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**A Phase III Randomized Study of Adjuvant Ipilimumab Anti-CTLA4 Therapy Versus High-Dose Interferon  $\alpha$ -2b for Resected High-risk Melanoma**

**Version Date: October 13, 2011**

**This is a clinical trial, a type of research study. Your doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your doctor for more explanation.**

You are being asked to take part in this study because you have skin cancer (melanoma) which, although it has been successfully treated with surgery, has a high probability of coming back.

**WHY IS THIS STUDY BEING DONE?**

The purpose of this study is to compare the effects, good and/or bad, of ipilimumab with interferon alfa-2b on you and your melanoma to find out which is better. In this study, you will get either ipilimumab or the interferon alfa-2b. You will not get both. We plan to determine whether ipilimumab stops or delays your cancer from returning in comparison to interferon alfa-2b.

High doses of interferon alfa-2b can reduce the risk of melanoma returning, but only some patients benefit from interferon. This interferon is commercially available. We hope to find a more effective and long-lasting treatment for your type of cancer. Ipilimumab is a biological agent that has been shown to have anti-tumor activity in advanced melanoma. Interferon alfa-2b is FDA-approved as an adjuvant treatment to surgery in adult patients with melanoma who are free of disease but at high risk for recurrence. Ipilimumab is investigational and has not been approved by the FDA for use in this cancer.

We also want to know your view of how your life has been affected by cancer and its treatment. For this "Quality of life" (QOL) study, you will be given short questionnaires at different times during the trial. The QOL study looks at how you are feeling physically and emotionally during your cancer treatment and at how you are able to carry out your day-to-day activities. If any questions make you feel uncomfortable, you may skip those questions and not give an answer. This information will help doctors better understand how patients feel during treatments and what effects the medicines are having.

**HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?**

About 1,000 people will take part in this study.

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

Please see the **study plan** that is listed later on this form.

**BEFORE YOU BEGIN THE STUDY**

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**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.**

- **Pregnancy test:** If you are a woman of childbearing potential, you will also be required to have a blood or urine pregnancy test prior to starting the study. The blood or urine pregnancy test must be negative within 72 hours before the start of the study drugs.  
*Note:* If you are pregnant or nursing, you will not be allowed to participate in this study because of the possibility of harm to your baby from the study drugs' administration. If you are a woman who can have children, you must use an adequate method of contraception to avoid pregnancy throughout the study, and for up to 12 weeks after the last dose of the study drugs, in such a manner that the risk of pregnancy is minimized. Men must avoid fathering children while receiving the study drugs.
- **HIV, Hepatitis B, or Hepatitis C:** These tests will involve having a small sample (about 1 teaspoon) of blood drawn prior to starting the study. You will not be able to participate in this study if any of these tests are positive. You will be presented with a separate HIV consent.
- **A medical history:** This may include questions about your health, current medications, and any allergies.
- **A physical examination:** The research doctor or another research healthcare professional will perform a complete physical assessment including blood pressure, pulse, rate of breathing, temperature, and height and weight.
- **An assessment of your body to rule out evidence of tumor:** This will be done using CT (Computerized Tomography) scans of your chest, abdomen and pelvis (must be performed within 28 days of starting study treatment), and MRI (Magnetic Resonance Imaging) of your brain. A PET scan or other imaging studies may also be done if indicated in your case.
- **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 sometimes to test for any infections.
- **Additional tests:** An ECG will be performed to assess the function of your heart.

If the screening examination indicates that you are eligible to participate in this trial, and if you agree to participate, you will be scheduled for these additional research related procedures:

- **Quality of Life (QOL) Questionnaire:** One purpose of this study is to measure the effect that treatment has on your quality of life. To measure this, we will ask you to fill out a questionnaire. The questionnaire takes about 5 to 15 minutes to complete.

## DURING THE STUDY

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If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures. They are part of regular cancer care.

- **A medical history:** This may include questions about your health, current medications, and any allergies.
- **A physical examination:** The research doctor or another research healthcare professional will perform a complete physical assessment including blood pressure, pulse, rate of breathing, temperature, and height and weight.
- **An assessment of your body to rule out recurrence of melanoma:** This will be done using a chest x-ray, chest CT scan or PET scan. More extensive testing will be done if your doctor determines that this is necessary. These studies will be done every 3 months.
- **Blood tests:** Blood (about 4-6 tablespoons) will be taken from a vein in your arm to check blood cell counts, how well your organs are functioning and sometimes to test for any infections. A urine test may sometimes be done.

