University of California, San Diego

Consent to Act as a Research Subject

A Phase I/II study of blinatumomab in combination with pembrolizumab (MK-3475) for adults with relapsed or refractory B-lineage acute lymphoblastic leukemia with high bone marrow lymphoblast count:

A University of California Hematologic Malignancies Consortium Study

Protocol No. 161287/UCHMC1504

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Matthew Wieduwilt, MD, PhD and his colleagues are conducting a research study sponsored by the University of California Hematologic Malignancies Consortium with Amgen Inc and Merck Inc to find out more about the experimental drug called pembrolizumab in combination with blinatumomab. You are being asked to take part because you have B-cell acute lymphoblastic leukemia (ALL) that is relapsed (disease came back after remission) or refractory (disease was not completely eliminated with treatment)."

Your participation in this research study is voluntary. The purpose of this Informed Consent Form is to inform you about the nature of this research study so that you may make an informed decision as to whether you would like to participate. If you have any questions, please ask your study doctor or coordinator to explain any words or information that you do not understand.

PURPOSE

The purpose of the study is to investigate the safety of the drug combination pembrolizumab (also known as MK-3475) and blinatumomab, and to determine whether this combination has an effect on your cancer and body. Blinatumomab is a standard treatment for relapsed or refractory B-cell acute lymphoblastic leukemia (ALL).

Pembrolizumab is a type of drug called an immunomodulatory drug. This drug is approved by the United States (U.S.) Food and Drug Administration (FDA) as a treatment for unresectable (cannot have surgery) or metastatic (the cancer has spread to other parts of the body) melanoma. Pembrolizumab is considered experimental because it is not approved by the FDA for the treatment of B-cell ALL.

Participation in this study is entirely voluntary. A total of 24 participants will take part in this multi-center study. Approximately 6 participants will be enrolled at UC San Diego.

DURATION OF THE STUDY / HOW LONG IS EACH VISIT?

The length of your participation in this study will be determined by how you react to the study

drugs. The study will involve a screening period, drug period (up to 28 weeks), and a follow-up period where we will follow your condition for up to 4 years.

Each of your study visits can last from approximately one to eight hours.

PROCEDURES

WHAT ARE MY OBLIGATIONS IF I TAKE PART IN THIS STUDY?

If you decide to take part in this study, you must be willing to do the following:

- Attend the scheduled visits
- Tell the study staff about any other medicines that you are taking
- Tell the study staff about any side effects of the drugs that you experience

WHAT WILL HAPPEN IF I TAKE PART IN THE STUDY?

If you agree to participate in this study, you will have the following tests and procedures to see if you are an appropriate candidate to participate further in the study. These tests are called "Screening Procedures."

Screening Procedures

The Screening Visit (Visit #1) may take between 2 and 8 hours to complete and the procedures may be scheduled over multiple days. Some of these may be part of your regular medical care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. Your study doctor will talk to you about these tests.

1. You will be asked about your medical history, including previous cancer therapies.
2. You will be asked for your demographic information (date of birth, gender, race, and ethnicity).
3. You will be given a physical exam and your weight, height and vital signs will be measured (your heart rate, blood pressure, and temperature).
4. You will be asked about any medications you are taking or have taken in the past.
5. You will be asked questions about your health and how your disease affects your daily life. You will also be asked to fill out a brief questionnaire about your quality of life.
6. Samples of your blood (approximately 2-3 tablespoons) will be drawn for laboratory tests:
    - Hematology or CBC (Complete Blood Count), which includes: white blood cell count, red blood cell count, platelet count, hemoglobin (oxygen-carrying pigment in red blood cells), hematocrit (measures the amount of space red blood cells take

up in the blood). This is to aid in diagnosing anemia (low red blood cell count which can result in fatigue), certain cancers of the blood, and to monitor blood loss and infection.

- Blood chemistry (which measures the levels of a number of chemical substances that are released from various tissues in the body to evaluate the function of the liver and kidneys).
- Coagulation studies (a test to determine how quickly your blood clots).
- Hepatitis screening: You will be informed of the results of the tests. The results of the tests, if positive, will be reported to the San Diego County health department as required by law and entered in your medical record. Your study doctor will discuss this with you

7. HIV testing is done to make sure that the study procedures are appropriate for you. If you test positive for HIV, the results must be entered in your medical record and provided to the California State Board of Health as required by law.

8. A pregnancy test will be performed if you are a woman of child-bearing potential. Pregnant women cannot be on the study.

