tacrolimus) to prevent graft versus host disease is experimental. Orca-T is designed to reduce the risk of graft versus host disease and thus possibly require less medication. However, we do not know if it will work as intended since this is still an experimental product.

Likely

- Headache and/or dizziness
- Uncontrollable shaking of a part of the body
- Diarrhea and/or constipation
- Nausea and/or vomiting
- Heartburn
- Stomach pain
- Loss of appetite

- Difficulty falling asleep and/or staying asleep

Less likely

- Damage to organs (heart, lungs, brain, others) which may cause changes in thinking, confusion, memory loss or shortness of breath
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Change in the heart rhythm, abnormal heartbeat, or heart stops beating
- Heart attack or failure which may cause chest pain, swelling of ankles, and tiredness
- A tear or a hole in the bowels which may cause belly pain or that may require surgery
- A new cancer resulting from treatment of earlier cancer
- Brain damage, which may cause headache, seizure, blindness

Rare but serious

- Decreased urination
- Pain or burning on urination
- Swelling of the arms, hands, feet, ankles, or lower legs
- Weight gain
- Unusual bleeding or bruising
- Seizures
- Coma (loss of consciousness for a period of time)

Letermovir

You will receive a drug called letermovir if you have a history of being infected with a virus called cytomegalovirus (CMV) unless you have a medical reason why you cannot take letermovir (such as a severe allergy to this drug).

Likely

- Bloating or swelling of the face, arms, hands, lower legs, or feet
- rapid weight gain
- tingling of the hands or feet
- unusual weight gain or loss
- Cough
- diarrhea

- headache
- nausea
- stomach pain
- unusual tiredness or weakness
- vomiting

Less likely

- Dizziness
- fainting
- fast, pounding, or irregular heartbeat or pulse

Cellular Infusions

Orca-T

Orca-T is developed using an experimental process, and its administration for allogeneic transplant is experimental.

Risks Associated with Orca-T

As of October 29, 2021, 109 subjects have been treated with Orca-T. Because of limited prior experience, the risks and side effects of Orca-T are still being identified. If important findings regarding the risks and side effects of Orca-T are discovered during the clinical trial, this information will be provided to you and your doctor. The following are possible risks:

- Manufacturing failure. The production of Orca-T is an experimental process. It is possible that an Orca-T may not be able to be created. If that happens, the available cells from the donor could be used to create a graft for you, but you may not be able to be enrolled in this research study. Alternative methods may be necessary to secure sufficient cells from your donor, for example a bone marrow harvest.
- Allergy or hypersensitivity. The manufacturing of Orca-T includes iron dextran, chemical products derived from cyanine dyes, and proteins derived from mice, cows, algae and a type of bacterium called *Streptomyces avidinii*. Some people have severe allergic reactions to these products, including anaphylaxis or other

potentially fatal reactions. You should not receive Orca-T if you have a known allergy or hypersensitivity to any of the above components.

- Infusion reactions. Infusion reactions have sometimes been reported when cells are infused into patients for allogeneic transplant. It is not known specifically what cells are responsible for such reactions, but they may include the cell types used in Orca-T. You will be given medications to lessen the risk of developing an infusion reaction. In addition, you will be monitored closely for signs of infusion reactions after being given Orca-T components, and appropriate treatment initiated as soon as possible.
- Worsening of transplant-related outcomes. Orca-T is designed to improve outcomes in transplantation by reducing the risk of complications like graft versus host disease, disease relapse and infection, while improving overall survival. However, until proven, it is possible that Orca-T may actually worsen one or more of these outcomes. The research team will be monitoring these events in all patients while the study is ongoing.
- One case of donor hematopoietic graft loss has been noted in a clinical trial patient who had autologous recovery of their own bone marrow without complication. The patient was given anti-inflammatory medication not usually given during transplantation which might have contributed to graft loss. Given this case, there is the possibility that graft loss may occur for other trial participants. Graft loss is seen under standard of care conditions as well in <1% of patients, and we currently do not have enough patient experience to know if there is an increased risk for trial participants as compared to standard of care transplantation.

Risks Related to the Transplant Procedure.

