INFORMED CONSENT

TITLE:	A Multicenter, Open-label, Phase 2 Study of Imprime PGG and Pembrolizumab in Subjects With Advanced Melanoma Failing Front-line Treatment with Checkpoint Inhibitors (CPI) or Triple Negative Breast Cancer (TNBC) Failing Front-line Chemotherapy for Metastatic Disease
PROTOCOL NO.:	BT-CL-PGG-MEL/BCA-1621/MK3475 PN-545/Amendment 001 WIRB® Protocol #20162506
SPONSOR:	Biothera Pharmaceuticals, Inc.
INVESTIGATOR:	Name Address City, State Zip Country
STUDY-RELATED PHONE NUMBER(S):	Name Phone number (24-hour number required)

Introduction

You have been asked to participate in a research study. In order to decide whether you agree to be part of this research study, you should read this informed consent, which describes how the study will be done and the possible risks and benefits.

Please take your time to make your decision about taking part. You may discuss your decision with your friends and family or your healthcare team. If you have any questions, you can ask your study doctor for more explanation.

If you agree to take part in this study, you will be asked to sign this form. You will be given a copy to keep. If you do not sign this form, you cannot take part in this study.

You are being asked to take part in this study because you have either:

- Metastatic Triple-Negative Breast Cancer (TNBC) and you have gotten worse after treatment with chemotherapy

or

- Advanced (unresectable [cannot be removed surgically] Stage III or Stage IV) melanoma and you have gotten worse after treatment with a type of medication called a “checkpoint inhibitor”

Why is this study being done?

The purpose of this study is to find out good and/or bad effects of the investigational drug, Imprime PGG, when given together with pembrolizumab which is also known as “Keytruda®” (a type of “checkpoint inhibitor”) in the treatment of your type of cancer. An investigational drug is one that is not approved by the United States Food and Drug Administration (FDA). Imprime PGG is a glucan. Glucans are molecules that are not normally present in your body. Imprime PGG when given with pembrolizumab may help the immune system to fight your type of cancer. Pembrolizumab is already approved by the FDA when given alone for the treatment of advanced metastatic melanoma, but not for TNBC. The combination of these drugs used in this study is also investigational.

Biothera is the sponsor supporting this study and is responsible for the manufacturing of Imprime PGG.

Pembrolizumab is manufactured by Merck.

The term “study drug” or “study medication” will be used throughout this document to refer to both Imprime PGG and pembrolizumab.

How many people will take part in the study?

The goal of the research study is for up to 94 people (up to 41 who have melanoma and up to 53 who have TNBC) to participate throughout the United States.

WHAT WILL HAPPEN IF I TAKE PART IN THIS RESEARCH STUDY?

Before you begin the study

You will have the following exams, tests, or procedures to find out if you can be in the study - this is called the screening period. These exams, tests, or procedures may be part of your regular cancer care and may be done even if you do not join the study. If you have had some of them recently (within days before the start of the treatment on this study), they may or may not need to be repeated. This will be up to your study doctor. These screening tests and procedures include the following:

- You will be asked to sign this consent form before any screening tests can be performed.
- If you are a female who is able to have children, a urine or blood pregnancy test will be done. You will not be allowed to enter the study if you are pregnant, or if you are breast-feeding.
- You will be asked about your past and present medical history including information about you, and medications (prescription, over the counter, and herbal) you are currently taking or have recently taken and the reason that you took them.
- Your performance status will be done which is a general assessment (questions) of how your cancer is affecting your daily life, and how well you can carry out daily activities.
- A physical examination including measurement of your vital signs (heart rate, breathing rate, blood pressure), weight, and height will be done.
- Blood samples (approximately 18 mL or about 3 and a half teaspoons) and a urine sample will be collected for routine tests.
- A screening blood sample (5 ml or 1 teaspoon) will also be collected to see if certain antibodies and proteins are present in your blood prior to your participation in the research

study; if you have previously been pre-screened with this blood test, you will not need to repeat it. Additional blood samples (5 ml or 1 teaspoon) will be collected during the study to see the effects of the study drug on your body.

