



Informed Consent

INFORMED CONSENT/AUTHORIZATION FOR PARTICIPATION IN RESEARCH WITH OPTIONAL PROCEDURES

A Phase I Trial of Bevacizumab, Temsirolimus Alone and in Combination
with Valproic Acid or Cetuximab in Patients with Advanced Malignancy and
Other Indications
2012-0061

Study Chair: Sarina Piha-Paul

Participant's Name _____

Medical Record Number _____

This is an informed consent and authorization form for a research study. It includes a summary about the study. A more detailed description of procedures and risks is provided after the summary.

STUDY SUMMARY

You are being asked to take part in this study because you have an advanced cancer that is refractory (has not responded to treatment) or has no standard treatment.

If you are reading and signing this form on behalf of a potential participant, please note: Any time the words "you," "your," "I," or "me" appear, it is meant to apply to the potential participant.

The goal of this clinical research study is to find the highest tolerable dose of Avastin (bevacizumab) and Torisel (temsirolimus) that can be given in combination with either valproic acid or cetuximab to patients with advanced cancer that is refractory. The safety of this drug combination will also be studied.

Bevacizumab is designed to block the growth of blood vessels, which may help to slow or block the growth of cancer.

Temsirolimus is designed to block the growth of cancer cells, which may cause

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cancer cells to die.

Valproic acid is an anti-seizure drug that may be able to activate tumor-fighting genes, causing cancer cells to die.

Cetuximab is designed to block a certain protein, called EGFR, that is thought to cause cancer cells to grow. This may cause cancer cells to die.

Bevacizumab is FDA approved and commercially available for the treatment of colorectal cancer and a type of lung cancer. Temsirolimus is FDA approved and commercially available for the treatment of kidney cancer that has spread. Cetuximab is FDA approved and commercially available for the treatment of colorectal cancer and a type of head and neck cancer. Valproic acid is FDA approved and commercially available to help control seizures.

The combination of bevacizumab and temsirolimus is not FDA approved to treat advanced cancer. The combination of bevacizumab and temsirolimus with cetuximab or valproic acid is not FDA approved to treat advanced cancer. At this time, the use of each study drug combination is investigational.

The study drugs may help to control the disease. Future patients may benefit from what is learned. There **may be** no benefits for you in this study.

Your participation is completely voluntary. Before choosing to take part in this study, you should discuss with the study team any concerns you may have, including side effects, potential expenses, and time commitment.

You can read a full list of potential side effects below in the Possible Risks section of this consent.

You may continue taking the study drug combination for as long as the doctor thinks it is in your best interest. You and/or your insurance provider will be responsible for the cost of the study drugs. You may choose not to take part in this study. Instead of taking part in this study, you may choose to receive standard therapy, which may include chemotherapy, radiation therapy, and/or surgery.

1. STUDY DETAILS

Screening Tests

Signing this consent form does not mean that you will be able to take part in this study. You will have screening tests to help the doctor decide if you are eligible to take part in this study. The following tests and procedures will be performed within 28 days before the first dose of study drugs:

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- Your medical and surgical history will be recorded.
- You will have a physical exam, including measurement of your weight and vital signs (blood pressure, breathing rate, heart rate, and temperature).
- You will have an electrocardiogram (ECG) to check your heart function.
- Blood (about 4 teaspoons) and urine will be collected for routine tests.
- If you have not had one performed in the last month, you will have a computed tomography (CT) scan or magnetic resonance imaging (MRI) scan to check the status of the disease.
- If you are able to become pregnant, you will have a blood (about 1 teaspoon) pregnancy test. To take part in this study, you must not be pregnant.

Study Groups

If you are found to be eligible, you will be assigned to a study drug combination that the study doctor thinks is in your best interest:

- Drug Combination 1: Temsirolimus, bevacizumab, and cetuximab
- Drug Combination 2: Temsirolimus, bevacizumab, and valproic acid
- Drug Combination 3: Temsirolimus and bevacizumab

Dose Escalation Group

You will be assigned to a dose level of your study drug combination based on when you joined this study.

Up to 11 dose levels will be tested for Study Drug Combination 1. Up to 10 dose levels will be tested for Study Drug Combinations 2 and 3. Three (3) participants will be enrolled at each dose level of each combination. The first group of participants will receive the lowest dose level. Each new group will receive a higher dose than the group before it, if no intolerable side effects were seen. This will continue until the highest tolerable dose of the study drug combination is found.

Dose Expansion Group

After the highest tolerable dose is found, up to an additional 10 participants, called the "dose expansion group," will receive each study drug combination at that dose.

Ovarian Expansion Group

Up to 14 additional participants with ovarian cancer, called the "ovarian expansion group," will receive Drug Combination 3 at the highest tolerable dose.

Study Drug Administration

The study drugs will be given in cycles. Cycles will be about 28 days or longer, depending on any side effects you may have.

