NATIONAL CANCER INSTITUTE
Center for Cancer Research

TO: Cancer Therapy Evaluation Program

FROM: Anish Thomas, MBBS, M.D., Principal Investigator,
Developmental Therapeutics Branch, CCR, NCI

DATE: 08/20/2024

RE: **Amendment Version Date: 08/20/2024 for CTEP Protocol #10268**:
"Randomized Phase II Trial of Topotecan plus M6620 (VX-970) vs. Topotecan alone in Patients with Relapsed Small-Cell Lung Cancer"

The purpose of this amendment is to update study personnel on the title page of the protocol.

SUMMARY OF CHANGES

1. **Headers:** Version date has been updated for consistency with protocol version date.

Research Study Informed Consent Document

Study Title for Participants: Randomized Trial of Topotecan With M6620, an ATR Kinase Inhibitor, in Small Cell Lung Cancers and Small Cell Cancers Outside of the Lungs

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: Protocol 10268, Randomized Phase II Trial of M6620 (VX-970, Berzosertib) vs. Topotecan alone in Patients with Relapsed Small-Cell Lung Cancer (NCT: NCT03896503)

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 study because you have been diagnosed with relapsed small cell lung cancer (SCLC) or small cell cancer outside the lungs. "Relapsed" means that the disease has grown or spread after prior treatment. Small cell cancers are an aggressive (fast-growing) cancer that can arise in the lungs and less commonly in "extrapulmonary" sites, also known as other parts of the body outside of the lungs. These tumors share many similarities including their fast growth and limited response to treatment when it comes back after initial chemotherapy.

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 questions:

Can we lower the chance of your relapsed SCLC growing or spreading by using M6620 and topotecan combination therapy?

Can we lower the chance of your small cell cancer outside of the lungs growing or spreading using M6620 and topotecan combination therapy?

M6620 is investigational and that it has not been approved by the FDA for this type of cancer.

We are doing this study because we want to find out if a new approach is better than the usual approach for your relapsed SCLC or outside of the lungs small cell cancer.

The usual approach is defined as care most people get for relapsed SCLC or for small cell cancer outside of the lungs.

The new approach we are testing is a combination of topotecan and M6620.

What is the usual approach to my relapsed small cell lung cancer or extrapulmonary small cell cancer?

The usual approach for patients with relapsed small cell lung cancer who are not in a study is treatment with topotecan. Topotecan is one of the U.S. Food and Drug Administration (FDA)-approved treatments for patients with relapsed SCLC.

The usual approach for patients with small cell cancer outside of the lungs follows the patterns of treatment for SCLC. There are no FDA approved drugs for small cell cancers outside of the lungs.

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 re-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 and have SCLC, you will be randomly assigned to one of two groups: to receive either the combination of M6620 and topotecan or topotecan alone. Outside of the lungs small cell cancer patients will only be assigned to receive the combination treatment of M6620 and topotecan. The treatment is continued for both patients with SCLC and patients with small cell cancer outside of the lungs as long as the cancer remains under control (*i.e.*, shrinking or not growing). If you are assigned to topotecan alone and your cancer worsens or spreads, you may be eligible to be re-assigned to receive the combination treatment of topotecan and the study drug M6620. Treatment may also be discontinued if you experience severe side effects.

After you finish your study treatment, your doctor will continue to follow your condition every 3 months through clinic visits and watch you for side effects and worsening of your condition until the study is completed.

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 M6620 and topotecan may not be as good as topotecan alone at shrinking your cancer or preventing it from coming back. There is also a risk that you could have side effects from the combination of M6620 and topotecan if you are assigned to receive the combination. These side effects may be worse and may be different than you would get with the usual approach for your relapsed SCLC or outside the lungs small cell cancer.