- An electrocardiogram (ECG) will be done to check the rhythm (tracing of the electrical activity) of your heart.
- A computed tomography (CT) scan with contrast (you will be injected with a dye prior to the procedure to make the organs and tissues that are being scanned more visible) or magnetic resonance imaging (MRI) of the head, chest, abdomen, and pelvis are required within 28 days of starting study drug. CT or MRI only needs to be performed if it hasn't been done within the required time period. If your study doctor believes your cancer has spread to your bones, you may be asked to have a bone scan. A bone scan is a diagnostic procedure used to evaluate abnormalities involving bones and joints.
- The pathology report describing your cancer upon initial diagnosis, and if available, a section of your archived cancer biopsy (which was taken from you in the past when you were first diagnosed with cancer), will be provided to the study researchers.

During the Study

Everyone in this study will get the same treatment of Imprime PGG in combination with pembrolizumab.

If the exams, tests, and procedures completed for the screening period show that you can be in the study, the study doctor feels it is safe for you to do so, and you choose to take part, you will be receiving Imprime PGG + pembrolizumab.

Treatment will occur in 3-week cycles.

Each cycle begins immediately after the end of the previous cycle so treatment continues without any gaps in the cycles for as long as you are receiving study drug.

Imprime PGG and pembrolizumab are both given through a needle in a vein as an intravenous (IV) line or through a previously surgically inserted venous access line, also known as a Port or PICC line.

You may receive medications before receiving the study medications, and these medications are called "pre-treatment". This pre-treatment is given to help your body tolerate the study medications better, and help to decrease the chance of an allergic type reaction. An anti-histamine drug (for example, Benadryl or equivalent) or other drugs which your doctor feels may help you will be given before administration of the study drug. You will then receive the Imprime PGG over a 2-4 hour period depending on your weight. After the Imprime PGG administration is completed, you will wait 15-30 minutes, (a rest period) and then receive the pembrolizumab over approximately 30 minutes.

You will need to be in the clinic for about 3 hours for each visit for all but 2 visits.

During 2 visits (Day 1 of Cycle 1 and Day 1 of Cycle 3) when extra blood samples will be drawn for a pharmacokinetic ("PK") analysis, you will need to stay in the clinic about 6 hours total. This includes your treatment time and 3 hour wait period to draw the PK blood work.

To find out how you are doing, the following tests and procedures will be done while you are on the study:

Tumor Biopsies

You will be asked if you are willing to undergo three procedures to provide the study researchers with biopsy samples of your cancer tumor. You need not agree to having these procedures done, but it will be very helpful to the study researchers in order to better understand how to help other people with your same disease. Even if you agree at the start of the study to undergo these procedures, you are free to change your mind for any reason and decline, without any negative consequences to you from your doctor or any of the research staff.

If any written documents or reports about the sample are also sent with your biopsy sample(s), your name and medical records number will be removed from them.

The biopsies will be collected at the following timepoints:

1. Before Beginning Day 1 of Week 1 (First Cycle)
2. After Finishing Cycle 2 But Before Beginning Day 1 of Cycle 3
3. At Time of Response or End of Study Visit (just one of these times)

☐ I agree to these optional biopsies

☐ I do not agree to these optional biopsies

Day 1 (All Cycles)

- A general assessment performance status (questions) of how your cancer is affecting your daily life and how well you can carry out daily activities will be done**.**
- Your weight (which is important to determine your correct dose of study medication) will be measured.
- You will be asked about your health, and any adverse events (any symptoms good or bad that you felt during the week after you received the study medications that are new or different for you than you normally feel) and any new medications or changes to medications you have taken.
- Blood samples will be collected for both routine tests and study-specific tests, unless these tests were performed less than 3 days prior to Day 1. The results of your blood tests will be reviewed by the study doctor prior to study drug administration. Therefore, this may require a separate visit each week for the blood draw prior to your treatment day, which can be scheduled up to 3 days prior to your treatment day, in order to allow for testing and processing of the blood sample.
- The maximum amount of blood taken on any one day will be on the first day of the study when 84 mL (or about 17 teaspoons) will be collected (this includes PK samples listed below). On all other first days of subsequent cycles, the amount will vary from 3 mL (a little over half a teaspoon) to 54 mL (about 11 teaspoons). The site staff have been given a chart showing exactly how much blood will be collected for which tests at every visit.

