Official Title:	A Phase II Single Arm Study of High-Dose IL-2 and Ipilimumab in Patients With Unresectable Stage III and Stage IV Melanoma
NCT number:	02203604
Document Type:	Study Protocol and Statistical Analysis Plan; Informed Consent Form Main
Date of the Document:	08/11/2016; 09/17/2015

[redacted]

CONSENT TO TAKE PART IN A RESEARCH STUDY

Title of Study: A Phase II Single Arm Study of High-Dose IL-2 and Ipilumimab in Patients with unresectable Stage III and Stage IV Melanoma

Principal Investigator: [redacted]

This consent form is part of an informed consent process for a research study and it will provide information that will help you to decide whether you wish to volunteer for this research study. It will help you to understand what the study is about and what will happen in the course of the study.

If you have questions at any time during the research study, you should feel free to ask them and should expect to be given answers that you completely understand.

After all of your questions have been answered, if you still wish to take part in the study, you will be asked to sign this informed consent form.

The study doctor (the principal investigator) or another member of the study team (an investigator) will also be asked to sign this informed consent form. You will be given a copy of the signed consent form to keep.

You are not giving up any of your legal rights by volunteering for this research study or by signing this consent form.

Sponsor of the study:
[redacted]

The costs that are usually covered include things such as research laboratory tests required by the study, and the costs of collecting all of the information required by the study.

Financial Disclosure
The Principal Investigator of this research study has a consulting relationship with the company

[redacted]
A Comprehensive Cancer Center Designated by the National Cancer Institute

IRB ID:
Approval Date: 9/17/2015
Expiration Date: 3/16/2016

that produces IL-2, a drug used in this study; Prometheus Laboratories Inc. Please feel free to ask any further questions you might have about this matter.

Why is this study being done?
The purpose of this study is to test the effects and safety of giving both ipilimumab and IL-2 at the same time as a treatment for the melanoma. This study will use both drugs together to develop information on whether the combination is useful for patients with advanced melanoma. We would also like to find out what effects, good and bad that this combination of drugs may have on your cancer. Both drugs are approved by the FDA for treatment of advanced melanoma but have not been used together.

Ipilimumab, which is also called Yervoy, is an antibody that acts against a molecule called Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4) that controls a part of your immune system by shutting it down. An antibody is a common type of blood protein. Your immune system (a system that defends your body against potentially harmful agents) uses antibodies to find and destroy harmful agents such as bacteria and viruses, which may cause sickness and disease. Antibodies can also be produced in the laboratory for treating patients. There are now several approved antibodies for treating cancer and other diseases.

Researchers think that one way cancers grow is by escaping the immune system. An antibody against CTLA-4 can prevent CTLA-4 from shutting down the immune system for a time. It is believed that this may help your body destroy cancer cells by allowing your immune system to continue fighting them. In laboratory studies, it has been possible to get rid of some cancers by using an antibody that acts against CTLA-4.

IL-2, also called Proleukin, is a protein that your body normally produces to signal to your body to make an immune response by stimulating T cells, part of the white blood cells. White blood cells are very important in the body's defense system as they help identify and destroy foreign invaders, such as viruses, and cells that don't belong, such as cancer cells.

Why have you been asked to take part in this study?
You have been asked to participate in this study because you have advanced melanoma, a serious type of skin cancer. Your cancer is not considered removable by a surgical procedure or has spread in the body.

Who may take part in this study? And who may not?
You may be included in this study if:

- You are 18 years of age or older
- You have a diagnosis of melanoma

Who may not participate?
You may not be included in this study if:

- You have ocular or mucosal melanoma

- A history of prior treatment with IL-2 or ipilimumab or CTLA4 inhibitor or agonist for metastatic disease
- You have to take corticosteroids on a chronic basis
- You are pregnant or breastfeeding

The study doctor and/or research team will also ask you other questions about your medical history in order to make sure qualify to be in this study.

How long will the study take and how many subjects will participate?
Your participation will last approximately one year for active treatment. In addition, you will be followed for up to 3 years to see how you are doing after the treatment.

You may be removed from this study without your consent for any of the following reasons: the study doctor decides that continued participation in the study will be harmful to you, you will need a treatment not allowed on the study, your disease becomes clinically worse, you are unable to take the treatment as indicated, or the study is canceled.

A total of 82 patients will take part in this study at several sites throughout the United States including the [redacted]

What will you be asked to do if you take part in this research study?
The study consists of four parts: Screening, Treatment Induction, Treatment Maintenance and Long Term Survival Follow-Up

Screening
The study doctor and possibly other study staff will explain the study to you and answer any questions you may have. If you decide that you may want to participate in the study, you will be asked to read and sign this Consent form. The screening visit with the study doctor will take approximately 1 hour.

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests, or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your doctor.

- **A medical history** (questions about your health, current medications, and any allergies).
- **A physical exam**. The research doctor or another research healthcare professional will complete a physical assessment, including blood pressure, pulse, rate of breathing, temperature, and height and weight.
- **An assessment of your tumor** by CT (Computerized Tomography, also known as a CAT scan. A CT scan is a very detailed x-ray exam.) Scans of your chest, abdomen, and pelvis must be performed within 28 days of starting study treatment, and an CT(Computerized

[redacted]
IRB ID:
Approval Date: 9/17/2015
Expiration Date: 3/16/2016

Tomography) or MRI (Magnetic Resonance Imaging) of your brain must be performed within 28 days of starting study treatment.

- **Blood tests**. Blood (about 2 tablespoons), will be taken from a vein in your arm to check blood cell counts, how well your organs are functioning, and to test for any infections. **Blood test for pregnancy**, if you are a woman of child-bearing potential. (This test must be collected within 3 days of study assignment.) Approximately one teaspoon of blood or less will be drawn for this test.
- **A sample of your tumor (optional)** to determine how the immune system is responding to the treatment a sample of your tumor from a previous biopsy that is available will be obtained or, if there is a melanoma that can be easily removed by a biopsy in the office a sample will be taken. **You may choose not to have this procedure if you do not want to. You may still be enrolled in this study if you say no.**

If these tests show that you are eligible to participate in the research study, you will begin the study treatment. If you do not meet the eligibility criteria, you will not be able to participate in this research study.

Treatment

Induction Phase (Weeks 1-12)

If you take part in this research study, you will receive ipilimumab by an infusion into a vein (I.V.) or central line (port-a-cath) at weeks 1, 4, 7, and 10 (cycles 1, 2, 3, and 4, where each cycle equals 21 days) for a total of four infusions. The infusion time is roughly 90 minutes in length. The infusion will occur at an outpatient facility. You will have your vital signs measured prior to the infusion, and every 30 minutes during the infusion process. One hour after the infusion has stopped, your vital signs will be measured one more time. Thus, the whole infusion process takes about 2 ½ to 3 hours.

In addition, you will receive high-dose IL-2 according to the usual standard at your hospital. You may need to undergo additional testing prior to IL-2 therapy, such as taking a stress test of your heart or pulmonary function studies to determine if your heart and lungs are able to tolerate IL-2. The IL-2 will be given after the second dose (week 4) and third dose (week 7) of Ipilumimab only. IL-2 is given in the hospital and will require you to be admitted to the hospital for treatment immediately after the Ipilumimab on week 4 and week 7. IL-2 is generally given through a central intravenous line every 8 hours up to a total of 14 doses. You will be monitored for vital signs and blood work based on your doctor's recommendations. Most patients will be in the hospital for about 5 days at a time.

- **Physical Exams**: During all treatment cycles, you will have a physical exam, including measuring your weight. You will be asked questions about your general health and specific questions about any problems that you might be having and any medications you may be taking.

  Please tell your doctor about any medical treatments that you will have to get during the study (such as elective surgery).

[redacted]

- **Blood Tests**: Every 3 weeks (every cycle) you will undergo blood tests to closely follow you while you are receiving the study drug. These tests will check blood cell counts and how well your organs are functioning. These tests will be done more often than if you were not on this study.. On certain visits an additional amount of blood will be taken for studies of your T cells to see how the treatment has affected them. This will be done at screening and again at weeks 1, 4, 12, and 24. Approximately 4-6 tablespoons of blood will be needed at each visit
- **Assessment of your cancer**: by CT (Computerized Tomography) of your chest, abdomen, and pelvis and a CT (Computerized Tomography) or MRI (Magnetic Resonance Imaging) of your brain. These assessments will be performed every 12 weeks. If your disease is found to be improving, you will be asked to repeat the CT and MRI scans in about 4 weeks.

Maintenance Phase
If your disease remains stable or continues to improve at week 24, you may receive additional doses of ipilimumab every 3 months after the last dose you received at week 12. Prior to receiving the doses you will be asked to undergo the following:

- **Physical Exam** (weight and vital signs) and questions about your current health, including any changes in your symptoms and any medications you are taking.

- **Routine blood tests** (about 4-6 tablespoons) to check your blood cell counts, how your organs are functioning, and any effects the drug may have on your blood. You will also be asked to take a pregnancy test if you are a woman of child bearing potential. On certain visits an additional amount of blood will be taken for studies of your T cells to see how the treatment has affected them. This will be done at screening, before treatment on weeks 1, 4, 7 and 12 and at 6 months and 12 months. Some of the blood and serum collected may be stored for future studies of the immune response.

  You will continue to undergo new CT and MRI scans to evaluate the extent of your disease every 12 weeks after week 24.

Experience with the drug ipilimumab has shown that for some patients, their disease may get larger before it stabilizes or gets smaller. In this situation, we will continue to follow and treat your disease at the discretion of you and your doctor.

Long Term Survival Follow- Up
After your end-of-treatment visit, you will be contacted every six months for up to 36 months total (3 years) from your first dose. During this time you may also be asked to return to the clinic to have biopsies done of your lesion(s).
If you leave the study for any reason, you will be contacted by phone every six months to see how you are doing.