9. You will have a chest X-ray. This test is performed by an x-ray technician. You will be asked to stand in front of the machine and must hold your breath when the x-ray is taken.
10. You will have a CT (or PET) scan of your chest, abdomen and pelvis to measure your disease.
    - CT scan: The CT (computed tomography) scanner is a free-standing machine with a large hole in the center. You will be asked to lie on your back with your arms raised above your head on a narrow table that slides into the hole. Patients who have difficulty with enclosed spaces such as those found with some MRI scanners do not usually have a problem with this type of test. A dye may be injected into a peripheral vein to better evaluate certain diseases and organs. The radiologist will decide if this is necessary. Tell the technician or radiologist if you have any allergies or have had difficulty with prior CT scans. It is very important that you remain still throughout the exam and hold your breath when asked. This will allow for better images. The actual scan time is usually about two minutes, although the entire procedure usually takes much longer.
    - Positron Emission Tomography (PET scan). You will be taken into a special injection room, where the radioactive substance is administered as an intravenous injection (although in some cases, it will be given through an existing intravenous line or inhaled as a gas). It will then take approximately 30 to 90 minutes for the

substance to travel through your body and accumulate in the tissue under study. During this time, you will be asked to rest quietly and avoid significant movement or talking. After that time, scanning begins.

11. You will have a bone marrow aspirate and biopsy. A bone marrow aspirate will be performed, usually before the biopsy is taken. The bone marrow sample is usually taken from the hip bone. The skin is cleansed, and a local anesthetic is injected to numb the skin. After the skin is numbed, the needle is inserted into the bone, and a syringe is used to withdraw the liquid bone marrow. You will feel a sting and slight burning sensation when the numbing medicine is applied. You may feel pressure as the needle is inserted into the bone, and a sharp and sometimes painful sucking sensation as the marrow is removed. This feeling lasts for only a few moments.

    The needle will be removed and either repositioned, or another needle may be used for the biopsy. The biopsy needle is then inserted into the bone. The core of the needle will be removed, and the needle is pressed forward and rotated in both directions. This forces a tiny sample of the bone marrow into the needle. The needle is then removed. Pressure is applied to the biopsy site to stop bleeding, and a bandage is applied. The biopsy needle may also cause a brief, usually more dull, pain. However, not all patients have such pain.

If the exams, tests and procedures show that you can be in the study and you choose to take part, you will receive the study drugs.

Study Procedures

At each study visit you will be asked about any current symptoms, whether you have had any side effects, and if there have been any changes to the medications you take since the last visit.

On day 29 during cycles 1 through 4 and day 38 of cycle 5 you will have a lumbar puncture (spinal tap) with intrathecal (delivered with a needle directly into the fluid surrounding your spinal cord) methotrexate. In this study you will have a total of 6 doses, including the dose given at screening.

Cycle 1 - Hospital admission required day 1-9	
Day 1	• Get physical exam and routine blood tests. • Receive dexamethasone IV once 1 hour before start of infusion • Start IV infusion of blinatumomab for days 1-7 • Have a sample of blood taken to measure drug levels.
Day 2-3	• Have a sample of blood taken to measure drug levels.

Day 8	• Receive dexamethasone IV once 1 hour before start of infusion • Start IV infusion of blinatumomab for days 8-28 • Have a sample of blood taken to measure drug levels.
Day 9-10	• Have a sample of blood taken to measure drug levels.
Day 14	• Get routine blood tests • Have a bone marrow aspirate and biopsy. An extra sample will be taken for research studies.
Day 15	• Have a sample of blood taken to measure drug levels. • Receive IV infusion of pembrolizumab.
Day 16-17	• Have a sample of blood taken to measure drug levels.
Day 21	• Have a sample of blood taken to measure drug levels.
Day 29	• Get routine blood tests • Have a bone marrow aspirate and biopsy. An extra sample will be taken for research studies. • May have an imaging scan (CT or PET) of your chest, abdomen and pelvis • Have a lumbar puncture with methotrexate.
Day 36	• Get routine blood tests • Receive IV infusion of pembrolizumab.

