Testing Therapy Sequence for Advanced BRAF Mutation Melanoma

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: DREAMseq (Doublet, Randomized Evaluation in Advanced Melanoma Sequencing) A Phase III Trial

What is the usual approach to treating my melanoma?

You are being asked to take part in this research study because you have been diagnosed with melanoma, a type of skin cancer, and the melanoma has spread beyond its local area and cannot be surgically removed. Further, your melanoma cells have been shown to have a mutation in a protein called BRAF that leads to uncontrolled growth of the tumor cells. People with BRAF mutant melanoma who are not in a research study usually receive either a combination of various oral agents that target the BRAF pathway (of dabrafenib and trametinib, vemurafenib and cobimetinib, or encorafenib and binimetinib) or the immunotherapy drugs. In addition, nivolumab or a similar drug, pembrolizumab or the combination of nivolumab and the distinct immunotherapy agent ipilimumab. All of these agents have been FDA approved for treatment of patients with advanced melanoma and thus could be alternative treatments for such patients not on a research study. For patients who receive the current approaches for advanced melanoma, about 40-50 out of 100 are anticipated to be free of cancer at five years.

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

If you decide not to take part in this study, you have other choices for your care. For example:

- you may choose to have the usual approach described above
- you may choose to take part in a different research study, if one is available
- you may choose not to be treated for cancer but you may want to receive comfort care [palliation] to relieve symptoms

Why is this study being done?

Given that there are multiple treatment approaches now available for patients with advanced melanoma that contains a mutation in the BRAF protein, patients have a choice which treatment to receive first and therefore the potential sequence of treatments. Currently there is no data on which treatment approach (initial treatment or sequence of treatments) yields the best outcome for a given patient or group of patients.

The purpose of this research study is to compare the good and bad effects of the sequence of immunotherapy followed by BRAF inhibitor therapy if and when the disease becomes resistant, to the sequence of BRAF inhibitor therapy followed by immunotherapy if and when the disease becomes resistant. The BRAF inhibitor component will include the combination of two drugs dabrafenib and trametinib that each have been approved by the FDA for the treatment of this patient population and have also been approved for use in combination due to superior effects relative to the single agent treatments. In addition, the study will involve the combination of FDA approved agents nivolumab and ipilimumab immunotherapy in the hopes that it might further improve the good effects of the immunotherapy component of the treatment sequence. The combination of ipilimumab and nivolumab has been shown in recent studies to produce superior antitumor effects but also more side effects than ipilimumab alone and nivolumab alone. An alternative dosing ratio of the nivolumab and ipilimumab will also be tested in this study. The alternative schedule has been shown to have less toxicity and nearly equivalent efficacy to the standard approved regimen, but as it is not itself FDA approved, it is considered "experimental."

This research study will allow the investigators to determine which sequence of treatment has the best outcome for patients. To be better, one sequence should significantly improve the number of patients alive at 2 and 3 years from start of treatment relative to the alternative sequence. There will be about 300 people taking part in this study.

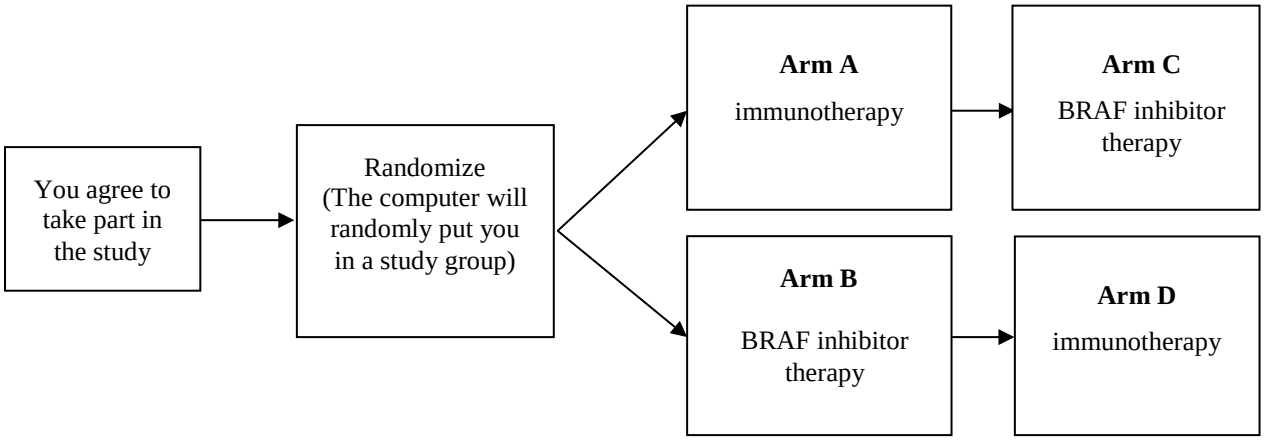
What are the study arms?

