Research study informed Consent Documentation

Study Title for Participants: Testing the addition of the pill chemotherapy, Cabozantinib, to the standard immune therapy Nivolumab compared to standard chemotherapy for non-squamous non-small cell lung cancer

Official Study Title for Internet Search on http://www.ClinicalTrials.gov:
EA5191, A Randomized Phase II Trial of Cabozantinib and Cabozantinib Plus Nivolumab Versus Standard Chemotherapy in Patients with Previously Treated Non-Squamous NSCLC (NCT04310007)

Version Date: November 8, 2024

Overview and Key Information

What am I being asked to do?

We are asking you to take part in a research study. This study has public funding from the National Cancer Institute (NCI), part of the National Institutes of Health (NIH) in the United States Department of Health and Human Services. We do research studies to try to answer questions about how to prevent, diagnose, and treat diseases like cancer.

You are being asked to take part in this research study because you have advanced non-squamous non-small cell lung cancer which has either grown or has recurred.

Taking part in this study is your choice.

You can choose to take part or you can choose not to take part in this study. You also can change your mind at any time. Whatever choice you make, you will not lose access to your medical care or give up any legal rights or benefits.

This document has important information to help you make your choice. Take time to read it. Talk to your doctor, family, or friends about the risks and benefits of taking part in the study. It's important that you have as much information as you need and that all your questions are answered. See the "Where can I get more information?" section for resources for more clinical trials and general cancer information.

Why is This Study Being Done?

This study is being done to answer the following question:

Can we lower the chance of your lung cancer from growing or spreading with an oral drug called cabozantinib? In this study, we are testing cabozantinib by itself and also with the immune drug, nivolumab.

We are doing this study because we want to find out if this approach is better or worse than the usual approach for your lung cancer. The usual approach is defined as care most people get for lung cancer, and for this study is chemotherapy given intravenously (IV).

What is the usual approach to my Non-Squamous NSCLC?

The usual treatment approach for patients being treated for second-line NSCLC is treatment with FDA approved chemotherapy such as docetaxel with or without ramucirumab, or other single agent chemotherapy agents. The usual treatment approach for patients with tumors with mutations in ROS1, RET, or MET can also include targeted pill therapy. It may also include platinum-based combination chemotherapy (such as carboplatin or cisplatin, and a second chemotherapy drug such as pemetrexed, paclitaxel, or gemcitabine) and/or immunotherapy (such as nivolumab, pembrolizumab, or atezolizumab) for patients that have not received these treatments before.

What are my choices if I decide not to take part in this study?

- 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.
- You may choose to only get comfort care to help relieve your symptoms and not get treated for your cancer.

What will happen if I decide to take part in this study?

If you decide to take part in this study, you will either get cabozantinib daily, a combination of cabozantinib daily with nivolumab every three weeks, or the standard chemotherapy until your tumor grows or you have symptoms serious enough to come off treatment.

After you finish your study treatment, your doctor will continue to follow your condition for 3 years and watch you for side effects. You will be followed every 3 months by either an office visit or telephone call.

What are the risks and benefits of taking part in this study?

There are both risks and benefits to taking part in this study. It is important for you to think carefully about these as you make your decision.

Risks

We want to make sure you know about a few key risks right now. We give you more information in the "What risks can I expect from taking part in this study?" section.

If you choose to take part in this study, there is a risk that the study approach may not be as good as the usual approach for your cancer preventing your cancer from coming back.

There is also a risk that you could have side effects from the study drugs. These side effects may be worse and may be different than you would get with the usual approach for your cancer.

Some of the most common side effects that the study doctors know about are:

- Loose, watery stools or diarrhea, usually manageable by using other medications or stopping the drug
- Tiredness
- Decreased appetite, nausea, or vomiting
- Skin changes including rash and peeling of the hands or soles
- Bleeding or blood clots

There may be some risks that the study doctors do not yet know about.

Benefits

There is evidence that this study approach is effective in shrinking your type of cancer. It is not possible to know now if the study drugs will extend your time without disease compared to the usual approach. This study will help the study doctors learn things that will help people in the future.

If I decide to take part in this study, can I stop later?

Yes, you can decide to stop taking part in the study at any time.

If you decide to stop, let your study doctor know as soon as possible. It's important that you stop safely. If you stop, you can decide if you want to keep letting the study doctor know how you are doing.

Your 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.

Are there other reasons why I might stop being in the study?

Yes. The study doctor may take you off the study if:

- Your health changes and the study is no longer in your best interest.
- New information becomes available and the study is no longer in your best interest.
- You do not follow the study rules.
- For women: You become pregnant while on the study.

