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UNIVERSITY OF WASHINGTON SCHOOL OF MEDICINE
FRED HUTCHINSON CANCER RESEARCH CENTER
SEATTLE CANCER CARE ALLIANCE

Consent to take part in a research study:

CC10075

A Phase II Trial of Umbralisib and Pembrolizumab in Patients with Relapsed or Refractory Classical Hodgkin Lymphoma

Sponsor-Investigator: Ryan Lynch, MD
825 Eastlake Ave. East
Seattle, WA 98109
(206) 606-1739

Emergency number (24 hours): 206-598-6190

University of Washington Medical Center paging operator. Please ask the operator to page the hematology-oncology fellow on call.

We would like you to join this research study

We are asking you to be in a research study. Research is not the same as treatment or medical care. The purpose of a research study is to answer scientific questions. The purpose of this consent form is to give you the information you will need to help you decide if you want to be in the study. Please read the form carefully. You may ask questions about the purpose of the research, what we would ask you to do, the possible risks and benefits, your rights as a volunteer, and anything else about the research or this form that is not clear. When we have answered all your questions, you can decide if you want to be in the study or not. This process is called 'informed consent.' We will give you a copy of this form for your records.

This consent form may contain words that you do not understand. Please ask the researcher or the study staff to explain any words or information that you do not clearly understand. You may take home an unsigned copy of this consent form to think about or discuss with family or friends before making your decision.

You do not have to be in the study. You are free to say "yes" or "no", or to drop out after joining. If you say "no," you would have no penalty or loss of benefits. Whatever you decide, your regular medical care would not change. You could choose to receive standard methods to treat your cancer.

We invite you to join this research study because you have relapsed or refractory Classical Hodgkin Lymphoma. Up to twenty (20) people will take part in this study.

Please read this description carefully. We will give you details about the purposes, procedures, risks and possible benefits related to this study. We will explain other choices that you have. We will also give you any other information that you need in order to make an informed decision about joining this study. Afterwards, you can ask questions that will help you decide whether to join the study. If you join this study, we would give you a signed copy of this form to keep for future reference.

PURPOSE OF THE STUDY

The purpose of this study is to study the effects (both good and bad) of using Umbralisib in combination with Pembrolizumab to treat patients with relapsed or refractory Classical Hodgkin Lymphoma. If you join this study, we would give you umbralisib and pembrolizumab and watch carefully for any side effects.

Classical Hodgkin Lymphoma is a type of cancer that affects the lymphatic system. The lymphatic system helps to fight infections and disease.

Pembrolizumab (MK-3475, Keytruda ®) is a type of drug that targets cancer cells. It is approved by the U.S. Food and Drug Administration (FDA) has recently been approved to treat individuals who have refractory Classical Hodgkin Lymphoma or those who have relapsed after 3 or more prior treatments.

Umbralisib belongs to a new class of drugs called "PI3K delta inhibitors". Umbralisib stops affected lymphocytes from increasing in numbers and shortens their life time.

Your study doctor can give you more information about the use of this medication.

PROCEDURES

If you join this study, we would do these tests and procedures. Most of these procedures are considered standard care for patients with relapsed or refractory Classical Hodgkin Lymphoma. The tests and procedures which are done only for research purposes are marked clearly below.

Screening/Baseline (within 4 weeks of starting treatment unless otherwise indicated):