- Allogeneic transplant is associated with the following risks:
  - **Graft-versus-host disease (GVHD):** GVHD condition is when the donor cells you receive attack some of your tissues and organs. Your study doctor can describe the possible manifestations of GVHD to you.
  - **Bleeding:** Your platelet count will drop leaving you at risk for bleeding. In some cases, bleeding can be a fatal complication. You will receive transfusion of platelets to minimize the risk of bleeding.

- **Veno-occlusive Disease (VOD):** High dose chemotherapy, radiation therapy and medications used to prevent graft versus host disease can cause veno-occlusive disease. Veno-occulsive disease can result in liver failure and in some cases, death.
- **Mouth Sores and Diarrhea:** The large doses of chemotherapy and radiation cause irritation in the lining of the mouth and intestines, resulting in painful mouth sores and diarrhea.
- **Capillary Leak Syndrome:** After chemotherapy and radiation, the blood vessels may become "leaky" and fluid enters your abdomen, lungs, and other tissues. Capillary leak syndrome can be difficult to manage if extra fluid enters your lungs and makes it hard to breathe. Capillary leak syndrome can be a fatal complication. .
- **Organ Damage:** You may experience life-threatening or long-term injury to the heart, lung, kidneys, brain or liver damage as a result of your transplant.
- **Infection**: The chemotherapy and radiation treatments, GVHD prophylaxis and treatment, as well as allogeneic HSCT are associated with increased risk for infections. You will be given medications as well as instructions to minimize the risk of infections. You will be monitored very closely for infections and treated promptly if there is suspicion of or documented infection.
  - **Antimicrobial Prophylaxis:**
    - Side effects may include nausea, vomiting diarrhea, loss of appetite, or rash
- **Graft Failure:** There is a risk of graft failure with allogeneic hematopoietic cell transplant procedures.
- **Late Effects:** You may experience late effects that occur months to many years after your transplant.
  - You may have problems with your thyroid gland that require you to take thyroid medication.
  - You may get cataracts earlier in life compared to a person who has not had a transplant. If you develop cataracts (cloudiness in the eyes) they may need treatment.
  - Your kidneys could be affected and cause anemia (low red blood cell count) or high blood pressure.

- You may develop a second cancer as a result of the chemotherapy, radiation and/or underlying disease. If secondary cancers happen, they generally do not develop until 10 to15 years after your transplant.
- Cancer therapies have the potential to accelerate the development of chronic health problems such as cardiovascular disease, cognitive changes, pulmonary, liver and kidney problems.

- **Unforeseen Risks:** New risks might appear at any time during the study that are different from the risks listed in this consent form. We will promptly tell you of any new information that may affect your decision to participate.
- **Additional Expected Risks:** Adenovirus infection, alopecia, anemia, constipation, cystitis, haemorrhagic, cytomegalovirus infection, diarrhea, Epstein-Barr virus infection, febrile neutropenia, fever, graft failure, hypertension, hypotension, incontinence, lymphoproliferative disorder, mucosal inflammation, nausea, neuropathy peripheral, edema, pain, rash, second primary malignancy, thromobocytopenia, thrombotic microangiopathy, veno-occlusive liver disease, and vomiting.

CD19-CAR T cell Therapy Associated Toxicities

CD19 CAR T gene-modified cells have been given to hundreds of individuals but CD22 CAR T cells have been given to far fewer individuals. There is still a lot we may not know and there may be risks that we cannot predict. At this time, over 35 adults and 5 children have received CD19/CD22-CAR T cells.

Dramatic and rapid expansion of CD19-CAR T cells is often associated with toxicity, including cytokine release syndrome and neurotoxicity.

Cytokine release syndrome (CRS)

Adult patients with ALL have been shown to develop severe CRS, only in patients with morphologic evidence of disease (>5% blasts in BM) at the time of T cell infusion. CRS will be graded using the American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading.

Severe CRS is defined by the presence of one of the following clinical and laboratory parameters:

- Hypotension: SBP<90 refractory to IV fluids requiring at least one vasopressor
- Respiratory distress/hypoxia requiring increasing supplemental oxygen or ventilatory support
- Acute coronary syndrome (ACS) with positive troponin, clinically significant arrhythmia, and/or ECG changes

Immune effector cell (IEC)-associated neurotoxicity syndrome (ICANS)

Patients with severe CRS may develop neurological complications including confusion, delirium, expressive aphasia, obtundation, myoclonus and seizure-like activity. Some of the previously treated adult ALL patients required ICU stay due to these side effects, and few patients required intubation.

