SUMMARY OF CHANGES – Consent

NCI Protocol #: 10313
Local Protocol #: 20-134
Protocol Version Date: 11/05/2024

Protocol Title: A phase IB and randomized open-label phase II study of Berzosertib (M6620, VX-970) in combination with carboplatin/gemcitabine/pembrolizumab in patients with chemotherapy-naïve advanced non-small cell lung cancer of squamous cell histology.

Informed Consent Version Date: 11/05/2024

#	Section	Change
1.	Drug Risks	These changes are in response to an RRA from Dr. Howard Streicher (streicherh@ctep.nci.nih.gov). New and/or modified risk information associated with Pembrolizumab was added based on the Revised CAEPR – Version Version 2.8, August 14, 2024. Added New Risk: • Rare and Serious: Inability to digest food which may cause bloating; Swelling of the bowels; Skin rash developing 1-8 weeks after a drug is given which may be accompanied by fever, lymph node swelling and organ failure Decrease in Risk Attribution: • Changed to Rare and Serious from Occasional: Lung problems (pneumonitis and other conditions). Symptoms may include: new or worsening cough, chest pain, shortness of breath. • Changed to Also Reported on Pembrolizumab MK-3475 Trials But With Insufficient Evidence for Attribution from Occasional (i.e. Removed from Risk Profile): Cough Provided Further Clarification: Reaction during or following a drug infusion which may cause fever, chills, rash (under Rare) is now reported as Reaction during or following a drug infusion which may cause fever, chills, rash, low blood pressure (under Occasional)
2.	Drug Risks	Gemcitabine and carboplatin side effects lists updated to the latest versions available on the CTEP website

Research Study Informed Consent Document – Phase 2

Study Title for Participants: Testing the addition of an anti-cancer drug, Berzosertib (M6620, VX-970), to the usual treatments (carboplatin and gemcitabine) and to pembrolizumab for patients with advanced squamous cell non-small cell lung cancer

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: Protocol 10313, A phase IB and randomized open-label phase II study of Berzosertib (M6620, VX-970) in combination with carboplatin/gemcitabine/pembrolizumab in patients with chemotherapy-naïve advanced non-small cell lung cancer of squamous cell histology (NCT# 04216316)

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.

We are asking you to take part in this research because you have advanced squamous cell non-small cell lung cancer (NSCLC) for which you have not been treated with chemotherapy in the past year.

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:

Is the combination of berzosertib (M6620, VX-970), gemcitabine, carboplatin, and pembrolizumab as effective in patients with advanced squamous cell non-small cell lung cancer compared to gemcitabine, carboplatin, and pembrolizumab?

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. This is the first time these drugs will be tested together in humans.

What is the usual approach to my advanced squamous cell NSCLC?

The usual approach for patients who are not in a study is treatment with Food and Drug Administration (FDA)-approved chemotherapy drugs, such as gemcitabine and carboplatin, or with immunotherapy. Your doctor can explain which treatment may be best for you.

Berzosertib (M6620, VX-970) is not FDA approved. This combination of drugs is not approved by the FDA for the treatment of advanced squamous cell NSCLC.

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 the combination of berzosertib (M6620, VX-970), gemcitabine, carboplatin, and pembrolizumab, or you will get gemcitabine, carboplatin, and pembrolizumab without berzosertib (M6620, VX-970) for up to four cycles (*i.e.*, 3 months), followed by pembrolizumab for up to 2 years total treatment (with or without berzosertib (M6620, VX-970) for the first 9 months [12 cycles], depending on what treatment group you are in) or until your cancer grows, or side effects require you to stop, or you decide to withdraw from the study.

After you finish your treatment, your doctor and study team will watch you for side effects. They will check you every 3 months for 12 months after treatment. This means your doctor will follow you through office visits or phone calls for at least 12 months after treatment.

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 drugs may not be as good as the usual approach for your cancer at shrinking or stabilizing your cancer. Combining the study drugs can result in greater similar side effects of those currently experienced by each drug individually.

