Document Coversheet

Study Title:

Phase I/IIa Clinical Trial Evaluating the Safety and Efficacy of Rintatolimod Combined with IFNa2b (Bioferon) to Enhance the Effectiveness of Pembrolizumab in Patients with Metastatic Triple Negative Breast Cancer

Institution/Site:	Roswell Park Comprehensive Cancer Center
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ROSWELL PARK CANCER INSTITUTE

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Roswell Park Study Number: I-3010822

Consent Form Given to Patient Taking Part in an Investigational/Clinical Research Study

KEY INFORMATION ABOUT THIS RESEARCH STUDY

This is a clinical research study being done by the doctors at the Roswell Park Comprehensive Cancer Center (study sponsor).

We are asking you to take part in this study because you have a form of breast cancer, called triple negative breast cancer, which is in an advanced stage and cannot be removed by surgery or be adequately controlled with radiation therapy. Current standard treatments consisting of chemotherapy regimens show benefit but are not curative in nature. Common chemotherapy regimens include but are not limited to paclitaxel, capecitabine, carboplatin, doxorubicin, eribulin.

Clinical research studies include only those patients who choose to take part.

- Your participation is voluntary. You may decide not to participate in this research study.
- You do not have to participate in this study to receive treatment for your condition.
- If you do participate, you may withdraw from the research study at any time.
- Please take your time to make your decision. Discuss it with your family and with people who are important to you.

Study Purpose: The purpose of this study is to find out what effects (good and bad) a type of treatment called "chemokine modulation therapy" or CKM will have on you and your type of cancer when given prior to an immune checkpoint inhibitor drug called pembrolizumab.

Immune checkpoint inhibitor drugs work by targeting molecules that act as a checks and balance system for immune responses. These treatments are designed to either "unleash" or "enhance" the cancer immune responses that already exist by either (1) blocking inhibitory molecules" or by (2) activating stimulatory molecules.

The CKM therapy will be given as a pre-treatment before you start on the pembrolizumab, in order to try to direct the immune cells to the cancer cells and maximize the effectiveness of pembrolizumab. The CKM pre-treatment therapy consists of these drugs: Rintatolimod, Interferon Alpha-2b and Celecoxib.

In addition, a new source of interferon alpha-2b is being used for this study, which is not approved by the U.S. FDA and is considered an investigational drug. This study will test 2 different dose levels of the new source of interferon alpha-2b to see if it is comparable to the drug formulation that is U.S. FDA-approved but is no longer being marketed.

Study Duration and Number of Participants: It is expected this study will take about 3 years or will continue until the needed number of participants are enrolled. We expect to enroll 12 patients from Roswell Park.

Your participation in this study will be approximately 8 weeks, with a 90-day follow-up period after your last dose of the study treatment to check for any adverse immune effects from the treatment. After that 90 days, you will be contacted by phone every 6 months up to 2 years to assess your survival status.

Exams, Tests and Procedures: This study involves exams, tests and procedures, some of which will be done as standard of care for your disease or condition, and some will be done for research-related purposes.

Listed below are key research-related tests and procedures that you will undergo during the study:

- Biopsies will be performed at baseline and on day 7.
- Certain blood tests for research will be done prior to starting treatment (thyroid, troponin, antinuclear antibodies, and research bloods) and at various separate time points throughout the study.
- An electrocardiogram (EKG) will be performed at 4 separate times throughout the study.

Section 3 of this document provides additional information on exams, tests and procedures involved with this study, including those being done as part of standard of care. Exams, tests and procedures being done as standard of care are required for your participation in the study according to the schedule outlined in Section 3.

Study Costs: Exams, tests and procedures and treatments that would routinely be needed to monitor and treat your illness even if you were not participating in the study are known as "standard of care" services. Charges for these services will be billed to you and/or your insurance company in the usual manner. You will be responsible for all co-payments, deductibles, and/or account balances as determined by your individual health insurance contract.

Exams, tests and procedures that are required only for the clinical research study and are not needed for the usual care of a patient with your disease are known as "research-related." You and/or your insurance company will not have to pay for research-related exams, tests and procedures done for research purposes only or that are covered by the study, including the research-related items listed in the section above.

The following drugs that you will be provided at no cost to you or your insurance company:

- Celecoxib
- Interferon-alpha 2b
- Rintatolimod
- 4 doses of Pembrolizumab while you are on the study.

You and /or your insurance company will be responsible for the costs of getting any drugs ready and administering (giving) them to you.

Section 10 of this document provides additional information on who to contact with questions about costs related to this research study.

Side Effects and Risks: While you take part in this study, you are at risk for side effects. The side effects may be mild, moderate, or severe. Many side effects go away shortly after the treatment stops, but occasionally, side effects can be serious, long lasting, or may be permanent or life-threatening. The most common side effects of the study drug(s) are:

- Celecoxib: Stomach pain, constipation, diarrhea, gas, heartburn, nausea, vomiting, dizziness, headache, respiratory tract infection.
- Interferon Alpha-2b: Pain, swelling and redness or skin damage at the injection site, hair loss, dizziness, changes in appetite, stomach or abdominal pain, diarrhea, nausea (feeling sick), viral infection, depression, mood swings, insomnia, anxiety, sore throat and painful swallowing, fatigue, chills and shivering, fever, flu-like reaction, feeling of general discomfort, headaches, weight loss, vomiting, irritability, weakness, changes in mood, cough (sometimes severe), shortness of breath, itching, dry skin, rash, sudden and severe muscle pain, joint pain, muscle and/or bone pain, changes in laboratory blood values including decreased white blood cell count, hepatic (liver) and renal (kidney) toxicity.
- Rintatolimod: Mild flushing, tightness of the chest, rapid heartbeat, anxiety, shortness of breath, feeling hot, sweating, nausea, liver enzyme level changes, diarrhea, itching, low blood pressure, rash, irregular heartbeat, low white blood cell count, dizziness, confusion.
- Pembrolizumab: Fatigue, decreased appetite, diarrhea, abdominal pain, rash, itching. Serious side effects may include heart attack, inflammation of the heart muscle and tissue surrounding the heart, inflammation of blood vessel walls, very severe blistering skin disease (with ulcers of the skin and digestive tract), shedding and scaling of the skin (possible fatal loss of bodily fluids), large skin blisters, hormone-regulation problems, type 1 diabetes mellitus.

Section 7 of this document provides more detailed information on possible side effects and risks.

Potential Benefits: It is not known if this treatment will help you or not. If the treatment is successful, you might see a decrease in your symptoms and improvement in your quality of life. It is also possible the investigational treatments may prove to be less useful or even harmful to you. You understand there is no guarantee that being on the study will help you. Future patients may be helped from the results and information gained from this study.