This research study has two treatment regimens, with a potential to crossover from one to the other. Arm A will receive the study drugs ipilimumab and nivolumab first, and at time of disease progression will crossover to Arm C to receive the study drugs dabrafenib and trametinib. Arm B will receive the study drugs dabrafenib and trametinib first, and at time of disease progression will crossover to Arm D to receive the study drugs ipilimumab and nivolumab.

- Ipilimumab will be given intravenously (through a vein in your arm) once on day 1 and 22 of cycles 1 and 2 (Induction period).
- Nivolumab will be given intravenously (through a vein in your arm) once on day 1 and 22 of cycles 1 and 2 (Induction period), then on day 1, 15, 29 of cycles 3 to 14 (Maintenance period).
- Dabrafenib will be taken by mouth twice a day (approximately every 12 hours) on an empty stomach (at least 1 hour before or two hours after a meal).
- Trametinib will be taken by mouth once a day (approximately the same time every day) on an empty stomach (at least 1 hour before or two hours after a meal). Take with the morning or evening dose of dabrafenib.

If you are eligible for the study, a computer will assign you by chance to beginning therapy on one of the two treatment arms (A or B) in the research study. This is called randomization. This is done by chance because no one knows if one study arm is better or worse than the other.

Another way to find out what will happen to you during this research study is to read the chart below. Start reading at the left side and read across to the right, following the lines and arrows.



How long will I be in this study?

The ipilimumab/nivolumab combination will be given for a maximum of two years. The dabrafenib/trametinib combination will be given for as long as it is controlling your tumor. You will be followed for as long as you are on therapy. After you finish the treatment regimens, your doctor will continue to watch you for side effects and follow your condition for up to 5 years from registration.

What extra tests and procedures will I have if I take part in this study?

Most of the exams, tests, and procedures you will have are part of the usual care for your cancer. However, there are some extra exams, tests, and surveys (to keep track of your symptom burden and overall function) that you will need to have if you take part in this research study.

During the study:

- You will be required to fill out a medication diary if placed on Arm B or Arm C, and medication bottles must be returned
- Surveys for all patients at various timepoints
- Samples of your tumor tissue 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 for this study only. The results of this review will not be returned to the site and will not impact patient care or participation in this trial.

What possible risks can I expect from taking part in this study?

If you choose to take part in this research study, there is a risk that:

- You may lose time at work or home and spend more time in the hospital or doctor's office than usual
- You may be asked sensitive or private questions which you normally do not discuss
- The study sequence that you receive may be the same, better, or worse than the approach that your physician would have chosen for your cancer.
- There can also be a risk in finding out new genetic information about you. New health information about inherited traits that might affect you or your blood relatives could be found during a study.

The drugs used in this research study may affect how different parts of your body work, such as your liver, kidneys, heart, pituitary gland, lungs, skin and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health. These risks are described in more detail below.

There is also a risk that you could have other side effects from the study drugs.

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drugs to try to reduce side effects.

The tables below show the most common and the most serious side effects that researchers know about for each treatment combination. There might be other side effects that researchers do not yet know about, particularly those that result from the use of these standard agents in a particular sequence. If important new side effects are found, the study doctor will discuss these with you.

Study Arms A or D – People on Study Arms A or D may also experience the possible Side Effects of ipilimumab listed below.