All these side effects were observed in patients with morphologic ALL at the time of T cell infusion. Patients will receive levetiracetam (Keppra) for seizure prophylaxis at least 2 days prior to T cell infusion and be monitored closely for these side effects. In case to allergic reactions to levetiracetam (Keppra), alternative anti-seizure medications will be used under the guidance of the Neurology team. Neurology service will be consulted immediately, and the following management algorithm will be utilized upon the first suspicion of any neurological side effects.

Baseline brain imaging should be conducted whenever feasible. Neurotoxicity, which is also referred to as immune effector cell (IEC)-associated neurotoxicity syndrome (ICANS) will be graded using the ASTCT consensus grading and the associated Immune Effector Cell-Associated Encephalopathy (ICE) score.

Lentiviral Gene Therapy Risks

Effect of DNA Integration

Most DNA integration is expected to cause no harm to the cell or to the patient. However, there is a chance that DNA integration might result in abnormal activity of other genes. In most cases, this effect will have no health consequences. However, in some cases, abnormal activity of a gene may cause unpredictable harm such as the development of cancer.

Discussion of delayed adverse event, leukemia-like malignancy, occurring in human studies:

It is important that you know about some cancers that occurred in another gene therapy research study. Clinical studies were conducted in France and United Kingdom to treat a disease called X-linked Severe Combined Immunodeficiency (SCID). Years after receiving cells that were modified by a retroviral vector, a significant number of the children in this small study developed a leukemia-like malignant disease (cancer). One child died from the cancer. A group of experts in this field studied the results from tests performed on these children's blood cells. They concluded that cancer was caused by the retroviral vector DNA. Still, most of the children with X-linked SCID who have received experimental gene therapy have not been found to have cancer at this time. Although they appear healthy, we still do not know whether they, too, will develop cancer.

Risk of malignancy for this study:

We do not know if the retroviral vector used in this protocol might cause cancer. However, you should be aware that the DNA contained in retroviral vectors will integrate into your DNA and that under some circumstances; this has been known to cause cancer months to years later.

Lentiviral Infection Risks

The cells we will be giving you have a type of virus (lentivirus) put into them along with the CD19/CD22 CAR gene. Although this lentivirus is not active, there is the rare possibility that it may regain the ability to make copies (replication competent lentivirus). Replication competent lentivirus has never been observed in human gene transfer studies to date. Lentivirus gene insertion could genetically alter your lymphocytes causing you to develop another type of cancer in your blood cells. This has been observed in studies inserting genes into stem cells, but has not yet been observed in clinical studies inserting genes into mature T-cells, like this study. You will be carefully monitored for 5 years after cell infusion for replication competent lentivirus and for 15 years after cell infusion for new cancers caused by the lentivirus.

The virus used in this study was built in a lab from parts of the HIV virus. While there is no chance you could contract HIV from the study treatment, future HIV tests may yield a "false positive" because the test detects virus segments that are similar on the two viruses.

Unknown Risk of Graft Failure

There is a risk of graft failure with allogeneic hematopoietic cell transplant procedures as well as an unknown risk of graft failure with administration of this novel CAR T therapy in the post-transplant setting.

The donors will be notified in the event of graft failure to propose recollection for a second transplant procedure. In the event of graft failure, we will perform an unmanipulated transplant from your donor.

Reproductive Risks

The effect of CD19/CD22-CAR T cell therapy on human sperm and eggs has never been studied. In addition, the effects on a developing fetus exposed to CD19/CD22-CAR T cells are unknown and may be unforeseeable. Chemotherapy used in this study can cause fetal harm. Therefore, both men and women on this study should not attempt pregnancy while CD19/CD22-CAR T cells are detectable in the blood.