You will need these tests and procedures that are part of regular cancer care. They are being done more often because you are in this study.

- **Pregnancy test:** If you receive ipilimumab and you are a woman of childbearing potential, you will also be required to have a blood or urine pregnancy test prior to each treatment with ipilimumab. The blood or urine pregnancy test must be negative within 72 hours before every ipilimumab treatment.
- **Assessment for side effects:** you will be monitored and questioned about possible side effects of the study drug as long as you are still receiving the study drug and up to 70 days after the last study drug administration.
- **Additional blood tests:** If you receive ipilimumab, additional hormonal studies will be done to monitor for known side effects of ipilimumab.

You will need these tests and procedures that are either being tested in this study or being done to see how the study is affecting your body.

- **Quality of Life (QOL) Questionnaire:** We will ask you to fill the QOL questionnaire every 12 weeks while you are still on treatment and every 24 weeks after you stop the study treatment for up to one year. The questionnaire takes about 5-15 minutes to complete.

**Interferon Diary:** If you receive interferon, you will be asked to keep track of your injections with a written interferon calendar which will be reviewed during visits to your doctor's office or clinic.

You will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance. A computer program will place you in one of the study groups. Neither you nor your doctor can choose the group you will be in. You will have an equal chance of being placed in any group.

If you are in group 1 (often called "Arm A") you will receive ipilimumab that will be given in 2 stages called induction phase and maintenance phase. In the induction phase, you will receive ipilimumab every 3 weeks for a maximum of 4 doses. In the maintenance phase,

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you will receive ipilimumab every 12 weeks (3 months), beginning at week 24, for a maximum of 4 doses (weeks 24, 36, 48, 60).

Ipilimumab will be administered by intravenous infusion, a method of putting the drug directly into the bloodstream through a vein. The infusion will take about 90 minutes and will take place at an outpatient facility. Prior to the infusion, you will have your vital signs measured. During the infusion your vital signs will be measured every 30 minutes and one hour after the infusion has stopped, your vital signs will be measured one more time.

A medical history, physical examination and blood tests will be done during all treatment visits when you come in for ipilimumab infusion. They may be done more often if your doctor thinks that this is necessary. In addition to the regular physical examination by your melanoma doctor, an eye examination by an eye specialist will be done at 6 and 18 months after the start of treatment. This will be done to monitor for potential side effects of ipilimumab. If melanoma recurrence occurs and you stop ipilimumab before these time points, the eye examination is not mandatory but will be done if your doctor decides it is necessary.

**If you are in group 2 (often called "Arm B") you will receive interferon Alfa-2b that will be given in 2 stages called induction phase and maintenance phase.** In the **induction phase**, you will receive interferon Alfa-2b given 5 consecutive days (M-F) out of 7 every week for four weeks by intravenous infusions over 20 minutes. These infusions will be given in the outpatient setting. In the **maintenance phase**, you will receive interferon Alfa-2b three times weekly, every other day (M, W, F) for 48 weeks by subcutaneous injections. You will be taught how to self administer the IFN subcutaneous injections. You will be asked to keep track of your injections with a written interferon calendar which will be reviewed during visits to your doctor's office or clinic.

A medical history, physical examination and blood tests will be done every week for 4 weeks during the induction phase, then every 4 weeks for 2 months, then every 6 weeks during the interferon treatment. They may be done more often if your doctor thinks that this is necessary.

#### **Central Review**

Pathology samples from your primary tumor, metastatic tumor, and tumor from your lymph nodes will be sent to a central laboratory to be examined by a central reviewer. This review will be used to confirm the results of the local institutional review.

#### **WHEN I AM FINISHED TAKING THE STUDY TREATMENT**

You will be asked to return to the clinic within 21 days following the last dose of ipilimumab or interferon. A medical history, physical examination, and blood tests will be done.

A quality of life questionnaire will be done 6 months and 1 year after your last dose of protocol treatment.

After the completion of the treatment, if you continue to have side effects related to the study treatment, you may be asked to return to the clinic more frequently. We would like to monitor you until all treatment related side effects have stopped.

STUDY CHART  
[Arm A: Ipilimumab]

If you are in Arm A, you will receive ipilimumab that will be given in 2 stages called induction phase and maintenance phase. In the induction phase, you will receive ipilimumab every 3 weeks for a maximum of 4 doses. In the maintenance phase, you will receive ipilimumab every 12 weeks (3 months), beginning at week 24, for a maximum of 4 doses (weeks 24, 36, 48, 60).