Possible Side Effects of Ipilimumab

(Table Version Date: December 20, 2017)

Special precautions

Side effects of ipilimumab (MDX-010) may happen anytime during treatment or even after your treatment has ended. Some of these problems may happen more often when ipilimumab (MDX-010) is used in combination with BMS-936558 (nivolumab). **Call or see your healthcare provider right away if you develop any problems listed below or the symptoms get worse.**

COMMON, SOME MAY BE SERIOUS

In 100 people receiving ipilimumab (MDX-010), more than 20 and up to 100 may have:

- Diarrhea, nausea
- Tiredness

Ipilimumab (MDX-010) may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:

- Skin: itching; rash, blisters including inside the mouth (can be severe); hives

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving ipilimumab (MDX-010), from 4 to 20 may have:

- Abnormal heartbeat
- Hearing loss
- Swelling and redness of the eye
- Pain
- Difficulty swallowing, eating
- Constipation, vomiting
- Weight loss, loss of appetite
- Fever
- Dehydration
- Pain or swelling of the joints
- Reaction during or following a drug infusion which may cause fever, chills, rash
- Low blood pressure which may cause feeling faint

Ipilimumab (MDX-010) may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:

- Lung problems (pneumonitis). Symptoms may include: new or worsening cough, chest pain, shortness of breath.
- Intestinal problems (colitis) that can rarely lead to tears or holes in your intestine. Signs and symptoms of colitis may include: diarrhea or increase in bowel movements, blood in your stools or dark, tarry, sticky stools, severe belly pain or tenderness.
- Kidney problems, including nephritis and kidney failure requiring dialysis. Signs of kidney problems may include: decrease in the amount of urine, blood in your urine, ankle swelling.
- Problem of the muscle, including swelling, which can cause muscle pain and severe muscle weakness sometimes with dark urine.
- Problem of the nerves that can cause paralysis. Signs and symptoms may include: numbness, tingling of hands and feet; weakness of the arms, legs and facial muscle movement.
- Liver problems (hepatitis) which can cause liver failure. Signs and symptoms of hepatitis may include: yellowing of your skin or the whites of your eyes, severe nausea or vomiting; drowsiness; pain in the right upper belly.
- Hormone gland problems (especially the thyroid, pituitary and adrenal glands, and pancreas). Signs and symptoms may include: headaches that will not go away or unusual headaches, extreme tiredness or changes in mood or behavior decreased sex drive; weight loss or weight gain; excessive thirst or urine; dizziness or fainting.

RARE, AND SERIOUS

In 100 people receiving ipilimumab (MDX-010), 3 or fewer may have:

- Bleeding
- Blockage of the bowels which may cause constipation
- Fluid around heart
- Severe illness with multiorgan failure
- Swelling of the brain which may cause headache, blurred vision, stiff neck, and/or confusion
- Confusion

Ipilimumab (MDX-010) may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:

- A condition with high blood sugar which leads to tiredness, frequent urination, excessive thirst, headache, nausea and vomiting, and can result in coma
- Heart problems including swelling and heart failure. Symptoms and signs of heart problem may include: Shortness of breath, swelling of the ankle and body.

RARE, AND SERIOUS In 100 people receiving ipilimumab (MDX-010), 3 or fewer may have:
• Complications associated with stem cell transplant using donor stem cells (allogeneic stem cell transplant). These complications are caused by attack of donor cells on the host organs (inducing liver, skin and gut), and can lead to death. If you are considering an allogeneic stem transplant after participating in this study, please tell your doctor that you have received ipilimumab therapy, since the risk and severity of transplant-associated complications may be increased.

Study Arms A or D – In addition to side effects outlined above, people who are in Arms A or D may also experience the possible side effects of nivolumab listed below.

Possible Side Effects of Nivolumab

(Table Version Date: June 18, 2018)

Special precautions
Side effects of BMS-936558 (nivolumab, MDX-1106) may happen anytime during treatment or even after your treatment has ended. Some of these problems may happen more often when BMS-936558 (nivolumab, MDX-1106) is used in combination with ipilimumab. **Call or see your healthcare provider right away if you develop any problems listed below or the symptoms get worse.**

COMMON, SOME MAY BE SERIOUS In 100 people receiving BMS-936558 (nivolumab, MDX-1106), more than 20 and up to 100 may have:
• Tiredness

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving BMS-936558 (nivolumab, MDX-1106), from 4 to 20 may have:
• Anemia which may require blood transfusion • Swelling and redness of the eye • Pain • Diarrhea, nausea • Dry mouth • Fever • Swelling and redness at the site of the medication injection • Bruising, bleeding • Pain or swelling of the joints