Women of Childbearing Potential

If you are a woman who is able to become pregnant, it is expected that you will use an effective method of birth control to prevent exposing a fetus to a potentially dangerous agent with unknown risk. If you are pregnant or currently breast feeding, you may not participate in this study. You understand that if you are pregnant, if you become pregnant, or if you are breast-feeding during this study, you or your child may be exposed to an unknown risk.

To confirm to the extent medically possible that you are not pregnant, you agree to have a pregnancy test done before beginning this research study and before staring myeloablative conditioning. You must agree to avoid sexual intercourse or use a birth control method judged to be effective by the investigator and which will not interfere with the proposed investigation. You must accept the risk that pregnancy could still result despite the responsible use of reliable method of birth control. You agree to notify the investigator as soon as possible of any failure of proper use of your birth control method, or if you become pregnant, either of which may result in your being withdrawn from the study.

Male Participants

If you are a man participating in this study and your partner is able to become pregnant, you and your partner must use adequate contraception while you are participating in the study and for at least 4 months after myeloablative conditioning and while CAR cells are seen in your blood. Your doctor will discuss with you what methods of birth control are considered adequate. You should inform your study doctor if your partner becomes pregnant.

Risks Associated with Research Procedures

Blood Draw

Drawing blood from your vein may cause pain where the needle is inserted, and there is a small risk of bruising, bleeding, infection at the place where the needle is inserted. Very rarely, a blockage of the vein or a small nerve injury can occur, resulting in numbness and pain; however, this will resolve with time. Some people experience dizziness, upset stomach or fainting when their blood is drawn.

Intravenous (IV) catheter

Prior to beginning the experimental therapy, your doctor may want to insert an intravenous (IV) catheter for the delivery of myeloablative conditioning, Orca-T graft, CD19/CD22 CAR-T cells, and to take blood samples. IV catheters can be placed in a hand, arm or leg. These are known as "peripheral" IVs. IVs placed in the central circulation, like the internal jugular vein (neck) or subclavian vein (just beneath the collar bone), are known as "central lines". You should discuss this with your doctor. For both types of catheter, the area will be numbed with an anesthetic before the catheter is inserted. During the insertion you could feel a pinch, and shortly thereafter bleeding, redness or a bruise could develop. Rarely an infection could occur if not kept clean. For central catheters, although rare, they can sometimes cause collapse of a lung or cause bleeding. Lung collapse is treated by putting a tube into your chest for a few days to allow your lung to expand. Pressure is placed on any area that might bleed.

Bone Marrow Aspirate/Biopsy

A bone marrow aspirate and biopsy is performed using a hollow needle to remove a small sample of bone marrow. Before the biopsy, a local anesthetic is used to numb the

area where the needle will be inserted. The procedure may cause discomfort, pain, bleeding, scarring or infection at the site of the aspirate/biopsy.

Dose-Escalation
You and other participants may receive a dose that is sub-therapeutic and may not be effective at treating your condition.

Lumbar Puncture
A lumbar puncture may be done to examine the cerebrospinal fluid, which is the fluid that surrounds your brain and spinal cord, to determine if your disease is affecting the brain. A lumbar puncture is done by inserting a thin hollow needle between two of the vertebrae (bones in the lower back). Prior to the lumbar puncture, you may be given a local anesthetic to numb the area. The procedure may cause headache that may be accompanied by nausea, vomiting and dizziness.

Testing for Notifiable Diseases
If you decide to participate in this study, the blood tests include tests for HIV, hepatitis B and C, and syphilis. The results of the tests could indicate that you have active HIV, hepatitis B, hepatitis C, and/or syphilis. If you test positive for HIV, counseling will be provided and we will refer you to a doctor who specializes in treating the condition. We will make every effort to keep your personal information confidential, but positive test results will need to be reported to the local health agency. Becoming aware of a diagnosis of one or more of these conditions would allow you to explore treatment that may extend your life and prevent passing infection to others, however it could have serious personal and/or social consequences, including difficulty obtaining health insurance or employment.

Risk Associated with Multi-gated Acquisition (MUGA)
MUGA scans may cause allergic reactions to the radioactive tracer, injection site soreness, and/or swelling. They may cause damage to cells or tissue from being exposed to the radiation used in the scan. However, the radioactive tracer you receive is generally safe for most people. Your body will get rid of it through your kidneys within about 24 hours.