You will be given bevacizumab by vein on Days 1 and 15 of each cycle. On Day 1 of Cycle 1, you will receive it over 90 minutes. If you tolerate it well in Cycle 1, you will receive it over 60 minutes in Cycle 2. If you then tolerate it well in Cycle 2, you will receive it over 30 minutes in Cycle 3. As long as you still tolerate it well, you will

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receive it over 30 minutes in Cycle 4 and further cycles.

You will be given temsirolimus by vein on Days 1, 8, 15, and 22 of each cycle. During Day 1 of Cycle 1, you will receive it over 60 minutes. If you tolerate it well on Day 1 of Cycle 1, it will be given over 30 minutes for all future doses, as long you continue to tolerate it well.

If you are taking Drug Combination 1, you will be given cetuximab by vein 1 time every week. The first time you receive cetuximab, it will be given over 2 hours. Every time you receive cetuximab after that, it will be given over 1 hour.

If you are taking Drug Combination 2, you will take valproic acid by mouth 1 time each day in each cycle. The drug can be taken with or without food.

Study Visits

One (1) time each week during **Cycle 1**, the following tests and procedures will be performed:

- You will have a physical exam, including measurement of your weight and vital signs.
- Blood (about 1 tablespoon) will be collected for routine tests.
- Urine will be collected for routine tests only during the first week of Cycle 1.

Every 4 weeks during **Cycles 2 and beyond**:

- You will have a physical exam, including measurement of your weight and vital signs.
- Blood (about 1 tablespoon) and urine will be collected for routine tests.

After Cycle 2, you will have a CT or MRI scan after every 2 cycles to check the status of the disease.

Ovarian Expansion Group

If you are in the **ovarian expansion group** you will have additional testing as follows:

- You will have extra blood (about 2 teaspoons each time) drawn **during Cycle 1**. The blood will be used for biomarker testing. Biomarkers are found in the blood/tissue and may be related to your reaction to the study drug. This blood will be drawn:
 - Before you begin taking the study drugs
 - On Day 1 at about 1, 4, 8, and 24 -36 hours after the start of your first infusion
 - On Day 6, 7, or 8
 - On Day 15
 - At the end of Cycle 1
- You will have 2 core needle biopsies for biomarker testing during **the screening visit and at the end of Cycle 1**. These samples will be used to learn how the study drug combination acts in the body and to learn its effect on

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cancer cells. To perform a core needle biopsy, a sample of tissue is removed using a hollow core needle that has a cutting edge.

- You will have a dynamic contrast enhanced MRI (DCE-MRI) and diffusion weighted MRI (DW-MRI) scan to check the status of the disease:
 - At screening
 - 24-48 hours after the start of Cycle 1
 - At the end of Cycle 1

Like a regular MRI scan, the DCE-MRI and DW-MRI scan involves passing part or all of the body into a long, narrow tube scanner that is open at both ends.

You may continue taking the study drug combination for as long as the doctor thinks it is in your best interest. You will no longer be able to take the study drugs if the disease gets worse, if intolerable side effects occur, or if you are unable to follow study directions.

Other Information

Because some over-the-counter and prescription drugs can decrease the effectiveness or increase the side effects of temsirolimus, you should discuss all over-the-counter drugs, health food supplements, and prescription drugs with the doctor and study nurse before taking them. For example, temsirolimus may interact with anti-seizure medication and/or Coumadin (warfarin). If it interacts with warfarin, it may result in the blood being made thinner and the risk of bleeding increased.

Patients with central nervous system (brain or spinal cord) tumors, including cancer that has spread to the brain and/or spinal cord, may also be at a higher risk of bleeding while taking temsirolimus.

Do not drink grapefruit juice or eat grapefruit or grapefruit products while taking temsirolimus. Do not drink alcoholic beverages (such as beer, wine, and liquor) while taking temsirolimus.

2. POSSIBLE RISKS

While on this study, you are at risk for side effects. These side effects will vary from person to person. The more commonly occurring side effects are listed in this form, as are rare but serious side effects that the drugs are known to cause. You should discuss these with the study doctor. You may also want to ask about uncommon side effects that have been observed in small numbers of patients but are not listed in this form. Many side effects go away shortly after the drugs are stopped, but in some cases side effects may be serious, long-lasting or permanent, and may even cause death.

Tell the study staff about any side effects you may have, even if you do not think they are related to the study drug.

Bevacizumab, temsirolimus, cetuximab, and valproic acid each may cause low blood cell

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counts (red blood cells, platelets, and/or white blood cells):

- A low red blood cell count (anemia) may cause difficulty breathing and/or fatigue. You may need a blood transfusion.
- A low platelet count increases your risk of bleeding (such as nosebleeds, bruising, stroke, and/or digestive system bleeding). You may need a platelet transfusion.
- A low white blood cell count increases your risk of infection (such as pneumonia and/or severe blood infection). Infections may occur anywhere and become life-threatening. Symptoms of infection may include fever, pain, redness, and difficulty breathing.