Other Options: If you do not join this study, you should discuss what other options there are with your doctor. Other options may include:

1. Usual/standard treatment for your disease or condition may be appropriate. This may include treatment with other drugs, drug combinations, or possibly other research programs here or at other centers which may be testing new drugs for your type of cancer.
2. No treatment, but medications and measures to keep you comfortable. This is sometimes called supportive care.

Feel free to talk with your health care team about your disease and your treatment choices.

The type of study, the risks, benefits, discomforts, and other important information about this study are discussed below.

ADDITIONAL INFORMATION ABOUT THIS RESEARCH STUDY

It is important that you read and understand the following facts that apply to anyone that takes part in our studies:

a) This study is considered research. It is investigational.

b) Taking part in the study is voluntary.

c) You may withdraw from the study at any time without penalty, loss of any benefits or access to care at Roswell Park to which you are otherwise entitled.

d) If you should decide not to take part in this study, it will not affect your care at Roswell Park now or in the future.

e) You should feel free to get a second opinion. This will not affect your ability to receive care and treatment here if you get one.

f) Your disease may not be helped from taking part in this study, but we may get information that will help others.

g) If we become aware of important new information that may relate to your willingness to participate in this study, we will inform you of this new information.

h) If you decide to stop being in the study, you should talk with your doctor first about this decision so you are informed whether stopping study participation may have any effects on your health.

1. What is the purpose of this study?

The purpose of this study is to find out what effects (good and bad) a type of treatment called chemokine modulation therapy, or CKM, will have on you and your type of cancer when given prior to an immune checkpoint inhibitor drug called pembrolizumab.

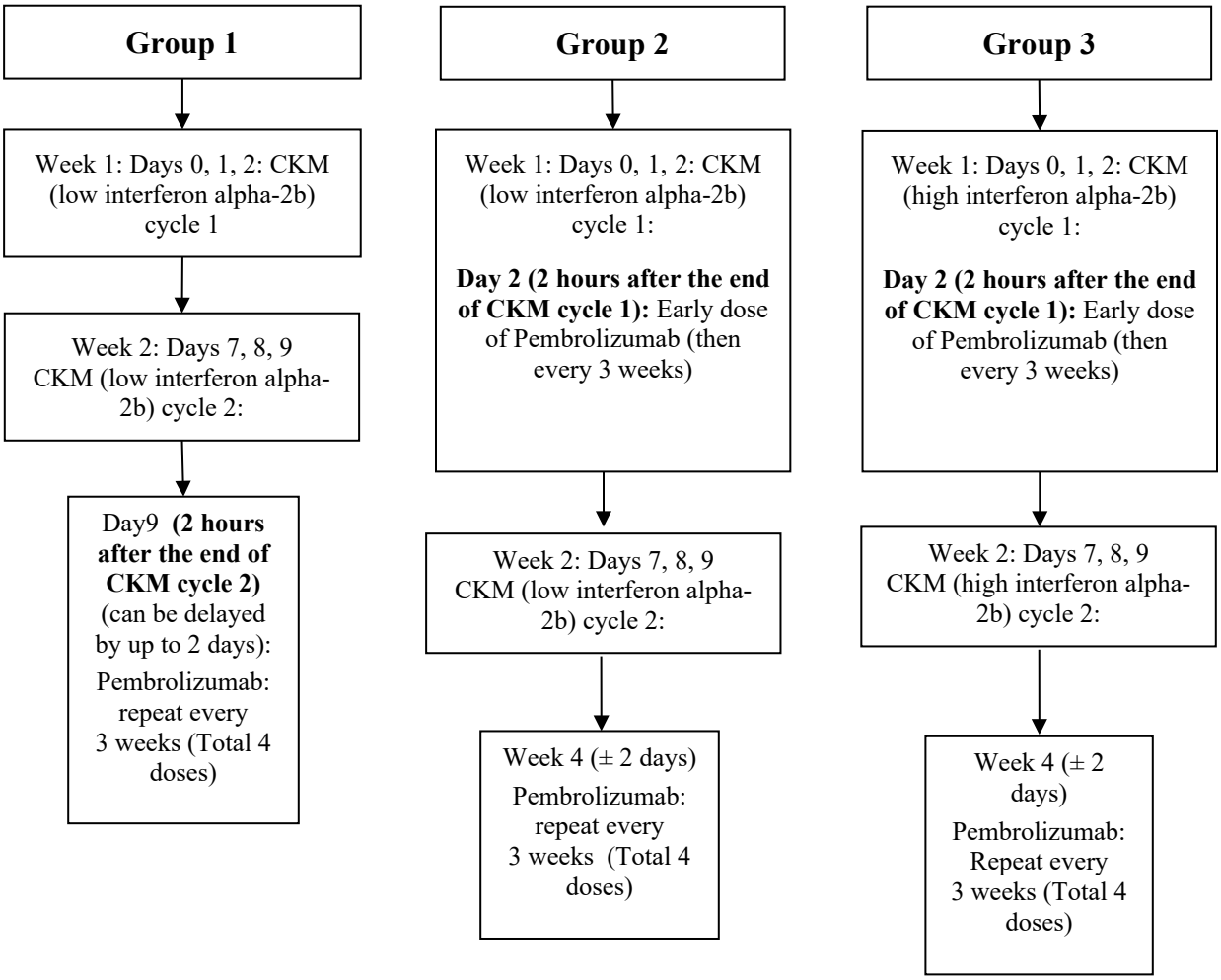
In addition, different doses of the study drug interferon alpha-2b (part of the CKM regimen) will be given to several study participants. The first several study participants will receive a low dose of this drug. If the drug does not cause serious side effects, it will be given to other study participants at a higher dose.

2. What are the study groups?

This study has three study groups. All study participants will get the same study drugs; however, depending on when you enroll to the study, you may receive the first dose of pembrolizumab in a different order (e.g., after the first or after the second CKM regimen) and, with a different dose of the interferon alpha-2b (a drug that is part of the CKM regimen).

The treatment phase of this study will be approximately 8 weeks for all groups and will include 2 rounds of CKM therapy, with the first dose of pembrolizumab administration occurring after the first or after the second CKM treatment regimen, depending on the group you are enrolled into.

The diagram below will show what the different groups are, the dose of interferon alpa-2b for each group (low or high) and, the order of pembrolizumab administration.



3. If I take part in this study, what exams, tests and procedures will I have done?

If you choose to take part in this research study, you will be asked to review and sign this consent form. You will then need to undergo a series of baseline tests to ensure that you are eligible to participate in the study.