- The study is stopped by the National Cancer Institute (NCI), Institutional Review Board (IRB), Food and Drug Administration (FDA), or study sponsor (ECOG-ACRIN). The study sponsor is the organization who oversees the study.

It is important that you understand the information in the informed consent before making your decision. Please read, or have someone read to you, the rest of this document. If there is anything you don't understand, be sure to ask your study doctor or nurse.

What is the purpose of this study?

The purpose of this study is to compare the two investigational treatments (cabozantinib alone to using cabozantinib plus the usual treatment nivolumab) to the current standard of care second line therapy. We know from prior studies that the pill therapy cabozantinib can control the growth of NSCLC by itself, but it is possible that it will work better by adding immunotherapy with nivolumab. The FDA approved treatment options for NSCLC after prior chemotherapy and immunotherapy includes chemotherapy with docetaxel, with or without ramucirumab. Other standard of care chemotherapies include gemcitabine, paclitaxel, and nab-paclitaxel. The addition of cabozantinib to the usual treatment (nivolumab) could shrink your cancer and/or prevent it from growing for a period of time. But, it could also cause side effects, which are described in the risks section below.

This study will help the study doctors find out if either treatment with cabozantinib, or treatment with cabozantinib plus nivolumab, is better, or the same as, the standard chemotherapy approach. To decide if it is better, the study doctors will be looking to see if either of these study treatments control cancer growth in patients for a longer time than the standard chemotherapy.

There will be about 117 people taking part in this study.

What are the study groups?

This study has 3 randomized study groups, Groups A, B and C. You will be told which group you are in.

- **Group A**

  If you are in this group, you will get the investigational pill therapy being studied in this type of cancer, cabozantinib. You will get this drug as a pill you take by mouth each day. You will receive a pill calendar to track your daily dose of cabozantinib. Take cabozantinib tablet(s) on an empty stomach – do not eat 2 hours before or 1 hour after each dose of cabozantinib. Do not crush or chew. Swallow the tablet(s) whole.

  Carbozantinib is not approved by the FDA for treatment of your disease.

  There will be about 39 people in this group.

  You will continue this therapy as long as your tumor remains controlled and your side effects are manageable.

- **Group B**

  If you are in this group, you get the investigational pill therapy being studied in this type

of cancer, cabozantinib, plus immunotherapy, nivolumab. You will get nivolumab by an IV infusion over 30 minutes every 3 weeks and you will get cabozantinib as a pill you take by mouth each day. You will receive a pill calendar to track your daily dose of cabozantinib. Take cabozantinib tablet(s) on an empty stomach – do not eat 2 hours before or 1 hour after each dose of cabozantinib. Do not crush or chew. Swallow the tablet(s) whole.

Cabozantinib is not approved by the FDA for treatment of your disease.

Nivolumab is approved by the FDA for treatment of your disease, but is unlikely to work by itself after prior immunotherapy

There will be about 39 people in this group.

You will continue this therapy as long as your tumor remains controlled and your side effects are manageable.

- **Group C**

  If you are in this group, you will get the standard chemotherapy regimen used to treat this type of cancer. The standard chemotherapy drugs and dosing schedule will be your treating physician's choice. The standard chemotherapy regimen used to treat this type of cancer has two options: the first is a combination of the drugs docetaxel and ramucirumab and the second option is the treating physician's choice for dosing and schedule of the drugs, docetaxel, gemcitabine, paclitaxel, or nab-paclitaxel. You will get these drugs intravenously (IV), but the schedule will be different based on what your treating physician chooses.

  These drugs are approved by the FDA for treatment of your disease, but only docetaxel with or without ramucirumab are specifically approved for second line treatment of NSCLC.

  There will be about 39 people in this group.

  We will use a computer to assign you to one of the study groups. This process is called "randomization." It means that your doctor will not choose and you cannot choose which study group you are in. You will be put into a group by chance. You will have an equal chance of being in Group A, Group B, or Group C.

  You will continue this therapy as long as your tumor remains controlled and your side effects are manageable. If your tumor does grow you may be eligible to receive study treatment in Group Z (below).

- **Group Z**

  This group is for patients whose cancer grows on standard chemotherapy (Group C) and are willing to continue on this study and receive the study therapy. We sometimes call this a "crossover" group. To participate, you must have been treated in Group C then have evidence of tumor growing in your body, but not in your brain. Additionally, you must still have good overall energy and good organ function, and recovered from side effects of chemotherapy. You can not have other treatments between treatment in Group C and treatment in Group Z, and need to be registered by your team for participation within 7 weeks of your last treatment.