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving BMS-936558 (nivolumab, MDX-1106), from 4 to 20 may have:

- Loss of appetite
- Reaction during or following a drug infusion which may cause fever, chills, rash

BMS-936558 (nivolumab, MDX-1106) may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:

- Lung problems (pneumonitis and pleural effusion). Symptoms may include: new or worsening cough, chest pain, shortness of breath.
- Intestinal problems (colitis) that can rarely lead to tears or holes in your intestine. Signs and symptoms of colitis may include: diarrhea or increase in bowel movements, blood in your stools or dark, tarry, sticky stools, severe belly pain or tenderness.
- Skin: itching; rash, blisters including inside the mouth; loss of skin pigment
- Liver problems (hepatitis) which can cause liver failure. Signs and symptoms of hepatitis may include: yellowing of your skin or the whites of your eyes, severe nausea or vomiting; drowsiness; pain in the right upper belly.
- Hormone gland problems (especially the thyroid, pituitary and adrenal glands, and pancreas). Signs and symptoms may include: headaches that will not go away or unusual headaches, extreme tiredness or changes in mood or behavior decreased sex drive; weight loss or weight gain; excessive thirst or urine; dizziness or fainting.

RARE, AND SERIOUS

In 100 people receiving BMS-936558 (nivolumab, MDX-1106), 3 or fewer may have:

- Dry eyes
- Sores in the mouth which may cause difficulty swallowing

BMS-936558 (nivolumab, MDX-1106) may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:

- Visual disturbances which may cause double vision, blurred vision, or loss of vision with a chance of blindness
- A condition with high blood sugar which leads to tiredness, frequent urination, excessive thirst, headache, nausea and vomiting, and can result in coma
- Kidney problems, including nephritis and kidney failure requiring dialysis. Signs of kidney problems may include: decrease in the amount of urine, blood in your urine, ankle swelling.
- Heart problems including swelling and heart failure. Symptoms and signs of heart problem may include: Shortness of breath, swelling of the ankle and body.

RARE, AND SERIOUS In 100 people receiving BMS-936558 (nivolumab, MDX-1106), 3 or fewer may have:
• Problem of the muscle, including swelling, which can cause muscle pain and severe muscle weakness sometimes with dark urine • Swelling of the brain (meningitis/encephalitis) which may cause: headache, stiff neck confusion, sleepiness, seizures or injury to the brain which may cause headache, seizure, blindness (also known as Reversible Posterior Leukoencephalopathy Syndrome) • Problem of the nerves that can cause paralysis. Signs and symptoms may include: numbness, tingling of hands and feet; weakness of the arms, legs and facial muscle movement • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Complications associated with stem cell transplant using donor stem cells (allogeneic stem cell transplant). These complications are caused by attack of donor cells on the host organs (inducing liver, skin and gut damage), and can lead to death. If you are considering an allogeneic stem transplant after participating in this study, please tell your doctor that you have received BMS-936558 therapy, since the risk and severity of transplant-associated complications may be increased.

Study Arms B or C- People who are in Arms B or C may also experience the possible side effects of dabrafenib listed below.

Possible Side Effects of Dabrafenib (based on CAEPR v. 2.3, May 20, 2016)

COMMON, SOME MAY BE SERIOUS In 100 people receiving dabrafenib mesylate, more than 20 and up to 100 may have:
• Nausea • Tiredness • Fever *(Fever and complications of fever are more frequent and severe when dabrafenib mesylate is used together with trametinib dimethyl sulfoxide.)* • Pain • Headache • Hair loss • Skin changes including rash, wart, thickening

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving dabrafenib mesylate, from 4 to 20 may have:
• Anemia which may require blood transfusion

OCCASIONAL, SOME MAY BE SERIOUS
In 100 people receiving dabrafenib mesylate, from 4 to 20 may have:

- Constipation, diarrhea, vomiting
- Chills
- Swelling of arms, legs
- Flu-like symptoms including body aches
- Bleeding *(The risk of bleeding is increased when dabrafenib mesylate is used together with trametinib dimethyl sulfoxide.)*
- Infection, especially when white blood cell count is low
- Loss of appetite
- A new skin cancer resulting from treatment of earlier cancer
- Dizziness
- Cough
- Dry skin
- Increased sweating
- Redness, pain or peeling of palms and soles
- Itching
- Change in hair
- Blood clot which may cause swelling, pain, shortness of breath *(The risk is increased when dabrafenib mesylate is used together with trametinib dimethyl sulfoxide.)*