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:

- Anemia, which may require blood transfusion
- Diarrhea, nausea, vomiting
- Tiredness
- Infusion related reactions

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

Benefits

There is some evidence in animals that berzosertib (M6620, VX-970) in combination with gemcitabine, carboplatin, or pembrolizumab may be effective in shrinking your type of cancer. It is unlikely that the combination of berzosertib (M6620, VX-970), gemcitabine, carboplatin, and pembrolizumab will help you live longer than the usual approach alone. This study may help the study doctors learn things that may help other 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. This may mean slowly stopping the study drugs so that there is not a sudden unsafe change, risk to your health, etc. 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 Institutional Review Board (IRB), Food and Drug Administration (FDA), or study sponsor (National Cancer Institute, [NCI]). 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 usual treatment (carboplatin, gemcitabine, and pembrolizumab) alone to using berzosertib (M6620, VX-970) plus the usual treatment. The addition of berzosertib (M6620, VX-970) to the usual treatment could prevent your cancer from getting worse. But, it could also cause side effects, which are described in the risks section below.

Another purpose of the study is to check the level of the study drugs in your blood (pharmacokinetics). Another objective of the study is to see if people with a certain genetic mutation respond better or worse to the study drugs.

This study will help the study doctors find out if this different approach is better, the same, or worse than the usual approach. To decide if it is better, the study doctors will be looking to see if the study drug increases the time that the patient lives without his or her disease getting worse compared to the usual approach.

There will be about 106 people taking part in this study, with about 6-18 people taking part in the first part of this study and 88 people taking part in the second part of the study.

What are the study groups?

This consent form covers the second part of the study.

This study has 2 study groups.

- **Group 1**

  If you are in this group, you will get the usual drugs used to treat this type of cancer, gemcitabine, carboplatin, and pembrolizumab, plus a study drug called berzosertib (M6620, VX-970). You will get these drugs through a vein in your arm on the following days of each cycle (a cycle is 21 days long):
  - Gemcitabine: Day 1 and Day 8
  - Carboplatin: Day 1
  - Pembrolizumab: Day 1
  - Berzosertib (M6620, VX-970): Day 2 and Day 9

You will get this 4-drug combination for four cycles (*i.e.*, 3 months).
After the initial 4 cycles (3 months) of treatment with the 4-drug combination, you may continue with pembrolizumab and berzosertib (M6620, VX-970) for up to another 12 cycles on Day 1 only (9 months). This is your first year of treatment. You will then receive pembrolizumab alone for up to another year, for a total of 2 years of treatment on the study. When you stop receiving gemcitabine and carboplatin beginning with Cycle 5, you may be allowed to receive berzosertib (M6620, VX-970) on the same day as your pembrolizumab treatment if it is more convenient for you. When you receive pembrolizumab alone beginning with Cycle 17, cycles will be 42 days long.

See the study calendar for more information.

There will be about 44 people in this group.

- **Group 2**

  If you are in this group, you will get the usual drugs used to treat this type of cancer, gemcitabine, carboplatin, and pembrolizumab. You will get these drugs through a vein in your arm on the following days of each cycle (a cycle is 21 days long):
  - Gemcitabine: Day 1 and Day 8
  - Carboplatin: Day 1
  - Pembrolizumab: Day 1

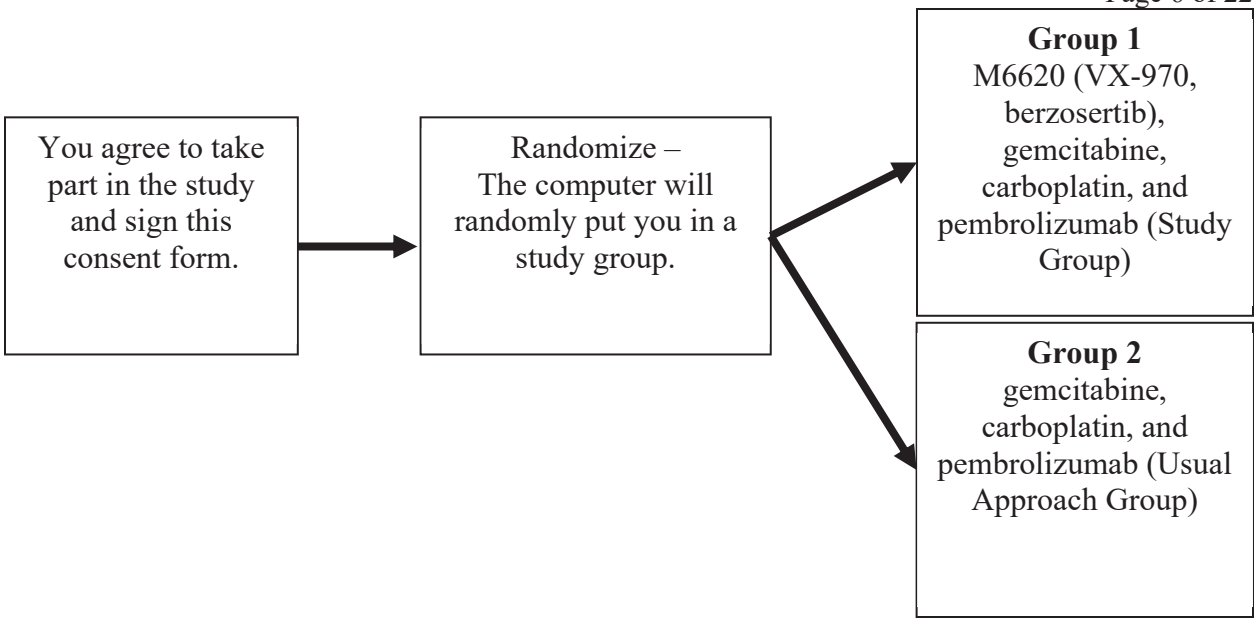
  You will get this 3-drug combination for four cycles (*i.e.*, 3 months) followed by pembrolizumab for up to 2 years of total treatment. Beginning with Cycle 17, cycles will be 42 days long. See the study calendar for more information.