MRI (Magnetic Resonance Imaging)

MRI machines use a strong magnet and radiofrequency magnetic fields to make images of the body interior. During the scan you will be asked to lie on a long narrow couch for a certain amount of time while the machine gathers information. During this time you will not be exposed to x-rays, but rather a strong magnetic field and radiofrequency magnetic fields, which you will not feel. You will, however, hear repetitive tapping noises that arise from the Magnetic Resonance scanner. We will provide earplugs or headphones that you will be required to wear. The space within the large magnet in which you lie is somewhat confined, although we have taken steps to relieve the "claustrophobic" feeling.

Risks:

Magnetic fields do not cause harmful effects at the levels used in the MRI machine. However, the MR scanner uses a very strong magnet that will attract some metals and affect some electronic devices. If you have a cardiac pacemaker or any other biomedical device in or on your body, it is very important that you tell the operator/investigator immediately. As metallic objects may experience a strong attraction to the magnet, it is also very important that you notify the operator of any metal objects (especially surgical clips), devices, or implants that are in or on your body before entering the magnet room. All such objects must be removed (if possible) before entering the magnet room. In some cases, having those devices means you should not have an MRI scan performed, so it is very important that you notify the operator. In addition, watches and credit cards should also be removed as these could be damaged. You will be provided a way to secure these items. If you have any history of head or eye injury involving metal fragments, if you have ever worked in a metal shop, or if you could be pregnant, you should notify the operator/investigator. You should also notify the operator/investigator if you have any tattoos on your body, including eyeliner and other permanent makeup. Tattoos could become warm and irritated during the scan and remain so for several days.

There is a possibility that you will experience a localized twitching sensation due to the magnetic field changes during the scan. This is not unexpected and should not be painful. However, you may have the scan stopped at any time if this occurs. There is also a possibility of tinnitus (ringing in the ears) after the MRI.

IF YOU FEEL DISCOMFORT AT ANY TIME, NOTIFY THE OPERATOR AND YOU CAN DISCONTINUE THE EXAM AT ANY TIME.

POTENTIAL BENEFITS

You and other participants may have the chance to help others get better treatment in the future based upon the knowledge that is gained from the clinical study.

We cannot and do not guarantee or promise that you will receive any benefits from this study.

ALTERNATIVES

You are not required to take part in this research study. Alternative options that may be available to you include:

- Chemotherapy and/or other cancer treatments
- Other experimental therapies under a different study
- Palliative or comfort care aimed at lessening the symptoms of cancer and making you as comfortable as possible. This type of care does not treat the cancer directly.
- No treatment at all

You should discuss each of these possible choices with the Protocol Director and/or your doctor.

PARTICIPANT'S RIGHTS

You should not feel obligated to agree to participate. Your questions should be answered clearly and to your satisfaction. If you decide not to participate, tell the Protocol Director.

You have the right to refuse to answer particular questions.

You will be told of any important new information that is learned during the course of this research study, which might affect your condition or your willingness to continue participation in this study.

ClinicalTrials.gov

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

CONFIDENTIALITY

The results of this research study may be presented at scientific or medical meetings or published in scientific journals. Your identity and/or your personal health information will not be disclosed except as authorized by you or as required by law**.** However, there is always some risk that even de-identified information might be re-identified.

Patient information may be provided to Federal and other regulatory agencies as required. The Food and Drug Administration (FDA), for example, may inspect research records and learn your identity if this study falls within its jurisdiction.

The purpose of this research study is to obtain information on the safety and effectiveness of Orca-T and CD19/CD22-CAR T cells; the results will be provided to the sponsor, the Food and Drug Administration and other federal and regulatory agencies as required.

Authorization To Use Your Health Information For Research Purposes

Because information about you and your health is personal and private, it generally cannot be used in this research study without your written authorization. If you sign this form, it will provide that authorization. The form is intended to inform you about how your health information will be used or disclosed in the study. Your information will only be used in accordance with this authorization form and the informed consent form and as required or allowed by law. Please read it carefully before signing it.

What is the purpose of this research study and how will my health information be utilized in the study?