Some of the most common side effects of M6620 that the study doctors know about are:

- Anemia (low red blood cell count) which may require blood transfusion
- Nausea, diarrhea, vomiting
- Tiredness
- Infection, especially when white blood cell count is low
- Dizziness, headache
- Flushing
- Infusion site reactions (occur at the body site where the drug is infused)

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

- Anemia which may require a blood transfusion
- Infection, especially when white blood cell count is low
- Constipation, diarrhea, nausea, vomiting
- Fever
- Bruising, bleeding
- Tiredness
- Shortness of breath
- Pain (*i.e.*, in the belly)

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

Benefits

There is preliminary evidence that M6620 combined with topotecan is effective in shrinking or stabilizing your type of cancer. However, it is not possible to know now if the M6620 combined with topotecan will extend your life or 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. 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.
- The study is stopped by the Institutional Review Board (IRB), Food and Drug Administration (FDA), or study sponsor (NCI). The study sponsor is the organization who oversees the study.
- For women: The study doctor will take you off the study treatment if you become pregnant while on 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 of M6620 plus topotecan to topotecan alone in patients with SCLC and to test the effects of M6620 combined with topotecan in patients with small cell cancer outside of the lungs. Topotecan, like most chemotherapies, works by damaging the deoxyribonucleic acid (DNA) in cancer cells, causing those cells to die and the tumor to shrink. However, some tumor cells can become less affected by chemotherapy because they have ways to repair the damaged DNA. The addition of M6620 to topotecan could help topotecan shrink your cancer and prevent it from returning.

For outside of the lungs small cell cancer patients, this study will help the study doctors find out if M6620 plus topotecan can treat your cancer or help you live longer.

What are the study groups?

This study has 2 study groups. All patients with small cell cancer outside of the lungs will be assigned to Group 2.

- **Group 1**

  If you are in this group, you will get topotecan to treat SCLC. You will get through a vein in the arm topotecan for approximately 30 minutes each day for five consecutive days (day 1 to 5) every 21 days. Each 21-day period is called a cycle, and the cycles will be repeated until as long as the cancer remains under control and there are no serious side effects. See the study calendar for more information. If you are assigned to topotecan alone and your cancer worsens or spreads, you may be eligible to be re-assigned to receive the combination treatment of topotecan and the study drug M6620.

  There will be about 18 people in this group.

- **Group 2**

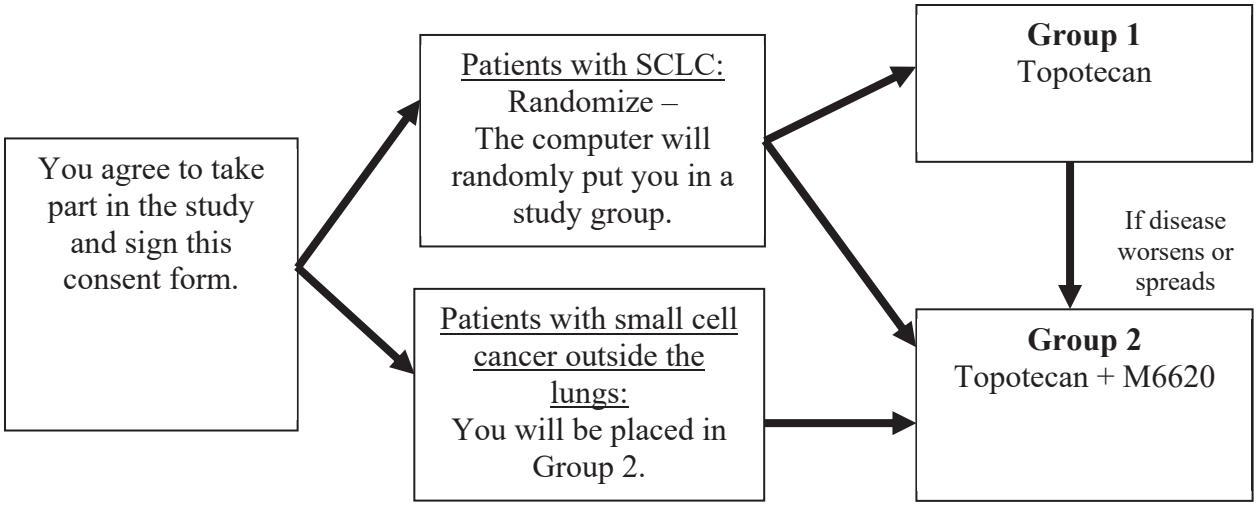
  If you are in this group, you will get topotecan, plus a study drug called M6620 to treat SCLC or small cell cancer outside of the lungs. You will get these drugs through a vein in the arm: topotecan for approximately 30 minutes each day for five consecutive days (day 1 to day 5) and M6620 for approximately 60 minutes (within 15 minutes after administration of topotecan is completed) on day 2 and day 5, every 21 days. Each 21-day period is called a cycle, and the cycles will be repeated until as long as the cancer remains under control and there are no serious side effects. See the study calendar for more information.