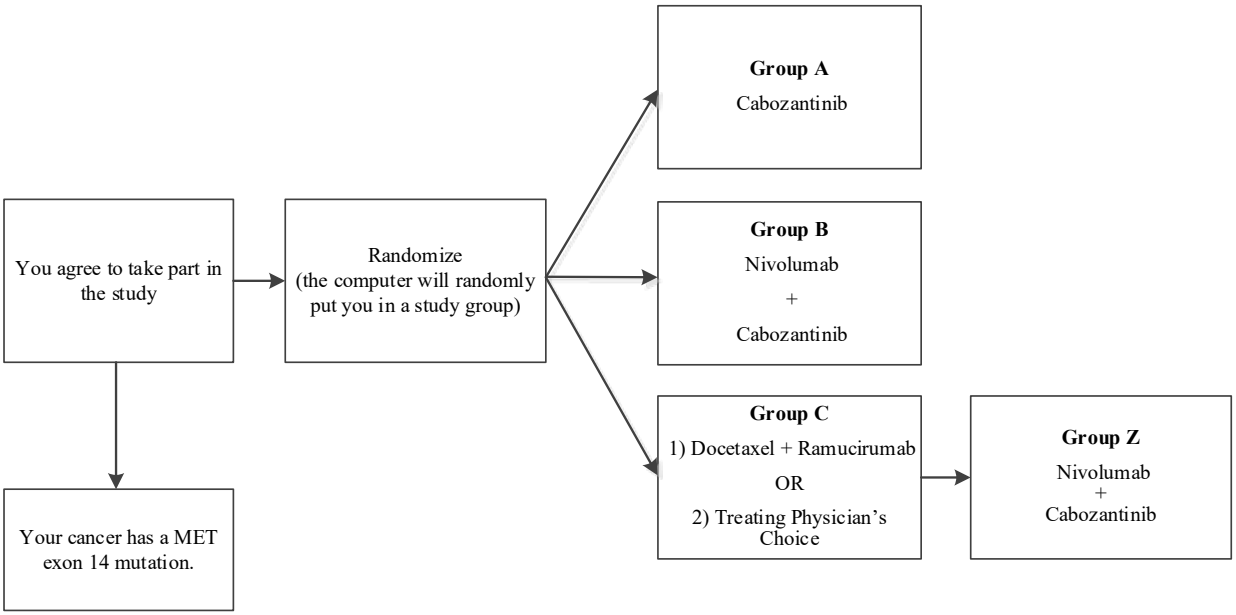
If you are in this group, you get the investigational pill therapy being studied in this type of cancer, cabozantinib, plus immunotherapy, nivolumab. You will get nivolumab by an IV infusion over 30 minutes every 3 weeks and you will get cabozantinib as a pill you take by mouth each day. You will receive a pill calendar to track your daily dose of cabozantinib. Take cabozantinib tablet(s) on an empty stomach – do not eat 2 hours before or 1 hour after each dose of cabozantinib. Do not crush or chew. Swallow the tablet(s) whole.

Cabozantinib is not approved by the FDA for treatment of your disease. Nivolumab is approved by the FDA for treatment of your disease.

There will be about 39 or fewer people in this group.

You will continue this therapy as long as your tumor remains controlled and your side effects are manageable.

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



What exams, tests, and procedures are involved in this study?

Before you begin the study, your doctor will review the results of your exams, tests, and procedures. This helps your doctor decide if it is safe for you to take part in the study. If you join the study, you will have more exams, tests, and procedures to closely monitor your safety and health. Most of these are included in the usual care you would get even if you were not in a study.

Listed below are exams, tests, and procedures that need to be done as part of this study to monitor your safety and health, but may not be included in the usual care. We will use them to carefully follow the effects of the study treatment, including preventing and managing side effects.

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These exams, tests, and procedures to monitor your safety and health may include:

- Echocardiogram (ECHO) or heart function test before beginning the treatment.
- Electrocardiogram (ECG) done before beginning the treatment, and during treatment only as clinically necessary.
- Thyroid testing done before beginning the treatment and every cycle as clinically necessary for participants on Arms A and B. This is also recommended for participants on Arm C, but not required by the study.

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

General Risks

If you choose to take part in this study, there is a risk that the study approach may not be as good as the usual approach for your cancer at preventing your cancer from coming back.

You also may have the following discomforts:

- Spend more time in the hospital or doctor's office.
- Be asked sensitive or private questions about things you normally do not discuss.
- May not be able to take part in future studies.

The study drugs used in this study could be very harmful to an unborn or newborn baby. There may be some risks that doctors do not yet know about. It is very important that you check with your study doctor about what types of birth control or pregnancy prevention to use during the study and up to 6 months after you have completed the study.