The left-hand column shows the day or week of treatment and the right-hand column tells you the main things that are planned for that day or week.

DAY/WEEK	WHAT IS PLANNED
Within 4 weeks of starting study	Medical history and physical examination, routine blood tests, electrocardiogram (ECG) and routine imaging studies
<b>Induction phase</b>	
Within 3 days of starting study	Blood or urine pregnancy test
Day 1 ± 3 days	Medical history and physical examination, routine blood tests, Ipilimumab infusion and assessment for toxicities
Day 22 ± 3 days	Medical history and physical examination, routine blood tests, Ipilimumab infusion and assessment for toxicities
Day 43 ± 3 days	Medical history and physical examination, routine blood tests, Ipilimumab infusion and assessment for toxicities
Day 64 ± 3 days	Medical history and physical examination, routine blood tests, Ipilimumab infusion and assessment for toxicities
Week 12 ± 2 wks	Medical history and physical examination, routine blood tests, assessment for toxicities
<b>Maintenance Phase (Until 12 weeks after the last ipilimumab dose or until recurrence of melanoma)</b>	
Week 24, 36, 48, 60 ± 2 weeks	Medical history and physical examination, routine blood tests, Ipilimumab infusion and assessment for toxicities
Every 6 weeks (± 1 week) during the maintenance phase	Medical history and physical examination, routine blood tests, assessment for toxicities
Every 3 months (± 2 weeks)	Routine imaging studies to assess for evidence of melanoma recurrence
Quality of Life Questionnaire	Every 12 weeks while you are still on treatment and every 24 weeks after you stop the study treatment for up to one year
End of Study Assessment	This will be done within 12 days of the last dose of Ipilimumab and will include medical history and physical examination, routine blood tests, assessment for toxicities
Follow Up after completing the study	Your doctor will explain to you how often you need to be seen. In general, your follow up visits may include medical history and physical examination,

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	routine blood tests, assessment for toxicities and imaging studies
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STUDY CHART  
**[Arm B: Interferon Alfa-2b]**

If you are in group Arm B you will receive interferon Alfa-2b that will be given in 2 stages called induction phase and maintenance phase. In the induction phase, you will receive interferon Alfa-2b given 5 consecutive days (e.g. M-F) out of 7 every week for four weeks by intravenous infusions over 20 minutes. These infusions will be given in the outpatient setting. In the maintenance phase, you will receive interferon Alfa-2b three times weekly, every other day (e.g. M, W, F) for 48 weeks by subcutaneous injections. The left-hand column shows the day or week of treatment and the right-hand column tells you the main things that are planned for that day or week.