The purpose of this research study is to assess the safety of administering allogenic, donor-derived CD19/CD22-CAR T cells that meet established release specifications in adults with B-cell ALL following a myeloablative conditioning regimen and Orca-T to determine if this will augment graft versus leukemia without increasing acute GVHD or graft failure.

Your health information will be used to verify the study conduct and data entry, assess the study treatment effects, and prepare regulatory documents for submission to the Sponsor, FDA, and/or other national regulatory agencies for marketing approval. Your coded information may also be used in research related to the study drug, your cancer and related diseases, and/or diagnostics to inform treatment.

Do I have to sign this authorization form?

You do not have to sign this authorization form. But if you do not, you will not be able to participate in this research study, including receiving any research-related treatment.

Signing the form is not a condition for receiving any medical care outside the study.

If I sign, can I revoke it or withdraw from the research later?
If you decide to participate, you are free to withdraw your authorization regarding the use and disclosure of your health information (and to discontinue any other participation in the study) at any time. After any revocation, your health information will no longer be used or disclosed in the study, except to the extent that the law allows us to continue using your information (e.g., necessary to maintain integrity of research). If you wish to revoke your authorization for the research use or disclosure of your health information in this study, you must write to:

Lori Muffly, MD, MS
875 Blake Wilbur Dr, Clinic F, MC 6560
Stanford, CA 94305
650-721-2785

What Personal Information Will Be Obtained, Used or Disclosed?
Your health information related to this study, may be used or disclosed in connection with this research study, including, but not limited to, your personal information (such as name, address, telephone number, date of birth); demographics (e.g. gender, race, ethnicity); medical history (especially cancer history and data relevant to stem cell transplant procedures and outcome); information from laboratory tests, radiology scans blood and urine tests, physical exams and other study tests or procedures; and information learned during telephone calls and office visits done as part of this research study.

Who May Use or Disclose the Information?

The following parties are authorized to use and/or disclose your health information in connection with this research study:

- The Protocol Director, Dr. Lori Muffly
- The IND Sponsor, Dr. Melody Smith
- The Stanford University Administrative Panel on Human Subjects in Medical Research and any other unit of Stanford University as necessary
- Stanford University Laboratory for Cell and Gene Medicine facility staff
- Research Staff

Who May Receive or Use the Information?

The parties listed in the preceding paragraph may disclose your health information to the following persons and organizations for their use in connection with this research study:

- The Office for Human Research Protections in the U.S. Department of Health and Human Services
- Orca Bio, Inc., its licensees and collaborators, and the clinical research organizations that help manage the study
- The Food and Drug Administration

Your information may be re-disclosed by the recipients described above, if they are not required by law to protect the privacy of the information.

When will my authorization expire?

Your authorization for the use and/or disclosure of your health information will end on December 31, 2057 or when the research project ends, whichever is earlier.

Will access to my medical record be limited during the study?
To maintain the integrity of this research study, you may not have access to any health information developed as part of this study until it is completed. At that point, you would have access to such health information if it was used to make a medical or billing decision about you (e.g., if included in your official medical record).

_____ _____
Signature of Adult Participant Date

_____
Print Name of Adult Participant

_____ _____
Signature of Legally Authorized Representative (LAR) Date
(e.g., parent, guardian or conservator)

_____
Print Name of LAR

LAR's Authority to Act for Participant
(e.g., parent, guardian or conservator)

FINANCIAL CONSIDERATIONS

Payment
You will not be paid to participate in this research study.

Costs
If you participate in this study, the study will pay for those services, supplies, procedures, and care associated with the study that are not a part of your routine medical care. However, there may be additional costs to you. These include basic expenses like transportation and the personal time it will take to come to the study visits. You and/or your health insurance must pay for services, supplies, procedures, and care that are required during this study for routine medical care. **You will also be responsible for any co-payments and/or deductibles as required by your insurance.** Participation in this study is not a substitute for health insurance.

Sponsor
Orca Bio, Inc. is providing financial support and/or material for this study.

Stanford University has a financial interest in Orca Bio, Inc., the company supplying materials for this study. Any equity or royalties will be held in an account managed by an independent third party, which will not know about the results of the human subjects research until publicly available.