Cycle 2 - Hospital admission required day 1-2	
Day 1	• Get routine blood tests • Receive dexamethasone IV once 1 hour before start of infusion • Start IV infusion of blinatumomab for days 1-28
Day 15	• Get routine blood tests • Receive IV infusion of pembrolizumab.
Day 29	• Get routine blood tests • Have a bone marrow aspirate and biopsy. An extra sample will be taken for research studies. • May have an imaging scan (CT or PET) of your chest, abdomen and pelvis • Have a lumbar puncture with methotrexate.
Day 36	• Get routine blood tests • Receive IV infusion of pembrolizumab
Cycle 3 and 4	

Day 1	• Get routine blood tests • Receive dexamethasone IV once 1 hour before start of infusion • Start IV infusion of blinatumomab for days 1-28
Day 15	• Get routine blood tests • Receive IV infusion of pembrolizumab.
Day 29	• Get routine blood tests • Have a bone marrow aspirate and biopsy. An extra sample will be taken for research studies. • Have an imaging scan (CT or PET) of your chest, abdomen and pelvis • Have a lumbar puncture with methotrexate.
Day 36	• Get routine blood tests • Receive IV infusion of pembrolizumab.
Cycle 5	
Day 1	• Get routine blood tests • Receive dexamethasone IV once 1 hour before start of infusion • Start IV infusion of blinatumomab for days 1-28
Day 15	• Get routine blood tests • Receive IV infusion of pembrolizumab.
Day 36	• Get routine blood tests • Receive IV infusion of pembrolizumab.
Day 38 (End of Treatment Visit)	• Get routine blood tests • Have a bone marrow aspirate and biopsy. An extra sample will be taken for research studies. • Have an imaging scan (CT or PET) of your chest, abdomen and pelvis • Have a lumbar puncture with methotrexate.

End of Treatment	
Day 38	• Get routine blood tests • Have a bone marrow aspirate and biopsy. An extra sample will be taken for research studies. • Have an imaging scan (CT or PET) of your chest, abdomen and pelvis • Have a lumbar puncture with methotrexate.
Every 3 months until	• Get physical exam and routine blood tests.

discontinuation of trial participation.	

Upon discharge from the hospital, your coordinator will arrange infusion center appointments to ensure that you continue receiving blinatumomab. You will continue receiving blinatumomab while using an ambulatory infusion pump and will come in to the infusion center for IV bag changes.

A participation information sheet and instructions about your infusion pump will be provided to you in a separate document.

Biological Samples

As described in the study Procedures above, blood samples will be collected from you throughout the study.

Additional research samples will also be collected throughout the study. Bone marrow will be collected with your standard of care bone marrow and sent to a central reader for evaluation of specific biomarkers (biological properties or molecules that can be detected and measured in parts of the body like the blood or tissue. These biomarker samples will be collected at screening, cycle 1 day 14, cycle 1 day 38-42, cycle 2 day 38-42, cycle 5 day 38-42, and relapse (if applicable). Serum cytokines will also be collected from peripheral blood on days 1, 2, 3, 8, 9, 10, 15, 16, 17, and 21 of cycle 1.

These samples will be analyzed for biomarkers that might help determine which patients have a higher or lower likelihood of responding to pembrolizumab and blinatumomab. There will be no direct benefit to you from this testing since you will not be provided with any results or information regarding the testing of your sample. Samples will be sent to the UCSD Lab of Gerald Morris, MD, PhD. They will be stored until the study is completed and batch analysis of the samples can be performed.

Dr. Matthew Wieduwilt will be responsible for deciding how your samples will be used. Blood/Bone marrow taken from you may be used to establish products that could be patented and licensed. There are no plans to provide you with financial compensation should this occur. Your blood/bone marrow may also be used in additional research to be conducted by the University of California personnel and the group collaborating in this research, Amgen Inc and Merck, Inc. Biospecimens (such as blood, tissue, or saliva) collected from you for this study and/or information obtained from your biospecimens may be used in this research or other research, and shared with other organizations. You will not share in any commercial value or profit derived from the use of your biospecimens and/or information obtained from them.

If you decide later that you do not want the specimens collected from you to be used for future research, you may tell this to Dr. Matthew Wieduwilt, who will use his best efforts to stop any additional studies. However, in some cases, such as if your samples have already been tested, the data from these tests are no longer linked to your identity and cannot be removed from the research database

Federal and State laws generally make it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

a) Health insurance companies and group health plans may not request your genetic information that we get from this research.

b) Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.

c) Employers with 5 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

Be aware that these laws **do not** protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

RISKS OF PARTICIPATION

Participation in this study may involve some added risks or discomforts. While you are on this study, you are at risk for the side effects listed below. You should discuss these with your doctor. There may also be other side effects that we cannot predict. Other drugs will be given to make side effects less serious and uncomfortable. Many side effects go away shortly after the study drug is stopped, but in some cases, side effects may be serious, long-lasting, and may even cause death.