- Part of the blood sample collected will include 20 mL (about 4 teaspoons) to see if certain antibodies and proteins are present in your blood and to see the effects of the study drug on your body.
- You will receive Imprime PGG first and then pembrolizumab.

Day 8 and Day 15 (All Cycles)

- You will receive an infusion of Imprime PGG.
- You will be asked about your health, and any adverse events (any symptoms good or bad that you felt during the week after you received the study medications that are different from you normally feel) and any new medications or changes to medications you have taken.

Cycle 1 and Cycle 3 Only (Week 1 and Week 7)

- Blood samples will be collected for pharmacokinetic (PK) testing. PK testing measures the amount of study drug that is circulating in the blood. You will spend additional time in the clinic for the study staff to collect the blood samples after the study drug administration. A total of 4 blood samples will be drawn, with the last one being about 6 hours after you start getting your first study drug infusion. A total of 20 mL (about 4 teaspoons) will be taken for this PK testing.

Every Other Cycle (Every 6 Weeks)

- In addition to the blood samples discussed earlier, a CT scan with contrast, or MRI scan of the head, chest, abdomen and pelvis, will be done. If necessary, a bone scan will be done.

These tests and procedures may be part of regular cancer care. However, these tests and procedures may be done more often because you are in this study or because your study doctor feels it is necessary.

End of Treatment Visit

Within 3 days after the end of the cycle in which you received your last dose of study medication, the following tests and procedures will be performed:

- A general assessment performance status (questions) of how your cancer is affecting your daily life and how well you can carry out daily activities will be done**.**
- A physical examination will be done and your weight will be measured.
- You will be asked about your health, and any adverse events (any symptoms good or bad that you felt during the week after you received the study medications that are new or different for you than you normally feel) and any new medications or changes to medications you have taken.
- A voluntary procedure to provide the study researchers with a biopsy sample of your cancer tumor, as discussed in detail earlier.
- Blood samples for routine tests and study-specific test totaling about 39 mL (about 8 teaspoons).

Post-Treatment Visit

Approximately 4 weeks after your last dose of study medication, the following tests and procedures will be performed:

- If you are a female who can have children, a urine or blood pregnancy test will be done.
- A general assessment performance status (questions) of how your cancer is affecting your daily life and how well you can carry out daily activities will be done.
- You will be asked about your health, and any adverse events (any symptoms good or bad that you felt during the week after you received the study medications that are new or different for you than you normally feel) and any new medications or changes to medications you have taken.
- Blood samples for routine tests and study-specific test totaling 23 mL (a little over 4.5 teaspoons).

Follow-up After Completion of the Post-treatment Visit

The study staff will call you every 2 months after your last study visit in the office to ask about any further treatment you may have received or are currently receiving for your cancer. You may be asked to have a CT with contrast or MRI scans every 6 weeks to monitor your cancer. This follow-up will end once the whole study finishes for everyone, which is expected to be approximately 3 years after the last patient who enrolled in this study took his/her first dose of study medication.

How long will I be in the study?

You will receive Imprime PGG + pembrolizumab in 3-week cycles. The 3-week cycles will continue until you have received treatment in the study for 2 years, until your cancer shows signs of progression, or you experience unacceptable toxicities, whichever occurs first.

Sometimes with checkpoint inhibitors such as pembrolizumab, your cancer may temporarily get worse (or show signs of progression) because the drug is helping your body to fight the cancer cells. This is sometimes called an “immune response”. If your doctor thinks this is happening to you, he/she will discuss with you the option to stay on the same study treatment you are on and check the size and number of your tumor(s) within about 4 weeks by taking an additional MRI or CT scan. During this time, your doctor will monitor your health carefully.