  There will be about 44 people in this group.

After completion of treatment, you will not be able to get additional doses of berzosertib (M6620, VX-970) or pembrolizumab. Berzosertib (M6620, VX-970) and pembrolizumab are not approved by the FDA for treatment of your disease.

We will use a computer to assign you to one of the study groups. This process is called "randomization" (like the flip of a coin). 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 50% chance of being in Group 1 or Group 2.

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.

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

- Two blood draws done during each cycle during the first and second weeks for the first four cycle. After cycle 4, the blood draw will only be done on Day 1 and 8 of each cycle.
- Thyroid testing done at the start of every cycle.
- Physical exams done at the start of each cycle.

This study will use genetic tests that may identify changes in the genes in your DNA. Your genes carry information about you and your family, from the color of your eyes to health conditions for which you may be at risk, such as certain kinds of cancer.

Finding these changes would not affect your treatment in this study. However, they could affect your health in other ways. If the changes in your genes were inherited, the changes could also affect the health of your family members.

You and your family may want to know about any genetic test findings that may be important to your health. You may use this form to grant us permission in advance to give this information to your doctor. If a genetic test result about you seems to be medically important and you have granted us permission to contact you, the following steps will occur:

1. Researchers will study the result further to decide if it may be medically important to you or your relatives.
2. The research laboratory that performed the genetic test will contact your doctor about the finding. The research laboratory, which will not have any identifying information about you, will provide your doctor with a code number assigned to your genetic test sample.
3. Your doctor will use the code number to identify you and will then contact you about the medically important finding. Your doctor may try to contact you several times.
4. You will require another genetic test to confirm the results. This test must be paid for at your own expense.
5. If it is confirmed that there are changes found that could cause health problems, then your doctor will discuss your options with you. We strongly suggest that you also talk to a genetic counselor. Genetic counseling services must be paid for at your own expense.

It is more likely, however, that you will not be contacted by us about a medically important finding. Even if we do not contact you, it does not mean that your genes do not contain changes that are important to your health. Researchers are always learning about new and medically important changes in genes and some information may be learned in the future. Researchers will only decide to contact you about genetic test results at the time your DNA is initially sequenced. You will not be contacted or consented for any research done using your samples in the future, and you will not receive any reports or information about any medically important findings learned in the future. Also, sometimes the meaning of genetic test results can be uncertain, and we may not know for sure what the results mean for your future health. Sharing an uncertain genetic test result with you could offer little benefit, no benefit at all, or could even be harmful.

Results from genetic testing will not be a part of your medical records, unless the results are confirmed by additional testing that you agreed to. See “Who will see my medical information?” for laws and risks in protecting your genetic information.

Some exams, tests, and procedures are a necessary part of the research study but would not be included in usual care. Listed below are procedures that will be done for research purposes only.

Your study doctor will need to use some of the tissue left over from your biopsy when you were diagnosed with cancer. This sample is a required part of the study. This tissue will be analyzed to learn about the tumor’s properties. You will not get the results of this testing, but your study doctor will.