Baseline Evaluations: Unless otherwise specified, the following will be performed within 21 days of receiving the first dose of study drug:

- Concomitant Medications: You will be asked to list any medications that you take on a regular basis (prescription and non-prescription and, any medications that you may be taking that will start or stop within 1 week of starting on the study.
- Your medical history will be obtained, especially relating to your cancer.
- Your doctor/provider will perform a physical exam. This will include recording your height (only at baseline) and weight, a general evaluation of your clinical condition, your blood pressure, pulse rate, respiratory rate and body temperature.
- Performance Status Assessment-you will be asked about how well you are able to perform ordinary tasks and carry out daily activities.
- You will undergo some blood tests in order to check your blood cell counts, electrolytes, heart, kidneys, thyroid and tumor marker level (approximately 2 tablespoons).

- For women of child-bearing potential: blood will be drawn for pregnancy test within 7 days of first study drug.
- Blood test for research-related studies (approximately 2 tablespoons) will be collected.
- Baseline eye examination
- You will have an electrocardiogram (EKG) done. This is a recording of the electrical activity of your heart.
- A biopsy of your tumor will be performed (this is optional for Group 1 and Group 2, but mandatory for Group 3).
- Baseline Disease Assessment: A CT scan and/or MRI will be done. If one has been done within 31 days of enrollment, this will not need to be repeated.

Once you are enrolled to the study, the following are the procedures that are part of the CKM treatment regimen:

CKM Treatment Regimen

The following will be performed during CKM Pre-Treatment #1 (on days 0, 1 and 2 unless otherwise specified):

- Concomitant Medications: You will be asked to list any medications that you take on a regular basis (prescription and non-prescription)
- Adverse Events will be recorded
- Your doctor/provider will perform a physical exam. This will include recording your weight and a general evaluation of your clinical condition.
- Vital Signs (temperature, blood pressure, pulse rate, and respiratory rate) will be performed prior to treatment. In addition, vital signs will be done before the Rintatolimod infusion as well as 30 and 60 minutes after finishing Rintatolimod.
- Performance Status Assessment-you will be asked about how well you are able to perform ordinary tasks and carry out daily activities.
- You will undergo some safety blood tests in order to check your blood cell counts, electrolytes and kidney function (approximately 2 tablespoons).
- Blood test for research (approximately 2 tablespoons) will be collected prior to start of CKM regimen and 2 hours after completion of Rintatolimod infusion

The following table describes the assessments and procedures that will occur while you are on the study:

Evaluation	Baseline	CKM Cycle #1 (Day 0, 1, 2)	CKM Cycle #2 (Day 7, 8, 9)	Pembrolizumab Dosing (every 3 weeks)					End of Treatment[15]	Follow-up[16]
				Cycle 2 Day 1 (*Pembrolizumab Dose #2*)	Cycle 2 Day 8	Cycle 2 Day 15	Cycle 3 Day 1 (*Pembrolizumab Dose #3*)	Cycle 4 Day 1 (*Pembrolizumab Dose #4*)		
Medical & Surgical History	X									
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Physical Examination	X	X	X	X			X	X	X	
Vital Signs	X	X	X	X	X	X	X	X	X	
Performance Status	X	X	X	X			X		X	
Standard safety blood tests	X	X	X	X	X	X	X	X	X	
Blood test for thyroid function testing	X						X		X	
Pregnancy test	X									
Blood test for heart function	X			X	X	X				
Blood test for tumor marker	X									
Blood draw for study related immune cell testing	X	X†	X††	X			X			
Antinuclear antibody testing	X									
EKG	X			X	X	X				
Tumor Biopsy	X		X							
CT and/or MRI	X								X	X
CKM regimen		X	X							
Pembrolizumab		X**	X*	X			X	X		
Adverse Events		X	X	X	X	X	X	X	X	X
Survival Status										X

†Before CKM regimen on Day 0 and after rintatolimod on Day 2.

††Before CKM regimen on Day7.

*Group 1: Day9 **(2 hours after the end of CKM cycle 2)** - can be delayed by up to 2 days. Pembrolizumab; and every 3 weeks thereafter for a total of 4 doses.

Group 2 and Group 3: **(2 hours after the end of CKM cycle 1): Early dose of Pembrolizumab, and every 3 weeks thereafter for a total of 4 doses.

Follow up:

If, at the end of the 8-week study period, it is determined that you are receiving clinical benefit from the treatment, you may be able to continue to receive pembrolizumab (every 3 weeks) beyond the 4 study doses. This will be at the discretion of the treating physician and the cost of any additional doses of pembrolizumab will be charged to you or your insurance carrier.

To capture all possible delayed immune-related adverse events, follow-up safety assessments will occur at least monthly for 90 days after the last dose of study drug or until resolution of any drug related toxicity (telephone contact is acceptable). Patients, who in consultation with their clinician will be continued on pembrolizumab after dose #4, will be included in the 90-day follow-up for immune mediated toxicities. Thereafter patients will be contacted by phone every 6 months up to 2 years to assess survival status.

Research on your biospecimens collected for this study (such as blood or tissue samples) might include whole genome sequencing, which looks at the complete set or large segments of DNA and how it may be changed or is different for people with diseases and those without. Body tissues are made up of cells that contain DNA (deoxyribonuclease acid), which is your unique genetic material that carries instructions on how your body develops and functions. Although your DNA is unique to you, you share some similarities with your children, parents, brothers, sisters, and other blood relatives.

4. Does this study involve genetic testing?

This study does not involve genetic testing.

5. Will I be informed of research results?

If we learn new information from research tests or analyses during this study that we believe may be important to your health or to your disease or condition, we may decide to share that information with you. Such information will be provided to you as part of your regular individual clinical care.

6. Why would I be taken off the study early?

You may be taken off the study for any of the following reasons:

- Your medical condition changes
- New information becomes known to us that would influence your decision to remain on the study
- The treatment is no longer helpful to you. Other options for your condition will then be discussed with you.
- The sponsor of the study may decide to stop or change the study
- You do not follow the study schedule or requirements
- You experience unacceptable side effects
- You no longer want to participate

7. What risks and discomforts are involved?

While you take part in this study, you are at risk for side effects. The side effects may be mild, moderate, or severe. Many side effects go away shortly after the treatment stops, but occasionally, side effects can be serious, long lasting, or may be permanent.

It is not possible to tell which side effect will affect you or how mild or severe the side effect might

be. We can only tell you what other people have experienced.

It is very important that you notify your doctor right away about **any** side effects, problems, or unusual experiences you may have while taking this medication/undergoing this procedure. This will decrease the chance that the side effects continue or become worse. Sometimes there are other medications that we can give you to make the side effects better or make you more comfortable. If severe side effects do develop, you and your doctor may decide it is in your best interest to stop taking part in the study.

There may be other side effects of the drugs/procedures that we do not know of yet.

Notify the study coordinator or study doctor before taking any new over-the-counter drugs or other medications to assure it is safe to take the new medication while on this study.

The drug(s)/procedures used in this study may cause all, some, or none of the side effects listed.

The risks and side effects for the drugs used in this study are listed below.