This study will use a sample of your tissue. Generally, your hospital will keep some of your tissue. This tissue may be used to help treat your cancer in the future. Because this study will need to use some of this tissue, there is a small risk that it could be used up.

Genetic Testing Risks

As part of this study, we are also studying a genetic test. The test is designed to find out if your tumor has the genetic changes that are needed for this study. If it does, we will assign you to a study group based on the genetic changes in your tumor.

Because this genetic test is still being studied, there is a risk that the test results may be wrong. If the test results are wrong, you may be included in this study even though it may not offer the best treatment option for you. Or, you may not be included in this study even though it may offer a good treatment option for you.

The exploratory research in this study may test your tumor, normal tissue, and blood for genetic changes. Changes found in your normal tissue may be passed down in families. For example, these genetic changes may be passed down to your children in the same way that eye and hair color are passed down.

Genetic tests of normal tissue can reveal information about you and also about your relatives. Your doctor will talk with you about what the tests results may mean for you and your family. He or she also may suggest you talk with a genetics counselor to learn more. You or

your insurance plan would have to pay for visits to a genetic counselor.

Side Effect Risks

The drugs used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will test your blood and let you know if changes occur that may affect your health.

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

Here are important things to know about side effects:

1. The study doctors do not know who will or will not have side effects.
2. Some side effects may go away soon, some may last a long time, and some may never go away.
3. Some side effects may make it hard for you to have children.
4. Some side effects may be mild. Other side effects may be very serious and even result in death.

You can ask your study doctor questions about side effects at any time. Here are important ways to make side effects less of a problem:

- If you notice or feel anything different, tell your study doctor. He or she can check to see if it is a side effect.
- Your study doctor will work with you to treat your side effects.
- Your study doctor may adjust the study drugs to try to reduce side effects.

This study is looking at a combination of the usual drugs used to treat this type of cancer plus a study drug. This different combination of drugs may increase your side effects or may cause new side effects.

Drug Risks

The tables below show the most common and most serious side effects doctors know about. Keep in mind that there might be other side effects doctors do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Study Groups A, B, and Z – Possible side effects of nivolumab and cabozantinib are listed in the tables below. Nivolumab is part of the usual approach for treating this type of cancer:

Possible Side Effects of Nivolumab

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Risk Profile for Nivolumab (Table Version Date: June 10, 2023)

Special precautions
Side effects of Nivolumab may happen anytime during treatment or even after your treatment has ended. Some of these problems may happen more often when Nivolumab 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 Nivolumab, more than 20 and up to 100 may have:

- Tiredness

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving Nivolumab, 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
- Loss of appetite
- Reaction during or following a drug infusion which may cause fever, chills, rash

Nivolumab 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 Nivolumab, 3 or fewer may have:

- Swelling of arms and legs which may cause a feeling of heaviness and tightness
- Dry eyes

RARE, AND SERIOUS

In 100 people receiving Nivolumab, 3 or fewer may have:

- Sores in the mouth which may cause difficulty swallowing
- A syndrome starting with flu-like symptoms and followed by swelling, tenderness which may cause flu-like symptoms, blurred vision, ringing in the ears, changes in hair or hair loss
- Swelling of the bowels

Nivolumab 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.
- 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 Nivolumab therapy, since the risk and severity of transplant-associated complications may be increased.

Possible Side Effects of Cabozantinib

Risk Profile for XL184 (Cabozantinib) (Table Version Date: August 29, 2024)

COMMON, SOME MAY BE SERIOUS In 100 people receiving cabozantinib, more than 20 and up to 100 may have:
• Diarrhea, nausea, vomiting • Tiredness • Weight loss, loss of appetite • Changes in taste • Redness, pain or peeling of palms and soles • High blood pressure which may cause headaches, dizziness, blurred vision

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OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving cabozantinib, from 4 to 20 may have:
• Anemia which may require blood transfusion • Pain • Constipation, heartburn • Dry mouth, skin • Sores in mouth which may cause difficulty swallowing • Swelling of arms, legs • Infection • Bruising, bleeding • Dehydration • Muscle weakness • In children or adolescents: may interfere with growth • Dizziness, headache • Cough, shortness of breath • Internal bleeding which may cause black tarry stool, blood in vomit, coughing up blood, or blood in urine • Bleeding from multiple sites including the nose • Changes in voice • Hair loss, rash • Change in hair color • Blood clot which may cause swelling, pain, shortness of breath

RARE, AND SERIOUS In 100 people receiving cabozantinib, 3 or fewer may have:
• A tear or hole in internal organs that may require surgery • Non-healing surgical site • Damage to the jaw bone which may cause loss of teeth • Bleeding in the brain which may cause confusion • Stroke which may cause paralysis, weakness • Brain damage which may cause headache, seizure, blindness (also known as Reversible Posterior Leukoencephalopathy Syndrome) • Lung collapse

Study Group C - In addition to side effects listed above, people who are in Group C may also have some side effects from the chemotherapy drugs, docetaxel, ramucirumab, gemcitabine, paclitaxel, or nab-paclitaxel. These drugs are part of the usual approach for treating this type of cancer and the risks should be discussed with your treating physician.