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Bevacizumab Side Effects

Common (occurring in more than 20% of patients)

<ul style="list-style-type: none"> ● high blood pressure ● blood clots in a vein (possible pain, swelling, and/or redness) ● pain ● headache ● dizziness ● fatigue ● hair loss (partial or total) ● abnormal salts, minerals, and/or acids in the blood (possible weakness, swelling, fatigue, low blood pressure, organ failure, heart problems, changes in mental status, and/or seizures) 	<ul style="list-style-type: none"> ● high blood sugar (possible diabetes) ● weight loss ● abdominal pain ● loss of appetite ● constipation/diarrhea ● mouth blisters/sores (possible difficulty swallowing) ● digestive system bleeding ● upset stomach ● vomiting ● abnormal taste 	<ul style="list-style-type: none"> ● failure of the ovaries to produce hormones, which may be permanent (possible stopped menstrual cycle) ● bleeding (including nosebleed) ● low white blood cell counts ● abnormal kidney test (possible kidney damage) ● bleeding in the lungs and/or airways ● difficulty breathing ● infection
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Occasional (occurring in 3-20% of patients)

<ul style="list-style-type: none"> ● swelling (arm/leg) ● blood clots in an artery (possible organ damage such as stroke and/or heart attack) ● low blood pressure (possible dizziness/fainting) ● heart failure ● fainting ● bleeding in the brain and/or spinal cord ● anxiety ● difficulty forming or speaking words ● dry skin ● skin sores ● opening of a wound/wound healing problems 	<ul style="list-style-type: none"> ● hand-foot syndrome (palms of hands/soles of feet having pain, swelling, and blistering) ● shedding and scaling of the skin (possible fatal loss of bodily fluids) ● dehydration ● dry mouth ● vein blockage in the abdomen ● intestinal blockage ● hole in the intestines (possibly leaking contents into the abdomen) ● bleeding gums 	<ul style="list-style-type: none"> ● inflammation of the intestines ● nausea ● uterine and/or vaginal bleeding ● low platelet counts ● nerve damage (loss of sensory function) ● weakness ● voice changes ● runny nose ● lung inflammation (possible difficulty breathing) ● infusion reaction (possible chills and/or hives) ● life-threatening allergic reaction (such as difficulty breathing, low blood pressure, and/or
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	organ failure)
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Bevacizumab may occasionally cause an abnormal opening that develops between one area of the body and another (for example, an abnormal connection and opening in one or more places between the trachea [breathing tube] and esophagus, which may interfere with swallowing, digestion, and/or choking. Another example is abnormal connections or passageways between different parts of the digestive system and/or the vagina). This may result in death.

Rare but serious (occurring in fewer than 3% of patients)

<ul style="list-style-type: none"> ● severe heart problems ● heart attack ● chest pain due to heart trouble ● severe increase in blood pressure (possible stroke) ● brain injury that may be reversible (possible headache, confusion, seizures, and/or vision loss) ● decreased brain function due to high blood pressure ● stroke ● decay of body tissue ● stomach and/or small intestine ulcer ● decreased blood flow to part of the bowel (possibly causing death of tissue) 	<ul style="list-style-type: none"> ● blood vessel blockage in the abdomen ● hole in the gall bladder (possible abdominal pain, gall stones, nausea, and/or infection) ● destruction of red blood cells ● low red blood cell counts ● bone destruction (including destruction of the jaw bone) ● inflammation inside the eye ● blurry vision ● permanent blindness ● detached retina (possible partial blindness) ● bleeding in the tissue lining the eye/in the eye ● deafness ● kidney failure 	<ul style="list-style-type: none"> ● abnormal blood clotting in small blood vessels of the kidney (possible kidney damage) ● coughing up blood ● increased blood pressure in the lungs (possible difficulty breathing and/or heart failure) ● blockage in the lung (possible pain and/or shortness of breath) ● abnormal hole inside the nose ● immune reaction ● severe life-threatening infection (possible low blood pressure, kidney failure, and/or heart failure)
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Rarely (in about 1-2% of patients), bevacizumab may cause bleeding in the brain in patients who have received bevacizumab for the treatment of primary brain tumors. You will be monitored for this complication and removed from the study if this were to occur.

If you are taking Coumadin (warfarin) or other blood-thinning drugs, you may be at higher risk of blood clots and/or bleeding.