- **Medical history** - You will be asked questions about your medical history. This includes ongoing medical conditions you have and drugs you are taking.
- **Physical exam** - Physical exams will assess your overall health status and include measuring your vital signs. This includes blood pressure, heart rate, temperature, and breathing rate. Your weight and height will also be recorded. You will also be asked how easily you perform daily activities.
- **Routine laboratory tests** - Blood samples will be taken for routine tests. About 2 - 3 teaspoons of blood will be taken and your blood will be tested for levels for certain components to see if it is safe for you to receive treatment. A little over a teaspoon of blood will be taken to test for hepatitis and HIV.
- **Pregnancy test** - If you are a female who could become pregnant, you will have a pregnancy test. A blood sample will be taken for this test.
- **Electrocardiogram (ECG/EKG)** - Sticky patches are placed on your chest, arms and legs. These patches are connected to a machine which shows the electrical activity of your heart. Radiation is not used to obtain an ECG. If you're sensitive to the adhesive on the sticky patches, you may have a little redness where the patch was attached to your skin.
- **PET Positron Emission Tomography (PET) scans**: PET scans use x-rays or radiation to allow doctors to see images of the part(s) of your body affected by cancer.
- **Optional research lab testing**: We will request up to 4 teaspoons of blood will be taken for research tests. The results will not be reported in your medical record.
- **Optional diagnostic tissue**: We will request 10 slides of your diagnostic tissue, if available.

Cycles 1 –16, Day 1 (+/- 3 days):

- **Physical exam** - Physical exams will assess your overall health status and include measuring your vital signs. This includes blood pressure, heart rate, temperature, and breathing rate. Your weight will also be recorded. You will also be asked how easily you perform daily activities and what drugs you are taking.
- **Routine laboratory tests** - Blood samples will be taken for routine tests. About a teaspoon of blood will be taken and your blood will be tested for levels for certain components to see if it is safe for you to receive treatment.
- **Side effects assessment (adverse events)** – Questions about symptoms and side effects

will be part of each visit, to determine what side effects that you are experiencing during treatment.
- **Research lab testing**: Up to 4 teaspoons of blood will be taken for research tests at day 1 of every cycle. The results will not be reported in your medical record.

Umbralisib alone - Every 4th cycle starting with Cycle 17 (e.g. 17, 21, 25, etc) until the end of treatment, Day 1 (+/- 3 days):

- **Physical exam** - Physical exams will assess your overall health status and include measuring your vital signs. This includes blood pressure, heart rate, temperature, and breathing rate. Your weight will also be recorded. You will also be asked how easily you perform daily activities and what drugs you are taking.
- **Routine laboratory tests** - Blood samples will be taken for routine tests. About a teaspoon of blood will be taken and your blood will be tested for levels for certain components to see if it is safe for you to receive treatment.
- **Side effects assessment (adverse events)** – Questions about symptoms and side effects will be part of each visit, to determine what side effects that you are experiencing during treatment.

Off-study visit (end of treatment visit):

- **Physical exam** - Physical exams will assess your overall health status and include measuring your vital signs. This includes blood pressure, heart rate, temperature, and breathing rate. Your weight will also be recorded. You will also be asked how easily you perform daily activities.
- **Routine laboratory tests** - Blood samples will be taken for routine tests. About a teaspoon of blood will be taken and your blood will be tested for levels for certain components to see if it is safe for you to receive treatment.
- **Side effects assessment (adverse events)** – Questions about symptoms and side effects will be part of each visit, to determine what side effects that you are experiencing during treatment.
- **PET Positron Emission Tomography (PET) scans**: PET scans use x-rays or radiation to allow doctors to see images of the part(s) of your body affected by cancer.

Long Term Follow-Up:

- Long term follow-up means keeping track of your medical condition. Your medical condition will be followed for one (1) year after your end of treatment. In order to do this, we will obtain the following information regarding your medical condition:
    - **Physical exam** - Physical exams will assess your overall health status and include measuring your vital signs. This includes blood pressure, heart rate, temperature, and breathing rate. Your weight will also be recorded. You will also be asked how easily you perform daily activities

Required Studies	Pre-Entry (within 4 weeks of cycle 1 day 1 unless indicated otherwise)	Within 3 days prior to each cycle (cycle 1-16)	Restaging	Within 3 days prior to every 4th cycle starting with cycle 17 while on umbralisib alone	EOT	Follow-up
Physical						
History and Physical	X	X		X	X	
Performance Status	X	X		X	X	
Clinical Disease Assessment	X	X		X	X	X
Adverse Event Assessment	X	X		X	X	
Concomitant Medication Assessment	X	X		X	X	
Lab						
TSH, T3, T4, LDH, ESR	X		X	X	X	
CBC with differential	X	X	X	X	X	
Comprehensive metabolic panel	X	X	X	X	X	
Serum Pregnancy test	X					
Hepatitis B/C serology, , direct and indirect coombs, CMV	X					
Radiology						
EKG	X					
PET/CT	X		X		X	
CT			X		X	
Correlative Studies	X	X	X		X	