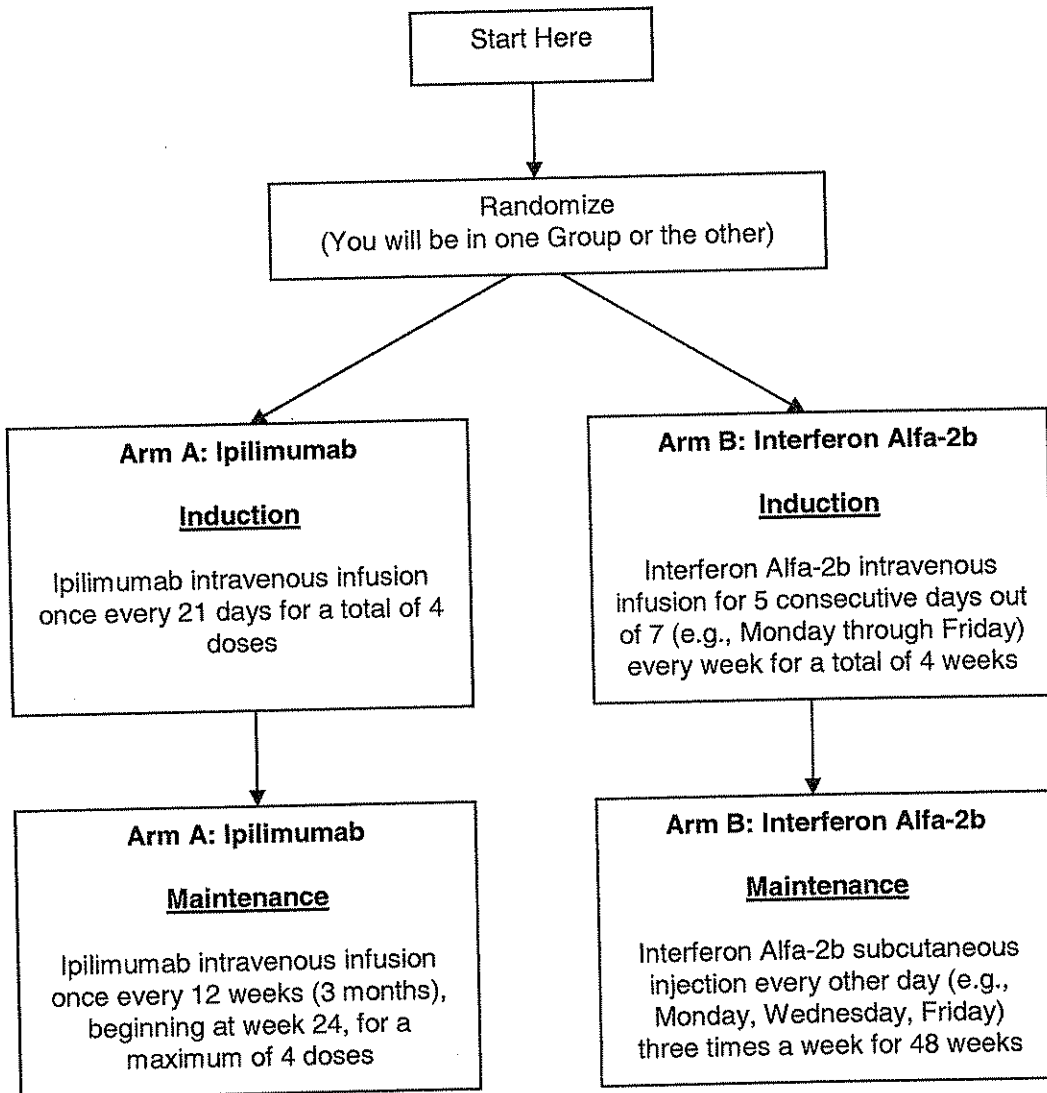
DAY/WEEK	WHAT IS PLANNED
Within 4 weeks of starting study	Medical history and physical examination, routine blood tests, electrocardiogram (ECG) and routine imaging studies
<b>Induction phase</b>	
Within 3 days of starting study	Blood or urine pregnancy test
Day 1	Medical history and physical examination, routine blood tests, interferon Alfa-2b infusion (also given on days 2,3,4,5) and assessment for toxicities
Day 8	Medical history and physical examination, routine blood tests, interferon Alfa-2b infusion (also given on days 9,10,11,12) and assessment for toxicities
Day 15	Medical history and physical examination, routine blood tests, interferon Alfa-2b infusion (also given on days 16,17,18,19) and assessment for toxicities
Day 22	Medical history and physical examination, routine blood tests, interferon Alfa-2b infusion (also given on days 23,24,25,26) and assessment for toxicities
Day 29	Medical history and physical examination, routine blood tests, and assessment for toxicities
<b>Maintenance Phase (Until 4 weeks after the last interferon dose or until recurrence of melanoma)</b>	
Every 4 weeks ( $\pm$ 1 week) for 2 months	Medical history and physical examination, routine blood tests, and assessment for toxicities. During this time you will be getting interferon Alfa-2b injections 3 times per week
Every 6 weeks ( $\pm$ 1 week; after the first 2 months)	Medical history and physical examination, routine blood tests, and assessment for toxicities. During this time you will be getting interferon Alfa-2b injections 3 times per week
Every 3 months ( $\pm$ 2 weeks)	Routine imaging studies to assess for evidence of melanoma recurrence
Quality of Life Questionnaire	Every 12 weeks while you are still on treatment and every 24 weeks after you stop the study treatment for up to one year
End of Study Assessment	This will be done within 21 days of the last dose of interferon. It will include medical history and physical examination, routine blood tests, and assessment for toxicities
Follow Up after	Your doctor will explain to you how often you need to be seen. In general,

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completing the study	your follow up visits may include medical history and physical examination, routine blood tests, assessment for toxicities and imaging studies.
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### STUDY PLAN

Another way to find out what will happen to you during the study is to read the chart below. Start reading at the top and read down the list, following the lines and arrows.