  This drug combination is not approved by the FDA for treatment of your disease.

  There will be about 56 people in this group, 36 patients with small cell lung cancer and 20 patients with small cell cancer outside of the lungs.

If you have SCLC, 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 a 1/3 chance of being in Group 1, and a 2/3 chance of being in Group 2. If you have small cell cancer outside of the lungs, you will be assigned to Group 2. If you are assigned to Group 1 and your cancer worsens or spreads, you may be eligible to be re-assigned to Group 2 and receive the combination treatment of topotecan and the study drug M6620.

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:

- Blood tests for complete blood count and health status done every cycle.
- Physical exams and clinical disease assessment done every cycle.
- Computed Tomography (CT) Exam performed every 6 weeks for tumor measurements
- For women: Serum pregnancy test done every 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 there are changes found that could cause health problems, then your study doctor will discuss your options with you. 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. We strongly suggest that you also talk to a genetic counselor. Genetic counseling services must be paid for at your own expense.
4. You may choose to have another genetic test to confirm the results. This test must be paid for at your own expense by you or your insurance plan.
5. If you choose to have another genetic test and it is confirmed that there are changes found that could cause health problems, then your doctor will discuss your options with you.

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.

- If you have small cell lung cancer, you will need to have one mandatory CT-guided biopsy in order to participate in the trial. If you have small cell cancer outside of the lungs, this biopsy is optional (please see Optional studies that you can choose to take part in). The study biopsy takes small pieces of cancer tissue from your body. This is like the biopsy you had that helped diagnose your cancer but will be done solely for research purposes to better predict how people with certain gene expressions may respond better to study treatment than others. The biopsy will be done before you begin the study drug. A sample from the tissue that was collected previously will also be used for research.

Researchers will obtain genetic material (DNA and ribonucleic acid [RNA]) from your tumor tissue. Your DNA and RNA will be sequenced to evaluate changes in your DNA and RNA. 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 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 M6620 (VX-970, berzosertib) 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 M6620 (VX-970, berzosertib) 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 will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drug(s)/study approach.

Here are important things to know about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, and some may never go away.
- Some side effects may make it hard for you to have children.
- 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.

The tables below show the most common and the 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.

The M6620 and topotecan combination or topotecan alone 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 treatment. If you are a woman who becomes pregnant while on the study treatment, the study doctor will stop you from taking the study treatment.

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 alterations of genes. 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.

Leftover tissue from your study may also be used for optional studies discussed later in this document under “Optional Studies”.

Blood Draw Risks

Some of the risks from drawing blood from your arm may include pain, bruising, light-headedness, and rarely, infection. For most people, needle punctures to get blood samples do not cause any serious harm. Let your study doctor know of any questions you have about possible side effects. You can ask the study doctor questions about side effects at any time.

Side Effect Risks

The study 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 the usual treatment for 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 Group 1 and Group 2 – Possible side effects of topotecan are listed in the tables below. This drug is part of the usual approach for treating this type of cancer:

Possible Side Effects of Topotecan (Table Version Date: August 4, 2016):

COMMON, SOME MAY BE SERIOUS In 100 people receiving Topotecan, more than 20 and up to 100 may have:
• Anemia which may require a blood transfusion • Constipation, diarrhea, nausea, vomiting • Fever • Pain • Bruising, bleeding • Infection, especially when white blood cell count is low • Tiredness • Shortness of breath • Hair loss

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Topotecan, from 4 to 20 may have:
• Blockage of the bowels • Sores in mouth which may cause difficulty swallowing • Headache • Cough • Rash

RARE, AND SERIOUS In 100 people receiving Topotecan, 3 or fewer may have:
• Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Swelling of the bowels which may require surgery • Scarring of the lungs

Study Group 2 - In addition to side effects listed above, people who are in Group 2 may also have some side effects from M6620. These side effects are listed below.