Table 1:

Procedure	Screening	Induction				Induction Assessment	Maintenance				End of Treatment	Long Term Follow up
	Pre-Treatment	Tx 1	Tx 2	Tx 3	Tx 4	F/U 1	Tx 5 F/U 2	Tx 6 F/U 3	Tx 7 F/U 4	Tx 8 F/U 5	F/U 6	LTFU every 6 months.
	-2	1	4	7	10	12	24	36	48	60	104	
Months		1				3	6	9	12	24	36	Every 6 months
Medical History	X					X	X	X	X	X	X	
Physical Examination	X					X	X	X	X	X	X	
Vital Signs (including height and weight)	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events Assessment/Con Meds		X	X	X	X	X	X	X	X	X		X
Blood Tests	X		X	X	X		X	X	X	X	X	
Urinalysis	X		X	X								
Pregnancy Test	X		X	X	X		X	X	X	X		
EKG	X		x	x								
Cardiac Stress Test	X											
Pulmonary Function Test	X											
CT or MRI	X					X	X	X	X	X	X	
Research Blood Tests	X	X	X	X		X	X			X	X	
Tissue collection(optional)	X						X				X	
Study Treatment												
IL-2			X	X								
Ipilimumab		X	X	X	X		X	X	X	X		

Can you stop being in the study?
Yes. You can decide to stop at any time. Tell the doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the doctor if you are thinking about stopping so any risks from the study drugs

can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest, if you do not follow the study rules, or if the study is stopped.

What are the risks and/or discomforts you might experience if you take part in this study?
You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any 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. Many side effects go away soon after you stop taking the study drugs. In some cases, side effects can be serious, long lasting, or may never go away. There is also the risk of death. You should talk to your doctor about any side effects that you have while taking part in the study.

Non immune-based Risks Associated with Ipilimumab:
While receiving treatment with ipilimumab, you may be at risk of side effects that occur during or shortly after the infusion (within 24 hours), or later after the infusion has finished. In isolated cases, some ipilimumab-related side effects may occur many months after the last dose of ipilimumab.

Likely:

- Diarrhea
- Nausea or the urge to vomit
- Fatigue or tiredness

Less Likely:

- Abnormally fast irregular heartbeat
- Belly pain
- Constipation
- Vomiting
- Chills
- Fever
- Lowered white blood cell count (may make you more likely to get infections)
- Loss of appetite
- Dehydration (when your body does not have as much water and fluid as it should)
- Joint pain
- Abnormal function of the nerve that controls facial expression
- Headache or head pain
- Sudden or traumatic injury to the kidney
- Itching
- Hives
- Low blood pressure

Rare but Serious:

- Partial or complete blockage of the small and/or large bowel.
- Progressive failure of blood clotting mechanisms

Immune-Based Events Considered to be Related to Ipilimumab

There are side effects that may also occur that are called immune-based events (where your immune system attacks your normal cells). The majority of the side effects seen so far have not been serious; however almost 50% of all participants receiving ipilimumab have experienced an immune-based event. Serious events are side effects which are fatal or life threatening; require you to be hospitalized; may permanently disable you or make you weak and unable to function at your current level; or may jeopardize you or require surgery or intervention by your doctor.

These immune-based side effects have usually been controlled by stopping ipilimumab treatment and if needed, with medications, including steroids (medications that are used to decrease inflammation). If you develop an immune-based event, the symptoms may take several months to improve.

Immune-based side effects observed in previous Ipilimumab research studies include:

- Esophagus/Stomach/Intestine: The most common stomach/intestinal event is diarrhea, which has occurred in about 10% of participants taking ipilimumab. Diarrhea due to ipilimumab ranges from mild to very severe with bleeding and may be life threatening. Some cases of diarrhea have started out as mild and then become severe. About 1% of participants have had diarrhea or stomach/intestinal complications that required surgical removal of part of their intestine or resulted in death. All other cases of diarrhea have been successfully treated by either stopping ipilimumab and/or treatment with anti-diarrhea medicine or with steroids. About 10% of participants treated with ipilimumab have also developed abdominal pain either alone or in combination with diarrhea. Rarely, constipation may be associated with ipilimumab.

  You should tell your doctor if you develop any diarrhea, constipation, any change in your bowel movements, have blood in your stool, or have abdominal pain. Your doctor may want to perform tests to better understand why you have these symptoms. These tests will allow your doctor to look at your intestine for damage. It may also help determine the type of treatment you might need, which may include the use of steroids. You may have to go into the hospital for doctors to investigate and treat the diarrhea or other stomach/intestinal symptoms.

  Also, there can be Inflammation of the esophagus (gullet or the tube that goes from mouth to stomach through which food passes) that can make swallowing difficult or painful.

  In addition, if you took IL-2 (another drug sometimes used for melanoma) before ipilimumab, or take IL-2 after, you may increase your chance of bowel perforation compared to taking IL-2 alone. A bowel perforation means that your bowel, small or large, has developed a hole which allows the contents of your intestine to leak into the abdomen. This is considered a medical

emergency as it causes a severe infection which can result in death. It has also been reported that patients with bowel metastasis of melanoma (melanoma cancer which has spread to the bowel) might be at higher risk of bowel perforation (tear), which could also result in death. If you know you have diverticulum (protrusion of soft tissue through the colonic wall) and/or diverticulitis (inflammation in the diverticulum), you need to tell your doctor and your doctor will evaluate whether it is appropriate to treat you with ipilimumab.

- Rash: Rash is a common immune-based event in participants treated with ipilimumab. Rash has occurred in about 20% of participants; most cases have been mild and less than 1% of cases have been serious. Some participants have had itching alone or together with the rash. There can also be Inflammation or damage to the tissue where a drug was injected

- The eye: In rare cases, administration of ipilimumab has been associated with inflammation in the various parts of the eye or with pigment (color) changes in the retina. There have been no known cases of permanent eye damage but these conditions could potentially interfere with your eyesight or even cause blindness if untreated. If these conditions develop, they may require treatment to reduce inflammation. In rare cases, double vision occurred as a result of muscle weakness. You should immediately tell your doctor if you think there is a change in your eyesight, if you develop double vision, or if you develop eye pain while you are on this study.

- Pancreas: Inflammation of the pancreas is called pancreatitis. Pancreatitis can occur suddenly (called "acute") or it can occur slowly over time (called "chronic"). Symptoms of pancreatitis usually include abdominal pain, nausea, vomiting, and fever. Your pancreas is responsible for producing digestive enzymes which help the body digest food as well as producing insulin which helps maintain your blood sugar levels. Mild acute pancreatitis usually doesn't permanently affect digestion or blood sugar levels, although a single severe attack can damage your pancreas and trigger chronic pancreatitis, which destroys the cells that produce both enzymes and insulin.

Ongoing damage to enzyme-producing tissue in chronic pancreatitis leads to poor absorption (malabsorption) of nutrients, especially fats; to weight loss; and to oily, malodorous stools. Damage to or destruction of insulin producing cells means blood sugar isn't metabolized properly, often leading to diabetes.

- Endocrine glands: Rarely (approximately 2%), participants have developed problems with particular glands (a gland is a group of cells or an organ that secretes a hormonal substance) such as the pituitary gland, the thyroid, or the adrenal gland. Symptoms that may be associated with problems of the pituitary or adrenal glands include fatigue, confusion, weight loss, inability to perform sexually (impotence), and headache.

- Liver: Approximately 4% of participants have developed serious problems with the liver as a result of ipilimumab treatment. Inflammation of the liver due to ipilimumab can range from mild to severe, and in very few cases, it can be life threatening. However, most severe cases have been successfully treated by stopping ipilimumab treatment and by administering anti-inflammatory

medications such as steroids. You should contact your doctor if you experience symptoms that may be associated with problems of the liver that include fatigue, weakness, vomiting, nausea, and abdominal pain. More frequent blood draws and a liver biopsy may be required if you develop serious liver abnormalities.

- Other organs: Rarely, participants have developed problems with the liver, kidney (proteinuria which is extra protein in urine), heart, muscles, blood vessels, and lung while taking ipilimumab. Acute failure resulting in death has occurred in less than 1% of participants. Symptoms that may be associated with problems of the liver include fatigue, weakness, vomiting, nausea, and abdominal pain. A liver biopsy may be required if you develop serious liver abnormalities. Too much bile in the blood causing a yellow color to the skin, gums, eye, and other tissues (jaundice) could occur.

- Meningitis (inflammation of the membrane surrounding the spinal cord and brain) has developed in less than 1% of participants treated with ipilimumab. This can cause headache, nausea and vomiting, stiff neck, and sensitivity of your eyes to light.

- In very rare cases, immune-related motor neuropathy (inflammation of the nerves that control muscles) such as Guillain-Barre Syndrome may occur, which could be life-threatening if not treated appropriately. You should tell your doctor if you experience weakness of your limbs with or without numbness or tingling. In addition, there can be progressive weakness caused by the body's immune system attacking the skeletal muscles (myasthenia gravis)

- Nephritis (inflammation of the kidneys) has developed in less than 1% of participants treated with ipilimumab. The cases of meningitis and nephritis resolved with treatment.

- A condition where the skin loses pigment and turns white (vitiligo), has occurred in less than 5% of participants. This condition is likely to be irreversible and permanent. A condition in which blistering and peeling of the top layer of the skin occurs and resembles a severe burn have been rarely reported. This is called toxic epidermal necrolysis. It can be very severe and may result in death.

- You should tell your doctor immediately if you think you are developing any unusual side effects even if they weren't listed here or any of the side effects or symptoms listed.

- Over-the-counter (OTC) drugs may cause major side effects. Acetominophen and NSAIDS found in most common OTC products for cold, headaches, muscle aches, and fever are safe and effective when used correctly, but too much can damage the liver. Be cautious when using OTC products. If you choose to take an OTC product, inform the nursing staff or your doctor about the drug.