If there is not enough tissue left over from your biopsy, your study doctor will need to do another biopsy to get this tissue. This biopsy will be taken before you begin the study drug. The study biopsy takes small pieces of cancer tissue from your body. This is like the biopsy you had that helped diagnose your cancer. This tissue will be analyzed to learn about the tumor’s properties. You will not get the results of this testing, but your study doctor will. If you agree to take part in

the study, you may need to sign a separate consent form for the study biopsy at the hospital or clinic where the biopsy is done.

If a tumor tissue sample cannot be obtained by biopsy or by using left over tissue, your study doctor will let you know if you are still able to participate in the study.

Blood samples will also be taken and are required for the study on three days to see how the body absorbs, distributes, and gets rid of the study drugs, and for other genetic testing purposes (germline). The first blood sample will be collected before you begin the study drug. Another blood sample will be collected on Cycle 1 Day 1 before you receive treatment and 25 minutes after treatment. You will have a third blood sample taken on Cycle 1 Day 2 at the following times: before your dose, 30 minutes after the start of the berzosertib (M6620, VX-970) dose, 55 minutes after the start of the berzosertib (M6620, VX-970) dose, 15 minutes after the end of the berzosertib (M6620, VX-970) dose, and 1 hour after the end of the berzosertib (M6620, VX-970) dose.

Researchers will obtain mandatory genetic material (DNA and RNA) from your tumor tissue and blood samples. Your DNA and RNA will be sequenced to evaluate changes in your DNA and RNA that may occur during treatment. You and your study doctor will not get any results of this testing. If you agree to take part in the study, you may need to sign a separate consent form for the study biopsy at the hospital or clinic where the biopsy is done.

A patient study calendar is attached at the end of this document. It shows how often these exams, tests, and procedures will be done.

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 drug may not be as good as the usual approach for your cancer or condition at shrinking or stabilizing your cancer.

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 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 for 6 months after you have completed the study.

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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

The genetic test used in this study will test your tumor and normal tissue for genetic changes, in the gene called ATM. 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.

Biopsy Risks

Common side effects of a biopsy are a small amount of bleeding at the time of the procedure, bruising, and pain at the biopsy site. Pain can be treated with regular pain medications. Rarely, an infection, significant bleeding, or collapsing of the lung can occur. You may sign a separate consent form for the study biopsy that describes the risks in more detail.

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 drug.

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.

Diarrhea is a common side effect associated with this drug combination. You should notify your doctor immediately at the first sign of poorly formed or loose stools or an increased frequency of bowel movements. Loperamide (Imodium) should be kept on hand and should be taken as recommended by your doctor.

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.

Possible Side Effects of M6620 (VX-970, berzosertib)
(Table Version Date: July 13, 2022)

COMMON, SOME MAY BE SERIOUS In 100 people receiving M6620 (VX-970, berzosertib), more than 20 and up to 100 may have:
• Anemia which may require blood transfusion • Diarrhea, nausea, vomiting • Tiredness • Bruising, bleeding

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving M6620 (VX-970, berzosertib), from 4 to 20 may have:
• Constipation • Fever • Flu-like symptoms including chills, body aches, muscle pain • Reaction during or following a drug infusion which may cause rash, low blood pressure • Loss of appetite • Dizziness, headache • Flushing

Possible Side Effects of Gemcitabine
(Table Version Date: January 18, 2023)

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 a blood transfusion • 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 • 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 • Drowsiness

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 • Brain damage, posterior reversible encephalopathy syndrome (PRES), which may cause headache, seizure, blindness • Stroke which may cause paralysis, weakness, headache • Liver damage which may cause yellowing of eyes and skin, swelling • Capillary Leak syndrome which may cause fluid in the organs, low blood pressure, shortness of breath, swelling of ankles • Hemolytic uremic syndrome (HUS) which may cause anemia, kidney problems, tiredness, bruising, swelling, or may require dialysis

Possible Side Effects of Carboplatin
(Table Version Date: October 11, 2024)

COMMON, SOME MAY BE SERIOUS In 100 people receiving Carboplatin, more than 20 and up to 100 may have:
• Infection, especially when white blood cell count is low

COMMON, SOME MAY BE SERIOUS In 100 people receiving Carboplatin, more than 20 and up to 100 may have:
• Bruising, bleeding • Anemia which may cause tiredness, or may require blood transfusions • Vomiting, nausea • Hair loss