Possible Side Effects of M6620 (VX-970, Berzosertib) (as of 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

Additional Drug Risks

The study drug M6620 could interact with other drugs. Certain other drugs can change how your body processes M6620. This could decrease the effect of M6620, or it could increase the side effects from M6620. 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.

There is a possibility that M6620 may make you more sensitive to sunlight. You should limit your exposure to the sun, including indoor tanning. It is recommended to use sunscreen and wear long sleeved clothes, hats, and sunglasses while outdoors.

There is a possibility that you may develop a severe blood infection in which the bloodstream is overwhelmed by bacteria.

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

Imaging Risks

The CT – guided biopsy 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 amount of radiation you will receive in this study is 0.8 rem which is below the guideline of 5 rem (or 0.5 rem in children) per year allowed for research subjects by the NIH Radiation Safety Committee.

The CT – guided biopsy that you get in this study will expose you to more radiation than you get from everyday background radiation. The amount of radiation from this scan is the same as 2.5 years worth of 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.

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 treatment. You should use an adequate form of birth control for at least 6 months after you have received your last dose of M6220.

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 relapsed SCLC or small cell cancer outside of the lungs. 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.
    - this includes the EKG(s) at any time that your study doctor determines it is necessary to do so.
- the costs of topotecan, getting it ready, and giving it to you
- the costs of getting M6620 ready and giving it 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 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 extra EKG performed at the beginning of this study.
- The blood tests performed every cycle.
- The CT-guided biopsy for testing for genetic expressions genes at the beginning of the study.

You or your insurance provider will not have to pay for the cost of M6620 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 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 these optional studies hope the results will help other people with small cell cancers 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 these studies for any reason, you can still take part in the main study.

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

Optional sample collections for known laboratory studies and/or storage 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.

Known future studies

Optional Circulating Cell-free DNA (cfDNA) and Circulating Tumor Cell (CTC) Biomarker Study

If you choose to take part in this optional study, researchers will collect blood for research on circulating tumor cells to better predict how certain people may respond better to treatment than others. The first blood sample for both studies will be collected before you start study treatment. Additional samples will be taken prior to treatment on Day 4 of cycle 1 and after treatment on Day 2 of cycle 1 for the CTC study and prior to treatment on Day 5 of cycle 1 for the cfDNA study, as well as Day 1 of cycle 2, Day 1 of cycle 3, and at the end of treatment for both studies.

Researchers will obtain genetic material (DNA and RNA) from the blood samples. Your DNA and RNA will be sequenced to evaluate changes in your DNA and RNA. You and your study doctor will not get any results of this testing.

Optional RNA Sequencing Biomarker Study (for patients with small cell cancer outside of the lungs only)

If you choose to take part in this optional study, researchers will collect your tumor tissue for research on evaluating the changes in your DNA and RNA. The tumor tissue will be obtained from a biopsy performed at the beginning of the study.

Optional Immunohistochemistry (IHC) Biomarker Study

If you choose to take part in this optional study, researchers will use leftover tumor tissue for research on evaluating whether the levels of certain proteins can predict how certain people respond to treatment.

Optional Whole Exome Sequencing (WES) Biomarker Study

If you choose to take part in this optional study, researchers will use remaining tumor tissue and collect blood for research on evaluating the changes in your DNA and RNA that occur during treatment.

Researchers will obtain genetic material (DNA and RNA) from both your tumor cells and your blood. Your DNA and RNA will be used for genomic sequencing, which is sequencing of all or 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 and allows researchers to identify your genetic code. This is usually done to look for changes in your genome that may cause health problems. 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. The genomic sequencing for the cfDNA, optional biopsy and WES biomarker studies will be done by an NCI-supported laboratory in Frederick, Maryland, known as the Molecular Characterization (MoCha) 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.

Unknown future studies

If you choose to take part in this optional study, any of your tumor tissue or blood samples left over from your biopsy or blood collection will be collected and stored. Storing samples for future studies is called "biobanking." The biobank is being run by the Nationwide Children's Hospital in Columbus, Ohio, 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. Your genomic sequence will also be stored in a secure NIH database for future use. 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.

Right now, we do not know what research may be done in the future using your tumor tissue and 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 the optional sample collections?