COMPENSATION for Research-Related Injury

All forms of medical diagnosis and treatment – whether routine or experimental – involve some risk of injury. In spite of all precautions, you might develop medical complications from participating in this study. If such complications arise, the Protocol Director and the research study staff will assist you in obtaining appropriate medical treatment. In the event that you have an injury or illness that is directly caused by your participation in this study, reimbursement for all related costs of care first will be sought from your insurer, managed care plan, or other benefits program. **You will be responsible for any associated co-payments or deductibles as required by your insurance.**

If costs of care related to such an injury are not covered by your insurer, managed care plan or other benefits program, you may be responsible for these costs. If you are unable to pay for such costs, the Protocol Director will assist you in applying for supplemental benefits and explain how to apply for patient financial assistance from the hospital.

You do not waive any liability rights for personal injury by signing this form.

CONTACT INFORMATION

Questions, Concerns, or Complaints: If you have any questions, concerns or complaints about this research study, its procedures, risks and benefits, or alternative courses of treatment, you should ask the Protocol Director, Dr. Muffly. You may contact her now or later at 650-721-2785.

Injury Notification: If you feel you have been hurt by being a part of this study, please contact the Protocol Director, Dr. Muffly at 650-721-2785.

Independent Contact: If you are not satisfied with how this study is being conducted, or if you have any concerns, complaints, or general questions about the research or your rights as a participant, please contact the Stanford Institutional Review Board (IRB) to speak to someone independent of the research team at (650)-723-5244 or toll free at 1-866-680-2906. You can also write to the Stanford IRB, Stanford University, 1705 El Camino Real, Palo Alto, CA 94306.

Appointment Contact: If you need to change your appointment, please contact Lindsay Danley at (650) -736-0304.

Alternate Contact: If you cannot reach the Protocol Director, please contact Dr. Smith at (650)-723-9519.

EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

As a research participant you have the following rights. These rights include but are not limited to the participant's right to:

- be informed of the nature and purpose of the experiment;
- be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized;
- be given a description of any attendant discomforts and risks reasonably to be expected;
- be given an explanation of any benefits to the subject reasonably to be expected, if applicable;
- be given a disclosure of any appropriate alternatives, drugs or devices that might be advantageous to the subject, their relative risks and benefits;
- be informed of the avenues of medical treatment, if any available to the subject after the experiment if complications should arise;
- be given an opportunity to ask questions concerning the experiment or the procedures involved;
- be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation without prejudice;
- be given a copy of the signed and dated consent form; and
- be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion or undue influence on the subject's decision.

May we contact you about future studies that may be of interest to you?
____ Yes ____ No

Signing your name means you agree to be in this study and that you will receive a copy of this signed and dated consent form.

_____ _____
Signature of Adult Participant Date

_____
Print Name of Adult Participant

_____ _____
Signature of Legally Authorized Representative (LAR) Date
(e.g., parent, guardian or conservator)

_____
Print Name of LAR

_____
LAR's Authority to Act for Participant
(e.g., parent, guardian or conservator)

_____ _____
(If available) Signature of Other Parent or Guardian Date

_____
Print Name of Other Parent or Guardian

_____
Authority to Act for Participant

_____ _____
Signature of Person Obtaining Consent Date

_____
Print Name of Person Obtaining Consent

The following witness line is to be signed only if the consent is provided as a summary form and accompanied by a short form foreign language consent.

_____ _____

Signature of Witness Date

_____

Print Name of Witness

(e.g., staff, translator/interpreter, family member)

- *Translated short form must be signed and dated by both the participant (or their LAR) AND the witness.*
- *The English consent form (referred to as the "Summary Form" in the regulations):*
  - *Must be signed by the witness AND the Person Obtaining Consent (POC).*
  - *The non-English speaking participant/LAR does not sign the English consent.*
  - *The non-English speaking participant/LAR should not sign the HIPAA participant line*
  - *If the participant or the LAR is non-English speaking, the Person Obtaining Consent (POC) must ensure that 1) the LAR's Description of Authority is completed and 2) that any questions or options presented by the consent form are documented and initialed by the POC on the Summary Form, per the participant's wishes, as they are understood during the consent process.*