RARE, AND SERIOUS
In 100 people receiving dabrafenib mesylate, 3 or fewer may have:

- Swelling and redness of the eye
- Changes in the eyes that may cause blurred vision or blindness
- Pain in belly (pancreas) that may require hospitalization
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Fainting
- Kidney damage which may cause swelling, may require dialysis *(The risk is increased when dabrafenib mesylate is used together with trametinib dimethyl sulfoxide.)*
- Swelling and redness of the skin

Study Arms B or C - In addition to the side effects listed above, people who are in Arms B or C may also experience the possible side effects of trametinib listed below.

Possible Side Effects of Trametinib (based on CAEPR v. 2.5 February 1, 2019)

COMMON, SOME MAY BE SERIOUS In 100 people receiving trametinib dimethyl sulfoxide (GSK1120212B), more than 20 and up to 100 may have:
• Diarrhea, nausea • Tiredness • Swelling of the body • Skin changes including rash, acne

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving trametinib dimethyl sulfoxide (GSK1120212B), from 4 to 20 may have:
• Anemia which may require blood transfusion • Abnormal heartbeat • Blurred vision or other visual disturbances • Dry eye, mouth, skin • Swelling of the eye • Pain • Constipation, heartburn, vomiting • Sores in the mouth which may cause difficulty swallowing • Chills, fever • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Infection • Change in heart function • Loss of appetite, dehydration • Dizziness, headache • Cough, shortness of breath • Hair loss, itching • Change in or loss of some or all of the finger or toenails • High blood pressure which may cause headaches, dizziness, blurred vision • Bleeding

RARE, AND SERIOUS In 100 people receiving trametinib dimethyl sulfoxide (GSK1120212B), 3 or fewer may have:
• Heart failure which may cause shortness of breath, swelling of ankles, and tiredness • Changes in the eyes (blood clot or retinal detachment) which may cause blindness • Blood clot which may cause swelling, pain, shortness of breath • A tear or hole in the bowels that may require surgery • Damage to muscle which may cause muscle pain, dark red urine • Damage to the lungs which may cause shortness of breath • Redness, pain or peeling of palms and soles

Let your study doctor know of any questions you have about possible side effects. You can ask the study doctor questions about side effects at any time.

Reproductive risks:

You should not become pregnant or father a baby while on this research study because the drugs in this study can affect a fetus.

If a woman becomes pregnant while on this research study or within 4 weeks after treatment with dabrafenib, or within 4 months after dabrafenib in combination with trametinib, or within 5 months after treatment with nivolumab (with or without ipilimumab), she will be asked information concerning the outcome of her pregnancy.

Women should not breastfeed a baby while on this research study.

It is important that you understand that you need to either practice “abstinence” (that is avoiding sexual activity) or use birth control while on this research 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). Dabrafenib has been shown to render ineffective hormonal birth control methods such as female use of prescribed “birth control pills” or a prescribed birth control implant therefore this cannot be used as the only means of birth control while on dabrafenib treatment. Whatever methods of birth control you choose they must be used for at least one week prior to the start of the research study and continue for at least 4 weeks after last dose of dabrafenib, 4 months after last dose of dabrafenib in combination with trametinib, and for at least 5 months after the last dose of nivolumab (with or without ipilimumab) if you are a woman of child-bearing potential, or 7 months if you are a sexually active male. 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.

What possible benefits can I expect from taking part in this study?

It is not possible to know at this time if the study approach with one or the other therapy to begin is better than the usual care for this cancer so this research study may or may not help you. But, this research study will help researchers learn things that will help people in the future.

Can I stop taking part in this study?

Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study.

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

The study doctor may take you out of the study:

- If your health changes and the study is no longer in your best interest
- If new information becomes available
- If you do not follow the study rules
- If the study is stopped by the sponsor, IRB or FDA.

What are my rights in this study?

Taking part in this research study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

For questions about your rights while in this study, you may contact the Operations Office of the National Cancer Institute (NCI) Central Institutional Review Board (CIRB) at 888-657-3711.

What are the costs of taking part in this study?