If this does happen, your doctor will review your treatment options with you before continuing study treatment, and will explain your treatment plan. If you decide to remain in the study, you will sign below, which means you understand your doctor thinks the study medications are helping you to fight your cancer, even though it looks like your cancer is getting worse. You agree to allow your doctor to continue treating you with the same study medications until your doctor knows the results of the additional MRI or CT scan. Your doctor will then review your results with you and if your cancer is improving, you will remain on the study. But if your cancer stays the same or has become even worse, your participation in the study will end.

Statement of Professional Obtaining Consent

I have fully explained what may be happening with the research participant's response to the study medications. In my judgment, there was sufficient access to information, including risks and benefits to make an informed decision.

Date: _____

Signature of Person Obtaining Consent: _____

Printed Name of Person Obtaining Consent: _____

After the last study visit in the office, study staff will call you every 2 months up until 3 years have passed since the last patient's first dose of study medication, and the study staff will ask about any additional cancer treatment you have received.

If you stop receiving study medication because you have achieved a Complete Response, and then your cancer recurs, you may be able to go back onto the study medication as long as the study is still ongoing.

It is possible that your study doctor or the sponsor will decide to end your participation in the study without your consent for any reason. Reasons for doing so include the following:

- If your study doctor does not think it is best for you to continue
- If your condition gets worse
- If you have serious side effects
- If you develop a serious illness, even if it is not related to your taking part in the study
- New information becomes available that shows this study in not the best option for you
- If you become pregnant, or you are nursing during this study
- If the entire study is discontinued
- If you are unable or are unwilling to follow the instructions for taking part in the study
- If you no longer meet the requirements for the study

Biothera, the FDA, an Institutional Review Board (IRB), an Ethics Committee, or other regulatory agencies may decide to stop the study before the study is done and without warning. If this happens to you, your study doctor will assist you with the plans for your continued care as appropriate.

What side effects or risks can I expect from being in the study?

You may have side effects while on the study. Everyone taking part in the study will be watched for side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Side effects may go away soon after you stop taking Imprime PGG and/or pembrolizumab. In some cases, side effects can be serious, long lasting, or may never go away. There is also a risk of death. You should talk to your study doctor about any side effects that you have while taking part in the study.

As with any new substance like Imprime PGG, new, previously unknown side effects may also occur.

This section uses symbols to describe the frequency of side effect occurrences. The following is included as a key to help you understand these symbols:

Symbol	Meaning
<	less than
≤	less than or equal to
>	greater than
≥	greater than or equal to

Imprime PGG

Common side effects seen in > 5% of patients treated with Imprime PGG in the healthy volunteer studies of Imprime PGG, when it was given as a single agent without premedication include the following:

- Shortness of breath
- headache
- tingling sensations
- rash
- nausea
- flushing (reddening of the face)
- red eyes
- blurred vision
- fatigue
- low red blood cell count
- dizziness
- numbness
- bruising
- sweating
- itching
- sore throat
- chest discomfort
- chills
- pain at injection site
- incidental back injury
- laceration or scratch
- fast heart-beat
- upper respiratory infection
- low white blood cell count
- joint aches or stiffness

Common side effects seen in more than 5% of subjects who received Imprime PGG in the healthy volunteer studies of Imprime PGG, when it was given in combination with filgrastim (Neupogen®):

- Abdominal (stomach) pain
- nausea
- chest discomfort
- chest pain
- chills
- injection site irritation
- injection site pain
- pain
- joint aches
- back pain
- musculoskeletal (muscles and bones in the body) pain
- pain in arms or legs
- dizziness
- headache
- shortness of breath
- rash
- hives

There were a few severe side effects which included:

- stomach pain
- hypersensitivity
- low blood pressure
- rapid heartbeat
- injection site pain and injection site swelling

Imprime PGG has been studied in patients with advanced cancer. The patients in these studies were also taking several other medications (eg antibodies, chemotherapy) to treat the cancer, in combination with Imprime PGG. The side effects seen in these studies have been similar to the side effects expected to be seen in patients that take these other medications (eg antibodies, chemotherapy).

In previous studies with another drug substance (Betafectin®) that contained the same active ingredient (PGG Beta Glucan) as Imprime PGG, other observed side effects included inflammation of the joints and eyes, permanent liver damage, fever, and dilation of blood vessels were observed. The side effects of Imprime PGG may be similar to those seen with Betafectin®.