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## HOW LONG WILL I BE IN THE STUDY?

We think you will be in the study for one to one and a half years. We would like to keep track of your medical condition for 15 years from study entry to look at the long-term effects of the study.

In the absence of melanoma relapse, you will be followed by your doctor every 3 months if you are less than 2 years from study entry, every 6 months if you are 2-5 years from study entry, and every 12 months if you are more than 5 years from study entry. You may be seen more often if your doctor determines that this is necessary.

If melanoma relapse occurs, we would also like to keep track of your medical condition for the rest of your life. We would like to do this by calling you on the telephone to see how you are doing. Keeping in touch with you and checking your condition helps us look at the long-term effects of the research study. We will call you every 3 months if you are less than 2 years from study entry, every 6 months if you are 2-5 years from study entry, and every 12 months if you are more than 5 years from study entry.

## CAN I 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 treatment 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 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 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 treatment. In some cases, side effects can be serious, long lasting, or may never go away. There also is a 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:

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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.

**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, ipilimumab may increase your chance of bowel perforation. 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.

- **Skin:** 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

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. It can be very severe and may result in death.

- **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.

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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, the adrenal gland, or the testes. 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.

Progressive failure of blood clotting and risk of bleeding is a rare but serious complication of ipilimumab.

- **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

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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.
- 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. Acetaminophen 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.

- **Infusion related reaction:** Reaction that can occur during or following the infusion of ipilimumab includes fever, chills, rash, low blood pressure, and difficulty breathing. This occurs in fewer than 20% of individuals treated with ipilimumab.

### Risks and Side Effects of Interferon Alpha-2b

#### Likely:

- Shortness of breath
- Changes in kidney function (abnormal kidney function tests which could indicate damage to your kidney)
- A decrease in your blood cell counts (making you more prone to infections) and bleeding
- Flu-like symptoms including fever, chills, nausea, vomiting, diarrhea, muscle aches, fatigue (tiredness), body aches
- Pain at the injection site
- Headache
- Numbness
- Pins and needles sensation in your fingers or hands
- Pain in your joints
- Reactivation of genital herpes
- Loss of appetite
- Weight loss
- Constipation
- Abdominal pain
- Hair loss
- Tremors (shaking)
- Taste changes

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- Fainting
  - Skin rash
  - Itching
  - Dryness of the mouth
  - Flatulence (gas)
  - Sweating

**Less Likely:**

- Chest pain
- High blood pressure
- Low blood pressure
- Flushing
- Rapid heartbeat
- Congestive heart failure (a reduced ability of the heart to pump and an accumulation of fluid in the heart)
- Changes in your heart rhythm such as an irregular beating of the heart
- Temporary anxiety or confusion
- Slowness of movement
- Feelings of persecution (paranoia)
- Hallucinations (seeing or hearing things that are not there)
- Mental depression
- Irritability
- Difficulty concentrating
- Aggressive reactions
- Suicidal thoughts
- Unconsciousness
- Visual disturbances
- Dizziness
- Sleep disturbances

**Rare:**

- Death
- Thromboembolic event (blocking of a blood vessel by a blood clot that has become detached from the site where it formed)
- Cardiac (heart) event
- Autoimmune (a condition where your body makes a substance that fights against your own system) thyroid disease

**Risks of Venipuncture/Intravenous Needle Insertion:**

**Less Likely:**

- Mild pain and discomfort at the injection or needle insertion site as well as possible infection, bleeding, bruising, and soreness.

**Rare:**

- Severe pain, swelling, infection from the actual injection, and fainting.

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**Reproductive risks:** You should not become pregnant or father a baby while on this study because the drugs in this study can affect a fetus. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your doctor about what kind of birth control methods to use and how long to use them.

Avoiding sexual activity is the only certain method to prevent pregnancy. However, if you choose to be sexually active, you must agree to use an appropriate double barrier method of birth control (such as female use of a diaphragm, intrauterine device (IUD), sponge and spermicide, in addition to the male use of a condom) or involve female use of prescribed "birth control pills" or a prescribed birth control implant. Both double barrier contraception and birth control pills or implants must be used for at least one week prior to the start of the research study and continuing for at least eight weeks following the last study visit. If you choose to be sexually active during the study, you must accept that pregnancy could still result, exposing you or your sexual partner to potential loss of pregnancy as well as other unknown effects on the developing fetus.

For more information about risks and side effects, ask your doctor.

