SUMMARY OF CHANGES – Consent

Consent changes for Protocol Amendment 15 to:

NCI Protocol #: 10183
Local Protocol #: ETCTN 10183
Protocol Version Date: July 22, 2024

Protocol Title: A Pilot Study of Tazemetostat and Pembrolizumab (MK-3475) in Advanced Urothelial Carcinoma (NCT03854474)

Informed Consent Version Date: July 22, 2024

#	Section	Comments
1	Header	Updates Protocol Version Date to: 07/22/2024

Research Study Informed Consent Document

Study Title for Study Participants: Testing the addition of tazemetostat to the immunotherapy drug, pembrolizumab (MK-3475), in advanced urothelial carcinoma

Official Study Title for Internet Search on http://www.ClinicalTrials.gov:
Protocol NCI 10183, A Pilot Study of Tazemetostat and Pembrolizumab (MK-3475) in advanced urothelial carcinoma (NCT03854474)

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 urothelial carcinoma (cancer that originated in the bladder or other parts of the urothelial tract) which has either grown/recurred after chemotherapy, or has spread and you are unable to receive treatment with platinum-containing chemotherapy or any chemotherapy due to medical reasons.

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:

- What is the safest dose of the drug tazemetostat to combine with pembrolizumab (MK-3475) to see if it shrinks your cancer cells or lowers the chance of your cancer cells growing and spreading.
- Can we improve the chance of your cancer responding to treatment by adding the study drug tazemetostat to pembrolizumab (MK-3475), which is approved as a single-agent for several types of cancer?

We are doing this study because we want to find out if this approach is better or worse than the usual approach for your urothelial carcinoma. The usual approach is defined as care most people get for urothelial carcinoma.

What is the usual approach to my urothelial carcinoma?

The usual approach for patients is treatment with chemotherapy or immune treatment, if applicable. Sometimes, combinations of these are used and your doctor can explain which may be best for you. These treatments can reduce symptoms and may stop the tumor from growing for several months or more.

Chemotherapy containing platinum is a preferred first treatment for patients with your type of cancer if it's medically safe to be treated with this therapy, however not all patients can get platinum-containing chemotherapyor other chemotherapy because of the side effects that can occur and/or medical reasons. For patients who are not able to receive platinum-containing chemotherapy or other chemotherapy, alternate treatments must be chosen carefully.

The drug in this study, pembrolizumab (MK-3475), is Food and Drug Administration (FDA) approved to treat your type of cancer, and it works by targeting a protein that is involved in your body's immune responses, called PD-L1. This treatment is approved for patients whose cancers progressed after receiving platinum-containing chemotherapy and for patients who are not able to receive platinum-containing chemotherapy.

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 receive the study drugs pembrolizumab (MK-3475) and tazemetostat for up to two years.

After you finish or discontinue your study treatment, your doctor and study team will continue to follow your condition for 1 year and watch you for side effects with clinic visits every 3 months.

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.
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 of pembrolizumab that the study doctors know about are:

- Tiredness
- Nausea
- Loss of appetite
- Pain in back
- Joint stiffness
- Cough
- Swelling and redness of the skin
- 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
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Reaction during or following a drug infusion which may cause fever, chills, rash
- Damage to organs in the body when donor cells attack host organs which may cause yellowing of eyes and skin, itchy dry skin'

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

- Anemia which may require blood transfusion
- Nausea, vomiting
- Tiredness
- Pain
- Constipation, diarrhea
- Fever
- Swelling of arms, legs
- Infection, especially when white blood cell count is low
- Cold symptoms such as stuffy nose, sneezing, sore throat
- Bruising, bleeding
- Weight loss, loss of appetite
- Headache
- Hair loss, dry skin

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

Benefits

There is some evidence in people with urothelial carcinoma that combining the two study drugs (pembrolizumab and tazemetostat) may have a better chance to shrink cancer cells or lower the chance of the cancer growing and spreading than pembrolizumab (MK-3475) alone. It is

unlikely that it will work in everyone with your cancer or help you live longer. 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. If you stop, you can decide if you want to keep letting the study doctor know how you are doing.

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

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

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

- Your health changes and the study is no longer in your best interest.
- New information becomes available and the study is no longer in your best interest.
- You do not follow the study rules.
- For women: You become pregnant while on the study.
- The study is stopped by the National Cancer Institute (NCI), Institutional Review Board (IRB), Food and Drug Administration (FDA), or study sponsor. The study sponsor is the organization who oversees the study.

It is important that you understand the information 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 see how people with your type of cancer respond to an approved treatment for urothelial carcinoma (pembrolizumab) in combination with the study drug tazemetostat (pembrolizumab with tazemetostat). Tazemetostat is not approved by the FDA for your type of cancer. Laboratory research indicates that combining the two drugs has the potential to have a better response than pembrolizumab (MK-3475) alone. But it could calso cause side effects, which are described in the risks sections below.

This study will help the study doctors find out the safest and most effective dose for tazemetostat when combined with pembrolizumab (MK-3475). It will also help doctors determine if the combination treatment has a better anticancer effect than treatment with pembrolizumab (MK-3475) alone. To decide if it is better, the study doctors will be looking to see if adding tazemetostat improves the response rates of patients compared to the usual approach.