Pembrolizumab

What is known about this study drug?

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

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

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

What side effects could the study drug cause?

VERY COMMON. SOME MAY BE SERIOUS (i.e. causing hospitalization, life-threatening or where noted, may cause death)

Out of 100 people who receive pembrolizumab, 20 or more people may have the following:

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

COMMON, SOME MAY BE SERIOUS (i.e. causing hospitalization, life-threatening, or where noted, may cause death)

Out of 100 people who receive pembrolizumab, at least 5 but less than 20 people may have the following:

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

UNCOMMON, SOME MAY BE SERIOUS (i.e. cause hospitalization, life-threatening, or where noted, may cause death)

Out of 100 people who receive pembrolizumab, at least 1 but less than 5 people may have the following:

- Inflammation of the lungs so you may feel short of breath and cough. Sometimes this might lead to death
- Too much thyroid hormone so you may feel anxious, angry, have trouble sleeping, feel weak, tremble, sweat, feel tired, have loose and watery stools
- Infusion reaction, where you may feel dizzy or faint, flushed, get a rash, have a fever, feel short of breath at the time of receiving your infusion (IV) or just after, or pain at the site of infusion

- Inflammation of the bowels/gut, which may cause severe pain in your belly with loose or watery stools, and black, tarry, sticky stools or stools with blood or mucus
- Inflammation of the skin so you may have peeling of the skin, itchiness, and/or skin redness. The skin inflammation (i.e. peeling, itching and redness) could also be widespread throughout your body. More severe skin reactions may involve the inside of your mouth, the surface of your eye and genital areas, and/or may cause the top layer of your skin to peel from all over your body which can cause severe infection. These severe conditions can sometimes lead to death.

RARE, SOME MAY BE SERIOUS (i.e. causing hospitalization, life-threatening, or where noted, may cause death)

Out of 100 people who receive pembrolizumab, less than 1 person may have the following:

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

- The formation of small clusters of immune cells (called granulomas) in parts of your body such as your lymph nodes, eyes, skin, or lungs
- Inflammation of the brain with confusion and fever. This may also include: disorientation, memory problems, seizures (fits), changes in personality and behavior, difficulty speaking, weakness or loss of movement in some parts of your body, and loss of consciousness

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

Patients with multiple myeloma who were treated with pembrolizumab in combination with either pomalidomide or lenalidomide (drugs related to thalidomide which affect the body's immune system) and dexamethasone (a steroid) had an increased number of serious side effects and deaths as compared to patients who received only dexamethasone and either pomalidomide or lenalidomide.

To date, there have been no studies conducted using a combination of Imprime PGG and pembrolizumab. Therefore, it is not known what types of side effects might be observed or which you might experience with this combination.

Due to the unknown effects of the study medication, you should be aware that the consumption of alcohol or the taking of any drugs or medication (with or without prescription or illegal ones), other than the study medications, at any time during the study without the consent of the study doctor or site staff might cause serious or even life-threatening reactions. Both new and current drugs can have unknown side effects, some of which might be serious.

0.9% Normal Saline (Sodium Chloride):

Infusion of normal saline can result in infusion site swelling, tenderness, redness, or infiltration (normal saline leaking into the tissue around the vein). More serious side effects may include increased heart rate, fever, rash, joint pain or shortness of breath.

Diphenhydramine (Antihistamine):

Diphenhydramine is used to treat symptoms of allergies such as runny nose, sneezing and itchy eyes, nose or throat. It is also used as a sleep aid or to decrease motion sickness. More common side effects include drowsiness, dry mouth (nose and throat), dizziness, nausea, headache, tightening of the chest and loss of appetite. More serious side effects may include change in vision, decrease or trouble urinating or trouble breathing.

Infusion Site Reaction:

It is possible to have what is called an infusion site reaction following an intravenous (IV) infusion (medication given through a needle in a vein). Symptoms of an infusion site reaction may include, pain, redness, burning sensation, and itching sensation. You may experience inflammation or infection at the infusion site. If you experience any of these report it to the clinic staff. The infusion site will be monitored throughout the study.