Possible Side Effects of Paclitaxel Protein-Bound Particles

(Table Version Date: September 26, 2017)

COMMON, SOME MAY BE SERIOUS In 100 people receiving Paclitaxel protein-bound particles, more than 20 and up to 100 may have:
• Swelling of the body • Infection, especially when white blood cell count is low which can be serious • Bruising, bleeding • Anemia, which may cause tiredness, or may require blood transfusions • Diarrhea, nausea, vomiting, or loss of appetite • Numbness and tingling of the arms and legs, muscle weakness • Fever • Tiredness • Dehydration • Hair loss, rash

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Paclitaxel protein-bound particles, from 4 to 20 may have:
• Heart stops beating • Mini stroke

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Paclitaxel protein-bound particles, from 4 to 20 may have:
• Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Abnormal heartbeat • Blood clot which may cause swelling, pain, shortness of breath • Damage to the lungs which may cause shortness of breath • Cloudiness of the eye, visual disturbances • Pain • Constipation • Paralysis, weakness, headache • Numbness and tingling of the arms and legs • Hoarseness

RARE, AND SERIOUS In 100 people receiving Paclitaxel protein-bound particles, 3 or fewer may have:
• None

Possible Side Effects of Paclitaxel

(Table Version Date: September 26, 2017)

COMMON, SOME MAY BE SERIOUS In 100 people receiving Paclitaxel, more than 20 and up to 100 may have:
• Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Infection, especially when white blood cell count is low • Bruising, bleeding • Anemia which may cause tiredness, or may require blood transfusions • Pain • Sores in mouth which may cause difficulty swallowing • Diarrhea, nausea, vomiting • Muscle weakness • Numbness, tingling or pain of the arms and legs • Hair loss

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Paclitaxel, from 4 to 20 may have:
• Abnormal heartbeat • Blood clot which may cause swelling, pain, shortness of breath • Damage to the lungs which may cause shortness of breath

RARE, AND SERIOUS In 100 people receiving Paclitaxel, 3 or fewer may have:
• Heart attack or heart failure which may cause shortness of breath, swelling of ankles, and tiredness • A tear or a hole in the bowels which may cause pain or that may require surgery • Severe skin rash with blisters and peeling which can involve mouth and other parts of the body

Possible Side Effects of Gemcitabine

(Table Version Date: October 18, 2021)

COMMON, SOME MAY BE SERIOUS In 100 people receiving Gemcitabine, more than 20 and up to 100 may have:
• Swelling of arms, legs, and body • Shortness of breath • Infection, including in the blood, especially when white blood cell count is low • Bruising, bleeding • Anemia which may cause tiredness, or may require blood transfusions • Blood in urine • Sores in mouth which may cause difficulty swallowing • Nausea, vomiting, diarrhea, constipation • Flu-like symptoms of muscle pain, fever, headache, chills and fatigue • Burning, numbness, tingling or "pins and needles" feelings • Difficulty sleeping • Rash, itching • Hair loss

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Gemcitabine, from 4 to 20 may have:
• Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Damage to the lungs and/or fluid around the lungs, which may cause shortness of breath, cough • Weight loss, loss of appetite

RARE, AND SERIOUS In 100 people receiving Gemcitabine, 3 or fewer may have:
• Heart failure or heart attack which may cause chest pain, shortness of breath, swelling of ankles, and tiredness • Stroke which may cause paralysis, weakness, headache • Liver damage which may cause yellowing of eyes and skin, swelling

Possible Side Effects of Docetaxel

(Table Version Date: April 29, 2021)

COMMON, SOME MAY BE SERIOUS In 100 people receiving Docetaxel, more than 20 and up to 100 may have:
• Swelling of the body • Infection, especially when white blood cell count is low • Anemia which may require blood transfusions • Vomiting, diarrhea, nausea • Sores in mouth which may cause difficulty swallowing • Tiredness • Fever • Pain in muscles • Watering, itchy eyes • Hair loss • Change in nails • Rash, itching

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OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Docetaxel, from 4 to 20 may have:
• Abnormal heart rate