Possible side effects of specific drugs used in this study include:

Pembrolizumab

You may develop side effects while participating in this study. You should tell the study staff about any side effects that you develop.

The side effects listed below have been reported by patients who have received pembrolizumab. These side effects can affect more than one of your normal organs and tissues at the same time.

VERY COMMON, SOME MAY BE SERIOUS (i.e. causing hospitalization, life-threatening or where noted, may cause death) Out of 100 people who receive pembrolizumab, 20 or more people may have the following:

- Itching of the skin
- Loose or watery stools

- Cough

COMMON, SOME MAY BE SERIOUS (i.e. causing hospitalization, life-threatening, or where noted, may cause death) Out of 100 people who receive pembrolizumab, at least 5 but less than 20 people may have the following:

- Joint pain
- Rash
- Fever
- Back pain
- 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
- Low levels 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

UNCOMMON, SOME MAY BE SERIOUS (i.e. causing hospitalization, life-threatening, or where noted, may cause death) Out of 100 people who receive pembrolizumab, at least 1 but less than 5 people may have the following:

- Inflammation of the lungs so you may feel short of breath and cough. Sometimes this 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, experience a decrease in your blood pressure 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, SOME MAY BE SERIOUS (i.e. causing hospitalization, life-threatening, or where noted, may cause death) Out of 100 people who receive pembrolizumab, less than 1 person may have the following:

- 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 eye 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 bellyaches, 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.
- Inflammation of the spinal cord with pain, numbness, tingling, or weakness in the arms or legs, bladder or bowel problems including needing to urinate more frequently, urinary incontinence, difficulty urinating, and constipation (myelitis).

Additionally, since pembrolizumab was approved in September 2014, the following side effects have been reported by people receiving pembrolizumab. These side effects were voluntarily

reported from a group of people of unknown size. It is not possible to estimate the frequency of this side effect:

- Inflammation of the joints which may include joint pain, stiffness and/or swelling
- Severe responses of the immune system that cause the body to attack its own blood cells, spleen, liver, lymph nodes, skin and brain. This may include fever, rash, inflammation of the liver, yellowing of the skin, an enlarged liver and spleen, low blood counts, and enlarged lymph nodes. The nervous system may also be affected and cause confusion, seizures, and even coma.

In addition to the above, if you have had an allogenic stem cell transplant (a procedure in which a person receives blood-forming stem cells from a donor), you may experience graft versus host disease (GvHD), which may include diarrhea, skin rashes, and liver damage, after receiving pembrolizumab. Sometimes this condition can lead to death.

If you have had a solid organ transplant (for example, if you have received a kidney or heart transplant), you may experience rejection of the transplanted organ. Your doctor will monitor you and should tell you what signs and symptoms you should report depending on the type of organ transplant that you have had.

There is also the potential for immune-mediated complications, including death, in patients who proceed to allogeneic hematopoietic stem cell transplantation (HCST) after treatment with pembrolizumab.

Patients treated with pembrolizumab before going on to allogeneic stem cell transplant (a procedure in which a person receives blood-forming stem cells from a donor), should inform their transplant physicians that they have received pembrolizumab in the past.

In patients with any hematologic malignancy (cancers of the blood like Hodgkin lymphoma, multiple myeloma): B-lineage acute lymphoblastic leukemia there is a potential for an increased risk of severe complications following allogeneic stem cell transplant in patients who previously received pembrolizumab before an allogenic stem cell transplant.

Reports clotting of blood within the liver and severe graft versus host disease (which can include skin, liver and gastrointestinal symptoms), including death, have been received for patients who received pembrolizumab before an allogeneic stem cell transplant.

Blinatumomab

Blinatumomab may cause all, some, or none of the side effects listed below. These side effects can be mild but could also be serious, life-threatening or even result in death. You may also experience an allergic reaction that has not been seen before.

As 02 June 2017 approximately 1060 people have received blinatumomab in research studies. Since it was first approved for sale in December 2014 through 02 June 2017, approximately 2,295 people have been prescribed blinatumomab (Blincyto™) for treatment.