RISKS AND DISCOMFORTS

Risks of Pembrolizumab

Pembrolizumab, which is approved in the USA and some other countries, is available by prescription to treat several different cancers, but may not be approved to treat your type of cancer.

Pembrolizumab works by helping your immune system to fight your cancer.

However, pembrolizumab can also cause your immune system to attack normal organs and tissues in your body and can affect the way they work, which can result in side effects that may become serious or life-threatening, and in some cases, may lead to death.

The study doctor believes that the following side effects may be caused by pembrolizumab

Common (greater than 20% of people)

- Itching of the skin
- Cough
- Loose or watery stools

Less Common (greater than or equal to 10% to less than or equal to 20% of people)

- Joint pain
- Fever
- Back pain
- Rash
- Low level of salt in the blood that may cause you to feel tired, confused, have a headache, muscle cramps, and/or feel sick to your stomach
- Pain in your belly
- Loss of skin color
- Not enough thyroid hormone so you may feel tired, gain weight, feel cold, have infrequent or hard stools

Uncommon (greater than or equal to 1% to less than 10% of people)

- Inflammation of the lungs so you may feel short of breath and cough. Sometimes this condition might lead to death
- Too much thyroid hormone so you may feel anxious, angry, have trouble sleeping, feel weak, tremble, sweat, feel tired, have loose and watery stools
- Infusion reaction, where you may feel dizzy or faint, flushed, get a rash, have a fever, feel short of breath at the time of receiving your infusion (IV) or just after, or pain at the site of infusion
- Inflammation of the bowels/gut, which may cause severe pain in your belly with loose or watery stools, and black, tarry, sticky stools or stools with blood or mucus
- Inflammation of the skin so you may have peeling of the skin, itchiness, and/or skin redness. The skin inflammation (i.e. peeling, itching and redness) could also be widespread throughout your body. More severe skin reactions may involve the inside of

your mouth, the surface of your eye and genital areas, and/or may cause the top layer of your skin to peel from all over your body which can cause severe infection. These severe conditions can sometimes lead to death

Rare (less than to 1% of people)

- Immune-mediated Inflammation of the nerves that may cause pain, weakness or tingling in your hands and feet, and may spread to your legs, arms and upper body leading to severe muscle weakness and possible temporary paralysis
- Inflammation of the muscles so you may feel weak or have pain in your muscles
- Inflammation of the pancreas (a gland in your abdomen that controls sugar levels) so you may have severe pain in the top part of your belly that may move to your back, feel sick to your stomach, and vomiting that gets worse when you eat
- Inflammation of the eye so you may have redness, blurred vision, sensitivity to light, eye pain, see floaters or have headaches
- Inflammation of the liver that may make you feel sick to your stomach and vomit, feel like not eating, feel tired, have a mild fever, have a pain in the right side of your belly, yellow eyes and skin, and dark urine
- Inflammation of the pituitary gland (a gland in the head), which may cause you to feel sick to your stomach or have headaches, changes in your behavior, double vision, few to no menstrual cycles, weakness, vomiting and dizziness or fainting
- Adrenal glands (glands on top of the kidneys) that may not make enough hormone, which could cause tiredness, weight loss, muscle weakness, feeling faint, joint, muscle and belly aches, nausea, vomiting, loose or watery stools, fever, salt craving, and sometimes darkening of the skin like a suntan
- Type 1 Diabetes, a condition that can cause too much sugar in your blood, feeling thirstier than usual, frequent urination and weight loss. You are likely to need regular insulin shots.
- Inflammation of the kidney so you may pass less urine or have cloudy or bloody urine, swelling and low back pain
- Inflammation of the middle layer of your heart wall that may cause your heart to have difficulty pumping blood throughout your body, which can cause chest pain, shortness of breath and swelling of the legs. You may experience a fast or irregular heartbeat that may cause dizziness or fainting. Sometimes this condition can lead to death
- Inflammation of the thyroid gland, an organ that makes and stores thyroid hormones. This condition may lead to change in your heart rate, blood pressure, body temperature, and the rate at which food is converted into energy.
- A condition that may make you feel weak and tired and might have drooping of the eyelids, blurred or double vision, difficulty swallowing, slurred speech, weakness in your arms and legs, or difficulty breathing
- The formation of small clusters of immune cells (called granulomas) in parts of your body such as your lymph nodes, eyes, skin, or lungs
- Inflammation of the brain with confusion and fever. This may also include: disorientation, memory problems, seizures (fits), changes in personality and behavior, difficulty speaking, weakness or loss of movement in some parts of your body, and loss of consciousness