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Carboplatin, from 4 to 20 may have:
• Diarrhea, constipation, belly pain • Changes in taste • Numbness and tingling in fingers and toes • Weakness • Swelling, redness, and pain at the site of the medication injection

RARE, AND SERIOUS In 100 people receiving Carboplatin, 3 or fewer may have:
• Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Visual loss • Difficulty hearing

Possible Side Effects of MK-3475 (Pembrolizumab)
(Table Version Date: August 14, 2024)

COMMON, SOME MAY BE SERIOUS In 100 people receiving pembrolizumab (MK-3475), more than 20 and up to 100 may have:
• Tiredness

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving pembrolizumab (MK-3475), from 4 to 20 may have:

- Nausea
- Loss of appetite
- Pain in back
- Joint stiffness
- Swelling and redness of the skin

Pembrolizumab (MK-3475) 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:

- Anemia which may require blood transfusion
- Pain in lymph nodes
- Blood clot which may cause bleeding, confusion, paralysis, seizures and blindness
- 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
- 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
- Diarrhea
- Sores in the mouth which may cause difficulty swallowing
- Pain in belly
- Sores in the bowels
- Chills, fever
- Reaction during or following a drug infusion which may cause fever, chills, rash, low blood pressure
- 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
- Pain or swelling of the joints
- Problem of the muscle, including swelling, which can cause muscle pain and severe muscle weakness sometimes with dark urine
- Skin: itching; acne; rash (can be severe); blisters and peeling on the skin, mouth; skin changes; hives

RARE, AND SERIOUS

In 100 people receiving pembrolizumab (MK-3475), 3 or fewer may have:

- 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
- Inability to digest food which may cause bloating
- Swelling of the gall bladder
- Swelling of the spinal cord
- Feeling of "pins and needles" in arms and legs
- Redness, pain or peeling of palms and soles

Pembrolizumab (MK-3475) 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:

- Heart problems including swelling and heart failure. Symptoms and signs of heart problems may include: Shortness of breath, swelling of the ankles and body.
- Swelling and redness of the eye which may cause blurred vision with a chance of blindness
- Swelling of the bowels
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Damage to organs in the body when donor cells attack host organs which may cause yellowing of eyes and skin, itchy dry skin
- Damage to organs in the body when the body produces too many white cells
- A condition with high blood sugar which leads to tiredness, frequent urination, excessive thirst, headache, nausea and vomiting, and can result in a coma
- Problem of the nerves that can cause paralysis. Signs and symptoms may include: numbness, tingling of hands and feet; weakness of the arms, legs.
- Swelling of the brain (encephalitis/meningitis) which may cause headache, confusion, sleepiness, seizures and stiff neck
- 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.
- Lung problems (pneumonitis and other conditions). Symptoms may include: new or worsening cough, chest pain, shortness of breath.
- Skin rash developing 1-8 weeks after a drug is given which may be accompanied by fever, lymph node swelling and organ failure
- Swelling or tenderness of blood vessels

Pembrolizumab works by helping your immune system to fight your cancer. However, pembrolizumab can also cause your immune system to attack normal organs and tissues in your body and can affect the way they work, which can result in side effects. These side effects may be serious (i.e. causing hospitalization or be life-threatening), may result in death, and/or may occur after you stop taking pembrolizumab. These side effects can affect more than one of your normal organs and tissues at the same time.

Additional Drug Risks

The study drug could interact with other drugs and food. Your study doctor will give you a drug information handout and wallet card that lists these possible interactions. Share this information with your family members, caregivers, other health care providers, and pharmacists.

The study drug berzosertib (M6620, VX-970) may also make you more sensitive to sunlight, so you should take protective measures to minimize sun exposure while taking berzosertib (M6620, VX-970).

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

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.

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 or within 6 months after your 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 lung 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 the carboplatin, gemcitabine, and pembrolizumab.
- the costs of getting the berzosertib (M6620, VX-970), carboplatin, gemcitabine, and pembrolizumab ready and giving it to you.
- the thyroid tests done at the start of every cycle.
- 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 and/or your insurance provider will not have to pay for exams, tests, and procedures done for research purposes only or that are covered by the study. These include:

- The EKG in this study done at the beginning of the study.
- The biopsy for research purposes at the beginning of the study (if no archival tissue is available).

You or your insurance provider will not have to pay for the berzosertib (M6620, VX-970) while you take part in this study.