In addition, immune-based reactions of any other organs, such as the joints or heart, could also occur. This could cause pain and swelling. Joint pain has been reported by less than 1% of

participants receiving ipilimumab. Inflammation of the heart or carditis may occur in all aspects of the heart and symptoms may include shortness of breath, fatigue, and chest pain. Treatment of the inflammation depends on the aspect of the heart which is affected. It may lead to decreased functioning of the heart.

IL-2 Risks

One of the most common side effects during Proleukin therapy is a condition known as capillary leak syndrome (CLS). CLS results in swelling caused by fluids leaking out of blood vessels into surrounding tissues (edema). CLS can cause a drop in blood pressure (hypotension) and decrease blood flow to body organs. It may also cause side effects such as changes in the rhythm of the heartbeat, severe chest pain, difficulty breathing, heart attacks, decreased function of the kidneys, and decreased mental alertness that may result in a coma. In general, adverse events are frequent, often serious, and sometimes fatal.

Patients should receive Proleukin therapy in treatment centers experienced in its administration of drug and prevention and management of side effects. Side effects are generally manageable and reversible, typically occur when the patient is still in the hospital, and tend to resolve within 3 days when treatment is stopped.
Other side effects associated with Proleukin therapy include impairment of the immune system, increased infections, and inflammatory disorders. Some patients may also experience flu-like symptoms (fever, chills, and muscle and joint pain), as well as fatigue, skin rash, and sweating. Any existing infection must be treated before starting treatment.

Proleukin therapy is typically given to patients in generally good health without any previous heart, lung, kidney, or central nervous system problems. Proleukin therapy must be administered in a hospital by a doctor and healthcare team experienced in treating patients with cancer and Proleukin.

Blood draw risks

You may experience pain or discomfort, bruising and/or bleeding at the site the needle enters the body, and in rare cases, fainting, light-headedness or infection.

Risks Related To Imaging Test Radiation

Radiologic testing, such as CT scans, will be used to assess the treatment of your disease at various times during therapy. The total radiation exposure from these tests is considered small and is not likely to affect you in a negative way, but can add up over time.

Risks Related To Imaging Procedures

The contrast solution (a dye that is injected to get a clearer picture) that may be given for a CT scan or MRI may cause an allergic reaction (rare). CT Contrast dye contains iodine and if you are allergic to iodine or shellfish you should notify your doctor and radiology lab prior to having the CT scan. The CT contrast solution can cause kidney damage, especially if you are diabetic, dehydrated, or elderly. When the contrast medium is injected during the CT scan, you may experience nausea, flushing, warmth, or a salty taste.

[redacted]
IRB ID:
Approval Date: 9/17/2015
Expiration Date: 3/16/2016

In MRI studies, you will be required to lie in a narrow tube, which may make you feel uncomfortable or claustrophobic. The MRI makes loud banging noises. You will be given earplugs if you would like them. If you are feeling uncomfortable, this study can be stopped at any time at your request. You should not have an MRI if you have a pacemaker, or metal plate in your body. In uncommon cases you may experience temporary or even permanent kidney damage due to the contrast medium

Are there any anticipated pregnancy risks?

Women

If you are pregnant or breastfeeding, you cannot take part in this study. A pregnancy test is required and will be given before you start the treatment and maintenance phase. You are responsible for using an effective birth control method such as birth control pills, barrier method (such as condoms or diaphragms), intrauterine device (IUD), hormone implants or surgical sterility while you are taking part in this study. Once you have completed treatment, you may discontinue birth control after 1 month of completing treatment. If you become pregnant, you must notify the study doctor immediately.

Men

You are responsible for using an effective birth control method, such as the ones listed above. If you are a male and your female partner becomes pregnant, you must notify your study doctor immediately. Once you have completed treatment, you may discontinue birth control after 1 month of completing treatment.

Are there any benefits for you if you choose to take part in this research study?

There may be no direct benefit to subjects for participating in this study. It is hoped that subjects will respond to treatment and have improvement in their condition. It is possible that the treatment may help reduce the tumor growth or tumors spread, or slow the tumor recurrence, or that it will not provide any benefit.

What are your alternatives if you don't want to take part in this study?

You do not have to take part in this study to receive treatment for your condition. You may choose not to take part in this study or you may discontinue your participation at any time without penalty or loss of benefits to which you are otherwise entitled.

Instead of participating in this study, there may be other treatment options available to you. You should discuss with the study doctor the potential advantages/disadvantages and benefits/risks of other treatments, which may include:

- No treatment other than care to make you feel more comfortable;
- Treatment with other FDA approved medications for melanoma;
- Other experimental therapy(ies).Talk to your doctor about your choices before you decide if you will take part in this study. You are under no obligation to take part in this research study. If you decide that you do not wish to take part in this study, you are free to leave the study at any time.

[redacted]

How will you know if new information is learned that may affect whether you are willing to stay in this research study?
During the course of the study, you will be updated about any new information that may affect whether you are willing to go on taking part in the study. If new information is learned that may affect you after the study or your follow-up is completed, you will be contacted.

Will there be any cost to you to take part in this study?
You and/or your insurance company will be billed for the costs of your treatment that are considered standard of care (for example, doctor/ Advanced Practice Nurse (APN) visits, nursing care to administer the treatments, routine lab tests, restaging scans, etc.) as you would have received these services even if you were not participating in this study. You will be responsible for any co-payments due for office visits, co-insurances and deductibles due on any tests and/or procedures that are required and considered standard care.

You or your insurance company will need to pay for the cost of supplies and personnel who give you the drug as well as hydration (fluids) and pre-medications given throughout the treatment.
Some health plans will not pay the costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

Procedures described in this consent form that will be provided at no cost to you are:

- All tests done at a central laboratory
- The study drug Ipilumimab

Some tests and procedures will be provided at no cost to you if they are done only for the purposes of this study. If the study doctor feels that any of these procedures are needed for your routine medical care, they will be billed to you or your insurance company. These procedures are:

- Physical exam done at screening
- Blood tests done at screening
- Urinalysis done at screening
- EKG done at screening
- CT/MRI scans done throughout the study

You or your insurance company will be responsible for the costs of your routine care, including the costs for:

- Physical exams done throughout the study and follow up
- Blood tests done throughout the study and follow up
- Treatment with IL-2, an FDA approved therapy for metastatic melanoma

If you have any questions about insurance coverage, including any out of pocket expenses you might incur, or which laboratory or facilities you are allowed to have tests at, a financial counselor will be made available to you upon request.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at:
http://www.cancer.gov/clinicaltrials/learningabout/payingfor

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.

Will you be paid to take part in this study?
You will not be paid for your participation in this research study.

How will information about you be kept private or confidential?
All efforts will be made to keep your personal information in your research record confidential, but total confidentiality cannot be guaranteed.

Your personal health information, identifiers and research data are stored and kept in a secure area in the [redacted]. Computer screens containing personal health identifiers are inaccessible to public view. Only the study doctor and research team will have direct access.

A description of this clinical trial will be available on 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 website at any time.

What will happen if you are injured during this study?
If you take part in this study, you will be exposed to certain risks of personal injury in addition to those associated with standard forms of treatment.

In addition, it is possible that during the course of this study, new adverse effects that result in personal injury may be discovered. Please refer to section 'What are the risks and/or discomforts you might experience if you take part in this study?".

The University will make appropriate referrals for medical and/or dental treatment for subjects who sustain personal injuries or illnesses as a direct consequence of participation in the research. The subject's health insurance carrier or other third-party payer will be billed for the cost of this treatment; provided that the University shall not submit to federally funded programs, e.g., Medicare, Medicaid or CHAMPUS, for reimbursement first if submission to such programs is prohibited by law. No financial compensation will be provided by the University and no other type of assistance is available from the University.

What will happen if you do not wish to take part in the study or if you later decide not to stay in the study?
Participation in this study is voluntary. You may choose not to participate or you may change your mind at any time.

[redacted]
IRB ID:
Approval Date: 9/17/2015
Expiration Date: 3/16/2016

If you do not want to enter the study or decide to stop participating, your relationship with the study staff will not change, and you may do so without penalty and without loss of benefits to which you are otherwise entitled.

You may also withdraw your consent for the use of your data, but you must do this in writing to Dr. [redacted]

Any data that has already been collected cannot be withdrawn because there may not be any identifiers to link the data with you. We are required by the Food and Drug Administration however, to continue to report anything that relates to the safety of these drugs.

At any time, the study doctor can take you out of this study because it would not be in your best interest to stay in it. Your study doctor can stop treatment even if you are willing to stay in the study.

If you decide to withdraw from the study for any reason, you may be asked to return for at least one additional visit for safety reasons.

Who can you call if you have any questions?
If you have any questions about taking part in this study or if you feel you may have suffered a research related injury, you can call the study doctor:

[redacted]

[redacted] have any questions about your rights as a research subject, you can call:

IRB Director
[redacted]

What are your rights if you decide to take part in this research study?
You have the right to ask questions about any part of the study at any time. You should not sign this form unless you have had a chance to ask questions and have been given answers to all of your questions.

PERMISSION (Authorization) TO USE OR SHARE HEALTH INFORMATION THAT IDENTIFIES YOU FOR A RESEARCH STUDY

Information about you and your health is personal and private, so this information generally cannot be used in research without your written permission. The next few paragraphs tell you about how researchers want to use and share your health information in this research study. Your

[redacted]
IRB ID:
Approval Date: 9/17/2015
Expiration Date: 3/16/2016

information will only be used as described here or as allowed or required by law. Ask questions if you do not understand any part of the research or the use of your health information. If you sign this consent form, you agree to let the researchers use your information in the research and share it with others as described below.

What is the purpose of the research and how will my information be used?
You are being invited to take part in this research study which is described at the beginning of this form. The purpose of collecting and using your health information for this study is to help researchers answer the questions that are being asked in the research.

What information about me will be used?