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Docetaxel, from 4 to 20 may have:
• Chest pain • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Bruising, bleeding • Liver damage, which may cause yellowing of eyes and skin, swelling • Constipation, bloating, weight loss • Numbness, pain, and/or tingling of the arms and legs, fingers, and/or toes • Change in taste

RARE, AND SERIOUS In 100 people receiving Docetaxel, 3 or fewer may have:
• Damage of the bone marrow, caused by chemotherapy, which may lead to cancer of bone marrow (leukemia) • Stevens-Johnson syndrome which may cause severe skin rash with blisters and peeling which can involve mouth and other parts of the body

Patients should be aware that Docetaxel may cause them to become intoxicated from the alcohol it contains. Patients should avoid driving, operating machinery, or performing other activities that are dangerous within one to two hours after the infusion of Docetaxel. In addition, some medications, such as pain relievers and sleep aids, may interact with the alcohol in the Docetaxel infusion and worsen the intoxicating effects.

Possible Side Effects of Ramucirumab

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving ramucirumab, from 4 to 20 may have:
• Anemia which may cause tiredness, or may require blood transfusion • Infection, especially when white blood cell count is low • Bruising • High blood pressure which may cause headaches, dizziness, or blurred vision • Swelling of arms or legs • Loss of appetite • Diarrhea • Sores in the mouth • Tiredness • Reaction during or following infusion of the drug which may cause fever, chills, rash, or low blood pressure

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving ramucirumab, from 4 to 20 may have:
• Headache • Nose bleed • Rash • Redness, pain or peeling of palms and soles • Bleeding

RARE, AND SERIOUS In 100 people receiving ramucirumab, 3 or fewer may have:
• Heart attack which may cause chest pain or shortness of breath • Heart stops beating • Stroke which may cause paralysis, weakness or headache • Blockage of the bowels which may cause pain, or vomiting • Internal bleeding which may cause blood in vomit • A tear or hole in the stomach and/or bowel which may cause pain and may require surgery • Damage to the liver which may cause damage to the kidneys, pain, bleeding, or confusion • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, or swelling of the face or throat • Severe blood infection • Reversible damage to the brain which may cause tiredness or changes in thinking

Additional Drug Risks

The study drug could interact with other drugs. Sometimes this can affect the levels of either drug in your body.

The study drug could interact with other drugs and food. Some foods like grapefruit juice. Drugs like Warfarin and Clopidogrel are not allowed to be taken.

Rarely, there are problems getting enough supplies of the study drug. If that happens, your doctor will talk with you about your options.

Inform your research healthcare team of over-the-counter products, herbal medicines/tea, and other prescribed drugs that you may have or about to buy. You will also be provided with a clinical trial wallet card that you need to carry with you at all time. Share the information that is in the clinical trial wallet card with your regular healthcare providers (example: doctor, nurse, pharmacist).

Imaging Risks

The CT, FDG-PET/CT, or MRI that you get in this study will expose you to low amounts of radiation. Every day, people are exposed to low levels of radiation that come from the sun and the environment around them. This type of radiation is called "background radiation." No one knows for sure whether exposure to these low amounts of radiation is harmful to your body.

The CT, FDG-PET/CT, or MRI that you get in this study will expose you to more radiation than you get from everyday background radiation. Most of the time, this amount of extra radiation is not harmful to you. However, scientists believe that being exposed to too much radiation can cause harmful side effects. This could include getting a new cancer. We estimate that this could happen in about 1 out of every 1000 people who get a very large amount of extra radiation.

As part of the CT that you get in this study, iodine will be injected into your vein. Some people are allergic to iodine. Let your study doctor know if you have an allergy to iodine or seafood or if you have kidney problems.

What are my responsibilities in this study?

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

- Keep your study appointments.
- Tell your doctor about:
  - all medications and supplements you are taking
  - any side effects
  - any doctors' visits or hospital stays outside of this study
  - if you have been or are currently in another research study.
- Write down in your pill calendar when you take the study drug at home.
- Participants must keep the wallet card with them to show providers as needed.
- Participants will be responsible for additional testing.

For women: Do not get pregnant or breastfeed while taking part in this study. **For men:** Do not father a baby while taking part in this study. **For all:** Tell your study doctor right away if you think that you or your partner have become pregnant during the study and for 6 months after the last dose of study drug.

What are the costs of taking part in this study?

You and/or your insurance plan will need to pay for the costs of medical care you get as part of the study, just as you would if you were getting the usual care for your cancer. This includes:

- the costs of tests, exams, procedures, and drugs that you get during the study to monitor your safety, and prevent and treat side effects.
- the costs of getting the study drugs ready and giving them to you.