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.

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 (Cancer Therapy Evaluation Program, NCI) and any 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.

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 and shared 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 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.

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

Circle your choice of "yes" or "no" for the following known future study.

Known future study

If you choose to take part in this optional study, researchers will use part of your tumor tissue that was previously collected for research on evaluating the changes in your RNA that occur

during treatment. You will not have to undergo any new biopsies. Researchers will obtain genetic material (RNA) from both your tumor cells and your blood. Your RNA will be used for genomic sequencing, which is sequencing part of your DNA. All your genetic information makes up your genome. Genomic sequencing is a test that records all or part of the pieces of DNA that are in your genes, piece by piece. This is usually done to look for changes in your genome that may cause health problems. The genomic sequencing will be done by an NCI-supported laboratory in Frederick, Maryland, known as the National Clinical Laboratory Network (NCLN) Genomics Laboratory at the Frederick National Laboratory for Cancer Research. The laboratory will compare the genomic sequences from your tumor and blood cells to identify how they differ. The differences between genomic sequences of your tumor and blood cells may be important to understand why you did or did not respond to the treatment you received. Researchers hope to find potential "biomarkers" (changes present in tumor tissue that predict how patients with your type of cancer may respond to current or future treatments). This optional study may improve the ability to select future treatments or treatment combinations for others in the future. This optional study will not affect the cancer treatment or approach that you receive.

Neither you nor your study doctor will be informed when the genetic sequencing research will be done. You and your study doctor will not receive reports of these studies, as they are intended for research purposes only and cannot be used to plan treatment.

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

Samples for known future studies:

I agree that my samples and related health information may be used for the laboratory study described above.

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

Study Calendar

	Pre-Study	Cycles 1-4 (1 Cycle = 21 days)				Cycles 5-16 (1 Cycle = 21 days)				Cycles 17-26 (1 Cycle = 42 days)				Disease Progression or End of Treatment	Follow Up
		Day 1	Day 2	Day 8	Day 9	Day 1	Day 2	Day 8	Day 9	Day 1	Day 2	Day 8	Day 9		Every 3 months[f]
Berzosertib (M6620, VX-970) [a]			X		X	X*									
Pembrolizumab [a]		X				X				X					
Gemcitabine [a]		X		X											
Carboplatin [a]		X													
Tumor tissue for research purposes [b] (from your previous biopsies)	X														
Tumor tissue for research purposes (if there is no previous tumor tissue available)	X														
Blood collection for research purposes	X	Cycle 1 only	Cycle 1 only												
Tumor measurements and radiologic evaluation to assess your response to treatment	X	*Assessments occur at 6, 12, and 18 weeks, then every 9 weeks.*												X	
Blood draws for complete blood count and general health status	X	X		X		X				X					
Thyroid tests [c]	X	X				X				X					
EKG [d]	X														
Physical exam, vital signs, weight, assessment of how you perform everyday tasks	X	X				X				X					
Pregnancy Test [e]	X														
Side effects evaluation		X ---------- X												X	
Concurrent medications	X	X ---------- X												X	
Informed consent, demographics, and medical history	X														

[a] Dose as assigned. The 4-drug combination of berzosertib (M6620, VX-970), Gemcitabine, and Carboplatin is to be given only during Cycles 1-4 (3 months). After the initial 4 cycles (3 months) of treatment with berzosertib (M6620, VX-970), gemcitabine, carboplatin, and pembrolizumab, you may continue with pembrolizumab and berzosertib (M6620, VX-970) on day 1 only for up to another 12 cycles (9 months, 1 year total), then pembrolizumab alone for up to 1 more year, for a total of 2 years of treatment on the study.

* During this time, you may be allowed to receive berzosertib (M6620, VX-970) on the same day as your pembrolizumab treatment if it is more convenient for you.

[b] Tumor Tissue: Tissue must be collected within 3 months before beginning treatment.

[c] Thyroid Tests: Testing will be done at the start of every cycle. Additional tests may be performed if your doctor indicates it is necessary.

[d] EKG: Will be done pre-study. Additional tests may be performed if your doctor indicates it is necessary.

[e] Women of childbearing potential will also receive a pregnancy test within 14 days before registration.

[f] Follow Up: Patient follow-up will occur via standard of care or a phone call every 3 months +/- (2 weeks) for 12 months following removal from study.