Side effects that other people have had in research studies that are thought to have been caused by blinatumomab are:

Very Common side effects (which may affect more than 1 person in 10):

- Anaemia (decreased red blood cells)
- Thrombocytopenia (decreased platelets, for clotting blood)
- Neutropenia (decreased neutrophils, a type of white blood cell that fights infection)
- Febrile neutropenia (decreased neutrophils with fever)
- Increased hepatic enzymes (in the blood, which may be due to inflammation or damage to liver cells)
- Tachycardia (rapid heart rate)
- Pyrexia (fever)
- Edema (swelling of hands, legs, ankles, feet, face, or trunk)
- Back pain
- Bone pain
- Headache
- Insomnia (difficulty falling and/or staying asleep)
- Cough
- Rash
- Hypotension (low blood pressure)
- Infections in the blood, including bacteria, fungai, viruses or infections in other organs. Serious infections can happen during and after treatment and can lead to death. Serious infections such as sepsis (infection in the bloodstream), and pneumonia (severe lung infection) have been reported in patients treated with blinatumomab. Your doctor may give you antibiotics to treat the infection or stop your treatment with blinatumomab.
- Infusion related reactions occur during or after the drug is given through the vein. Symptoms of infusion reaction may include headache, rash, itching, flushing, swelling, shortness of breath, nausea and sometimes vomiting. Severe infusion reactions can cause dizziness, severe skin reactions, difficulty breathing or swallowing, a decrease in blood pressure, and could be life threatening. Signs and symptoms of infusion reaction can be very similar to cytokine release syndrome.
- Cytokine release syndrome is when your body releases substances called cytokines during the blinatumomab infusion. This can cause fever, chills, headache, decreased blood pressure, increased liver enzymes, nausea, and vomiting. Cytokine release syndrome symptoms generally are mild to moderate but occasionally can be serious or life threatening, or may even lead to death. Your doctor may give you medications such as steroids and/or other medications to prevent or treat cytokine release syndrome.

Common side effects (which may affect between 1 and 10 people in every 100):

- Leukopenia, Lymphopenia (decreased types of white blood cells)
- Leukocytosis (increased white blood cells)
- Lymphadenopathy (swelling in lymph nodes)
- Hyperbilirubinemia (high levels of bilirubin in the blood)
- Decreased immunoglobulins (in the blood, proteins made by the body's immune system to fight against infections and foreign substances)
- Increased alkaline phosphatase (in the blood can be due problems in your liver or in your bones)
- Chills
- Chest pain
- Pain in the arms, legs and hands
- Overdose, Accidental overdose
- Weight increased
- Hypertension (high blood pressure)
- Flushing
- Dyspnea (difficulty breathing, wheezing or respiratory failure)
- Hypersensitivity, allergic reactions to blinatumomab, including hypersensitivity, have been reported. Signs and symptoms of allergic reactions can be very similar to infusion reaction. If you have symptoms of an allergic reaction, you should contact the study doctor or his/her study staff immediately.
- Hematophagic histiocytosis can occur with cytokine release syndrome, described above. It is a life threatening overactivity of your immune system caused by releasing large amount of inflammatory cytokines. Your doctor may give you medications such as steroids and/or other medications to prevent or treat cytokine release syndrome.
- Tumor lysis syndrome (a group of complications from release of large amounts of potassium, phosphate, and nucleic acid caused by the breakdown of tumor cells after cancer treatment). Tumor lysis syndrome may cause kidney failure, abnormal heart rhythm, and can even lead to death. Patients with moderate kidney failure showed an increased rate of tumor lysis syndrome compared with patients with mild kidney failure or normal kidney function. However, this did not lead to permanent discontinuation of treatment with blinatumomab. Your doctor may give you medicines before your treatment to help prevent tumor lysis syndrome.
- Nervous system problems such as tremor (shaking), dizziness, seizures, somnolence (changes in alertness), paresthesia (abnormal skin sensation such as burning, prickling, tingling), hypoaesthesia (numbness), aphasia (difficulty speaking or slurred speech), cognitive disorder (difficulty understanding words), encephalopathy (loss of consciousness, brain malfunction), memory impairment (memory loss), confusion and/or disorientation, or loss of balance. These nervous system problems can be serious or life threatening, or may even lead to death. Patients with a medical history of neurologic signs and symptoms had a higher rate of neurologic events (such as tremor, dizziness, confusion, encephalopathy and poor coordination). Your doctor will be closely monitoring you and may give you medications such as steroids and/or other medications to treat nervous system problems or stop your treatment with blinatumomab.