The study agents will be supplied at no charge while you take part in this research study. It is possible that one or more of the study agents may not continue to be supplied while you are on the study. Although not likely, if this occurs, your study doctor will talk to you about your options.

You and/or your health plan/insurance company will need to pay for all of the other costs of treating your cancer while in this research study, including the cost of study drug preparation and administration, tests, procedures, or medicines to manage any side effects, unless you are told that certain tests are being done at no charge. Before you decide to be in the research

study, you should check with your health plan or insurance company to find out exactly what they will pay for.

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

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

If you are injured or hurt as a result of taking part in this research study and need medical treatment, please tell your study doctor. Contact information for your study doctor is listed on the consent cover page. The study sponsors will not offer to pay for medical treatment for injury. Your insurance company may not be willing to pay for research study-related injury. If you have no insurance, you would be responsible for any costs.

If you feel this injury was a result of medical error, you keep all your legal rights to receive payment for this even though you are in a research study.

No funds have been set aside to compensate you in the event of injury.

Who will see my medical information?

Your privacy is very important to us and the researchers will make every effort to protect it. Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, the researchers will do their best to make sure that any information that is released will not identify you. Some of your health information, and/or information about your specimen, from this study will be kept in a central database for research. Your name or contact information will not be put in the database.

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

There are organizations that may inspect your records. These organizations are required to make sure your information is kept private, unless required by law to provide information. Some of these organizations are:

- Montana Cancer Consortium
- The study sponsor, ECOG-ACRIN Cancer Research Group.
- Bristol-Myers Squibb, the manufacturer of ipilimumab and nivolumab, or other pharmaceutical collaborator

- Novartis, the manufacturer of dabrafenib and trametinib, or other pharmaceutical collaborator
- The Institutional Review Board, IRB, is a group of people who review the research with the goal of protecting the people who take part in the study.
- The Food and Drug Administration and the National Cancer Institute in the U.S. and similar ones if other countries are involved in the study.

Optional Studies Section:

This section is about optional studies you can choose to take part in.

This part of the consent form is about optional studies that you can choose to take part in. You will not get health benefits from any of these studies. The researchers leading these optional studies hope the results will help other people with cancer in the future.

The results will not be added to your medical records and you or your study doctor will not know the results.

You will not be billed for these optional studies. You can still take part in the main study even if you say 'no' to any or all of these studies. If you sign up for but cannot complete any of the studies for any reason, you can still take part in the main study.

Circle your choice of "yes" or "no" for each of the following studies.

A. Tobacco Use Assessment Substudy

If you agree to participate in this study you will be asked to do an online survey regarding your tobacco use. Regardless if you have used tobacco or not, the information you provide is important to us. You will complete the survey online at 3 different timepoints (before the study treatment, 3 months after starting treatment, and 6 months after starting treatment). Each survey should take you about 6 minutes to complete. To participate, you will be asked for your email address so we can send you a link to the ECOG-ACRIN Systems for Easy Entry of Patient Reported Outcomes (EASEE-PRO).

Up to 1500 patients will be enrolled in this study.

Please read the question below and circle "Yes" or "No".

I agree to participate in the Tobacco Use Assessment Substudy.

Yes No

B. Optional Sample Collections for Laboratory Studies and/or Biobanking for Possible Future Studies

Researchers are trying to learn more about cancer and other health problems. Much of this research is done using samples of tissue, blood, urine, or other fluids. Through these studies, researchers hope to find new ways to prevent, detect, treat, or cure health problems.

Some of these studies may be about genes. Genes carry information about features that are found in you and in people who are related to you. Researchers are interested in the way that genes affect how your body responds to treatment.

If you choose to take part, we are requesting that you allow the collection and submission of blood and tissue leftover from the central review for research.

If you choose to take part, we are also requesting that you allow the storage of your leftover blood and tissue samples for future research projects that may be done at a later date. These samples will be stored in a "biobank". The Biobanks are run by ECOG-ACRIN staff and researchers and are financially supported by the National Cancer Institute.

What is involved if you provide your samples for research?