Temsirolimus Side Effects

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Common (occurring in more than 20% of patients)

<ul style="list-style-type: none"> ● swelling (arm/leg) ● pain ● fever ● skin rash ● high blood sugar (possible diabetes) ● low blood levels of potassium (possible weakness/muscle cramps) 	<ul style="list-style-type: none"> ● low blood levels of phosphate (possible bone damage) ● high blood levels of fat and/or cholesterol (possible heart disease and/or stroke) ● mouth blisters/sores (possible difficulty swallowing) ● nausea ● loss of appetite ● diarrhea 	<ul style="list-style-type: none"> ● abdominal pain ● low blood cell counts (red, white, platelets) ● abnormal liver test (possible liver damage) ● weakness ● abnormal kidney test (possible kidney damage) ● difficulty breathing ● cough ● infection
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Occasional (occurring in 3-20% of patients)

<ul style="list-style-type: none"> ● chest pain ● headache ● difficulty sleeping ● itching 	<ul style="list-style-type: none"> ● nail changes ● dry skin ● constipation ● abnormal taste 	<ul style="list-style-type: none"> ● vomiting ● weight loss ● pain (back/joint) ● nosebleed ● sore throat
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Exact frequency unknown but occurring in fewer than 10% of patients:

<ul style="list-style-type: none"> ● high blood pressure ● blood clots in the veins (possibly in a deep vein and/or lung) ● chills ● depression ● acne 	<ul style="list-style-type: none"> ● holes in the intestines (possible leaking contents into the abdomen) ● abnormal liver tests (possible yellowing of the skin and/or eyes) ● muscle pain ● painful red eyes 	<ul style="list-style-type: none"> ● runny nose ● lung inflammation (possible difficulty breathing) ● wound healing problems ● infusion reaction (possible chills and/or hives)
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The intravenous (IV) infusion of temsirolimus may commonly cause you to have an allergic reaction and/or infusion reaction. These reactions include severe allergic reaction, breathing interruptions, chest pain, difficulty breathing, flushing, low blood pressure, and/or loss of consciousness. Life-threatening reactions, including fatal reactions, have occurred.

Rare but serious (occurring in fewer than 1% of patients)

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● build up of fluid in the tissue around the heart	● breakdown of muscle tissue (possible kidney	● kidney failure ● build up of fluid around
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<ul style="list-style-type: none"> ● seizure ● very severe blistering skin disease (with ulcers of the skin and digestive tract) 	failure) <ul style="list-style-type: none"> ● increased sensitivity to pain (possible burning, sweating, and/or swelling of the arms and legs) 	the lungs <ul style="list-style-type: none"> ● fungal lung infection ● pneumonia ● drug leakage from injection site
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Valproic Acid Side Effects

Common (occurring in more than 20% of patients)

<ul style="list-style-type: none"> ● headache ● sleepiness ● dizziness ● hair loss (partial or total) 	<ul style="list-style-type: none"> ● nausea ● vomiting ● diarrhea ● abdominal pain ● upset stomach 	<ul style="list-style-type: none"> ● low blood counts (platelet, white) ● tremors ● weakness
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Occasional (occurring in 3-20% of patients)

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<ul style="list-style-type: none"> ● swelling (possibly of the arm, leg, and/or face) ● high blood pressure ● low blood pressure (possible dizziness/fainting) ● irregular or fast heartbeat ● flushing ● difficulty sleeping ● difficulty walking ● memory loss ● mood swings ● fever ● abnormal thinking or dreams ● depression, agitation, nervousness, anxiety, and/or confusion ● inability to move or talk ● chills ● loss of coordination ● fatigue/lack of energy ● hallucinations (seeing or hearing things that are not there) 	<ul style="list-style-type: none"> ● loss of appetite ● weight gain or loss ● increased appetite ● constipation ● dry mouth ● burping ● inability to control bowel movements ● gas ● inflammation of the stomach and/or intestines ● swollen tongue ● vomiting of blood ● inflammation of the pancreas (possible abdominal pain) ● mouth blisters/sores ● abnormal taste ● bladder inflammation (possible pain and/or urge to urinate) ● difficult and/or painful urination ● frequent urination ● loss of bladder control 	<ul style="list-style-type: none"> ● muscle tension ● difficulty forming or speaking words ● decreased ability to move ● leg cramps ● abnormal or uncontrolled muscle movements ● pain (including back, joint, muscle, and/or neck pain) ● stiff neck ● abnormal sensation (such as pins and needles) ● overactive reflexes ● vision problems (including double vision, dry eyes, blurry vision, eye twitching, lazy eye, eye pain, and painful red eyes) ● ringing in the ears ● ear pain ● deafness
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<ul style="list-style-type: none"> ● personality disorder (abnormal thoughts and actions) ● speech disorder ● skin rash ● lupus (an immune system disease) ● itching ● dry and/or oily skin 	<ul style="list-style-type: none"> ● stopped menstrual cycle ● painful menstruation ● uterine and/or vaginal bleeding ● vaginal inflammation ● abnormal liver tests (possible liver damage) 	<ul style="list-style-type: none"> ● sore throat ● difficulty breathing ● cough ● nosebleed ● runny nose ● lung inflammation ● flu-like symptoms ● injection site pain
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Frequency unknown but occurring in between 1 and 10% of patients

<ul style="list-style-type: none"> ● abnormal kidney test (possible kidney damage) 	<ul style="list-style-type: none"> ● difficulty swallowing 	<ul style="list-style-type: none"> ● hiccups
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Rare but serious (occurring in fewer than 3% of patients)