Allergic Reaction:

It is possible to have what is called an allergic (or hypersensitivity) reaction during or soon after the administration of any investigational or non-investigational medicine. Some subjects have experienced difficulty breathing, wheezing, hives or swelling around the vein where the needle was placed, face, mouth, lips, gums, tongue, or neck. If you have any allergies that you are aware of, you should tell the study doctor before agreeing to take part in this study. Since Imprime PGG is investigational when taken alone or in combination with other medications, there may be other risks that are unknown.

All drugs have a potential risk of an allergic reaction, which if not treated promptly, could become life threatening. If you experience any such symptoms, you should get medical help and contact the study doctor right away.

Risks and possible discomforts you might experience from the study procedures include:

Blood draws: Temporary discomfort from the needle in your arm, bruising, bleeding, and swelling at the needle insertion site or vein [phlebitis], and infection. Standard medical care will be taken to avoid these complications.

ECG: The risks from an ECG can include skin irritation and a rash from the gel that is used or from wearing or removing the patches.

CT Scan Risks: In this study, you will be exposed to some radiation from the CT scans. The amount of radiation you will get is like the amount from other x-ray exams routinely used in medicine. Public policy is to keep exposure levels as low as possible.

Contrast dye may be used, which has a small possibility of a severe allergic reaction and kidney problems.

MRI Scan risk: You may have risks from MRI if you have metallic objects in your body. You may also become anxious from lying in a tight space without moving.

Other Risks:

Since Imprime PGG is investigational, there may be other risks that are unknown. For your own safety and for the safety of other subjects in the study, you must inform the study doctor or study staff about any side effects or other health problems you experience during the study. Other medicines or supplements could cause side effects if you use them while you are receiving Imprime PGG. Because of this, you must tell the study doctor or a member of the study staff about all of your past and present illnesses and allergies. You must also tell them about all drugs, vitamins, supplements, and medicines you are taking.

It is important that you report all symptoms and side effects that you experience as soon as they occur, whether or not you think they are caused by the study drug. The phone numbers for the study team are on the first page of this document.

REPRODUCTION RISKS

Pregnancy Related Risks / Use of Birth Control Females

The effects of Imprime PGG on pregnancy, an unborn baby, or a nursing child are not known. If you are currently pregnant, planning to become pregnant, or are breastfeeding a child, you should not take part in this study.

All females who are able to get pregnant and males whose partners are able to get pregnant and who are sexually active are required to use an acceptable form of contraception (birth control) during the study and continue contraception for 120 days after the last dose of study drug. Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% when used consistently and correctly. The study doctor will instruct you in correct use of your selected birth control method and review with you at each visit your responsibility to use your selected birth control method consistently and correctly.

The following are highly effective methods of acceptable birth control:

- Abstinence (refraining from intercourse for the required study period)
- Correctly placed copper containing intrauterine device (IUD).
- Contraceptive rod implanted into the skin
- Male sterilization of subject or female subjects' partner with confirmed absence of sperm in the post-vasectomy ejaculate.
- Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

Use of 2 of the following:

- Diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- Cervical cap with spermicide
- Contraceptive sponge
- Male condom or female condom (cannot be used together)
- Hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill, contraceptive skin patch, vaginal contraceptive ring, or subcutaneous (under the skin) contraceptive injection

Discuss any other forms of birth control with your study doctor to see if they are acceptable.

Birth control methods, even when used consistently and correctly, are not perfect. If you become pregnant or want to stop your required birth control while you are in the study, you should tell the study doctor immediately. You will be withdrawn from the study if you discontinue birth control or you become pregnant.

Males

The effects of Imprime PGG on sperm or a pregnancy are not known. If you are planning to father a child you should not join this study. If you and your partner are physically able to have children and you are sexually active, you must use an acceptable form of the birth control from the methods listed above consistently and correctly beginning with the first infusion of the study drug and at least 120 days after the last injection of the study drug. The study doctor will discuss

with you the permitted methods of birth control for this study and will help you select birth control that is appropriate for you. The study doctor will instruct you in correct use of your selected birth control method and review with you at each visit your responsibility to use your selected birth control method consistently and correctly.