- All information in your medical record
- Hospital discharge summaries
- Radiology records or images (MRI, CT, PET scans)
- Medical history or treatment
- Medications
- Consultations
- Laboratory/diagnostic tests or imaging
- EKG and/or EEG reports
- Psychological testing, surveys or questionnaires
- Pathology reports, specimen(s) or slide(s)
- Operative reports (about a surgery)
- Emergency Medicine reports

Who may use, share or receive my information?
The research team may use or share your information collected or created for this study with the following people and institutions:

- [redacted]
- Representatives of the National Cancer Institute (NCI), Food and Drug Administration (FDA), and other U.S. and international governmental regulatory agencies involved in overseeing research

Those persons or organizations that receive your information may not be required by Federal privacy laws to protect it and may share your information with others without your permission, if permitted by the laws governing them.

[redacted] **be able to review my research record while the research is ongoing?**
No. We are not able to share information in the research records with you until the study is over. To ask for this information, please contact the Principal Investigator, the person in charge of this research study.

Do I have to give my permission?
No. You do not have to permit use of your information. But, if you do not give permission, you cannot take part in this research study. (Saying no does not stop you from getting medical care or other benefits you are eligible for outside of this study.)

If I say yes now, can I change my mind and take away my permission later?
Yes. You may change your mind and not allow the continued use of your information (and to stop taking part in the study) at any time. If you take away permission, your information will no longer be used or shared in the study, but we will not be able to take back information that has already been used or shared with others. If you say yes now but change your mind later for use of your information in the research, you must write to the researcher and tell him or her of your decision: [redacted]

How long will my permission last?
There is no set date when your permission will end. Your health information may be studied for many years.

Where can you get more information?
You may call the National Cancer Institute's Cancer Information Service at:
Voice: 1-800-4-CANCER (1-800-422-6237)

You may also visit the NCI Web site at http://cancer.gov/
For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

If you do not have access to a personal computer, you may access these websites and other information at a computer in the Resource and Learning Center on the second floor of the [redacted]

[redacted]
If you agree a biopsy will be used to determine how the immune system is responding to the treatment. The first sample of your tumor can be from a previous biopsy that is available, will be obtained or, if there is a melanoma that can be easily removed by a biopsy in the office a sample will be taken. The second sample will be taken at the beginning of the maintenance phase (around week 24). The third sample will be taken around the time you come off treatment.

Risks Associated with Optional Biopsies

[redacted]
IRB ID:
Approval Date: 9/17/2015
Expiration Date: 3/16/2016

- Pain and discomfort at the biopsy site
- Minor bleeding at the biopsy site
- Tenderness at the biopsy site
- Scarring at the biopsy site
- Rarely, an infection at the biopsy site.

PLEASE INITIAL ONE OF THE FOLLOWING:
You may choose not to have this procedure if you do not want to. You may still be enrolled in this study if you say no.

_____ I agree to have a biopsy of my tumor, if my doctor feels it is appropriate for me.

_____ I do not agree to have a biopsy of my tumor.

Text continued on next page

Request to Store Leftover Tissue* Samples for Future Research Use

*We use the term "tissue" to refer to specimens such as blood, urine, existing already taken tumor tissue from a previous surgery before entering this study, or tissue taken from a surgery as part of this research study.

We ask your permission to store left over tissue samples collected from you during a previous surgery and/or during this study for future research. Following are details about our request. Please know that you may still participate in the main study even if you say no to this request to store tissue for future research.

How and where will your leftover tissue be stored and by whom?
Your leftover tissue samples will be stored in the [redacted] Biorepository [redacted] which is owned and operated by the [redacted]. The [redacted]

The purpose of the repository is to store leftover tissue samples to be used for future research to be conducted by the Principal Investigator and the research staff at [redacted]. The goal of the research is to better understand and develop better means to prevent, diagnose and treat disease.

All of the subjects in this study will be asked to allow leftover tissue to be stored and used for future use in the repository. The more samples and health information available in storage, the more useful the repository will be for medical research.

How will samples be collected?
Only the leftover tissue that was collected during a previous surgery and/or as a part of this research study for future research would be stored and used for future use.

Psychological or Social Risks Associated with Loss of Privacy:
While the databases developed for this project will be coded to protect your personal information, people may develop ways in the future that would allow someone to link your medical information back to you. It is also possible that there could be violations to the security of the computer systems.

There also may be other privacy risks that we have not foreseen.

What are the benefits of participation?
You will not benefit personally from providing tissue samples for this tissue bank because research usually takes a long time to produce meaningful results. However, your participation may help investigators understand, prevent, or treat the diseases and conditions studied in the future.

[redacted] information about you and your tissue samples be kept private and confidential?
Information obtained from this research with material obtained from your tissue sample(s) will be kept confidential so that neither the investigator nor the Sponsor can link your individual research results with your identity.

Your sample(s), and materials derived from your sample(s), will be given a code number, and only information related to your age, sex, race, health condition and other relevant clinical information collected in the main study will be linked with the sample's code number. Your name, date of birth, address, or other personal identifying information, will not be linked with the sample(s) you give.

Is there other important information to consider?
Yes. There is no cost to you to allow us to store and use your tissue and information for future research. Nor will you be paid to participate in this repository. Should any products or services result from research using your samples and information, there is no plan to share any of the profits with you.

The research we are doing is only a stepping stone in understanding disease. It may take a long time for our research to produce useful health-related information. Therefore, tests done for our research using your samples and information will not be useful in directing your medical care. Information from our research will not be returned to you, your family members, your doctor, or outside parties. It is possible, however, that members of regulatory authorities, such as the U.S. Food and Drug Administration, [redacted] Review Board, or other persons required by law may be allowed to look at this information.

What are your rights if you agree to the storage and use of your tissue for future research?
You have the right to ask questions about any part of our storage and future research at any time. You should not sign this form unless you have a chance to ask questions and have been given answers to all of your questions. Your participation in this part of the study is voluntary. You do not have to participate. If you do, you can change your mind at any time.

What are the procedures for withdrawing consent?
If you agree to allow your tissue to be stored for future research at the [redacted] nd tell him to destroy any remaining tissue samples and data that are currently being stored in the repository.

However, please note that it may not be possible to destroy samples, information and data created from your samples that may have already been used in research studies prior to your request. The [redacted] will keep records linking your identity with the tissue sample(s) indefinitely. Until those records are destroyed, you may ask that your tissue sample(s) and materials obtained from your sample(s) be destroyed.

[redacted]
IRB ID:
Approval Date: 9/17/2015
Expiration Date: 3/16/2016

Permission to Store Leftover Tissue for Future Research Use:
Please tell us if and how you wish your samples and information to be used for future research.

Initial next to the ways you permit your samples and information to be used. **Leave this section blank** if you do not want your samples or information used for future research.

- My leftover tissue may be stored and used for future research as follows:

  _____ on Disease such as cancer

  _____ on any research topic important to researchers such as for future studies of the immune response.

Permission to Contact You with Additional Requests to Participate in Research
Please tell us if we may contact you in the future to tell you about other ways you may participate in this research or other research we are conducting by initialing next to your choice.

The investigators may contact me in the future to ask me to take part in more research.

Yes _____ No _____

What are your rights if you agree to the use of your blood/tissue for other types of research for future research?
You have the right to ask questions about any part of the future study at any time. You should not sign this form unless you have had a chance to ask questions and have been given answers to all of your questions.

Authorization to use your health information for future research purposes
Because information about you and your health is personal and private, it generally cannot be used in this future research studies without your written authorization (permission). If you sign this addendum consent form, it will provide that authorization. The details of what information we will collect and how we will use it are discussed in the main consent under the heading, "Authorization of use your health information for research purposes" near the end of the main consent document.

Also, if you authorize the use of your health information for future use, we will collect information about your cancer diagnosis, treatment, and outcome. And, if you agree to allow us to use your health information for future research, you are permitting us to share this information with our research collaborators at our institution and with [redacted].

Thank you for considering participation in this research.

SIGNATURE PAGE FOLLOWS IMMEDIATELY.

[redacted]
IRB ID:
Approval Date: 9/17/2015
Expiration Date: 3/16/2016

AGREEMENT TO PARTICIPATE

You have read this entire form, or it has been read to you, and you believe that you understand what has been discussed.

All of your questions about this form or this study have been answered.

I agree to take part in this study.

Subject Name:_____

Subject Signature:_____ Date:_____

FOR NON-ENGLISH SPEAKING SUBJECTS:

Signature of Reader/Translator If the Subject Does Not Read English Well:

The person who has signed above, _____, does not read English well. You read English well and are fluent in _____ (*name of the language*), a language that the subject (his/her parent(s)/legal guardian) understands well. You understand the content of this consent form and you have translated for the subject (his/her parent(s)/legal guardian) the entire content of this form. To the best of your knowledge, the subject (his/her parent(s)/legal guardian) understands the content of this form and has had an opportunity to ask questions regarding the consent form and the study, and these questions have been answered (his/her parent(s)/legal guardian).

Reader/Translator Name:_____

Reader/Translator Signature:_____ Date:_____

Witness Name:_____

Witness Signature:_____ Date:_____

Signature of Investigator/Individual Obtaining Consent:

Investigator/Person Obtaining Consent:_____

Signature:_____ Date: _____

[redacted]
IRB ID:
Approval Date: 9/17/2015
Expiration Date: 3/16/2016

SUBJECT REGISTRATION FORM

Protocol Number: CA184-084

Investigator Identification

Institution and affiliate name _____

Investigator's name_____

Investigator phone _____

Patient Identification

Patient's initials (Last, First) _____

Registration number _____

Patient demographics

Sex _____ M _____ F

Birth date (mm/yyyy) _____/_____

Race _____

Ethnicity _____

Prior therapy

_____

_____

_____

Informed Consent

Subject signed date (mm/dd/yyyy) ____/____/_____

Please attach a copy of the signed consent document to this form.