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<ul style="list-style-type: none"> ● slow heartbeat ● coma ● dementia (loss of mental capacity) ● progressive multifocal leukoencephalopathy (PML – a disease with brain damage that may likely result in paralysis and/or coma, which may be permanent, or death) ● mood changes ● low body temperature ● psychosis (loss of contact with reality) ● decrease in the size of an organ/tissue ● allergic skin reaction ● very severe blistering skin disease (with ulcers of the skin and digestive tract) ● very severe blistering skin disease (loss of a large portion of skin) ● high blood levels of ammonia (possible changes in mental 	<ul style="list-style-type: none"> ● inability to process fats (possible weakness, enlarged heart, or decreased brain function) ● high blood levels of glycine ● low blood levels of sodium (possible headache, confusion, seizures, and/or coma) ● abnormal production of the hormone that regulates salt and fluid excretion ● problems with red blood cell production (possible skin rashes, blistering, abdominal pain, and/or altered mental status) ● bruising ● thyroid function tests abnormal ● swelling of the salivary gland 	<ul style="list-style-type: none"> ● cysts in ovaries (possible difficulty becoming pregnant) ● increased risk of bleeding ● low red blood count ● blood vessel inflammation (possible bleeding and/or bruising) ● abnormal liver tests (possible yellowing of the skin or eyes) ● liver failure ● liver damage ● seeing "spots before the eyes" ● decreased kidney function (rare in children) ● allergic reaction (possibly life-threatening, such as difficulty breathing, low blood pressure, and/or organ failure)
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status)		
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Valproic acid may cause suicidal thoughts and/or suicidal behavior.

Valproic acid may cause birth defects, such as spina bifida (when the backbone and spinal canal do not close before birth). If valproic acid is taken during pregnancy, your child may have lower mental function.

Cetuximab Side Effects

Common (occurring in more than 20% of patients)

<ul style="list-style-type: none"> ● heart attack ● fatigue/lack of energy ● headache ● difficulty sleeping ● fever ● skin rash (possibly acne-like), peeling, and/or itching ● dry skin ● nail changes ● low blood levels of magnesium (possible weakness and/or seizures) 	<ul style="list-style-type: none"> ● weight loss ● dehydration ● abdominal pain ● constipation ● diarrhea ● mouth blisters/sores (possible difficulty swallowing) ● vomiting ● nausea ● loss of appetite ● low white blood cell count 	<ul style="list-style-type: none"> ● abnormal liver tests (possible liver damage) ● weakness ● pain ● nerve damage (loss of sensory function) ● difficulty breathing ● cough ● sore throat ● infection ● severe rash at the site of previous radiation ● life-threatening allergic reaction (such as difficulty breathing, low blood pressure, and/or organ failure)
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Occasional (occurring in 3-20% of patients)

<ul style="list-style-type: none"> ● confusion ● depression ● anxiety ● chills/shivering ● skin sores ● hair loss (partial or total) ● hand-foot syndrome (palms of hands/soles of feet having pain, swelling and blistering) 	<ul style="list-style-type: none"> ● low blood levels of calcium and/or potassium (possible weakness and/or cramping) ● dry mouth ● abnormal taste ● upset stomach 	<ul style="list-style-type: none"> ● painful red eyes ● immune reaction ● infusion reaction (possible chills and/or hives) ● severe life-threatening infection (possible low blood pressure, kidney failure, and/or heart failure)
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Frequency unknown but occurring in 1-10% of patients

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- hair growth

Rare but serious (occurring in fewer than 3% of patients)

<ul style="list-style-type: none"> ● heart attack ● stoppage of heart and lung function ● decreased blood supply to the heart ● low blood pressure (possible dizziness/fainting) ● irregular heartbeat ● inflammation of the membranes around the spinal cord and brain (possible headache and/or coma) 	<ul style="list-style-type: none"> ● shock ● loss of consciousness ● large skin blisters ● very severe blistering skin disease (with ulcers of the skin and digestive tract) ● very severe blistering skin disease (loss of large portion of skin) ● changes in body salts such as sodium and/or potassium (possible fatigue and/or weakness) 	<ul style="list-style-type: none"> ● eye ulcer ● kidney failure ● lung inflammation (possible difficulty breathing) ● difficulty breathing due to narrowing of the airways ● blockage in the lung (possible pain, shortness of breath, and/or failure to breathe)
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Using the study drugs together may cause side effects that are not seen when each is given alone. The study drug combinations may also increase the frequency and/or severity of the side effects listed above.

Other Risks

Blood draws may cause pain, bleeding, and/or bruising. You may faint and/or develop an infection with redness and irritation of the vein at the site where blood is drawn. Frequent blood collection may cause anemia (low red blood cell count), which may create a need for blood transfusions.