Pregnancy Follow Up

If you become pregnant during the study or within at least 120 days, after the last infusion of the study drug, please tell the study doctor immediately. Please also tell the doctor who will be taking care of you during the pregnancy that you took part in this study. The study doctor will ask if you or your pregnancy doctor are willing to provide updates on the progress of the pregnancy and its outcome. If you agree, this information will be provided to the study sponsor for safety monitoring follow-up.

What if New Information Becomes Available?

The study doctor will tell you in a timely manner of any information learned during the course of the study that might cause you to change your mind about taking part in the study. You may contact the study doctor at any time after your participation ends to find out if any new information about this study has become available.

As with any new substance, new and/or previously unknown side effects may also occur with the use of Imprime PGG.

Are there benefits to taking part in the study?

Taking part in this study may or may not help your cancer. The information learned from this study may help doctors learn more about the combination of Imprime PGG and pembrolizumab as a treatment for people with cancer such as yours. This information could help future cancer patients.

What other choices do I have if I do not take part in this study?

Your other choices may include:

- Getting treatment or care for your cancer with a different cancer drug without being in a study
    - If you have advanced melanoma, the following is a list of other medication options available to you (in alphabetical order):
        - Aldesleukin for metastatic melanoma
        - Cobimetinib in combination with vemurafenib for BRAF-mutated unresectable or metastatic melanoma (BRAF is a protein which is involved in sending signals in cells and cell growth, and a mutation in BRAF can increase the growth and spread of cancer cells)
        - Dabrafenib for BRAF-mutated unresectable or metastatic melanoma
        - Dacarbazine for metastatic melanoma
        - Ipilimumab for adjuvant treatment after surgical removal of melanoma at high risk of recurrence OR for unresectable or metastatic melanoma

    - Nivolumab used with Ipilimumab for BRAF-unmutated unresectable or metastatic melanoma OR alone in refractory melanoma after treatment with Ipilimumab or BRAF inhibitor if BRAF-mutated tumor
    - Peginterferon Alfa-2b for melanoma spread to lymph nodes after surgical removal of skin melanoma
    - Pembrolizumab for unresectable or metastatic melanoma (if you decide to participate in this study, you will receive pembrolizumab + Imprime PGG)
    - Talimogene Laherparepvec for local injection into recurrent melanoma of the skin or lymph nodes that are unresectable
    - Trametinib for BRAF-mutated unresectable or metastatic melanoma
    - Vemurafenib for BRAF-mutated unresectable or metastatic melanoma
- Taking part in another study
- Getting no treatment
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Talk to your doctor about all of your choices before you decide if you will take part in this study. There may be new treatments your doctor can tell you about, which were not yet approved at the time this Informed Consent Form was written.

What are my responsibilities if I decide to participate?

If you decide that you want to participate in the study, you will be asked to come to all of your scheduled study visits, to follow the study doctor's directions, and to inform the study staff about any new medications you are taking and how you have been feeling.

Will my medical information be kept private?

Every effort will be made to keep your study records private. It is the responsibility of the study staff to make sure that your research records are protected. If information from this study is used in any reports or publications, your name and anything else that could identify you will not be used. The study staff will review your records and require access to your medical information.

Other organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The National Cancer Institute (NCI) and other government regulatory agencies like the US Food and Drug Administration (FDA)
- Biothera the study sponsor, Merck (manufacturer of pembrolizumab), and representatives working on behalf of the sponsor
- Regulatory agencies in other countries
- Western Institutional Review Board® (WIRB®)

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.

What are the costs of taking part in this study?

The sponsor will provide Imprime PGG and pembrolizumab at no cost to you or your health insurance. You and/or your health plan/insurance company will be charged for the costs of treating your cancer including the costs of the:

- Imaging scans
- Doctor visits
- Regular tests of blood to test your health

You/your insurance will NOT be charged for the following:

- Blood tests for research purposes only
- ECGs required for research purposes only
- Tests on your tumor for research purposes only

Some health plans will not pay the costs for taking part in studies. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment. Check with your health plan or insurance company to find out what they will pay for.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

If, during the study, Imprime PGG becomes approved for use in your cancer, you and/or your health plan may have to pay for drug needed to complete this study.