- your insurance co-pays and deductibles.

Talk to your insurance provider and make sure that you understand what your insurance pays for and what it doesn't pay for if you take part in this clinical trial. Also, find out if you need approval from your plan before you can take part in the study.

Ask your doctor or nurse for help finding the right person to talk to if you are unsure which costs will be billed to you or your insurance provider.

You or your insurance provider will not have to pay for the cabozantinib and nivolumab while you take part in this study.

Rev. Add3 You and/or your insurance provider will not have to pay for the baseline ECG performed prior to randomization.

Taking part in this study may mean that you need to make more visits to the clinic or hospital than if you were getting the usual approach to treat your cancer. You may:

- Have more travel costs.
- Need to take more time off work.
- Have other additional personal costs.

You will not be paid for taking part in this study. The research may lead to new tests, drugs, or other products for sale. If it does, you will not get any payment.

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

If you are injured as a result of taking part in this study and need medical treatment, please talk with your study doctor right away about your treatment options. The study sponsors will not pay for medical treatment for injury. Your insurance company may not be willing to pay for a study-related injury. Ask them if they will pay. If you do not have insurance, then you would need to pay for these medical costs.

If you feel this injury was caused by medical error on the part of the study doctors or others involved in the study, you have the legal right to seek payment, even though you are in a study. Agreeing to take part in this study does not mean you give up these rights.

Who will see my medical information?

Your privacy is very important to us. The study doctors will make every effort to protect it. The study doctors have a privacy permit to help protect your records if there is a court case. However, some of your medical information may be given out if required by law. If this should happen, the study doctors will do their best to make sure that any information that goes out to others will not identify who you are.

Some of your health information, such as your response to cancer treatment, results of study tests, and medicines you took, will be kept by the study sponsor in a central research database. However, your name and contact information will not be put in the database. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

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

Some of these organizations are:

- The study sponsor and any drug company supporting the study now or in the future. This would include any organization helping the company with the study.
- The NCI Central IRB, which is a group of people who review the research with the goal of protecting the people who take part in the study.
- The FDA and the groups it works with to review research.
- The NCI and the groups it works with to review research.
- The NCI's National Clinical Trials Network and the groups it works with to conduct research including the Imaging and Radiation Oncology Core (IROC).

In addition to storing data in the study database, data from studies that are publicly funded may also be shared broadly for future research with protections for your privacy. The goal of this data sharing is to make more research possible that may improve people's health. Your study records may be stored for future use in public databases. However, your name and other personal information will not be used.

Some types of future research may include looking at your information and information from other patients to see who had side effects across many studies or comparing new study data with older study data. However, right now we don't know what research may be done in the future using your information. This means that:

- You will not be asked if you agree to take part in the specific future research studies using your health information.
- You and your study doctor will not be told when or what type of research will be done.
- You will not get reports or other information about any research that is done using your information.

There are laws that protect your genetic information. However, there is a risk that someone could get access to your genetic information and identify you by name. In some cases, employers could use your genetic information to decide whether to hire or fire you. The study doctors believe the risk of this happening is very small. However, the risk may increase in the future as people find new ways of tracing information. For more information about the laws that protect you, ask your study doctor.

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.

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 the study doctor _____ (*insert name of study doctor[s]*) at _____ (*insert telephone number, and email address if appropriate*).

For questions about your rights while in this study, call the (*insert name of organization or center*) Institutional Review Board at (*insert telephone number*).

Optional studies that 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. They are separate from the main study described above. These optional studies will not benefit your health. The researchers leading this optional study hope the results will help other people with your condition in the future. The results will not be added to your medical records and you or your study doctor will not know the results.

Taking part in these optional studies is your choice. You can still take part in the main study even if you say "no" to any or all of these studies. There is no penalty for saying "no." You and your insurance company will not be billed for these optional studies. If you sign up for, but cannot complete any of these studies for any reason, you can still take part in the main study.

Optional Sample Collections for Bio-banking for Possible Future Studies

Researchers are trying to learn more about cancer and other health problems using blood and tissue samples from people who take part in clinical trials. By studying these samples, researchers hope to find new ways to prevent, detect, treat, or cure diseases.

Some of these studies may be about how genes affect health and disease. Other studies may look at how genes affect a person's response to treatment. Genes carry information about traits that are found in you and your family. Examples of traits are the color of your eyes, having curly or straight hair, and certain health conditions that are passed down in families. Some of the studies may lead to new products, such as drugs or tests for diseases.