#### **ARE THERE BENEFITS TO TAKING PART IN THE STUDY?**

Taking part in this study may or may not make your health better. While doctors hope that ipilimumab will be more useful against cancer compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help doctors learn more about ipilimumab and interferon Alfa-2b as a treatment for cancer. 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 without being in a study
- Taking part in another study
- Getting no treatment

Talk to your doctor about your choices before you decide if you will take part in this study.

#### **WILL MY MEDICAL INFORMATION BE KEPT PRIVATE?**

The Eastern Cooperative Oncology Group (ECOG) is conducting this study. ECOG is a cancer research group that conducts studies for the National Cancer Institute. Your doctor is a member of ECOG or another group that is participating in this study. To help protect your privacy, ECOG has obtained a Confidentiality Certificate from the Department of Health and Human Services (DHHS).

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With this Certificate, ECOG cannot be forced (for example, by court subpoena) to disclose information that may identify you in any federal, state or local civil, criminal, administrative, legislative or other proceeding. Disclosure will be necessary, however, upon request of DHHS for audit or program evaluation purposes.

You should know that a Confidentiality Certificate does not prevent you or a member of your family from voluntarily releasing information about you or your involvement in this research. If an insurer or employer learns about your participation and obtains your consent to receive research information, then ECOG may not use the Certificate of Confidentiality to withhold this information. This means that you and your family must also actively protect your privacy.

You should also understand that your doctor and ECOG may take steps, including reporting to authorities, to prevent you from seriously harming yourself or others.

Finally, the Certificate does not prevent the review of your research records under some circumstances by certain organizations for an internal program audit or evaluation. Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as:

- Eastern Cooperative Oncology Group (ECOG)
- National Cancer Institute (NCI)
- Food and Drug Administration (FDA)
- Other regulatory agencies and/or their designated representatives
- Drug manufacturers and/or their representatives
- Central laboratories, banks and/or reviewers

#### **WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?**

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these 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.

The cost of additional laboratory tests, such as pregnancy tests for patients on Arm A, might not be covered by your insurance.

The Division of Cancer Treatment and Diagnosis, NCI, will provide the investigational agent ipilimumab at no charge while you take part in this study. The NCI does not cover the cost of getting ipilimumab ready and giving it to you, so you or your insurance company may have to pay for this.

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Even though it probably won't happen, it is possible that the NCI may not be able to continue to provide the ipilimumab for some reason. If this would happen, the study may have to close. Your study doctor will talk with you about this, if it happens.

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

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.

### WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?

It is important that you tell your doctor, \_\_\_\_\_ [investigator's name(s)], if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at \_\_\_\_\_ [telephone number].

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

### WHAT ARE MY RIGHTS IF I TAKE PART IN THIS STUDY?

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.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

### WHO CAN ANSWER MY QUESTIONS ABOUT THE STUDY?

You can talk to your doctor about any questions or concerns you have about this study. Contact your doctor \_\_\_\_\_ [name(s)] at \_\_\_\_\_ [telephone number].

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For questions about your rights while taking part in this study, call the Kansas City Clinical Oncology Program Institutional Review Board (a group of people who review the research to protect your rights) at 913-948-5588.

Please note: This section of the informed consent form is about additional research studies that are being done with people who are taking part in the main study. You may take part in these additional studies if you want to. You can still be a part of the main study even if you say 'no' to taking part in any of these additional studies.

You can say "yes" or "no" to each of the following studies. Please mark your choice for each study.

### ABOUT PROVIDING SPECIMENS FOR RESEARCH

Please read this form and ask about anything that is not clear to you. This is part of the **informed consent** process for research. This is to inform you of the possible risks, benefits, and limits of giving your samples for research.

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You are being asked to give some of your samples (called **specimens**) and related information to be stored (banked) for future research. This may help researchers learn more about how to prevent, find and treat cancer and other diseases.

The choice to have your samples used for research is up to you. No matter what you decide, it will not affect your medical care.

Below is some general information you should know before agreeing to allow the use of your specimens for research. After the general information there are descriptions of the research projects. Each project is described separately, including the types of samples requested and how they are collected. Each description is followed by questions concerning your participation in the project. Your samples will be used only for the projects in which you agree to participate.