You will not be paid for taking part in this study.

What happens if I am injured because I took part in this study?

It is important that you tell your doctor if you feel that you have been injured because of taking part in this study. They will treat you or refer you for treatment. If, during the course of the study, you experience any injury as a direct result of the administration of study drug, the sponsor agrees to pay all medical expenses necessary to treat such injury (1) to the extent you are not otherwise reimbursed by medical insurance, a government program, or a third party, and (2) provided you have followed the directions of the study doctor.

You will not be financially compensated for your participation in this trial beyond what may be provided for time and travel. Payment for such things as lost wages, expenses other than medical care, or pain and suffering is not available.

To help avoid injury, it is very important to follow all study directions. By signing and dating this form, you have not waived any of the legal rights to pursue a claim through the legal system, which you would have otherwise, if you were not a participant in a drug research study.

Is my participation voluntary?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

Who can answer my questions about the study?

You can talk to your study doctor about any questions, complaints, or concerns you have about this study or if at any time you feel you have had a research-related injury or reaction to the study drugs.

If you have any questions about your rights as a research subject or if you have questions, concerns, or complaints about the research, please contact:

Western Institutional Review Board® (WIRB®)
1019 39th Avenue SE Suite 120
Puyallup, Washington 98374-2115
Telephone: 1-800-562-4789 or 360-252-2500
E-mail: Help@wirb.com

WIRB is a group of people who perform independent review of research.

WIRB will not be able to answer some study-specific questions, such as questions about appointment times. However, you may contact WIRB if the research staff cannot be reached or if you wish to talk to someone other than the research staff.

About Using Tissue and Blood Specimens for Research

You have had a biopsy (or surgery) of your cancer tumor(s) in the past to see if you have cancer. Your doctor removed some body tissue to do some pathology tests (tests and examination of your cancer tissue under a microscope). The results of these tests (the pathology report) confirmed that you have cancer. You will need to provide permission for this pathology tissue to be further examined for use this study.

You will need to provide permission for your pathology tissue sample to be sent to a central testing facility for this study. It may be tested for biomarkers (a substance that can be measured which is indicative of your disease). Additional biomarkers may be evaluated as new information becomes available from research studies. These results will become part of the study record. All possible measures will be used to protect your privacy and confidentiality, such as the use of a study number specific to you in place of your name on the results. Any unused tumor tissue samples will be returned to your study doctor 6 months after the study has ended, or sooner should you request them earlier. There will also be 3 additional tumor biopsy samples that we would like to collect. You will need to provide permission for these samples to be collected.

As described earlier, an additional blood sample (20 mL or approximately 1.5 tablespoons) will also be collected at the timepoints specified previously in this document. The blood will be tested for markers that may be associated with side effects or response to therapy, and to learn more about the immune system and cancer.

Statement of Professional Obtaining Consent

I have fully explained this research study to the research participant. In my judgment, there was sufficient access to information, including risks and benefits to make an informed decision.

Date: _____

Signature of Person Obtaining Consent: _____

Printed Name of Person Obtaining Consent: _____

Research Participant Statement

I have read this Informed Consent. I have had the opportunity to discuss this study with my family or any trusted friends, as I desired. I have had the opportunity to discuss this study with the consenting professional and all my questions have been answered to my satisfaction. I understand that my participation is voluntary. I understand the purpose, risks, and benefits of the research study. I agree to take part in this study.

Date: _____

Patient Signature: _____

Patient Printed Name: _____

The following section is only to be used after a discussion about continuing on treatment after possible pseudo-disease progression.

Research Participant Statement to Continue Research Participation

I have read the section of the Informed Consent about why my cancer may be improving even though the results look worse. I have had the opportunity to discuss this result with my family or any trusted friends, as I desired. I have had the opportunity to discuss this situation with the consenting professional and all my questions have been answered to my satisfaction. I understand that my participation is voluntary. I understand the purpose, risks, and benefits of continuing in this research study. I agree to continue taking part in this study.

Date: _____

Patient Signature: _____

Patient Printed Name: _____