Pathology

Please attach a copy of the original pathology report to this form

PLEASE NOTE THAT SUBJECTS MUST MEET ALL OF THE ELIGIBILITY REQUIRMENTS LISTED IN SECTION 4.0 OF THE CLINICAL PROTOCOL

[redacted]

Please note that blood and tumor specimens must be submitted as detailed in Section 12 of the clinical protocol and using the **SPECIMEN SUBMISSION FORM located in the Laboratory Manual**.

SUBJECT ELIGIBILITY CHECKLIST

Protocol Number: CA184-084

[redacted]

Title: A Phase II Single Arm Study of High-Dose IL-2 and Ipilimumab in Patients with Unresectable Stage III and Stage IV Melanoma
Protocol Version Date: 03 Oct 2014
Protocol Number: CA184-084

Investigator Identification

Institution and Affiliate name: _____

Investigator's Name: _____

Investigator phone: _____

Participant Name: (Print First and Last)	Patient IWRS Screening Number:
Attending: (Print First and Last)	Consenting Professional : (Print First and Last)
Registering Individual: (Print First and Last)	Registering Individual Phone Number:
Date of Consent: ____/_____/_____	

Consent Questions:

1.0	Is the participant fluent in English? (Yes/No) *If Yes, skip to the Eligibility Criteria section; if NO, continue with Consent Question 2.0*	_____
2.0	What is the participant's primary language?_____	_____
3.0	Was an IRB-approved translated informed consent used in the participant's or legally authorized representative's primary language ?(YES/NO)	_____

[redacted]

4.0	Was an IRB-approved short-form given to the participant or legally authorized representative in their primary language? (YES/NO or NA)	_____
5.0	Was the IRB-approved English consent or summary signed by the consenting professional? (Yes/No/NA)	_____
6.0	Was an interpreter (non-family member or caregiver) used for the discussion? (YES/No/NA)	_____

The subject must meet the following criteria to be eligible for the trial (please check):

ELGIBILITY CRITERIA:

1.0	How old is the patient? (≥ 18 yes of age) DOB: ____/_____/_____ **Race** (Must circle AT LEAST one choice): American Indian/Alaskan Native Asian Black/African American White Native Hawaiian/other Pacific Islander **Ethnicity**(Must circle AT LEAST one choice): Hispanic Non Hispanic **Gender:** M/F	_____ _____ _____ _____
2.0	Does the patient have histologically or cytologically confirmed diagnosis of cutaneous melanoma that is considered unresectable (Stage III or IV) ? (YES/NO) Stage : T:_____N:_____M:_____ (Note: stage at study start) Date of Initial Diagnosis: _____/_____/_____	_____
2a.	Does the patient have Ocular or Mucosal melanoma? (No)	_____
4.0	Does the patient have measurable disease that is at least 20 mm by CT scan or ≥10 mm for spiral CT according to RECIST and WHO (mWHO) ? (Yes)	_____

5.0	Is the patient's life expectancy ≥ 3 months? (Yes)	_____
6.0	What is the patient's ECOG performance status? (0 or 1) Date: / /	_____
7.0	Is the patient accessible and able to comply with treatment, PK and immune-monitoring sample collection, and required study follow-up? (Yes)	_____
8.0	If the patient is a woman of childbearing potential (WOCBP), does she have a negative serum or urine pregnancy test (minimum sensitivity 25 UI/L or equivalent units of HCG) within 72 hours before the start of ipilimumab, or Day 1, which is acceptable per the sponsor ? (Yes/ NA- only if the patient is male or not of child bearing potential) Date: _____/_____/_____ If the woman is a women of NON-childbearing potential , please give reason for status: • Post –menopausal Date of last menstrual period: ___/_____/_____ • Hysterectomy and/or oophorectomy Date of surgery: ____/_____/___ • Other: Please explain: _____ ***Note: Non-childbearing potential is defined as:*** • Hysterectomy , bilateral tubal ligation, or bilateral oophorectomy • Amenorrhea ≥ 12 consecutive months without another cause and documented serum follicle stimulating hormone (FSH) level ≥40 mIU/ml • Irregular menstrual periods and a documented serum follicle stimulating hormone (FSH) level ≥40 mIU/ml and Receiving hormone replacement therapy (HRT) ***Note: FSH level testing is not required for women ≥ 62 years old with amenorrhea of > 1 year.***	_____

9.0	If the patient is a WOCBP, does she agree to use an acceptable method of contraception to avoid pregnancy throughout the study and for at least 4 weeks prior to initiation of drug and for at least 26 weeks after the last dose of investigational product in such a manner that the risk of pregnancy is minimized? (Yes/ NA –only if the patient is male or not of childbearing potential)	
10.0	If the patient is a sexually active male, does he agree to use an acceptable method of contraception throughout the study and for at least 4 weeks prior to initiation of the drug and for at least 8 weeks after the last dose of investigational product in such a manner that the risk of pregnancy is minimized? (Yes/NA-only if the patient is a female)	
11.0	Is the patient pregnant or breastfeeding? (No/NA-only if the patient is a male)	
12.0	Does the patient have known or suspected brain metastasis? (Yes/NO)	
13.0	**If Yes to 12.0,** have the brain metastases been previously treated? (Yes/NA- only if the answer to question 14.0 is No)	
14.0	**If Yes to 12.0,** has an MRI with and without contrast or CT of the brain been performed to rule out brain metastases or to show no evidence of progression for at least 4 weeks? (Yes/NA-only if the answer to question 14.0 is No)	
15.0	**If Yes to 12.0**, has the patient been off immunosuppressive doses of systemic medications, at least 4 weeks at time of enrollment? (Yes/NA-only if answer to question 14.0 is No) Note: Corticosteroids have a washout period of 14 days prior to randomization.	
16.0	Does the patient have prior malignancy active with the previous 5 years? (No)	

[redacted]

17.0	Does the patient have any active autoimmune disease or a documented history of autoimmune disease? (No)	
18.0	Does the patient have a history of a syndrome that required systemic steroid or immunosuppressive medications? (No) Note: Subject with vitiligo , psoriasis in active within the past 2 years , resolved childhood asthma/atophy , or thyroid disease controlled by replacement therapy without the need for immunosuppression are eligible	
19.0	Does the patient have known or suspected human immune deficiency virus (HIV) , hepatitis B or C infection? (No)	
20.0	Does the patient have or a history of extensive pulmonary metastases or chronic pulmonary disease history? (No) Date: _____/_____/_____ Note: FEV1 and FVC > 65% Note: Only for patients with pulmonary function: FEV1 and FVC > 65% of prediction for those patients with extensive pulmonary metastases or chronic pulmonary disease history.	
22.0	Is the patient on beta-blockers? (Yes/No) *Note: Patients may be weaned off of beta-blockers two weeks prior to study enrollment under the supervision of their primary cardiologist.*	
23.0	Does the patient have an underlying heart condition and those 50 years or older who have reversible ischemic changes on cardiac stress test who are deemed ineligible for surgery by cardiology consult? (No) Date of Cardiac Stress Test: _____/_____/_____	
24.0	Has the patient been treated with IL-2, ipilimumab or prior CTLA-4 inhibitor or agonist? (Yes/No) Note: not for metastatic disease.	
25.0	If yes to 26.0, has it been at least 6 months since the final adjuvant treatment from start of study treatment?	

	(Yes/NA only if answered NO to 26.0) Date: _____/_____/_____	
26.0	If yes to 26.0 did the patient have Grade 3 or greater adverse events with prior adjuvant ipilimumab therapy that did not resolve with limited corticosteroid use? (No/ NA only if answered NO to 26.0)	
27.0	Does the patient have presence of an underlying medical condition that in the opinion of the investigator or Sponsor could adversely affect the ability of the subject to comply with or tolerate study procedures and/or study therapy ? (No)	
28.0	Does the patient have evidence of organ dysfunction or any clinically significant deviation from normal in physical examination, vital signs, ECG or clinical laboratory determinations beyond what is consistent with the target population? (No)	
29.0	Has the patient been treated with systemic anti-cancer treatment (including investigation drugs) within 4 weeks of first dose of study medication? (No) Date of Last Treatment: _____/_____/_____	
30.0	Has the patient been treated with immunosuppressive medications or immunosuppressive doses of systemic corticosteroids (doses ≥ 10 mg/dcay prednisone or equivalent) within 14 days of first dose of study medication? (No)	
32.0	Did the patient have surgery or radiotherapy within 4 weeks prior to enrollment without any sequelae of the enrollment of study medication? (No)	
33.0	Did the patient have any non-oncology live viral vaccine therapies used for prevention of infectious disease within 1 month of the first dose of study medication? (No)	
34.0	Did the patient have prior treatment with Ipilimumab	

[redacted]

	or IL-2? (No)	
35.0	Has the patient been treated with anti-CTLA 4? (No)	_____
36.0	Is the patient a prisoner or involuntarily incarcerated? (No)	_____
37.0	Is the patient compulsorily detained for treatment of either a psychiatric or physical (e.g., infectious disease) illness? (No)	_____
38.0	What is the patients ANC? (≥ 1000/uL) Date: _____/_____/_____	_____
39.0	What is the patient's platelet count? (≥ 75,000 /uL) Date: _____/_____/_____ ***Note: Transfusion to achieve the required levels respectively is not permitted.***	_____
40.0	What is the patient's Hemoglobin? (≥ 9.0 g/dL) Date: _____/_____/_____ ***Note: (≥ 80 g/L; may be transfused)***	_____
41.0	What is the patient's total creatinine? (≤ 2.0 x ULN) Date: _____/_____/_____	_____
42.0	What is the patient's total bilirubin? (≤ 2.0 x ULN) Date: _____/_____/_____ Does have patient Gilbert's Syndrome? (Yes/No) Note: patients with Gilbert's Syndrome, who must have a total bilirubin less than 3.0 mg/dL)	_____ _____ _____
43.0	What is the patient's AST? (≤ 2.5 x ULN for patients without liver metastasis, ≤ 5 times for patients with liver metastases) Date: _____/_____/_____	_____
44.0	What is the patient's ALT? (≤ 2.5 x ULN for patients without liver metastasis, ≤ 5 times for patients with liver metastases) Date: _____/_____/_____	_____
45.0	Is the patient willing and able to provide signed informed consent, including consent for any screening procedures conducted to establish eligibility for registration, required prior to trial participation? (Yes)	_____