Celecoxib:

Unlikely Side Effects: In 100 people who received this drug, approximately 5 - 9 experienced the following:

- Indigestion, stomach upset
- Blockage of the airway which may cause shortness of breath, cough, wheezing
- Elevated liver enzymes in blood
- Abnormal heartbeat which may cause fainting
- Diarrhea, nausea
- Headache
- High blood pressure which may cause dizziness, blurred vision
- Kidney damage which may cause swelling
- Sores in stomach which may cause belly pain
- Swelling of the stomach
- Stroke which may cause paralysis, weakness

Rare but Serious Side Effects: In 100 people who received this drug, less than 5 experienced the following:

- Heart attack which may cause chest pain
- Swelling of the legs
- Belly pain
- Vomiting
- Severe liver enzyme elevation which may cause yellow eyes and skin, tiredness
- Bowel perforation
- Internal bleeding which may cause belly pain, black tarry stool, or blood in vomit
- Severe skin rash
- Severe allergic reaction with low blood pressure or trouble breathing
- Blood clot

Interferon Alpha-2b

The following side effects have been reported:

Very Common Side Effects: In 10 people who received this drug, more than 1 experienced the following:

- Pain
- Swelling and redness or skin damage at the injection site
- Hair loss
- Dizziness
- Changes in appetite
- Stomach or abdominal pain, diarrhea, nausea (feeling sick)
- Viral infection
- Depression, mood swings
- Insomnia
- Anxiety
- Sore throat and painful swallowing
- Fatigue
- Chills and shivering
- Fever
- Flu-like reaction
- Feeling of general discomfort
- Headaches
- Weight loss
- Vomiting
- Irritability
- Weakness
- Changes in mood
- Cough (sometimes severe)
- Shortness of breath
- Itching, dry skin, rash
- Sudden and severe muscle pain, joint pain, muscle and/or bone pain
- Changes in laboratory blood values including decreased white blood cell count.

Common Side effects: In 100 people who received this drug, between 1 to 10 patients experienced the following:

- Thirst
- Dehydration
- High blood pressure
- Migraines
- Swollen glands
- Flushing
- Menstrual problems
- Decreased sexual drive
- Vaginal problem
- Breast pain
- Pain in testicle
- Problems with thyroid gland
- Red gums, dry mouth, red or sore mouth or tongue

- Tooth ache or dental disorders
- Herpes simplex (fever blisters)
- Taste disorders
- Upset stomach
- Heartburn
- Constipation
- Liver enlargement (liver disorders, sometimes severe)
- Loose stools
- Sinus infection
- Lung inflammation
- Eye pain
- Disorders in the tear ducts
- Irritation and redness of the thin membrane covering the eye
- Agitation
- Sleepiness
- Sleepwalking
- Behavioral disorders
- Nervousness
- Stuffy or runny nose
- Sneezing
- Rapid breathing
- Pale or reddened skin
- Bruising
- Skin or nail disorders
- Red, dry, scaly patches of thickened skin (psoriasis)
- Increased sweating
- Increased need to pass urine
- Slight tremors
- Decreased sensitivity to touch, and
- Joint inflammation and swelling.

Uncommon Side Effects: In 1,000 people who received this drug, between 1 to 10 patients experienced the following:

- Bacterial infection
- Tingling feeling, and
- Inflammation of the tissue around the heart (possible chest pain).

Rare Side Effects: In 10,000 people who received this drug, between 1 to 10 patients experienced the following:

- The study treatment may cause an increased risk of infection, such as pneumonia (an infection of the lungs). A low number of white blood cells may increase the risk of infection. It may become life-threatening. Symptoms of infection may include fever, pain, redness, and/or difficulty breathing.

Very Rare Side Effects: In 10,000 people who received this drug, less than 1 patient experienced the following:

- Low blood pressure

- Puffy face
- Diabetes
- Leg cramps
- Back pain
- Kidney disorders
- Nerve alteration
- Bleeding gums
- A disorder caused by decreased production of red blood cells, white blood cells and platelets which may cause severe anemia, infection and bleeding may occur. This may be serious or life-threatening without treatment.
- Pure red cell aplasia, a condition where the body stopped or reduced the production of red blood cells, has been reported. This condition causes severe anemia, symptoms which would include unusual tiredness and lack of energy.
- Sarcoidosis, (a disease characterized by persistent fever, weight loss, joint pain and swelling, skin lesions and swollen glands) has been very rarely reported.
- Loss of consciousness has occurred very rarely, mostly in elderly patients treated at high doses.
- Cases of stroke (cerebrovascular events) have been reported. Seek your doctor immediately if you have any of these symptoms.

Side Effects of Unknown Frequency:

- Gum disease and dental disorders
- Change in color of the tongue
- Altered mental condition
- Loss of consciousness
- Acute hypersensitivity reactions including hives, swelling of hands, feet, ankles, face, lips, mouth, or throat which may cause difficulty in swallowing or breathing, difficulty breathing due to narrowing of the airways and a severe, whole-body allergic reaction have been reported (at unknown frequency).
- Vogt-Koyanagi-Harada syndrome (an autoimmune inflammatory disorder affecting the eyes, skin and the membranes of the ears, brain and spinal cord)
- Thoughts about threatening the life of others
- Mood disorder with extremes of happiness and sadness
- Heart failure
- Pericardial effusion (a fluid collection that occurs between the heart lining and the heart itself, scarring of the lungs that can affect the ability to breathe and may make you short of breath, and reactivation of hepatitis B infection (liver damage) have been reported with interferon alpha 2b use.
- Pulmonary arterial hypertension – a disease of severe narrowing of the blood vessels in the lungs resulting in high blood pressure in the blood vessels that carry blood from the heart to the lungs may occur particularly in patients with risk factors such as HIV infection or severe liver disorders (cirrhosis). The episodes were reported at different time points during the treatment, typically several months after starting treatment with interferon alpha 2b.