Unknown future studies

If you choose to take part in this optional study, a sample of tissue from your previous diagnostic biopsy and blood will be collected and stored. Storing samples for future studies is called "bio-banking." The biobank is being run by ECOG-ACRIN and is supported by the NCI. This is a publicly funded study. Samples from publicly funded studies are required to be shared as broadly as possible. However, we will protect your privacy. The goal of this is to make more research possible that may improve people's health.

The biobank is a public research resource. It has controlled access. This means that researchers who want to get samples and data from it must submit a specific research request. The request identifies who they are and what their planned research project is. Before getting the samples and data, the researchers must agree to keep the data private, only use it for their planned research project, and never use it to try to identify you. Also, any health-related information, such as your response to cancer treatment, results of study tests, and medicines you took, will be stored for future use.

Right now, we don't know what research may be done in the future using your tissue and/or blood samples. This means that:

- You will not be asked if you agree to take part in the future research studies.
- You and your study doctor will not be told when or what type of research will be done.
- You will not get reports or other information about any research that is done using your samples.

Unknown future research studies may include sequencing of all or part of your DNA. This is called genomic sequencing. Sequencing allows researchers to identify your genetic code. Changes in your genetic code may just be in your tumor tissue. These are called somatic changes. Changes may also be in your normal tissue and passed down through your family. For example, these genetic changes may be passed down to your children in the same way that eye and hair color are passed down. These are called germline changes.

If only tumor tissue is sequenced, we will not know if a genetic change in your tumor is also in your normal tissue. This is why sometimes both normal tissue and tumor tissue are sequenced. This helps researchers understand if a genetic change happened only in your cancer tissue, or in your normal tissue as well.

What is involved in this optional sample collection?

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

1. Tumor tissue that was collected at the time of your diagnostic biopsy will be sent to the biobank for research. Only tumor tissue from procedures performed as part of your standard of care will be sent.
2. About five (5) tablespoons of blood will be collected from a vein in your arm before you start treatment, on cycle three day one prior to treatment, and if your cancer worsens. The blood will usually be collected at the same time as the blood collected for your clinical tests to monitor your health. In most cases an additional needle stick will not be required to collect the blood.
3. Your samples will be stored in the biobank. There is no limit on the length of time we will keep your samples and research information. The samples will be kept until they are used for research or destroyed.
4. Researchers can only get samples from the biobank after their research has been approved by experts. Researchers will not be given your name or contact information.
5. Some of your genetic and health information may be placed in central databases for researchers to use. The databases will not include your name or contact information.

What are the risks in this optional sample collection?

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

Generally, hospitals will keep some of your tissue. This tissue may be used to help treat your cancer in the future. There is a small risk that when this tissue sample is submitted to the biobank for this optional sample collection, your tissue could be used up.

Your medical and genetic information is unique to you. There is a risk that someone outside of the research study could get access to your study records or trace information in a database back to you. They could use that information in a way that could harm you. Researchers believe the chance that someone could access and misuse your information is very small. However, the risk may increase in the future as people find new ways of tracing information.

In some cases, this information could be used to make it harder for you to get or keep a job and get or keep health insurance.

How will information about me be kept private?

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

1. They will remove identifiers, such as your initials, from your samples and information. They will replace them with a code number. There will be a master list linking the code numbers to names, but they will keep it separate from the samples and information.
2. Researchers who study your samples and information will not know who you are. They also must agree that they will not try to find out who you are.
3. Your personal information will not be given to anyone unless it is required by law.
4. If research results are published, your name and other personal information will not be used.

What are the benefits to taking part in this optional sample collection?

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 to this optional sample collection?

There are no costs to you or your insurance. You will not be paid for taking part in this study. The research may lead to new tests, drugs, or other products for sale. If it does, you will not get any payment.

What if I change my mind about this optional sample collection?

If you decide you no longer want your samples to be used, you can call the study doctor, _____, (*insert name of study doctor for main trial*), at _____, (*insert telephone number of study doctor for main trial*), who will let the biobank know. Then, any samples that remain in the biobank will be destroyed or returned to your study doctor. This will not apply to samples or related health information that have already been given to or used by researchers.

What if I have questions about this optional sample collection?

If you have questions about the use of your samples for research, contact the study doctor, _____, (*insert name of study doctor for main trial*), at _____, (*insert telephone number of study doctor for main trial*).

Please circle your answer below to show if you would or would not like to take part in each optional study:

Samples for unknown future studies:

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

I agree that my samples and related health 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.

My signature agreeing to take part in the study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed and dated copy of this form. I agree to take part in the main study. I also agree to take part in any additional studies where I circled "yes".

Participant's signature _____

Date of signature _____

Signature of person(s) conducting the informed consent discussion _____

Date of signature _____