[redacted]

Protocol: A Phase II Single Arm Study of High-Dose IL-2 and Ipilimumab in Patients with Unresectable Stage III and Stage IV Melanoma
Principal Investigator: [redacted]

[redacted] **Team** (Physician or Consenting Professional)

Reviewed and Approved by : (Print First and Last Name)	Title:
Reviewed and Approved by: (Signature)	Date: _____/_____/_____
By signing above I attest that I have reviewed and confirmed that the above eligibility has been met	

External Registration Instruction Section	
1.0	**Registration will be performed by Theradex's IWRS System** ____/____/___ Patient Identification Patient's initials (Last, First) _____ IWRS Screening Number _____

Pre-Treatment Evaluation:		
	TO BE COMPLETED WITHIN 1 MONTHY OF STUDY DRUG ADMINISTRATION	
1.0	Informed Consent	____/____
2.0	Medical History including toxicities or allergy related to previous treatments	____/____
3.0	ECOG Performance Status	____/____
4.0	Complete Physical Examination	____/____
5.0	Concomitant Medication Review (Checking for protocol-excluded medications)	____/____
6.0	Clinical Complaints and Adverse Events	____/____
7.0	CT/MRI of chest, abdomen and pelvis (w/w/o contrast)	____/____
8.0	CT/MRI of Brain (w/w/o contrast)	____/____
9.0	Cardiac Stress Test	____/____
10.0	Pulmonary Function Test(if needed)	____/____

[redacted]

[redacted]

TO BE COMPLETED WITHING 2 WEEKS OF STUDY DRUG ADMINISTRATION		
11.0	Fresh Tumor Biopsy (optional)	____/__/____
12.0	Biochemistry-Electrolytes (sodium, potassium, calcium, chloride and magnesium, serum creatine, BUN)	____/__/____
13.0	Phosphorous	____/__/____
14.0	ALT/AST/ALP, Total Bilirubin (Hepatic Function)	____/__/____
15.0	Hematology(CBC w/ Differential , Platelets)	____/__/____
16.0	T3,TSH,T4,	____/__/____
17.0	LDH	____/__/____
18.0	12- Lead ECG	____/__/____
19.0	Serum Protein	____/__/____
20.0	Albumin	
21.0	Urinalysis	____/__/____
22.0	Vital Signs Temp:_____BP:_____Respiratory Rate:_____ Heart Rate:_____; Height: ;Weight:_____	____/__/____
TO BE COMPLETED WITHIN 72 HOURS OF Study Drug ADMINISTRATION		
24.0	Pregnancy Test (Serum)- if applicable Note: Day 1 is OK	____/__/____

[redacted] **OFF STUDY FORM**

Protocol Number: A Phase II Single Arm Study of High-Dose IL2 and Ipilimumab in Patients with Unresectable stage III and Stage IV Melanoma.
Protocol [redacted] CA -184-084. [redacted]

Investigator Identification
Institution and affiliate name _____
Investigators name _____

Patient Identification
Patient's initials (Last, First) _____
Registration number _____

Date Subject is Off Study (mm/dd/yyyy) ____/____/_____

Reason Subject is Off Study:
_____ best response achieved; date ____/____/_____
_____ progressive disease; date ____/____/_____
_____ toxicity; describe
_____ lost to follow-up
_____ physician preference
_____ patient withdrawal; reason
_____ patient never received tx; reason
_____ other; describe

_____
Investigator Name (print)

_____ _____
Signature of Investigator Name Date

[redacted]

[redacted]

ECOG performance status table:

Description	Grade
Fully active, able to carry on all pre-disease performance without restriction	0
Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, i.e. light housework, office work.	1
Ambulatory and capable of self-care , but unable to carry out any work activities. Up and about more then 50% of waking hours.	2
Capable of only limited self- care, confined to bed or chair more than 50% of waking hours	3
Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair	4
Dead	5

Karnofsky Performance Status (KPS) to ECOG Conversion Table:

KPS	ECOG
100	0
90	1
80	1
70	2
60	2
50	3
40	3
30	4
20	4
10	4
0	5

Karnofsky Performance Status
(D.A. Karnofsky and J.H. Burchenal, The clinical evaluation of chemotherapeutic agents in cancer. In: C.M. MacLeod, Editor, Evaluation of chemotherapeutic agents in cancer, Columbia University Press, New York (1949), pp. 191-205).

- 100%- normal, no complaints, no evidence of disease.
- 90%- Able to carry on normal activity, minor signs or symptom of disease.
- 80%- Normal activity with effort, some signs or symtoms of disease.
- 70%- Cares for self, unable to carry on normal activity or to do work.
- 60%- Requires occasional assistance from others but able to care for most needs.
- 50%- Requires considerable assistance from others and frequent medical care.
- 40%- Disabled, requires special care and assistance.
- 30%- Severly disabled, hospitalization indicated, death not imminent.
- 20%- Very sick, hospitalization necessary, active supportive treatment necessary.
- 10%- Moribound, fatal processes progressing rapidly.
- 0%-Dead.

Tumor Assessment Form:

RECIST 1.1: BI-DIMENSIONAL RESPONSE ASSESSMENT FORM (WHO)

Protocol #:			Disease:					
TARGET LESIONS								
Target Lesion #	Organ (maximum 10 target lesions & 5 per organ)	Series/Image at Baseline	Baseline Date: ☐ sent to EMR for scanning	Follow-up #: Date: ☐ sent to EMR for scanning		Follow-up #: Date: ☐ sent to EMR for scanning		Follow-up #: Date: ☐ sent to EMR for scanning	
	SCAN TYPE: CT:CAP, Brain MRI		Diameter(mm)	Series/Image	Diameter(mm)	Series/Image	Diameter(mm)	Series/Image	Diameter(mm)
1									
2									
3									
4									
5									
6									
7									
8									
9									
10									
				From baseline	From nadir	From baseline	From nadir	From baseline	From nadir
		SUM	N/A						
		% change							
Overall Response of Target Lesions				☐CR ☐PR ☐SD ☐PD		☐CR ☐PR ☐SD ☐PD		☐CR ☐PR ☐SD ☐PD	
NON-TARGET LESIONS									
Non-Target Lesion #	New Lesions (check if applicable)	Organ and location							
1	☐		☐ Pres	☐ Pres ☐ Abs ☐ PD		☐ Pres ☐ Abs ☐ PD		☐ Pres ☐ Abs ☐ PD	
2	☐		☐ Pres	☐ Pres ☐ Abs ☐ PD		☐ Pres ☐ Abs ☐ PD		☐ Pres ☐ Abs ☐ PD	
3	☐		☐ Pres	☐ Pres ☐ Abs ☐ PD		☐ Pres ☐ Abs ☐ PD		☐ Pres ☐ Abs ☐ PD	
4	☐		☐ Pres	☐ Pres ☐ Abs ☐ PD		☐ Pres ☐ Abs ☐ PD		☐ Pres ☐ Abs ☐ PD	
5	☐		☐ Pres	☐ Pres ☐ Abs ☐ PD		☐ Pres ☐ Abs ☐ PD		☐ Pres ☐ Abs ☐ PD	
6	☐		☐ Pres	☐ Pres ☐ Abs ☐ PD		☐ Pres ☐ Abs ☐ PD		☐ Pres ☐ Abs ☐ PD	
Overall Response of Non-Target Lesions				☐CR ☐SD ☐PD		☐CR ☐SD ☐PD		☐CR ☐SD ☐PD	
OVERALL RESPONSE				☐CR ☐PR ☐SD ☐PD		☐CR ☐PR ☐SD ☐PD		☐CR ☐PR ☐SD ☐PD	

SUMMARY FOR BEST OVERALL RESPONSE

Best Overall Response _____ PI Signature (confirmation of summary responses): _____

Date of Best Overall Response _____ Date: _____

Date of Progression _____ Comments (if any changes have been made to prior measurements, please explain): _____

THIS DOCUMENT MUST BE SCANNED INTO THE EMR AFTER EACH ASSESSMENT

Page____ ☐ Check if final assessment

Target lesions (the min. size of a measurable lesion must be at least double the slic

-non-nodal must be LD ≥ 10 mm on CT/MRI

-measurable lymph nodes must be ≥ 15 mm in the short axis on CT/MRI

-clinically must be ≥ 10 mm when measured with calipers

Response of target lesions

CR: Disappearance of all target lesions. lymph nodes must be < 10 mm short axis.

PR: At least a 30% decrease in the sum of diameters.

PD: At least a 20% increase in the sum of diameters

SD: Neither PR nor PD.

Non-Target lesions : All other lesions, including sma lesions (LD <10mm or pe

Response of non-target lesions

CR: Disappearance of all non-target lesions and normalisation of tumour mark

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or ma

PD: Progression of existing non-target lesions/new lesions.