Risks of Umbralisib

The following side effects have been reported as at least possibly related to umbralisib in other studies:

Common (greater than or equal to 10%)

- Anemia (decrease in the number of red blood cells)
- ALT increase
- AST increase
- Blood creatinine increase
- Diarrhea
- Fatigue/tiredness
- Low levels of lymphocytes
- Low platelet levels
- Fever
- Nausea
- Decrease in number of white blood cells
- Vomiting
- Decreased appetite
- Rash

Uncommon (greater than or equal to 1% to less than 10% of people)

- Fever with decrease in white blood cells, white blood cells above normal range, decreased number of platelets
- Vision blurred
- Abdominal bloating, abdominal pain, constipation, dry mouth, indigestion, inflammation of the bowel that can cause, severe diarrhea which may require hospitalization
- Fever, weakness, chills, general discomfort, swelling of hands, arms, legs, ankles, and/or feet
- Yeast infection in the mouth, pneumonia, infection of the mouth or throat
- Increase in liver enzymes, increase in levels of creatinine in blood which can indicate decreased kidney function, increase in lymphocyte count (type of white blood cell), weight loss
- Dehydration, increase in blood sugar levels, decrease in levels of potassium in blood, decrease in levels of phosphate in blood which can lead to bone weakness
- Pain in joints, muscle spasms, pain in arms and/or legs
- Dizziness, change in taste, headache, numbness and/or tingling of the hands and/or feet, involuntary shaking or trembling
- Difficulty sleeping
- Cough
- Hair loss, night sweats, itching
- Damage to multiple organs (sepsis)
- Inflammation of the colon (colitis)

- Edema (swollen limbs)
- Sepsis including septic shock
- Maculo-papular rash

Rare (less than to 1% of people)

- Blood disorders
- Ringing in the ears
- Problems with eyesight
- Gas (flatulence)
- Stomach pains
- Mouth sores
- Pancreas inflammation (Pancreatitis)
- Fungal skin infections and eczema
- Tingling in arms, legs and mouth
- Anxiety, hallucinations or poor memory
- Erectile Dysfunction
- Hot flashes

Women who are pregnant or nursing a child may not take part in this study. Before entering the study, you and your study doctor must agree on the method of birth control you will use during the entire study. If you think that you have become pregnant during the study, you must tell your study doctor immediately. Pregnant women will be taken out of the study.

Men who are in this study should not get a sexual partner pregnant while taking the study drug and for 4 months after the last dose of study drug. The effect of the study drug on sperm is not known.

Electrocardiogram (ECG/EKG)

Electrocardiogram (ECG) is a recording of the heart's beats. An ECG shows the electrical activity of the heart. You may have mild irritation, slight redness, or itching at the sites on your skin where the recording patches are placed.

Blood Draws

Blood draws may cause pain, bleeding, and/or bruising. You may faint and/or get an infection. Infection rarely happens. There may be redness and irritation at the place where the needle enters your vein.