Rintatolimod:

Very likely Side Effects: In 100 people who received this drug, approximately 15 experienced the following:

- Mild, short-lived pain at the infusion site
- Flu-like symptoms which may include, but not limited to: fever, chills, mild muscle or joint aches, headache, fatigue and possibly nausea and vomiting
- Flushing, occasionally, it can be accompanied by a tightness of the chest, increased heart rate, anxiety, shortness of breath, reports of "feeling hot", excessive sweating, and nausea

Less likely side effects: In 100 people who received this drug, approximately 5 - 14 experienced the following:

- A more pronounced fever with chills and fatigue in response to a single infusion. This typically resolves over 12 to 24 hours, responds to acetaminophen (pain and fever reducing medication), and does not recur on subsequent dosing.
- Diarrhea, itching, hives, drop in blood pressure, sensitivity to light, rash, irregular heart rate, and vision problems

Rare side effects: In 100 people who received this drug, less than 5 experienced the following:

- Temporary increased swelling around the tumor or even increased enhancement of the tumor
- Complications from the infusion that include infection, bleeding, or nerve damage
- Decreased liver function
- Fainting caused by low blood pressure

Pembrolizumab:

Likely Side Effects: In 100 people who received this drug, approximately more than 15 experienced the following:

- Increase in blood pressure also known as high blood pressure
- Loss of hair from areas of the body where hair is usually found
- Itching
- Rash
- Increased blood sugar levels
- Increased triglyceride levels (high blood levels of fat)
- Decreased albumin levels, a protein made by the liver that enters your bloodstream and helps keep fluid from leaking out of your blood vessels into other tissues (low blood levels of this protein can cause swelling, weakness, and/or fatigue)
- Decreased sodium levels
- Constipation
- Decreased appetite
- Diarrhea
- Nausea
- Increased liver enzyme (may indicate possible liver damage)
- Joint, back, or muscle aches
- A nerve problem that causes pain, numbness, tingling, swelling, or muscle weakness in different parts of the body.
- Cough

- Shortness of breath
- Fatigue (tiredness)
- Immune mediated toxicities (immune cells attack the normal cells in the body)
- Fever
- Abdominal pain
- Loss of skin color
- Decreased thyroid hormone levels causing weight gain, fatigue, feeling cold, constipation

Less likely Side effects: In 100 people who received this drug, approximately more than 14 experienced the following:

- Anemia (decreased red blood cells)
- Veno-occlusive disease of the liver (immune cells in the body cause the small veins in the liver to become obstructed, leading to symptoms such as enlarged liver, yellowing of the eyes/skin, and fluid build-up in the abdomen)
- Blood infection

Rare but Serious Side Effects In 100 people who received this drug, less than 4 experienced the following:

- Vasculitis (inflammation of the blood vessels)
- A rare skin condition that causes large fluid filled blisters (Bullous pemphigoid)
- Erythroderma (an intense reddening of the skin)
- Inflammation of the pituitary gland
- A rare type of anemia where the body attacks its own red blood cells.
- Inflammation of the liver caused by the body's immune cells attacking the liver cells
- Inflammation of the pancreas
- Rare condition in which the body attacks its own tissues
- Rhabdomyolysis-rare condition in which the muscle tissue breaks down, leading to
- Muscle pains, weakness, vomiting, confusion and possible kidney failure.
- Confusion
- Inflammation of the optic nerve or uvea (parts of the eye)
- Inflammation of the kidneys
- Kidney failure
- Build-up of fluid around the lung
- Pneumonia
- Inflammation of the lungs
- Respiratory failure
- Infusion reaction (may include dizziness or fainting (low blood pressure), flushing, rash, fever, shortness of breath or sick to your stomach, or pain at the site of infusion).
- Heart problems including inflammation and heart failure with heart inflammation as a
- complication of therapy being reported to lead to death in less than 3 patients out of 1000 who receive the drug. Symptoms and signs of heart problem may include: shortness of breath, swelling of the ankle and body.
- Stevens-Johnson Syndrome is a severe skin and digestive tract reaction that may include rash and sloughing or breakdown of tissue. This may manifest as various blisters, hives, and other rashes in various locations on the body including palms and soles, face and other extremities. This is serious and may be life threatening.

- Toxic Epidermal Necrolysis (TEN) is a rare, life-threatening skin condition that is usually caused by a reaction to a drug. The top layer of skin detaches from the lower layers of skin all over the body. This is similar to the skin damage from a severe burn and is serious and life threatening.
- Increased thyroid hormone levels causing feeling anxious, mood swings, having trouble sleeping, feeling weak, tired, trembles, sweating, diarrhea
- Inflammation of large intestine causing diarrhea with or without blood or mucous
- Inflammation of the skin with peeling, itchiness, skin redness
- Guillain-Barré Syndrome; inflammation of the nerves causing pain, weakness, tingling in hands and feet
- Inflammation of the muscles
- Decrease in adrenal gland hormone levels (may cause possible weakness and/or low blood pressure)
- Type 1 diabetes (symptoms may include extreme thirst, increased hunger-especially after eating), dry mouth, upset stomach and vomiting, frequent urination, unexplained weight loss even though you're eating and feel hungry, fatigue, blurry vision; heavy, labored breathing; frequent infections of your skin, urinary tract, or vagina; crankiness or mood changes
- Inflammation of the thyroid: low thyroid hormone levels can lead to fatigue, weight gain, constipation, dry skin, depression, reduced exercise tolerance and problems with concentration and mental focus, whereas high thyroid levels in the blood can lead to anxiety, trouble sleeping, fast heart rate, fatigue, weight loss, irritability, sweating, and increased appetite. Other symptoms may include pain in the thyroid gland and tremors (involuntary shaking of the body or limbs)
- Myasthenic syndrome; condition that causes weakness, fatigue, eyelid droopiness, blurred or double vision, difficulty swallowing
- Formation of small immune cell clusters (granulomas) in parts of the body, such as lymph nodes, eyes, skin, lungs
- Inflammation of the brain with confusion and fever which may include disorientation, memory problems, seizures, changes in behavior, difficulty speaking, weakness or loss of body part movements, loss of consciousness
- Inflammation of the spinal cord which may include pain, numbness, tingling, weakness in arms or legs, bladder or bowel problems including urinating more frequently, leakage of urine, unable to urinate, constipation
- Inflammation of the joints
- Vogt-Koyanagi-Harada syndrome; changes in eyesight, eye pain, white patches on the skin, hearing loss
- Inflammation and scarring of the bile ducts
- Inflammation of the lining of the stomach
- Anemia due to the destruction of red blood cells
- Not enough pancreatic enzymes (proteins that break down food) that leads to poor digestion of food

Procedure Risks:

Tumor Biopsy:

A biopsy is the removal of a sample of body tissue for examination. The most common risks of a biopsy can include pain from the procedure, bruising and soreness at the site of the biopsy and, scarring at the site of the biopsy. The soreness is generally diminished within 48 hours of the procedure. In rare instances there may be infection and/or bleeding. To reduce these risks, the site of the biopsy will be numbed, and sterile techniques will be used. Your doctor will discuss with you the safest method and location to perform these biopsies.

Intravenous (IV) insertion:

The risk of IV insertion is similar to the risk of blood draw: momentarily painful with insertion of the IV and bruising/swelling at the IV site. There is a small risk of fainting, infection and inflammation of the vein (called phlebitis). There is also a rare risk of the fluid from the IV leaking into the tissues around the vein if the IV becomes dislodged or is not inserted correctly. This "leakage" of fluid into the surrounding tissue could potentially cause swelling, pain, redness or tissue damage.