Evaluation of best overall response

Target lesion	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/ non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
PD	Any	Yes or No	PD

[redacted]

REFERENCES

1. Cesana, GC et al., Characterization of CD4+CD25+ Regulatory T Cells in Patients Treated With High-Dose Interleukin-2 for Metastatic Melanoma or Renal Cell Carcinoma. J Clin Oncol 2006. 24(7):1169-1177.
2. Sabatino, M et al., Serum Vascular Endothelial Growth Factor and Fibronectin Predict Clinical Response to High-Dose Interleukin-2 Therapy. J Clin Oncol, 2009. 27(16):2645-2652.
3. Ugurel, S et al., Impact of the CCR5 gene polymorphism on the survival of metastatic melanoma patients receiving immunotherapy. Cancer Immunol Immunother 2008 57(5):685-691.
4. Van Elsas, A, Hurwitz, AA and Allison, JP. Combination immunotherapy of B16 melanoma using anti-cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and granulocyte/macrophage colony-stimulating factor (GM-CSF)-producing vaccines induces rejection of subcutaneous and metastatic tumors accompanied by autoimmune depigmentation. J Exp Med 1999 190(3):355-66.
5. Hodi, SF, O'Day, SJ, McDermott, DF et al. Improved survival with ipilumimab in patients with metastatic melanoma. N Engl J Med 2010.
6. Comis, RL. DTIC (NSC-45388) in malignant melanoma: a perspective. Cancer Treat Rep 1976 60(2):165-76.
7. Legha SS, Ring S, Bedikian A et al. Treatment of metastatic melanoma with combined chemotherapy containing cisplatin, vinblastine and dacarbazine (CVD) and biotherapy using interleukin-2 and interferon-alpha. Ann Oncol. 1996 Oct;7(8):827-35.
8. Legha, SS, Ring S, Eton O, et al. Development of a biochemotherapy regimen with concurrent administration of cisplatin, vinblastine, dacarbazine, interferon alfa, and interleukin-2 for patients with metastatic melanoma. J Clin Oncol. 1998 16(5):1752-9.
9. McDermott DF, Mier JW, Lawrence DP et al. A phase II pilot trial of concurrent biochemotherapy with cisplatin, vinblastine, dacarbazine, interleukin 2, and interferon alpha-2B in patients with metastatic melanoma. Clin Cancer Res. 2000 Jun;6(6):2201-8.
10. Atkins, MB, Gollob, JA, Sosman, JA et al. A phase II pilot trial of concurrent biochemotherapy with cisplatin, vinblastine, temozolomide, interleukin 2, and IFN-alpha 2B in patients with metastatic melanoma. Clin Cancer Res. 2002 8(10):3075-81.
11. Eton O, Legha SS, Bedikian AY et al. Sequential biochemotherapy versus chemotherapy for metastatic melanoma: results from a phase III randomized trial. Clin Oncol. 2002 20(8):2045-52.
12. Atkins, MB, Hsu J, Cohen GI, et al. Phase III trial comparing concurrent biochemotherapy with cisplatin, vinblastine, dacarbazine, interleukin-2, and interferon alfa-2b with cisplatin, vinblastine, and dacarbazine alone in patients with metastatic malignant melanoma (E3695): a trial coordinated by the Eastern Cooperative Oncology Group. J Clin Oncol. 2008 26(35):5748-54.
13. Lotze, M., Grimm, E., Mazumder, A., Strausser, J., and Rosenberg, S. 1981. In vitro growth of cytotoxic human lymphocytes. IV. Lysis of fresh and cultured autologous tumor by lymphocytes cultured in T cell growth factor (TCGF). Cancer Res. 41:4420-.
14. Mazumder, A., and Rosenberg, S. 1984. Successful immunotherapy of natural killer-resistant established pulmonary metastases by the intravenous adoptive transfer of syngeneic lymphocytes activated in vitro by interleukin-2. J Exp Med 159:495.

[redacted]
Approval Date: 1/8/2018
Expiration Date: 9/27/2018

15. Rosenberg, S., Mule, J., Spiess, P., Reichert, C., and Schwarz, S. 1985. Regression of Established Pulmonary Metastases and Subcutaneous Tumor Mediated by the Systemic Administration of High-Dose Recombinant Interleukin 2. J Exp Med 161:1169-1188.
16. Rosenberg, S., Lotze, M., Muul, L., Leitman, S., Chang, A., Ettinghausen, S., Matory, Y., Skibber, J., Shiloni, E., Vetto, J., et al. 1985. Observations on the systemic administration of autologous lymphokine-activated killer cells and recombinant interleukin-2 to patients with metastatic cancer. N Eng J Med 313:1485-1492.
17. Lotze, M., Chang, A., Seipp, C., Simpson, C., Vetto, J., and Rosenberg, S. 1986. High-dose recombinant interleukin-2 in the treatment of patients with disseminated cancer. JAMA 256:3117-3124.
18. Rosenberg, S., Lotze, M., Muul, L., Chang, A., Avis, F., Leitman, S., Linehan, W., Robertson, C., Lee, R., Rubin, J., et al. 1987. A progress report on the treatment of 157 patients with advanced cancer using lymphokine-activated killer cells and interleukin-2 or high-dose interleukin-2 alone. N Eng J Med 316:889-897.
19. Rosenberg, S., Yang, J., White, D., and Steinberg, S. 1998. Durability of complete responses in patients with metastatic cancer treated with high-dose interleukin-2: identification of the antigens mediating response. Ann Surg. 228:307-319.
20. Atkins, M, Lotze, M, Dutcher, J et al. High-dose recombinant interleukin-2 therapy for patients with metastatic melanoma: analysis of 270 patients treated between 1985 and 1993. J Clin Oncol 1999 17:2105-2116.
21. Atkins, MB, Kunkel L, Sznol M and Rosenberg SA. High-dose recombinant interleukin-2 therapy in patients with metastatic melanoma: long-term survival update. Cancer J Sci Am, 2000. 6 Suppl 1: p. S11-4.
22. Kammula, US, White DE and Rosenberg SA. Trends in the safety of high dose bolus interleukin-2 administration in patients with metastatic cancer. Cancer 1998 83(4):797-805.
23. Schwartzentruber, DJ. Guidelines for the safe administration of high-dose interleukin-2. J Immunother. 2001 24(4):287-93.
24. Baskar, S et al., Rejection of MHC class II-transfected tumor cells requires induction of tumor-encoded B7-1 and/or B7-2 costimulatory molecules. J Immunol, 1996. 156(10): p. 3821-7.
25. Chambers, CA and Allison, JP. Costimulatory regulation of T cell function. Curr Opin Cell Biol, 1999. 11(2):203-10.
26. Greene, JL et al., Covalent Dimerization of CD28/CTLA-4 and Oligomerization of CD80/CD86 Regulate T Cell Costimulatory Interactions. J. Biol. Chem., 1996. 271(43):6762-26771.
27. Carreno, BM et al., CTLA-4 (CD152) can inhibit T cell activation by two different mechanisms depending on its level of cell surface expression. J Immunol, 2000. 165(3):1352-6.
28. Egen, JG, Kuhns, MS and Allison, JP. CTLA-4: new insights into its biological function and use in tumor immunotherapy. Nat Immunol, 2002. 3(7):611-8.
29. Walunas, TL et al., CTLA-4 can function as a negative regulator of T cell activation. Immunity, 1994. 1(5):405-413.
30. Krummel, MF and Allison, JP. CD28 and CTLA-4 have opposing effects on the response of T cells to stimulation. J Exp Med, 1995. 182(2):459-65.

[redacted]
Approval Date: 1/8/2018
Expiration Date: 9/27/2018

31. Carreno, BM et al., CTLA-4 (CD152) Can Inhibit T Cell Activation by Two Different Mechanisms Depending on Its Level of Cell Surface Expression. J Immunol, 2000. 165(3):1352-1356.
32. O'Day, SJ, Hamid, O and Urba, WJ. Targeting cytotoxic T-lymphocyte antigen-4 (CTLA-4): a novel strategy for the treatment of melanoma and other malignancies. Cancer, 2007. 110(12):2614-27.
33. Leach, DR, Krummel, MF and Allison, JP. Enhancement of antitumor immunity by CTLA-4 blockade. Science, 1996. 271(5256):1734-6.
34. Kwon, ED et al. Manipulation of T cell costimulatory and inhibitory signals for immunotherapy of prostate cancer. Proc Natl Acad Sci U S A, 1997. 94(15):8099-103.
35. van Elsas, A., A.A. Hurwitz, and J.P. Allison, Combination immunotherapy of B16 melanoma using anti-cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and granulocyte/macrophage colony-stimulating factor (GM-CSF)-producing vaccines induces rejection of subcutaneous and metastatic tumors accompanied by autoimmune depigmentation. J Exp Med, 1999. 190(3): p. 355-66.
36. Hurwitz, A.A., et al., CTLA-4 blockade synergizes with tumor-derived granulocyte-macrophage colony-stimulating factor for treatment of an experimental mammary carcinoma. Proc Natl Acad Sci U S A, 1998. 95(17): p. 10067-71.
37. Hurwitz, A.A., et al., Combination immunotherapy of primary prostate cancer in a transgenic mouse model using CTLA-4 blockade. Cancer Res, 2000. 60(9): p. 2444-8.
38. Quezada, S.A., et al., CTLA4 blockade and GM-CSF combination immunotherapy alters the intratumor balance of effector and regulatory T cells. J Clin Invest, 2006. 116(7): p. 1935-45.
39. van Elsas, A et al., Elucidating the autoimmune and antitumor effector mechanisms of a treatment based on cytotoxic T lymphocyte antigen-4 blockade in combination with a B16 melanoma vaccine: comparison of prophylaxis and therapy. J Exp Med, 2001. 194(4):481-9.
40. Attia, P et al., Autoimmunity correlates with tumor regression in patients with metastatic melanoma treated with anti-cytotoxic T-lymphocyte antigen-4. J Clin Oncol, 2005. 23(25):6043-53.
41. Downey, SG et al. Prognostic factors related to clinical response in patients with metastatic melanoma treated by CTL-associated antigen-4 blockade. Clin Cancer Res, 2007 13(22 Pt 1):6681-8.
42. Hodi, FS et al., Biologic activity of cytotoxic T lymphocyte-associated antigen 4 antibody blockade in previously vaccinated metastatic melanoma and ovarian carcinoma patients. Proc Natl Acad Sci U S A, 2003 100(8):4712-7.
43. Maker, AV et al., Tumor regression and autoimmunity in patients treated with cytotoxic T lymphocyte-associated antigen 4 blockade and interleukin 2: a phase I/II study. Ann Surg Oncol, 2005 12(12):1005-16.
44. Dai, D, et al. Model-based evaluation of ipilimumab dosage regimen in patients with advanced melanoma. J Clin Oncol (Meeting Abstracts), 2008 26(15_suppl):9073.
45. Powderly, JD et al., Prolonged survival in objective responders to ipilimumab therapy. J Clin Oncol (Meeting Abstracts), 2008 26(15_suppl):2004.
46. Thompson, JA et al. Effect of prior treatment status on the efficacy and safety of ipilimumab monotherapy in treatment-naive and previously treated patients with advanced melanoma. J Clin Oncol (Meeting Abstracts), 2008 26(15_suppl):9055.