Uncommon side effects (which may affect between 1 and 10 people in every 1000):

- Speech disorder
- Cytokine storm, is a severe form of cytokine release syndrome described above
- Pancreatitis, inflammation of the pancreas that can be life-threatening or may even lead to death. Symptoms can include severe and persistent stomach pain, with or without nausea and vomiting.
- Leukoencephalopathy, a rare, serious disorder of the white matter in the brain that can lead to severe disability and death and for which there is no known prevention, treatment, or cure. Symptoms can include difficulty thinking, loss of balance, changes in speech or walking, weakness on one side of your body, or blurred or lost vision.
- Capillary leak syndrome(leakage of fluid from small blood vessels into other body spaces that could cause swelling of the trunk, arms and legs)
- Macrophage activation syndrome, a severe, potentially life-threatening, complication which can lead to continuous fevers, tiredness, headaches, and confusion.

What are the risks of using blinatumomab in combination with other drugs?

Tell the study doctor or the study staff about any drugs you are taking, have recently taken, or are planning to take, including herbal remedies, supplements, and drugs you take without a prescription. The side effects of using blinatumomab in combination with other drugs are unknown at this time. Please discuss any concerns you may have with the study doctor.

Additional Risks and Discomforts Associated with Study Procedures

Risk of Testing for HIV: Participation in this study will require that you be tested for HIV. These tests are necessary to make sure that these study procedures would be appropriate for you. Testing for HIV may result in a diagnosis of infection with this virus. You will be informed of the results of these tests; if you do not wish to know the results, you should refuse to participate in this study. In the event that you are diagnosed with HIV, your doctor will give you the results in a face-to-face discussion (not by telephone or mail), counseling will be offered to you, and the results will be entered in your medical record and provided to the California State Board of Health. In the event that you are diagnosed with HIV, you may be referred to a doctor who specializes in these illnesses. The diagnosis of HIV may result in earlier treatment and/or prevention of many complications from the illnesses. Efforts will be made to keep your personal information confidential. Awareness of a diagnosis of these illnesses may have serious personal or social consequences. Some of these consequences include possible difficulty obtaining health insurance or employment, and difficulty traveling to some foreign countries.

***Allergic Reactions*:** As with any drug, there is the chance of an allergic reaction, which may include difficulty breathing, rash, flushing, weakness, dizziness, lightheadedness, and swelling.

Intravenous (IV) Injection Side Effects: If the drug leaks from the vein, where the needle was inserted, it may cause skin irritation at the needle site and surrounding tissue. All injections into your vein can cause swelling, a burning sensation, tightness, bruising, bleeding, and/or nerve damage have a slight risk of pain, bleeding, infection, and rarely, fainting and/or nerve damage

Risks of blood draws: There is a risk of discomfort or pain, bleeding, swelling and a small arm bruise and swelling when blood is drawn. Rarely, a clot or infection may occur at the site of the blood draw. Some people also become faint, dizzy, or light-headed during or immediately after the blood draw.

Risks of bone marrow aspirate and biopsy: It is very painful when bone marrow is removed but pain will last only last 15 – 30 seconds. However, the area may be sore for a day or two. It is very rare, but you may have an allergic reaction to the numbing medicine; this reaction may include swelling in the throat, difficulty breathing, changes in heart rate or blood pressure, rashes or even death in rare cases. A large amount of bleeding or an infection are possible but are rare.

Risks of lumbar puncture: There is a risk of headache and nausea, discomfort or pain in the back, bleeding and infection.

Reproductive Risks: It is not known if blinatumomab is harmful to an unborn or breastfed baby.

If you become pregnant during this study, potential risks could include complications such as miscarriage (loss of the pregnancy) or birth defects.

In order to participate in the study you adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period.

Non-pregnant, non-breast-feeding women may be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 2 years will be considered postmenopausal), or 3) not heterosexually active for the duration of the study.

The two birth control methods must be two barrier methods OR a barrier method plus a hormonal method to prevent pregnancy. If you are female, you should start using birth control from study Day 1 throughout the study period and for 120 days after the last dose of study therapy.

The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

You should not become pregnant or father a baby while on this study because the drugs in this study can affect a fetus and cause serious birth defects. Women should not breastfeed a baby while on this study and for 60 days after the last study treatment. It is important you understand that you need to use birth control while on this study. If you are female and capable of child-bearing, a pregnancy test will be done before the study begins in order to be as sure as possible that you are not pregnant. Your participation requires that you use two contraception methods (such as abstinence, diaphragm, condom, or intrauterine device) to prevent pregnancy for the duration of the study. Ask about counseling and more information about preventing pregnancy.