Blood Draw:

The blood draw is momentarily painful while the needle is penetrating the skin. There is a small risk of fainting, of some bruising (bleeding under the skin), and a rare (1 in 1,000) risk of infection. *Less common* side effects include mild pain, discomfort, and/or bruising at the needle insertion site, inflammation of the vein, as well as possible infection, bleeding and, soreness. *Rare* side effects include severe pain, swelling, possibly an infection from the needle insertion site, and fainting.

CT scan: (Computed Tomography)

When you have a CT scan, you will be exposed to radiation. In addition, you might be allergic to the dye used during CT scan procedures.

When the contrast medium is injected during the CT scan, you may experience nausea, flushing, warmth and a salty taste. You must not move during the test but relax and breathe normally. You might be uncomfortable while you are in the tunnel-shaped machine. You may feel claustrophobic (confined feeling) during this test.

MRI: (Magnetic Resonance Imaging)

There are no known harmful effects from the strong magnetic field used for MRI. However, the magnet is so powerful that it can send unsecured metal objects flying across the room. The magnet may affect pacemakers, artificial limbs and other medical devices that contain iron. Also, there is a risk that metal objects coming near the magnet may become dangerous as they are pulled toward the magnet. The magnetic field will stop a watch that is within several yards of the magnet. Severe injury or death can occur when patients with implanted neurological stimulators undergo MRI scans. You should discuss any metal devices in your body with the study staff.

Electrocardiogram: There are generally no risks. This procedure examines how efficiently your heart is working.

8. Reproductive risks:

This study may involve risks to you or your unborn child that are not known at this time therefore, you should not become pregnant or father a baby while you are participating in this study. Also,

you should not nurse your baby while on this study. If you plan to have children in the future, discuss with your doctor whether it may be necessary to have your eggs or sperm preserved prior to participating in this study. Women of childbearing potential will be required to take a pregnancy test before being allowed to take part in this study. You may also be asked to take pregnancy tests while receiving the study treatment. The pregnancy test must be negative before you enter this study.

Women of childbearing potential will be asked to practice an effective method of birth control while on this study and for a time after treatment ends. This includes, but is not limited to, oral birth control pills, an IUD, condoms with spermicide, or abstinence. Since interactions between the study drug and oral birth control pills cannot be ruled out, a "barrier" method of contraception (condom, diaphragm) must be used as well. In certain cases, oral birth control pills cannot be used for birth control. When taking part in this study, you should continue use of birth control and should not donate your eggs for six (6) months after the last treatment to ensure the drug/treatment has cleared from the body. Please discuss this with your doctor.

When you sign this consent form, to the best of your knowledge, you are not pregnant and do not plan to become pregnant while taking part in this study. Should you become pregnant during this study, you need to immediately tell your study doctor and obstetrician. If you wish you may request a referral for counseling or ask about counseling (such as genetic counselor, social worker, or psychologist.) to discuss this further.

Male patients must use an effective method of birth control. This can include, but is not limited to, condoms with spermicide, abstinence, or having a vasectomy. When taking part in this study, you should continue use of birth control and should not donate sperm for three months after receiving the last dose of the drug to be sure the drug has cleared from the body. Discuss birth control measures with your doctor.

9. What are my responsibilities in this study?

If you choose to take part in this study, you will need to:

- Keep your study appointments.
- Tell your doctor about:
    - All medications and supplements you are taking
    - Any side effects
    - Any doctors' visits or hospital stays outside of this study
    - If you have been or are currently in another research study.
- Keep the study medication out of the reach of children and do not share the study drug with any other person.

10. Who should I contact with questions about costs related to this study?

As discussed in the "Study Costs" section on page 2 above, certain services will be billed to you or your insurance carrier. There are many different types of insurance plans and contracts. It is not possible to tell you in advance the exact amount your insurance will pay and what your financial responsibility will be.

There are certain insurance plans that will not cover charges for any care related to an experimental or investigational therapy or study. These plans may deny coverage for even the routine, standard of care medical services you will need to receive during the time you are enrolled in the study. If you have an insurance plan that does not cover participation in a clinical research study, or if you currently have no insurance coverage, a financial counselor can meet with you to provide an

estimate of the costs that would be associated with participation in this study. A payment schedule can be developed if needed.

If you wish, a financial counselor can meet with you to help answer your questions regarding insurance coverage issues, to discuss a payment schedule, or to answer questions you may have regarding study-related billing. A Financial Counselor can be reached at 716-845-4782.

In addition, a representative from the Patient Access Department can help you obtain authorizations from your insurance carrier when needed. A representative from the Patient Access Department can be reached at 716-845-1049.

11. What happens if I am injured as a result of this study?

If you believe you have been injured as a direct result of your participation in this research study, notify the Roswell Park Patient Advocate at (716) 845-1365 or the Study Doctor at (716) 845-1486.

If you develop complications or side effects from your participation in this clinical research study, medical treatment and/or medications to help with side effects will be provided at the usual charge and will be billed to you and /or your insurance company.

Medical diagnosis and treatment for the injury will be offered, and a determination will be made regarding appropriate billing for the diagnosis and treatment of the injury. A financial counselor can be reached at 716-845-4782 to provide an explanation of coverage and to answer questions you may have regarding study related billing.

You do not give up any legal rights by signing this form. You are not prevented from seeking to collect compensation for injury related to malpractice, fault, or blame on the part of those involved in the research.

12. Will I be paid for joining this study?

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

It is possible that this research project may result in developing treatments, devices, new drugs, or procedures that could be used for commercial profit by the sponsor or other entities. If this happens, you understand that you will not receive any financial payment or share in any commercial profit for the use of your information and biospecimens (such as blood or tissue samples) collected as part of this research.

13. Where can I find more information?

You may call the NCI's Cancer Information Service at 1-800-4-CANCER (1-800-422-6237).

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.

For accurate cancer information including Physician Data Query (PDQ), visit https://www.cancer.gov.

14. Who do I contact with questions?

You are free to ask questions at any time about this study and to ask for more information from the doctor identified on this document. If you have any questions, concerns or complaints about this study, you should contact the study doctor identified on the first page of this document. In

case of an emergency after regular hospital hours, you should telephone (716) 845-2300 and ask for the medical oncology doctor on call.

If you have questions about your rights as a research subject or you feel you have been injured as a result of your participation in this research study, you can call the Roswell Park Patient Advocate (Support) Office at (716) 845-1365. You should also feel free to contact the Patient Advocate Office at any time while considering participation, during participation or once your participation is complete. This office is unaffiliated with any specific research study. They can help you obtain additional information regarding your research participation and your rights as a research subject or how to proceed should you feel you have been injured as a result of your participation. They are available to discuss any problems, concerns, questions or input you may have.

It may be necessary to contact you at a future date regarding new information about the medication or procedures that you have received. For this reason, we ask that you notify the Patient Access office at 716-845-1049 or stop at the Registration Desk in the Lobby of Roswell Park to update us of any change in your address.