[redacted]

47. Lenschow, DJ et al. CD28/B7 system of T cell costimulation. Ann Rev Immunol 11996 4:233-258.
48. Schwartz, RH. Costimulation of T lymphocytes: the role of CD28, CTLA4, and B7/BB1 in interleujin-2 production and immunotherapy. Cell 1992 71(7):1065-1068.
49. Chen, LS et al. Costimulation of antitumor immunity by the B7 counterreceptor for the T lymphocyte molecules CD28 and CTLA-4. Cell 1992 71(7):1093-1102.
50. Townsend, SE et al. Tumor rejection after direct costimulation of CD8+ T cells by B7-transfected melanoma cells. Science 1993 259(5093):368-370.
51. Townsend, SE et al. Specificity and longevity of antitumor immune responses induced by B7-tarnsfected tumors. Cancer Res 1994 54(24):6477-6483.
52. Allison, JP et al. Manipulation of costimulatory signals to enhance antitumor T cell responses. Curr Opin Immunol 1995 7(5):682-686.
53. Linsley, PS et al. CTLA-4 is a second receptor for the B cell activation antigens B7. J Exp Med 1991 174(3)561-569.
54. Thompson, CB and Allison, JA. The emerging role of CTLA-4 as an immune attenuator. Immunity 1997 7(4):445-450.
55. Walunas T.L., et al., CTLA-4 can function as a negative regulator of T cell activation. Immunity, 1994. 1(5): p. 405-413.
56. Kearney E.R., et al., Antigen-dependent clonal expansion of a trace population of antigen-specific CD4+ T cells in vivo is dependent on CD28 costimulation and inhibited by CTLA-4. J Immunol, 1995. 155(3): 1032-1036.
57. Krummel M.F. and Allison J.P. CD28 and CTLA-4 have opposing effects on the response of T cells to stimulation. J Exp Med 1995; 182(2): 459-465.
58. Krummel M.F., et al., Superantigen responses and co-stimulation: CD28 and CTLA4 have opposing effects on T cell expansion in vitro and in vivo. Int Immunol, 1996. 8(4): 519-523.
59. Tivol E.A., et al., Loss of CTLA-4 leads to massive lymphoproliferation and fatal multiorgan tissue destruction, revealing a critical negative regulatory role of CTLA-4. Immunity, 1995. 3(5): 541-547.
60. Waterhouse P. et al., Lymphoproliferative disorders with early lethality in mice deficient in CTLA-4. Science, 1995. 270(5238): 985-988.
61. Chambers C.A., et al., Lymphoproliferation in CTLA-4-deficient mice is mediated by costimulation-dependent activation of CD4+ T cells. Immunity, 1997, 7(6): 885895.
62. Asim Amin A, De Pril V, Hamid O, et. al. Systemic Corticosteroids for the Treatment of Immune-Related Adverse Events (irAEs) Do Not Impact the Development or Maintenance of Ipilimumab Clinical Activity. [Poster presentation: #9037]. Presented at the 2009 American Society of Clinical Oncology Annual Meeting; May 29-June 2, 2009. Orlando, FL, USA.
63. Blansfield JA, Beck KE, Khoi T, et al. Cytotoxic Tlymphocyte-associate antigen-4 blockage can induce autoimmune hypophysitis in patients with metastatic melanoma and renal cancer. J Immunother 2005;28(6): 593-598.
64. Jaber SH, Edward W, et al. Skin reactions in a subset of patients with stage IV melanoma treated with anti-cytotoxic Tlymphocyte antigen 4 monoclonal antibody as a single agent. Arch Dermatol 2006;142:166-172.

[redacted]

65. Robinson MR, Chi-Chao C, Yang JC, et al. Cytotoxic Tlymphocyte-associate antigen-4 blockage in patients withmetastatic melanoma: A new cause of uveitis. J Immunother 2004;27(6):478-479.
66. CA184022 Clinical Study Report. A Randomized, Double-Blind, Multi-center, Phase II Fixed Dose Study of Multiple Doses of Ipilimumab (MDX-010) Monotherapy in Patients with Previously Treated Unresectable Stage III or IV Melanoma. Bristol-Myers Squibb Company and Medarex Inc, 2008. Document Control No. 930026869.
67. CA184008 Clinical Study Report. A Multicenter, Single Arm Phase 2 Study of MDX-010 (BMS734016) Monotherapy in Patients with Previously Treated Unresectable Stage III or IV Melanoma. Bristol-Myers Squibb Company and Medarex Inc, 2008. Document Control No. 930025464.
68. CA184007 Clinical Study Report. Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study Comparing the Safety of Ipilimumab Administered With or Without Prophylactic Oral Budesonide (Entocort™ EC) in Patients with Unresectable Stage III or IV Malignant Melanoma. Bristol-Myers Squibb Company and Medarex Inc, 2008. Document Control No. 930026874.
69. CA184004 Clinical Study Report. An Exploratory Study to Determine Potential Predictive Markers of Response and/or Toxicity in Patients with Unresectable Stage III or IV Malignant Melanoma Randomized and Treated with Ipilmumab (MDX-010/BMS-734016) at Two Dose Levels. Bristol-Myers Squibb Company and Medarex Inc, 2008. Document Control No. 930027670.
70. MDX010-19 Clinical Study Report. A Study of Intra-patient Escalating Doses of MDX-010 Given Alone or in Combination With Two GP100 Peptides Emulsified with Montanide ISA-51 in the Treatment of Patients with Stage IV Melanoma. Medarex Inc. and Bristol-Myers Squibb Company, 2007. Document Control No. 930023186.
71. Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, Lebbé C, Maio M, Binder M, Bohnsack O, Nichol G, Humphrey R, Hodi FS. Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-Related Response Criteria. Clin Cancer Res 2009;15(23):7412-7420.
72. Schwartzentruber, D. Guidelines for the safe administration of high-dose interleukin-2. J Immunother 2001;24(4):287-293.
73. Mavroukakis SA, Muehlbauer PM, White RL, Schwartzentruber DJ. Clinical pathways for managing patients receiving interleukin 2. Clin J Oncol Nurs 2001;5(5):207-217.
74. Korn EL, Liu P-Y, Lee S, et al. Meta-analysis of phase II cooperative group trials in metastatic stage IV melanoma to determine progression-free and overall survival benchmarks for future phase II trials. J Clin Oncol. 2008;26:527-534.
75. Chapman PB, Einhorn E, Meyers ML, Saxman S, Destro AN, Panageas KS, Begg CB, et al. Phase III Multicenter Randomized Trial of the Dartmouth Regimen Versus Dacarbazine in Patients with Metastatic Melanoma. J Clin Oncol. 1999;17(9)2745-2751.
76. Middleton MR, Grob JJ, Aaronson N, Fierlbeck G, Tilgen W, Seiter S, Gore M, et al. Randomized Phase III Study of Temozolomide Versus Dacarbazine in the Treatment

[redacted]

of Patients With Advanced Metastatic Malignant Melanoma. J Clin Oncol. 2000;18:158-166.

77. Bedekian AY, Millward, M, Pehamberger H, Conry R, Gore M, Trefzer U, Pavlick AC, et al. Bcl-2 Antisense (oblimersen sodium) Plus Dacarbazine in Patients With Advanced Melanoma: the Olimersen Melanoma Study. J Clin Oncol. 2006:24:4738 4745.
76. Schwartz, RN, Stover, L and Dutcher, J. Managing toxicities of high-dose interleukin-2. Oncology (Williston Park), 2002. 16(11 Suppl 13):11-20.
78. Rochlitz, C, et al., Immunotherapy of metastatic melanoma by intratumoral injections of Vero cells producing human IL-2: phase II randomized study comparing two dose levels. Cancer Gene Ther, 2002. 9(3):289-95.
79. Kaufman, H, et al., Targeting the local tumor microenvironment with vaccinia virus expressing B7.1 for the treatment of melanoma. J Clin Invest, 2005. 115:1903 - 1912.
80. Szabo, SJ et al., Distinct Effects of T-bet in TH1 Lineage Commitment and IFN-gamma Production in CD4 and CD8 T Cells. Science, 2002. 295(5553):338-342.
81. Zhang, DH et al., Transcription Factor GATA-3 Is Differentially Expressed in Murine Th1 and Th2 Cells and Controls Th2-specific Expression of the Interleukin-5 Gene. J. Biol. Chem., 1997. 272(34):21597-21603.
82. Fontenot, JD, Gavin, MA and Rudensky, AY. Foxp3 programs the development and function of CD4+CD25+ regulatory T cells. Nat Immunol, 2003. 4(4):330-6.
83. Mucida, D et al. Reciprocal TH17 and regulatory T cell differentiation mediated by retinoic acid. Science, 2007. 317(5835):256-60.
84. Bunce, M., et al. Phototyping: comprehensive DNA typing for HLA-A, B, C, DRB1, DRB3, DRB4, DRB5 & DQB1 by PCR with 144 primer mixes utilizing sequence-specific primers (PCR-SSP). Tissue Antigens. 46:355–367, 1995.