#### What are samples and where are they stored?

A sample is any material taken from your body such as tissue, blood, urine and other fluids. If you agree, your samples will be sent to laboratories to be used in research or will be stored for research in a Cooperative Group bank. These banks are supported by the National Cancer Institute. Cooperative Group banks contain samples and information. Your samples are kept along with those from other people in the banks. Researchers then ask for samples from the banks to study them.

#### What information will be collected?

When your samples are sent by the institution treating you to any research laboratory or bank, some personal information will be sent with the samples. Any personal information sent with the samples is not given to other researchers. The personal information is used only by the

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laboratory or bank to identify your samples. Your privacy will be protected to the fullest extent possible. This will be discussed later in the section "How will information related to my samples be protected?"

Examples of other information that might be used for research include:

- Dates of medical procedures
- Any diagnosis and stage of your disease (if you have cancer)
- Your age and race
- Medical and family history
- Treatments you had
- How you responded to treatments

### **What will happen to my samples if I agree to give them for research?**

If you agree to let your samples be kept for future research (research not yet defined), your samples will be stored in a Cooperative Group bank. The samples will be kept until they are used up or destroyed. The samples are given a code to protect your privacy before they are used. Any related information given to researchers will also be coded. Researchers will receive the code instead of any information that might directly identify you.

You or your doctor will not be given reports or other information about the research that uses your samples. This information will not be put into your health record. Results may be used for future research.

You will not be named or identified by other personal information if any results are published. Most publications contain results from many patients.

Your samples and related information will be used only for research and will not be sold. It is possible that research may help to create new products or treatments. If this should happen, you will not be paid.

Coded data from some research studies that use samples could be put into secure Internet databases that can be shared by other approved researchers. This could include genetic data. Current safety rules are followed to safeguard your privacy. Your name or contact information will not be put in the database.

### **What kind of research will be done with my samples?**

Many types of research use normal or diseased (**cancerous**) samples. Researchers can study proteins, RNA and DNA (genes). The study of genes (DNA) is often called **genetic research**.

For example, your samples may be looked at:

- To see if a trait is passed down in families from one generation to the next (**inherited**). This type of research may help to explain why some cancers run in families or why some people have side effects from treatment while others do not. This is often studied through blood cells and DNA (**genes**).
- To learn about changes in the body that happen after you were born (**non-inherited**). For example, being in the sun too much can cause changes in cells that lead to skin cancer.

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### **Will it help me if I give my samples for research?**

Using your samples for research will probably not help you. We do hope the research results will help people in the future. The best way to prevent, find or treat cancer and other diseases is by studying human samples and data.

### **What are the risks of giving my samples for research?**

There is a risk that your information could be misused. The chance of this happening is very small. We have many protections in place to lower this risk. See the next section, "How will the information related to your samples be protected?" Your privacy will be protected to the fullest extent possible.

There can be a risk in knowing genetic information. New health information about inherited traits that might affect you or your blood relatives could be found during a research study. Even though your genes are unique, you share some of the same genes with your blood relatives. Very rarely health or genetic information could be misused by employers, insurance companies, and others. For example, life insurance companies may charge a higher rate based on this information.

Some states have laws to protect against genetic discrimination [*list appropriate state information if your state has such laws*]. A new federal law called the Genetic Information Non-Discrimination Act, or GINA is in effect. This law helps to lower the risk of health insurance or employment discrimination. The law does not include other types of misuse by life insurance or long term care insurance. To learn more about the GINA Law, please check the Internet or ask the study staff.

Although we are not able to know all of the risks from taking part in research on inherited traits, we believe that the risks to you and your family are very low, because research results will not be returned to you or your doctor.

### **How will information related to my samples be protected?**

We have many ways to protect the information related to your samples:

Your samples and information receive a unique code. Researchers only receive coded samples and information, and will not be able to link the code to you. Only approved people in the Eastern Cooperative Oncology Group can match you to the code on your samples and related information.

Strict security safeguards are in place to reduce the chance of misuse or unplanned release of information. Steps we take include password protected access to databases and restricted access to freezers or rooms that contain samples.

Before samples are given to researchers, studies are reviewed for the quality of the science and for patient protection. Records from research studies can be reviewed by the Cooperative Group, by the sponsor, and by government agencies. This is to make sure the research follows the rules of the Cooperative Group and state or federal laws.

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Research results will not be returned to you or your doctor. If research results are published, your name and other personal information will not be given.

ECOG also has a Certificate of Confidentiality from the U.S. Department of Health and Human Services. The Certificate protects against the forced release of personal information from the Cooperative Group bank or database.