Having **tumor biopsies** performed may cause pain, bruising, bleeding, redness, low blood pressure, swelling, and/or infection at the site of the biopsies. An allergic reaction to the anesthetic may occur. A scar may form at the biopsy site.

During the **DCE-MRI/DW-MRI**, you may feel mild vibrations throughout your body. The machine will produce a loud knocking noise. This is normal. You will be given earplugs to protect your ears. Some people, especially those who tend to feel uncomfortable in small or closed spaces, may feel “closed in” and become anxious while in the scanner. The scanner has an intercom, which will allow you to speak to the staff during the procedure. If you feel ill or anxious during scanning, tell the MRI staff and the scanning will be stopped if you wish. The MRI will require a catheter to be inserted into one of your veins in order to inject the MRI contrast agent. This may cause skin irritation, bleeding, and/or infection. You may have an allergic reaction to the contrast agent.

The magnetic field used in MRI scanning may harm people who have metal in their bodies (pacemakers, neurostimulators, certain clips, or staples from surgery). It may

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cause problems with devices, such as pacemakers. If you have metal in your body or a pacemaker, you should not have an MRI.

This study may involve unpredictable risks to the participants.

Pregnancy Related Risks

Taking part in this study can result in risks to an unborn or breastfeeding baby, so you should not become pregnant, breastfeed a baby, or father a child while on this study. You must use birth control during the study if you are sexually active.

Birth Control Specifications: Acceptable forms of birth control include:

- Birth control pills plus a barrier method (such as condom)
- Intrauterine devices (IUD) plus a barrier method (such as condom)
- Implantable or injectable birth control (NorplantR or Depo-ProveraR started at least 3 months before joining the study) plus a barrier method (such as condom)
- Double-barrier methods (such as condom and diaphragm)
- Surgical sterilization

Males: Tell the doctor right away if your partner becomes pregnant or suspects pregnancy.

Females: If you are pregnant, you will not be enrolled on this study. If you become pregnant or suspect that you are pregnant, you must tell your doctor right away.

Getting pregnant [will](#) result in your removal from this study.

OPTIONAL PROCEDURES FOR THE STUDY

If you are in the **dose expansion group** of the study, and if you agree, you are being asked to have additional testing, as follows:

Optional Procedure #1: If you agree, you will have extra blood (about 2 teaspoons each time) drawn **during Cycle 1**. The blood will be used for biomarker testing. Biomarkers are found in the blood/tissue and may be related to your reaction to the study drug. This blood will be drawn:

- Before you begin taking the study drugs
- On Day 1 at about 1, 4, 8, and 24 -36 hours after the start of your first infusion
- On Day 6, 7, or 8
- On Day 15
- At the end of Cycle 1

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Optional Procedure #2: If you agree, you will have 2 core needle biopsies for

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biomarker testing during **the screening visit and at the end of Cycle 1**. These samples will be used to learn how the study drug combination acts in the body and to learn its effect on cancer cells. To perform a core biopsy, a sample of tissue is removed using a hollow core needle that has a cutting edge.

Optional Procedure #3: If you agree, you will have a dynamic contrast enhanced MRI (DCE-MRI)* scan performed to learn how the study drug combination may be affecting the disease:

- At screening
- 24-48 hours after the start of Cycle 1
- At the end of Cycle 1

*Like a regular MRI scan, the DCE-MRI scan involves passing part or all of the body into a long, narrow tube scanner that is open at both ends.

There will be no cost to you for taking part in the optional procedures.

Optional Procedure Risks:

Blood draws may cause pain, bleeding, and/or bruising. You may faint and/or develop an infection with redness and irritation of the vein at the site where blood is drawn. Frequent blood collection may cause anemia (low red blood cell count), which may create a need for blood transfusions.

Having **tumor biopsies** performed may cause pain, bruising, bleeding, redness, low blood pressure, swelling, and/or infection at the site of the biopsies. An allergic reaction to the anesthetic may occur. A scar may form at the biopsy site.

During the **DCE-MRI**, you may feel mild vibrations throughout your body. The machine will produce a loud knocking noise. This is normal. You will be given earplugs to protect your ears. Some people, especially those who tend to feel uncomfortable in small or closed spaces, may feel “closed in” and become anxious while in the scanner. The scanner has an intercom, which will allow you to speak to the staff during the procedure. If you feel ill or anxious during scanning, tell the MRI staff and the scanning will be stopped if you wish. The MRI will require a catheter to be inserted into one of your veins in order to inject the MRI contrast agent. This may cause skin irritation, bleeding, and/or infection. You may have an allergic reaction to the contrast agent.

The magnetic field used in MRI scanning may harm people who have metal in their bodies (pacemakers, neurostimulators, certain clips, or staples from surgery). It may cause problems with devices, such as pacemakers. If you have metal in your body or a pacemaker, you should not have an MRI.