If you agree to take part in the optional sample collections, here is what will happen next:

1. Optional cfDNA and CTC Biomarker Study: About 2 tablespoons of blood will be collected from a vein in your arm at each timepoint: before you begin study drug, Cycle 1 Day 2 (~4 hours after treatment), Cycle 1 Day 4, Cycle 1 Day 5, Cycle 2 Day 1, Cycle 3 Day 1 and at end of treatment for a total of about 12 tablespoons throughout the study.

2. Optional RNA Sequencing Biomarker Study (for patients with small cell cancer only outside of the lungs): A sample of tissue will be collected before you begin study drug. For the biopsy procedure, the study doctor will use a needle to take pieces of your tumor. This process may be repeated several times in the same appointment in order to get

enough tissue. A sample from the tissue that was collected previously may also be sent to the biobank.

3. Optional IHC Biomarker Study: A sample from the tissue that was collected at the time of your study biopsy will also be sent to the biobank. A sample from the tissue that was collected previously may also be sent to the biobank.

4. Optional WES Biomarker Study: A sample from the tissue that was collected at the time of your study biopsy will also be sent to the biobank. A sample from the tissue that was collected previously may also be sent to the biobank. About 1 tablespoon of blood will also be collected from a vein in your arm at baseline.

5. 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.

6. 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.

7. 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 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. 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. There are laws against the misuse of genetic information including non-US participants, but they may not give full protection. For more information about the laws that protect you, ask your study doctor or visit: https://www.genome.gov/10002328/

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 sample 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. Only your study doctor and a few study researchers will have access to the master list linking the code numbers to names. The biobank and the genomic sequencing laboratory will receive your samples with the following information only: your sample code number; your age, race/ethnicity, and gender; your type of cancer; any previous treatments you received for your cancer; and the treatment you will receive for this current study.
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. The researchers must be trained in the handling of private information. Any researcher who wants to study your stored samples and genetic information must apply and be approved to do so.
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.

If your doctor contacts you about a medically important finding from this optional study and you choose to see a genetic counselor or choose to have another genetic test to confirm the results, these tests and visits must be paid at your own expense by you or your insurance plan.

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 sample that remains in the biobank will be destroyed or returned to your study doctor. This will not apply to any samples or related health information that have already been given to or used by researchers.

What if I need my tissue or blood samples to be returned?

Tumor tissue or blood samples that remain in the biobank can be returned if needed for medically necessary events or procedures to assure appropriate medical care, such as for DNA or RNA analysis. Specimens may also be returned if tissue is needed to determine eligibility for enrollment in a research protocol or clinical trial. Every effort will be made to facilitate medically necessary events or procedures to assure appropriate medical care for a patient with a serious or life-threatening illness.

Tumor tissue or blood samples and genetic material (DNA and RNA) that is no longer in the biobank or that has already been given to or used by researchers cannot be returned. No samples will be returned for matters related to patients needing or wanting genetic testing to determine medically important risks.

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 known future studies:

I agree that my samples and related health information may be used for the optional cfDNA and CTC Biomarker Study described above.

YES NO

I agree that my samples and related health information may be used for the optional RNA Sequencing Biomarker (for patients with small cell cancer outside of the lungs only) Study described above.

YES NO

I agree that my samples and related health information may be used for the optional IHC Biomarker Study described above.

YES NO

I agree that my samples and related health information may be used for the optional WES Biomarker Study described above.

YES NO

I agree that my study doctor, or someone on the study team, may contact me or my doctor to see if I wish to learn about results from these studies.

YES NO

Samples for unknown future studies:

I agree that my samples and related health information may be kept in a biobank for use in future health research.

YES NO

Contact for Future Research

I agree that my study doctor, or someone on the study team, may contact me or my doctor to see if I wish to participate in other research in the future.

YES NO

Contact for Medically Important Genetic Test Results

I agree that my study doctor, or someone on the study team, may contact me and my doctor if the laboratory finds a possible genetic test result that may be important to the health of me and/or my family members.

YES NO

Before you join this study, you may wish to talk with family members to see if they would like to learn of any genetic test results that may be important to their health. You have the right to decide how to handle sharing this information with your family members. However, if you were to become unable to share this information with family members due to illness or injury, or if you were no longer alive, please select and sign one of the options below on releasing genetic information to family members. Only genetic test results that may be medically important to your family members would be released.