If you or your partner become pregnant while you are participating in this study, you must report it to your study doctor immediately. Dr. Wieduwilt will then ask for permission to follow what happens to during and after the pregnancy using a separate informed consent document.

Risks from X-rays and/or Scans: During your participation in this research study, you will be exposed to radiation from scheduled x-rays and/or imaging scans. The total exposure resulting from these imaging studies is calculated to be 39.2-99.5 mSv, depending on which scans are required to adequately monitor your illness. This amount is more than you would receive from one year of natural exposure in the San Diego area, which is approximately 1.6 mSv. Cumulative exposure from radiation may increase your risk of developing certain types of cancer in the future.

The principal investigator for this research study has determined and verified that all of the imaging scans prescribed for this study would typically be performed as part of the standard medical care required to adequately monitor your current illness. Scans are typically done as part of your standard care to assess your disease. If you are especially concerned with radiation exposure, or you have had a lot of x-rays or imaging scans already, you should discuss this with study doctor for this study, Dr. Wieduwilt, or your regular doctor.

Risks of IV Contrast: As part of this study a CT scan may be done. There may be some reactions related to the contrast dye used in CT scans. Contrast dye is usually administered when you get a CT scan. Contrast dye may also be used in PET/CT scans and MRI scans. Some people may develop hives and itching or other allergic symptoms from this dye, swelling of the heart, cramps of the voicebox, breathing distress caused by narrowing of the airways in lungs, low blood pressure, with loss of consciousness, and in rare cases, severe loss of blood and fluids leading to shock and death, fainting, seizures, and irregular heartbeats. In addition, if you have low kidney function, this dye can temporarily or permanently decrease your kidney function.

Risks of Loss of Confidential Information: There is also a small risk that information from your health records will be released to an unauthorized party. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small. An identification code assigned by the study team to each participant will be used in place of your name to protect your identity when reporting trial-related data.

There may be other risks associated with participation in this study that are currently unforeseeable. You will be informed of any significant new findings.

BENEFITS OF PARTICIPATION

If you agree to take part in this study, there may not be direct medical benefit to you. Other patients in the future, however, may benefit from the information learned from this research study, and the investigators may learn more about pembrolizumab and the combination of pembrolizumab and blinatumomab in B-cell ALL.

ALTERNATIVES TO PARTICIPATION

If you choose not to take part in or stop participating in this research study, there may be other treatments. Refusal to take part in this study will not cause penalty or loss of benefits to which you are otherwise entitled.

You do not have to participate in this study to receive treatment for your cancer. Other possible treatments could include treatment with other drugs or drug combinations, or other research studies. Please talk to your doctor about these and other options.

You do not have to participate in this study to receive blinatumomab. Blinatumomab (Blincyto) is commercially available.

Please talk to your doctor about these and other options.

COSTS/COMPENSATION

The study drugs, pembrolizumab and blinatumomab will be supplied at no cost while you take part in this study. The cost of getting the study drugs, Pembrolizumab and Blinatumomab ready is also provided at no cost. The cost of giving you the study drug is not paid by the study sponsor so you or your health plan/insurance company may have to pay for this.

It is possible the study drugs, pembrolizumab and blinatumomab, may not continue to be supplied while you are on the study. Although not likely, if this occurs, your study doctor will talk to you about your options.

You and/or your health plan/insurance company will also need to pay for all of the non-research costs of caring for your cancer while in this study, including the costs of tests, procedures, or medicines to manage any side effects related to your standard of care, unless you are told that certain tests are supplied at no cost. Before you decide to be in the study, you should check with your health plan/insurance company to find out exactly what they will pay for.

Examples of procedures and drugs that may be billed include the following: blood tests for routine analysis (blood cell count, blood chemistry, pregnancy tests), physical exams, imaging

scans, infusion of the study drugs, lumbar punctures, bone marrow aspiration and biopsies, and other standard tests and procedures used to evaluate your disease.

The costs of hospitalization will be billed to insurance.

There will be no payment to you for participating in this study.

COMPENSATION FOR RESEARCH-RELATED INJURY

If you are injured as a direct result of participation in this research, the University of California will provide any medical care you need to treat those injuries. The University will not provide any other form of compensation to you if you are injured. You may call the Human Research Protections Program Office at (858) 246-HRPP (858-246-4777) for more information about this, to inquire about your rights as a research subject or to report research-related problems.