CONSENT/PERMISSION/AUTHORIZATION FOR OPTIONAL PROCEDURES

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Circle your choice of “yes” or “no” for each of the following optional procedures:

Optional Procedure #1: If you are asked, do you agree to allow extra blood to be drawn for biomarker testing?

YES

NO

Optional Procedure #2: If you are asked, do you agree to allow 2 tumor biopsies to be performed and used for biomarker testing?

YES

NO

Optional Procedure #3: If you are asked, do you agree to allow DCE-MRI scans to be performed to learn how the study drug combination may be affecting the disease?

YES

NO

3. COSTS AND COMPENSATION

If you suffer injury as a direct result of taking part in this study, MD Anderson health providers will provide medical care. However, this medical care will be billed to your insurance provider or you in the ordinary manner. You will not be reimbursed for expenses or compensated financially by MD Anderson for this injury. You may also contact the Chair of MD Anderson's IRB at 713-792-2933 with questions about study-related injuries. By signing this consent form, you are not giving up any of your legal rights.

Certain tests, procedures, and/or drugs that you may receive as part of this study may be without cost to you because they are for research purposes only. However, your insurance provider and/or you may be financially responsible for the cost of care and treatment of any complications resulting from the research tests, procedures, and/or drugs. Standard medical care that you receive under this research study will be billed to your insurance provider and/or you in the ordinary manner. Before taking part in this study, you may ask about which parts of the research-related care may be provided without charge, which costs your insurance provider may pay for, and which costs may be your responsibility. You may ask that a financial counselor be made available to you to talk about the costs of this study.

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Samples that are collected from you in this study may be used for the development of treatments, devices, new drugs, or patentable procedures that may result in commercial profit.

There are no plans to compensate you for any patents or discoveries that may result from your participation in this research.

You will receive no compensation for taking part in this study.

Additional Information

4. You may ask the study chair (Dr. Sarina Piha-Paul, at 713-563-1930) any questions you have about this study. You may also contact the Chair of MD Anderson's Institutional Review Board (IRB - a committee that reviews research studies) at 713-792-6477 with any questions that have to do with this study or your rights as a study participant.
5. You may choose not to take part in this study without any penalty or loss of benefits to which you are otherwise entitled. You may also withdraw from participation in this study at any time without any penalty or loss of benefits. If you decide you want to stop taking part in the study, it is recommended for your safety that you first talk to your doctor. If you withdraw from this study, you can still choose to be treated at MD Anderson.
6. This study or your participation in it may be changed or stopped without your consent at any time by the study chair, the U.S. Food and Drug Administration (FDA), the Office for Human Research Protections (OHRP), or the IRB of MD Anderson.
7. You will be informed of any new findings or information that might affect your willingness to continue taking part in the study, and you may be asked to sign another informed consent and authorization form stating your continued willingness to participate in this study.
8. MD Anderson may benefit from your participation and/or what is learned in this study.

Future Research

Your personal information and/or samples are being collected as part of this study. These data and/or samples may be used by researchers at MD Anderson or shared with other researchers and/or institutions for use in future research.

Before being shared for future research, every effort will be made to remove your identifying information from any data and/or samples. If all identifying information is

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removed, you will not be asked for additional permission before future research is performed.

In some cases, all of your identifying information may not be removed before your data or samples are used for future research. If this research is performed at MD Anderson, the researchers must get approval from the Institutional Review Board (IRB) of MD Anderson before your data and/or samples can be used. At that time, the IRB will decide whether or not further permission from you is required. The IRB is a committee of doctors, researchers, and community members that is responsible for protecting study participants and making sure all research is safe and ethical.

If this research is not performed at MD Anderson, MD Anderson will not have oversight of any data and/or samples.

Genetic Research

Any samples collected from you as part of this study will be used for genetic research, which may include whole genome sequencing. Whole genome sequencing is a type of testing in which researchers study your entire genetic makeup (DNA). This may help researchers learn how changes in the ordering of genes may affect a disease or response to treatment.

Authorization for Use and Disclosure of Protected Health Information (PHI):

- A. During the course of this study, MD Anderson will be collecting and using your PHI, including identifying information, information from your medical record, and study results. For legal, ethical, research, and safety-related reasons, your doctor and the research team may share your PHI with:
 - Federal agencies that require reporting of clinical study data (such as the FDA, National Cancer Institute [NCI], and OHRP)
 - The IRB and officials of MD Anderson
 - Study monitors and auditors who verify the accuracy of the information
 - Individuals who put all the study information together in report form
- B. Signing this consent and authorization form is optional but you cannot take part in this study or receive study-related treatment if you do not agree and sign.
- C. MD Anderson will keep your PHI confidential when possible (according to state and federal law). However, in some situations, the FDA could be required to reveal the names of participants.

Once disclosed outside of MD Anderson, federal privacy laws may no longer protect your PHI.