Select and sign ONE option from below:

(1) **You have my permission** to release my genetic test results to **any and all** family members involved, in the event that I am unable to or have not survived to grant permission myself.

Participant's signature

Date of signature

Witness's signature

Date of signature

(2) **You have my permission** to release my genetic test results or stored DNA **only** to the family members listed. Please write the name of the family member(s) in the space provided below.

Provide name of family member(s)

Participant's signature

Date of signature

Witness's signature

(3) **You do NOT have my permission** to release my genetic test results or stored DNA to any family members. I request that this information be kept private.

Participant's signature

Date of signature

Witness's signature

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

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Date of signature

Attachment A: Study Calendar

	Pre-Study	Cycle 1								Cycles 2 and onward								
		Before you begin the study drug	Day 1	Day 2	Day 3	Day 4	Day 5	Day 8	Day 15	Day 1	Day 2	Day 3	Day 4	Day 5	Day 8	Day 15	End of Treatment/ Disease Progression	Post-Treatment (Follow-up)
M6620 (VX-970, berzosertib)[A]				X			X				X			X				
Topotecan[B]			X	X	X	X	X			X	X	X	X	X				
Pre-study procedures including informed consent, height, demographics, medical history	X																	
EKG (this will occur at pre-study and at any time your physician determines is necessary)	X																	
Physical exam[C]	X		X							X							X	
Vital Signs	X		X	X	X	X	X			X[H]	X	X	X	X			X	X
General well-being (performance status)	X		X							X							X	X
Weight	X		X							X							X	X
Concurrent meds	X		X----------X														X	
Blood draw to assess how your blood is clotting	X																X	
Blood draws for complete blood count and health status[D]	X		X					X	X	X							X	
Serum Pregnancy test[E]	X		X							X								

	Pre-Study	Cycle 1								Cycles 2 and onward								
		Before you begin the study drug	Day 1	Day 2	Day 3	Day 4	Day 5	Day 8	Day 15	Day 1	Day 2	Day 3	Day 4	Day 5	Day 8	Day 15	End of Treatment/ Disease Progression	Post-Treatment (Follow-up)
Clinical disease assessment	X									X[F]							X	
Computed Tomography (CT) imaging scans for tumor measurements	X		Tumor measurements will be repeated every 6 weeks during treatment.														X	
Side effects evaluation			X----------X															
Blood draws for CTC Biomarker Study (optional)		X[I]		X[L]		X[K]				X[G, K]							X	
Blood draws for cfDNA Biomarker Study (optional)		X					X[K]			X[G, K]							X	
Blood draw for WES Biomarker Study (optional)		X[I]																
Tumor biopsy and tumor sample collection		X																
Tumor biopsy for small cell cancer outside of the lungs patients (optional)		X																
Follow-up phone call																		X[J]

A. M6620 (VX-970, berzosertib) will be given at the assigned dose intravenously (IV) for 60 minutes (+/- 10 minutes) within 15 minutes after the completion of the topotecan on Days 2 and 5 of each 21-day cycle.
B. Topotecan will be given at the assigned dose IV for 30 minutes on Day 1, 2, 3, 4, and 5 of each 21-day cycle.
C. Symptom-directed physical examinations will also be performed, as clinically indicated.
D. Blood will be drawn in Cycle 1 and only when your study doctor says it's necessary.
E. For women of child bearing potential only.
F. Performed every 2 cycles, starting with Cycle 3 (e.g., Cycle 3, Day 1 and then Cycle 5, Day 1)
G. Blood draws will only occur in Cycles 2 and 3.
H. Your vital signs will be collected on Day 1 of each cycle.

	Pre-Study	Cycle 1								Cycles 2 and onward								
		Before you begin the study drug	Day 1	Day 2	Day 3	Day 4	Day 5	Day 8	Day 15	Day 1	Day 2	Day 3	Day 4	Day 5	Day 8	Day 15	End of Treatment/ Disease Progression	Post-Treatment (Follow-up)
I. Your blood will be drawn at the same time the tumor biopsy is being taken. J. Every 3 months. K. Blood samples will be taken prior to drug administration on the same day as the biopsy. L. Blood sample will be taken about 4 hours after drugs are administered.																		