What this means is that ECOG cannot be forced to disclose your identity to any third party. It is possible that for some legal proceedings, the Certificate of Confidentiality could be over-ridden by a court of law.

### **Making your choice**

The choice to take part is up to you. You may choose not to let us store and use your samples. If you decide not to let us store and use your samples, you will still receive the same medical care and you may still participate in the treatment part of this clinical trial. You may also take part in other research studies.

If you decide that your samples can be kept, you may change your mind at any time. Contact the study staff at your hospital and let them know that you do not want your samples used for research \_\_\_\_\_. Then, any sample that remains in the bank will no longer be used. Samples that have already been given to or used by researchers cannot be returned or destroyed.

Please read the research study descriptions below, review the questions carefully and circle "Yes" or "No". **If you have any questions, please talk to your doctor or nurse, or call the institution's research review board at 913-948-5588.**

### **USING SPECIMENS FOR FUTURE RESEARCH**

We would like to keep the tumor tissue specimens that are leftover from the central review for future research. If no tumor tissue specimens are leftover, we would like permission to obtain additional tumor tissue specimens if available, for future research. We would also like to collect biopsy specimens (if performed) if your disease returns or becomes worse, for banking for future research.

Additionally, we would like to collect blood for banking for future research. The specimens will be collected by using a needle to draw some blood from a vein in your arm. If you agree, approximately nine (9) to ten (10) tablespoons of blood will be collected before you start treatment, and eight (8) to nine (9) tablespoons will be collected at the following time points: 12 weeks after treatment, at 48 weeks, at 96 weeks and if your disease returns or becomes worse. Blood draws can result in bruising.

If you agree to provide additional blood for future research, we wish to examine the effects of both of these treatments on the different cells that make up your blood and to look for special markers that may help us define patients who are more likely to benefit from these two drugs. This is done to develop a deeper understanding of biological cancer treatments and will not affect your medical treatment in any way.

Although most future research studies will focus on cancer, some research projects may also include other diseases, such as heart disease, diabetes or Alzheimer's disease.

As indicated above, the specimens will only be given to researchers approved by scientific reviewers appointed by the Eastern Cooperative Oncology Group. Any research done on the specimens must also be reviewed by the researcher's institutional review board.

**Please review the points listed in the "Voluntary Participation" and the risks associated with donating your specimens for research (including genetic research) outlined in the section above. Then read the questions below carefully and circle "Yes" or "No."**

May we have some blood for future research about cancer?

**I agree to provide additional blood for research.**

Yes No

May we have additional tissue from your surgeries or biopsies, if available, for future research about cancer?

**I agree my tissue will be submitted for research.**

Yes No

May we keep any tissue leftover after the central review for future research about cancer?

**May your coded samples and related coded information be kept for use in research to learn about, prevent, find or treat cancer? This may also include research on inherited traits (genes passed on in families).**

Yes No

May we keep any samples submitted for future research about other diseases?

**May your coded samples and related coded information be kept for use in research to learn about, prevent, find or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease). This may also include research on inherited traits (genes passed on in families).**

Yes No

### **PERMISSION TO CONTACT YOU IN THE FUTURE**

We request your permission to contact you in the future about taking part in more research studies. If you agree and we decide to contact you in the future, we will first contact your doctor or some one at your hospital. They will tell you why we would like to contact you and, if you agree, they will send us your contact information. We will not attempt any direct contact without obtaining this second permission from you.

**Someone from my hospital or the Eastern Cooperative Oncology Group may contact me in the future to ask me to take part in more research.**

CALGB 50904  
Approval Date: 12/1/11 to 7/13/12  
Assurance #: FWA00003582

Yes	No
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**WHERE CAN I GET MORE INFORMATION?**

You may call the National Cancer Institute's Cancer Information Service at:  
1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

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/>

You will get a copy of this form. If you want more information about this study, ask your doctor.

**Release**

By signing this form you authorize KCCOP to access and obtain information that is required for the study. This may include your medical records, labs, radiologic films and reports and pathology specimens. This authorization to disclose your medical records shall not expire, even upon death, unless specifically revoked in writing by you.

You will get a copy of this form. If you want more information about this study, ask your study doctor.

**Signature**

I have been given a copy of all 22 pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant \_\_\_\_\_

Date \_\_\_\_\_

Signature of Person Obtaining Consent \_\_\_\_\_

Date \_\_\_\_\_