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- D. The permission to use your PHI will continue indefinitely unless you withdraw your authorization in writing. Instructions on how to do this can be found in the MD Anderson Notice of Privacy Practices (NPP) or you may contact the Chief Privacy Officer at 713-745-6636. If you withdraw your authorization, you will be removed from the study and the data collected about you up to that point can be used and included in data analysis. However, no further information about you will be collected.
- E. 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.

CONSENT/AUTHORIZATION
(Adult Participants Only)

I understand the information in this consent form. I have had a chance to read the consent form for this study, or have had it read to me. I have had a chance to think about it, ask questions, and talk about it with others as needed. I give the study chair permission to enroll me on this study. By signing this consent form, I am not giving up any of my legal rights. I will be given a signed copy of this consent document.

SIGNATURE OF PARTICIPANT

DATE

LEGALLY AUTHORIZED REPRESENTATIVE (LAR)

The following signature line should only be filled out when the participant does not have the capacity to legally consent to take part in the study and/or sign this document on his or her own behalf.

SIGNATURE OF LAR

DATE

RELATIONSHIP TO PARTICIPANT

WITNESS TO CONSENT

I was present during the explanation of the research to be performed under Protocol 2012-0061.

SIGNATURE OF WITNESS TO THE VERBAL CONSENT
PRESENTATION (OTHER THAN PHYSICIAN OR STUDY
CHAIR)

DATE

A witness signature is only required for vulnerable adult participants. If witnessing the assent of a pediatric participant, leave this line blank and sign on the witness to assent page instead.

PERSON OBTAINING CONSENT

I have discussed this research study with the participant and/or his or her authorized representative, using language that is understandable and appropriate. I believe that I have fully informed this participant of the nature of this study and its possible benefits and risks and that the participant understood this explanation.

PERSON OBTAINING CONSENT

DATE

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PARENT/GUARDIAN PERMISSION

I have read and understand the description of this research. I have had a chance to discuss the study and ask questions. My questions have been answered. I give permission for my child or ward to take part in this study.

SIGNATURE OF PARENT/GUARDIAN

DATE

SIGNATURE OF PARENT/GUARDIAN

Signature of Other Parent (Optional, unless required by the IRB.)

DATE

☐ The IRB has determined that the signature of both parents is required.

If not obtaining both parental signatures, please indicate reason below:

☐ Other parent is deceased, unknown, incompetent, or not reasonably available.

☐ Parent/Guardian signing above has sole legal responsibility for the care and custody of the child.

☒ The IRB has determined that the signature of both parents is NOT required.

WITNESS TO PARENTAL/GUARDIAN PERMISSION

I was present during the explanation of the research to be performed under Protocol 2012-0061. The child participant was also present. In my opinion, the parent(s)/guardian provided permission for the child to participate in the research.

SIGNATURE OF WITNESS TO THE PARENTAL/GUARDIAN
PERMISSION (OTHER THAN PARENT/GUARDIAN OR
MEMBER OF THE STUDY TEAM)

DATE

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ASSENT OF MINOR

(Entire section must be completed if the participant's intellectual age is at least 7 and less than 18 years. Participants with an intellectual age of 7 - 12 are not required to sign.)

If written assent is not obtained on an age-appropriate participant, check reason why not:

- _____ 1.) The participant's intellectual age is less than seven.
- _____ 2.) The participant dissented, but the participant's parent(s)/guardian felt that the intervention(s) or procedure(s) involved in the research hold out the possibility of a direct benefit that is important to the health and/or well being of the participant and is available only in the context of this research study.
- _____ 3.) Other: _____

I have been told what I will be asked to do in this study.

I have been told that I do not have to be in this study. If I decide not to be in this study, no one will be mad at me. I may quit at any time, but if I do, I may need to take a different treatment.

I have had a chance to talk about the study and ask the study doctor questions. All of my questions have been answered. I agree to be in this study and do what I am asked to do so long as I want to stay in this study. I agree that the study doctor can put me on this study. By signing this paper, I am not giving up any of my legal rights. I have been given a copy of this document.

SIGNATURE OF MINOR (Age 13-17)

DATE

WITNESS TO ASSENT

I was present during the explanation of the research to be performed under Protocol **2012-0061**. The child participant was also present. In my opinion, the child assented to participate in the research. (Note: If obtaining assent, a witness signature is required.)

SIGNATURE OF WITNESS TO THE ASSENT (OTHER THAN
PARENT/GUARDIAN OR MEMBER OF THE STUDY TEAM)

DATE

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TRANSLATOR

I have translated the above informed consent as written (without additions or subtractions) into _____ and assisted the people

(Name of Language)

obtaining and providing consent by translating all questions and responses during the consent process for this participant.

NAME OF TRANSLATOR

SIGNATURE OF TRANSLATOR

DATE

☐ Please check here if the translator was a member of the research team. (If checked, a witness, other than the translator, must sign the witness line below.)

SIGNATURE OF WITNESS TO THE VERBAL TRANSLATION
(OTHER THAN TRANSLATOR, PARENT/GUARDIAN,
OR STUDY CHAIR)

DATE

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