15. What about confidentiality of my information?

Your privacy is very important and the study doctors and those involved with this research study will make every effort to protect it.

Some of your health information, such as your response to treatment, results of study tests, and medicines you took, will be kept by the study sponsor in a research database. As required by law, only the minimum, necessary information that identifies you will be used to conduct this research study . If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

There are organizations that may look at or receive copies of some of the information in your study records. Your health information in the research database also may be shared with these organizations. They must keep your information private, unless required by law to give it to another group.

Information that identifies you may be removed from your health information and/or biospecimens (such as blood or tissue samples, if applicable). The de-identified health information or biospecimens may then be used or disclosed for other purposes, including for future research studies or distributed to another investigator for future research studies, without additional informed consent or authorization from you.

Your health information may also be stored in a research database or repository. This information may then be used for other research, either de-identified or identified. Future research studies using your health information will be reviewed by an oversight board known as an Institutional Review Board if required by law. This information will be kept indefinitely.

Sharing information is part of the research process and may increase what we can learn from the research. Researchers share information by putting data from the study into one or more scientific databases, where it is stored along with information from other people and studies; this is referred to as large scale data sharing. Researchers can then study the combined information to learn even more about health and disease. Often, sharing data is required as a condition of

funding or for publishing study results. It is also needed to allow other researchers to validate study findings and to come up with new ideas. There are many different kinds of scientific databases; some are maintained by Roswell Park, some are maintained by the federal government, and some are maintained by private companies. Your name and other information that could readily identify you (such as your address) will not be shared or placed into an external scientific database. All requests for data sharing will be reviewed by Roswell Park and we will use many safety procedures to protect your privacy. However, we cannot guarantee that no one will ever be able to use the information to identify you.

Certificate of Confidentiality

As an additional measure to protect your privacy, a Certificate of Confidentiality has been issued from the United States Government, National Institutes of Health, for this study. With this Certificate, the investigators and institutions involved in this study cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceeding. We will use this Certificate to resist any demands for information that would identify you, with the following exceptions:

- The Certificate cannot be used to resist a request for your information from the United States Government when the information is to be used for auditing or evaluation of federally funded projects or for information that must be disclosed to meet the requirements of the Food and Drug Administration (FDA).
- State law requires we report cases of diseases that spread easily, or abusive behavior (toward a child, a partner, or an elderly person), and people who say they are going to hurt themselves or someone else.
- The Certificate does not prevent you or a member of your family from voluntarily releasing information about yourself or involvement in this research. Also, if you have given written consent to an insurer, employer, or other person to receive research information, then we may not use the Certificate to withhold the information.

AUTHORIZATION TO USE YOUR HEALTH INFORMATION

If you volunteer to take part in this research study, and you sign this document, you give permission to the study doctor and research staff to use or disclose (release) your health information that identifies you and is collected as part of the research study described in this consent. This means that others may know or be able to find out your identity, use your health information and share it with others. We want you to know who may use this information and how they may use it. We also want to tell you about your rights before you agree to take part in the study.

If you volunteer to take part in this research study, you consent to the release of your health information from other medical facilities for any moderate to life-threatening or fatal adverse events that occur while on study treatment through 90 days after treatment ends.

Who may see this information?

- Dr. Gandhi and all the members of the study/research team and other health care professionals at Roswell Park
- The Sponsor of this study, its' affiliates, successor companies, assigns, companies that may buy information from the Sponsor, and business collaborators, individuals and organizations working with the Sponsor and their representatives, including authorized study monitors, auditors and clinical research organization representatives

- Government or Regulating Agencies such as the FDA, DHHS, NCI, NIH or other agencies worldwide
- Government agencies that must receive reports about certain diseases and conditions
- Institutional Review Boards or Data Safety and Monitoring Boards at Roswell Park and its affiliates or outside of Roswell Park.

What information may be collected, used and shared?

Health information that identifies you and relates to your participation in this study will be collected and created. This may include the following:

- Health information, sometimes known as "Protected Health Information" (PHI) can include your name; address, patient identification number; medical record number; date of birth; photographs; information about your health, including past medical history, treatment, diagnosis, test results and any other information about your health or medical condition; or about payment of charges for medical treatment found in your medical record or other records maintained by Roswell Park.
- Information from the procedures used to find out whether you are eligible to take part in this study. This may include physical examinations, blood and urine tests, x-rays and other procedures or tests, and any other information that you may release to us, including information about your health history.
- Information obtained in the course of the study including information about your response to any treatments you receive, information related to study visits and phone calls, physical examinations, blood and urine tests, genomic or genetic tests, x-rays and other procedures or tests, and any other information about your participation in this study.

Why will this information be used and/or shared?

PHI and other information that may identify you will be used and given out to others to carry out the research study. The sponsor will analyze (test) and evaluate the results of the study. The sponsor, its agents, assigns, government agencies, and others may visit the research site to follow how the study is being done and may review your information for this purpose.

This information may be given to the FDA. It may also be shared with other governmental agencies in this country and in other countries. This is done for participant protection and so the sponsor can receive marketing approval for any new products that may result from this research. The information may also be used to meet the reporting needs of the governmental agencies.

The results of this research may be published in scientific journals or presented at medical meetings, but your identity will not be disclosed (shared).

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

If you refuse to authorize the collection, use and disclosure of your health information as indicated above, you will not be able to be in this research study.

Your decision not to sign this authorization or to withdraw from the study will not involve any penalty or loss of benefits to which you are otherwise entitled and will not affect your access to non-research related health care here.

What happens if I want to withdraw my authorization?

You may change your mind and revoke (take back) this authorization at any time, except to the extent that Roswell Park has already acted (used or disclosed health information) based on this authorization. To revoke/withdraw this authorization, you must write to the study doctor (name

and address is on the first page of this form) and let the doctor know that you are withdrawing your authorization to use and disclose your information.

If you should die while enrolled in or after taking part in this study, your health information may be used or disclosed solely for research purposes without getting any added authorization.

The results of clinical tests or therapy performed as part of the research may be included in your medical record and will not be removed from the record if you withdraw.

May I review or copy the information obtained from me or created about me?

You may not have the right to review or copy aspects of your Protected Health Information (PHI) that are considered to impact the integrity (truthfulness) of this research study. At the end of this research study and at your written request, you may have access to your health information that relates to the research study. Information is kept in your medical record, which is a set of data that includes medical information or billing records used in whole or in part by your doctors or other health care providers at Roswell Park to decide about care and treatment. Access to your health information in your medical record is described in the Notice of Privacy Practices provided to you by Roswell Park. If it is necessary for your care and/or treatment, your PHI will be provided to you or your referring or primary care doctor. You will not have access to your blood, tissue, and diagnostic research study results that are performed in a laboratory/facility that is not approved to report clinical results.