VOLUNTARY PARTICIPATION

Participation in this study is entirely voluntary. If you choose not to participate or wish to withdraw your consent to participate in these study procedures at any time, it will in no way affect your regular treatments or medical care at this institution or loss of benefits to which you are entitled. Please contact Dr. Matthew Wieduwilt or a member of his/her study team if you wish to withdraw from participation.

You will be informed of any new findings that might affect your willingness to continue participating in the study.

If health conditions occur which would make your participation in this study possibly dangerous, or if other conditions occur that would make participation in this study detrimental to you or your health, then your study doctor may discontinue your participation in this study.

DO YOU HAVE ANY QUESTIONS?

Dr. Matthew Wieduwilt and/or _____has explained this study to you, and answered your questions. You may contact Dr. Wieduwilt at 858-822-8644. You may also call the hospital 24-hour paging system at (858) 657-7000 and ask for the bone marrow transplant physician on-call. If you have other questions or research-related problems, you may call the Moores UCSD Cancer Center Clinical Trials Office at (858) 822-5354.

If you have questions about your rights as a research participant, your participation in this study, and/or concerns about this study, you may call the UCSD Human Research Protections Program (a group of people who review the research study to protect your rights and welfare) at (858) 246-HRPP (858-246-4777).

A description of this clinical trial will be available on 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 confidentiality of your research records will be maintained to the extent allowed by law. This includes using locked filing cabinets and the use of passwords will be required to access your personal data on computers. Access to your information will be limited to study personnel who need to use it for the purpose of the research in this study. Only the minimum necessary information required will be collected, stored, used and reported. Your medical information will not be made publicly available unless disclosure is required by law or regulation.

Data obtained from this study will be given to the sponsors of this study, Amgen, Inc, and Merck& Co, Inc, and/or its representatives, and may be published or given to regulatory authorities, including the Food and Drug Administration (FDA), Department of Health and Human Services (DHHS) agencies, the UCSD Institutional Review Board, the Moores UCSD Cancer Center Data and Safety Monitoring Board (DSMB) and other governmental agencies in the United States or other countries in which regulatory approval of pembrolizumab or blinatumomab may be sought. Your identity will remain confidential. Study data is labeled with a code instead of your name or other information that can easily identify you.

You will be asked to sign a separate HIPAA authorization form to allow the study team to access and share information from your medical record. Your permission as described in this informed consent and HIPAA document does not have an automatic expiration date.

SIGNATURE AND CONSENT

Your participation in this study is voluntary, and you may refuse to participate or withdraw from the study at any time without prejudice or loss of benefits to which you are otherwise entitled. You will receive a signed copy of this consent document and a copy of "The Experimental Subject's Bill of Rights" to keep.

You agree to participate.

_____
Printed Name of Participant

_____ _____
Signature of Participant Date

_____
Printed Name of Person Obtaining Consent

_____ _____
Signature of Person Obtaining Consent Date

Human Research Protections Program
(858) 246-4777
(858) 246-3329 (FAX)

University of California, San Diego
9500 Gilman Drive, Mail Code 0052
La Jolla, CA 92093-0052

EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

The faculty and staff of the University of California, San Diego wish you to know:

Any person who is requested to consent to participate as a subject in a research study involving a medical experiment, or who is requested to consent on behalf of another, has the right to:

1. Be informed of the nature and purpose of the experiment.
2. Be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be used.
3. Be given a description of any attendant discomforts and risks reasonably to be expected from the experiment.
4. Be given an explanation of any benefits to the subject reasonably to be expected from the experiment, if applicable.
5. Be given a disclosure of any appropriate alternative procedures, drugs, or devices that might be advantageous to the subject, and their relative risks and benefits.
6. Be informed of the avenues of medical treatment, if any, available to the subject after the experiment if complications should arise.
7. Be given an opportunity to ask any questions concerning the experiment or the procedures involved.
8. Be instructed that consent to participate in the medical experiment may be withdrawn at any time, and the subject may discontinue participation in the medical experiment without prejudice.
9. Be given a copy of a signed and dated written consent form when one is required.
10. 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.

If you have questions regarding a research study, the researcher or his/her assistant will be glad to answer them. You may seek information from the Human Research Protections Program - established for the protection of volunteers in research projects - by calling (858) 246-4777 from 7:30 AM to 4:00 PM, Monday through Friday, or by writing to the above address.