Intravenous Line (IV Line)

Infusion of the Pembrolizumab may cause discomfort, irritation, mild bruising, bleeding, leakage of the drug solution, and rarely infection, nausea and lightheadedness.

Radiation risks

Some of the tests that you will have in this research study will expose you to radiation. Everyone receives a small amount of radiation every day called "background radiation". This radiation is natural and comes from space, air, water, soil, and the food you eat. Each year you are exposed to about 3 milliSieverts (mSv) of this background radiation. A milliSievert is a unit of radiation dose. For comparison, the estimated radiation dose from each of these tests is listed below. The risk to your health from this level of radiation exposure is too low to be detectable and may be nonexistent.

18-FDG PET/CT Scan: 19 mSv
CT-chest: 7 mSv
CT-abdomen: 8 mSv
CT-pelvis: 6 mSv
CT-head: 2 mSv
CT-neck: 3 mSv

NEW INFORMATION
You will be told about any new information that might change your decision to be in this study. You may be asked to sign a new consent form if this occurs.

BENEFITS

We do not know if this study would help you. We are testing umbralisib in combination with pembrolizumab to see its effects on people with relapsed or refractory Classical Hodgkin Lymphoma. You might get better if you receive umbralisib and pembrolizumab, but your condition could stay the same or even get worse. We hope the information from this study will help other people with relapsed or refractory Classical Hodgkin Lymphoma in the future.

COSTS
TG Therapeutics, Inc. will provide the study drug (umbralisib) free of charge during this study. The cost of Pembrolizumab will be billed to you or your insurance company. Tests and procedures that are done only for the study will not be billed to you or your insurance company.

You or your insurance company may be billed for any standard medical care given during this research study.

You may want to talk with your insurance company about its payment policy for standard medical care given during a research study. If your insurance company does not pay, you may be billed for those charges.

You might have unexpected expenses from being in this study. Ask your study doctor to discuss the costs that will or will not be covered by the sponsor. This discussion should include who will pay the costs of treating possible side effects.

PAYMENT FOR PARTICIPATION
You will not be paid for taking part in this study. You might have unexpected expenses from being in this study. You may want to talk with your insurance company about its payment policy for standard medical care given during a research study. If your insurance company does not pay, you may be billed for those charges. If you have any questions about what is billed to you or your insurance company, you may call a study staff member.

Reimbursement for travel expenses may be available. Please talk with the Principal Investigator or study staff about this option.

ALTERNATIVE TREATMENT
If you decide not to enter this study, there are other choices available. Ask the study doctor to discuss these alternatives with you. You do not need to be in this study to receive treatment for your cancer. The other choices include:

- Standard treatment
- Another research study
- No treatment
- Comfort care

The study team strongly suggests that you do not take any type of "alternative" or "naturopathic" medications because they may interfere with the study medications.

CONFIDENTIALITY
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.

Your participation in this study will be noted in your UW medical record.

The information may also be given to the U.S. Food and Drug Administration (FDA). It may be given to governmental agencies in other countries where the study drug may be considered for approval. Medical records which identify you and the consent form signed by you will be looked at and/or copied for research or regulatory purposes by:

- the sponsor, TG Therapeutics, Inc., and any agent for the sponsor
- Seattle Cancer Care Alliance, University of Washington and Fred Hutchinson Cancer Research Center
- Fred Hutchinson Cancer Research Center Institutional Review Board (an IRB is a group that reviews the study to protect the right and welfare of research participants).
- Food and Drug Administration (FDA)
- Office for Human Research Protections (OHRP)
- Department of Health and Human Services (DHHS) agencies,

We will do our best to keep personal information confidential. Absolute confidentiality cannot be guaranteed because of the need to give information to these parties. The results of this research study may be presented at meetings or in publications. Your identity will not be disclosed in those presentations. Personal information may be given out if required by law. For example, workplace safety rules may require health workers to contact you about lab tests. Or a court may order study information to be disclosed. Such cases are rare.