When does this authorization end?

This authorization does not have an end date.

What happens to my health information after it is given to others?

If you sign this form, the health information collected from you and shared as indicated above, may be re-disclosed to third parties who are not subject to the same laws as those in the United States and may no longer be protected. There is a risk that your information will be given to others without your permission; however, the Sponsor also has protections in place to assure the security of your health information.

Authorization

As a participant in this study, you agree to allow the use of your health information for research purposes. You understand that your health information will be used/disclosed by Roswell Park as indicated in this document. You understand that you have a right to withdraw your authorization for use of your health information in writing, but the information which has already been used or disclosed before your written withdrawal will continue to be used for research purposes. Finally, you understand your health information that has been disclosed by Roswell Park through this authorization to the study sponsor, government agencies, or others may be further disclosed by them, as the health information will no longer be protected by the federal privacy laws.

OPTIONAL RESEARCH: Group 1 and Group 2 ONLY

During the course of your participation in this you will have the opportunity to provide optional tumor biopsy tissue at two timepoints throughout the study: at baseline (before starting on the study treatment) and, after completion of the second CKM treatment regimen This part of the

consent form is about the optional biopsies of tumor tissue that you may provide for research studies to see what affect the treatment may or may not have had on tumor cells.

You will not get health benefits from any of these studies. The research from these studies may help other people with cancer or other diseases in the future. You can still take part in the main study even if you say "no" to this optional research.

These samples will be kept in a secured research laboratory at Roswell Park. Samples will be used for planned study analyses as well as for future analysis for other yet to be identified biomarkers that may be related to the clinical outcome of the patients receiving this type of treatment.

These stored samples will be used for future research studies that might involve genetic or genomic studies and looking for links between genes and factors like diet or lifestyle, other cancers, or other diseases that are common in your age group. Body tissues are made up of cells that contain DNA (deoxyribonuclease acid), which is your unique genetic material that carries instructions on how your body develops and functions. Genetic studies look at certain genes (small segments of the DNA) and genomic studies, which may include whole genome sequencing, looks at the complete set or large segments of the DNA and how it may be changed or is different for people with diseases and those without. Although your genomic information is unique to you, you share some genomic similarities with your children, parents, brothers, sisters, and other blood relatives.

The samples will be labeled so your name and your identity will remain unknown to the researchers. The results of any genetic or other studies will not be given to you or your doctor, as your identity will not be known. It is not possible for us to know now all the different ways the samples may be studied in the future. We would also like to store information collected on you in this clinical study along with information from your medical records, including your age, ethnic background, diagnosis, disease history, medical treatments and response to treatments. This information along with your samples help researchers learn more about cancer and other diseases and to understand why some people respond to certain treatments while others do not.

Information from studies using your samples and your medical information will be collected along with information from other people who volunteer for this optional research. Researchers can request to study the samples and medical information stored in the specimen and data bank.

This includes researchers at Roswell Park as well as from other universities, the government, and drug or health-related companies in the United States or other countries. Information from studies of your samples and your medical information might also be shared broadly by placing the information into one or more large scientific databases maintained at Roswell Park or at other institutions or by the federal government where it is stored along with information from many other people and from other studies. Researchers can request to study the combined information to learn more about cancer or other diseases. Some information from these large databases may be made freely available to the public (unrestricted access) but will not contain any information specific to you or any other participant. Information from studies using your samples and your medical information may also be put in a controlled-access database in which researchers need to get permission to use the information for a research project. Researchers who are approved to access the information in the controlled-access database will need to agree not to attempt to identify you.

We will not give researchers information that could directly identify you. We will take many steps to protect the privacy of people who take part. We will remove your name and any other information that could directly identify you from your samples and information. We will replace

the direct identifiers with a code number and only certain study staff will have access to the key that will link the code number to your identity. By protecting your identity in this manner, researchers who study your samples and information will not know who you are. There is a risk that someone could get access to the data we have stored about you. It is also possible that the information from your genome, when combined with information from other public sources could be used to identify you. We believe the chance of this happening is very small but we cannot make guarantees. Your privacy and the confidentiality of your information are very important to us and we will make every effort to protect them.

It is not possible for us to know now what tests will be discovered in the future. We cannot give you a list of all the possible ways the sample will be used. We are asking that you give your permission for us to take, store and do research on the sample without contacting you again in the future. None of this research is a direct help to you but could help us learn other ways to prevent cancer or other diseases and might be helpful to others in the future. It is possible that future research projects may result in developing treatments, devices, new drugs, or procedures that could be used for commercial profit. If this happens, you understand that you will not receive any financial payment or share in any commercial profit for the use of your biospecimens (such as blood or tissue samples) that had been stored for future research.

If you give permission for the sample now and change your mind later, you will need to write to the doctor listed on the first page of this form and let him/her know that you changed your mind. If we have not already used the sample, it will be destroyed and not used. If you have any questions, please ask your doctor.

BASELINE: Prior to the start of the study treatment, my tumor tissue can be taken and used in research to learn about, prevent, treat, or cure cancer

PLEASE CHECK ONE BOX

YES ☐ **NO** ☐

AFTER COMPLETION OF CKM Cycle #2: Following the second CKM treatment regimen (and prior to pembrolizumab dosing), my tumor tissue can be taken and used in research to learn about, prevent, treat, or cure cancer

PLEASE CHECK ONE BOX

YES ☐ **NO** ☐

Statement of Investigator/Person Conducting the Informed Consent Discussion:

I certify that the nature and purpose, the potential benefits and possible risks associated with participation in this research study have been explained and that any questions about this information have been answered. A signed copy of this consent will be given to the participant.

SIGNATURE_____ **DATE**_____ **TIME**_____

PRINTED NAME _____

Participant's Statement of Consent:

By signing below, you agree that:

- You have been told of the reasons for this study.
- You have had the study explained to you.
- You have had all of your questions answered, including those about areas you did not understand, to your satisfaction.
- You have carefully read this consent form and will receive a signed copy of this form.
- You do **not** waive any **legal** rights you have under federal or state laws and regulations.
- You willingly give your consent to voluntarily join in this research study.

Participant:

SIGNATURE_____ **DATE**_____ **TIME**_____

PRINTED NAME _____

Witness Signature is needed in the following circumstances – check below:

☐ Not Applicable

☐ The person consenting cannot write – mark must be made as appropriate.

☐ The person consenting cannot read - consent has been read to him/her.

☐ The person consenting cannot understand English and the consent has been verbally interpreted.

(The witness should be fluent in both English and the language of the person consenting.)

Witness Statement:

The person consenting has signed this document in my presence.

SIGNATURE_____**DATE**_____ **TIME**_____

PRINTED NAME _____

RELATIONSHIP TO PARTICIPANT_____