If you agree to take part, here is what will happen next:

1. About four to five (4 - 5) tablespoons of blood will be collected from a vein in your arm before you start treatment, every six (6) weeks (initial treatment and crossover), at the time of crossover, and at the time of progression (if your cancer gets worse). An additional four (4) teaspoons of blood will be collected weekly if you have severe side effects, until your side effects improve, and then weekly until you are tapered off of immunosuppressive treatment. The blood will be collected at the same time as the blood to monitor your health is collected. However, sometimes an additional stick may be done to collect the blood samples.
2. Tumor tissue leftover from the central review and laboratory research studies (described above) will be sent to the Biobank for research.
3. Your samples and some related information will be stored in the Biobanks, along with samples and information from people who took part in this or other research studies. The samples will be kept until they are used up.
4. Only qualified researchers can submit a request to use the materials stored in the Biobanks. A committee of experts at ECOG-ACRIN, and/or the National Cancer Institute, will review each request to use the samples for research. All research projects using these samples will also be reviewed by an ethics or institutional review board to ensure that the request is necessary and proper. Researchers will not be given your name or any other information that could directly identify you.
5. Neither you nor your study doctor will be notified when research will be conducted or given reports or other information about any research that is done using your samples.
6. Some of your genetic and health information may be placed in central databases that may be public, along with information from many other people. Information that could directly identify you will not be included.

What are the possible risks in providing your samples for research?

1. The most common risks related to drawing blood from your arm are brief pain and possibly a bruise.

2. There is a risk that someone could get access to the personal information in your medical records or other information researchers have stored about you.
3. There is a risk that someone could trace the information in a central database back to you. Even without your name or other identifiers, your genetic information is unique to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information.
4. In some cases, this information could be used to make it harder for you to get or keep a job or insurance. There are laws against the misuse of genetic information, but they may not give full protection. There can also 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 study. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.

When my samples are used for research, how will information about me be kept private?

Your privacy is very important to the researchers and they will make every effort to protect it. Here are just a few of the steps they will take:

1. When your samples are sent to the researchers, no information identifying you (such as your name) will be sent. Samples will be identified by a unique code only.
2. The list that links the unique code to your name will be kept separate from your samples and health information. Any Biobank and ECOG-ACRIN Cancer Research Group staff with access to the list must sign an agreement to keep your identity confidential.
3. Researchers to whom ECOG-ACRIN Cancer Research Group sends your samples and information will not know who you are. They must also sign an agreement that they will not try to find out who you are.
4. Information that identifies you will not be given to anyone, unless required by law.
5. If research results are published, your name and other personal information will not be used.

What are the Possible Benefits of allowing my samples to be used for research?

You will not benefit from taking part. The researchers, using the samples from you and others, might make discoveries that could help people in the future.

Are there any costs or payments associated with providing my samples for research?

There are no costs to you or your insurance. You will not be paid for taking part. If any of the research leads to new tests, drugs, or other commercial products, you will not share in any profits.

What if I change my mind about allowing my samples to be used for research?

If you decide you no longer want your samples to be used, you can call the study doctor, who will let the researchers know. Contact information for your study doctor is listed on the

consent cover page. Then, any samples that remain in the Biobank will no longer be used and related health information will no longer be collected. Samples or related information that have already been given to or used by researchers will not be returned.

What if I have more questions?

If you have questions about the use of your samples for research, contact the study doctor. Contact information for your study doctor is listed on the consent cover page.

Please circle your answer to show whether or not you would like to take part in each option:

Samples for use in laboratory research studies:

May we have samples of your blood and tissue for laboratory research studies?

I agree to have my samples collected and I agree that my samples and related information may be used for the laboratory studies described above.

YES NO

Samples for use in future research studies:

May we keep any blood and tissue leftover after the central review and laboratory research studies for future research?

My samples and related information may be kept in a Biobank for use in future health research.

YES NO

This is the end of the section about optional studies.

Where can I get more information?

You may visit the NCI Web site at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Who can answer my questions about this study?

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact information for your study doctor is listed on the consent cover page.

Signature:

This study has been explained to me, and I have been told what my enrollment in the study involves. I have read all pages of this consent and have had my questions answered to my satisfaction at this time. I consent to participate in this study and any additional studies where I circled 'yes'. I understand that by signing this form I have not given up any of my legal rights. I will be given a copy of this consent form. I may also request a copy of the protocol (full study plan).

Participant Signature: _____

Date: _____

Signature of Person Obtaining Consent: _____

Date: _____

Time of consent: _____ (AM) (PM)
(Required for initial consent only)