If you join this study, information about your participation would be made part of your permanent medical record. This information would include a copy of this consent form. If an insurance company or employer or anyone else were authorized to see your medical record, they would see a copy of this consent form.

COMPENSATION FOR INJURY

In the event of injury to a research participant, resulting from research procedures, appropriate medical treatment will be available at the University of Washington to the injured research participant; however, financial compensation will not be offered.

No money has been set aside to pay for things like lost wages, lost time, or pain. However, you do not waive any rights by signing this consent form.

VOLUNTARY PARTICIPATION AND WITHDRAWAL

Your participation in this study is voluntary. You may decide not to participate, or you may leave the study at any time. Your decision will not result in any penalty or loss of benefits to which you are entitled.

Your participation in this study may be stopped at any time by the study doctor or the sponsor without your consent for any reason, including:

- if it is in your best interest,
- you do not consent to continue in the study after being told of changes in the research that may affect you

If you leave the study before the planned final visit, you may be asked by the study doctor to have some tests or procedures done so that you leave the study safely.

SOURCE OF FUNDING FOR THE STUDY

The sponsor TG Therapeutics, Inc. is paying for this research study.

QUESTIONS

WHO CAN ANSWER MY QUESTIONS ABOUT THE RESEARCH STUDY?

If you have questions about:	**Call:**
This study (including complaints and requests for information)	206-606-1739 (Ryan Lynch, MD, Principal Investigator)
If you get sick or hurt in this study	206-606-1739 (Dr. Ryan Lynch)

Your rights as a research participant	206-667-5900 or email irodirector@fredhutch.org (Director of Institutional Review Office, Fred Hutchinson Cancer Research Center) 206-543-0098 (Human Subjects Division, University of Washington)
Your bills and health insurance coverage	206-606-1377 (Patient Financial Services, Seattle Cancer Care Alliance)
24-hour emergency number	(206) 598-6190 (UWMC Paging Operator)

Contact Ryan Lynch, MD at (206) 606-1739 for any of the following reasons:

- if you have any questions about your participation in this study,
- if you feel you have had a research-related injury or a reaction to the study drug, or
- if you have questions, concerns or complaints about the research

You may also contact:

Human Subjects Division
University of Washington
Box 359470
Seattle, Washington 98195-9470
Telephone: 206-543-0098
(You may also call collect at 206-221-5940 if you do not otherwise have access to a telephone)
Email: hsdinfo@uw.edu

Do not sign this consent form unless you have had a chance to ask questions and have gotten satisfactory answers.

If you agree to be in this study, you will receive a signed and dated copy of this consent form for your records

CONSENT

I have read this consent form (or it has been read to me). All my questions about the study and my part in it have been answered. I freely consent to be in this research study.

By signing this consent form, I have not given up any of my legal rights.

☐ I agree to have the optional blood draws collected as part of this Study.

☐ I do **NOT** agree to have the optional blood draws collected as part of this Study.

☐ I agree to allow the collection of my tissue from my diagnosis, if available.

☐ I do **NOT** agree to allow the collection of my tissue from my diagnosis, if available.

_____
Subject Name (printed)

_____ _____
Signature of Subject Date

_____
Person Conducting Informed Consent (printed)

_____ _____
Signature of Person Conducting Informed Consent Discussion Date

---------- Use this section only if applicable ----------

If this consent form is read to the subject because the subject is unable to read the form, an impartial witness not affiliated with the research or investigator must be present for the consent and sign the following statement:

I confirm that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject. The subject freely consented to be in the research study.

_____
Printed Name of the Impartial Witness

_____ _____
Signature of the Impartial Witness Date

If you served as an interpreter or witness during the consent process, sign below to indicate you attest to the accuracy of the presentation to the participant and the apparent understanding of the research by the participant.

_____

Printed Name of Interpreter

_____ _____

Signature of Interpreter Date

Copies to: Researcher's file
Subject
Subject's medical record (if applicable)