Up to 30 participants will be enrolled in this study.

What are the study groups?

All study participants will get the same study interventions. Treatment will include an approved immunotherapy, pembrolizumab (MK-3475). All study participants will also get the study drug tazemetostat.

Patients in this study will have either received platinum-containing chemotherapy (the standard of care treatment), or were not eligible to receive this treatment or another chemotherapy because of the risk of side effects or other medical reasons.

The study will start with a lead in phase group where participants in groups of 3 at a time will be given the study drugs. At the beginning of the study, 3 participants will be treated with pembrolizumab in combination with the recommended dose for tazemetostat. If this dose does not cause bad side effects, another 3 participants will be treated at the same dose level. If there are any bad side effects, the dose of tazemetostat will be made lower as new participants enter the study. A total of up to 6 participants will be treated in this way. Once we have found the highest dose that is safe and does not cause bad side effects, we will treat an additional 6 participants at this dose in the expansion part of the study. The dose of tazemetostat to be used in the remainder of this study was set as of October 14, 2020.

Participants may receive this combination treatment for up to two years. Tazemetostat will be taken by mouth twice daily, in combination with pembrolizumab every three weeks continuously in a 21-day cycle. Pembrolizumab will be given intravenously on day 1 of each 3-week treatment cycle.

Tazemetostat can be taken with or without food, with doses at least 8 hours apart. If you miss a dose or experience vomiting, you should skip the dose and take the next scheduled dose.

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 tests and procedures that may need to be done as part of this study to look at research outcomes, but may not be included in the usual care. We will use them to look at research outcomes based on your tumor and genetic characteristics and help us learn more about treating your type of cancer.

The tests and procedures for research purposes include:

You will need to have blood samples collected for the study. These blood samples will be taken on Cycle 1 Day 1 (pre-dose), Cycle 2 Day 1, and Cycle 3 Day 1. A blood sample will also be taken if your disease becomes worse and you stop study treatment or at one year if you are still on therapy. You and your study doctor will not get the results of this testing.

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 if it's available. You will also be asked if you would like to undergo an optional biopsy at baseline (only if your old tissue is not available), after 2 cycles of treatment, and if your disease becomes worse. The tissue will be used to test for mutations and other characteristics of your cancer that will help researchers assess the study treatment. You and your study doctor will not get the results of this testing.

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 combination pembrolizumab (MK-3475) and tazemetostat may not be as good as the usual approach at shrinking your cancer.

You may also have the following discomforts:

- You may lose time at work or home and spend more time in the hospital or doctor's office than usual
- You may be asked sensitive or private questions which you normally do not discuss

The treatments 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 (3 months for males) after you have completed the study.

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

Blood Draw Risks

The risks of taking blood include pain, a bruise at the point where the blood is taken, redness and swelling of the vein and infection, and a rare risk of fainting.

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 can occur. You may sign a separate consent form for the study biopsy that describes the risks in more detail.

Side Effect Risks

The treatments 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 be testing 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 drugs.

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.

- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

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

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drugs to try to reduce side effects.
- The study doctor will provide you with information about other drugs you may need to avoid while receiving the study drug.

Drug Risks

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

Possible Risks of Pembrolizumab (MK-3475)

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

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

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

MK-3475 (pembrolizumab) 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
- 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
- Lung problems (pneumonitis and other conditions). Symptoms may include: new or worsening cough, chest pain, shortness of breath.
- Skin: itching; acne; rash (can be severe); blisters and peeling on the skin, mouth; skin changes; hives

RARE, AND SERIOUS

In 100 people receiving MK-3475 (pembrolizumab), 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
- 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

MK-3475 (pembrolizumab) 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
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Reaction during or following a drug infusion which may cause fever, chills, rash
- 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.
- 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.

Possible Risks of Tazemetostat

COMMON, SOME MAY BE SERIOUS
In 100 people receiving tazemetostat (EPZ-6438), more than 20 and up to 100 may have:

- Anemia which may require blood transfusion
- Nausea, vomiting
- Tiredness

OCCASIONAL, SOME MAY BE SERIOUS
In 100 people receiving tazemetostat (EPZ-6438), from 4 to 20 may have:

- Pain
- Constipation, diarrhea
- Fever
- Swelling of arms, legs
- Infection, especially when white blood cell count is low
- Cold symptoms such as stuffy nose, sneezing, sore throat
- Bruising, bleeding
- Weight loss, loss of appetite
- Headache
- Hair loss, dry skin

RARE, AND SERIOUS
In 100 people receiving tazemetostat (EPZ-6438), 3 or fewer may have:

- Cancer of bone marrow caused by chemotherapy
- Damage to the bone marrow (irreversible) which may cause infection, bleeding, may require transfusions
- A new cancer resulting from treatment of earlier cancer
- Cough, shortness of breath
- Increased risk of sunburn

You should avoid prolonged exposure to sunlight during treatment with tazemetostat. You should should wear protective clothing, sunscreen, and avoid tanning beds.

Risks when pembrolizumab and tazemetostat are given together
A lot of the side effects seen with pembrolizumab and tazemetostat are mild to moderate. However, some side effects can be very serious and life-threatening and may even result in death. Some side effects do not need treatment while others generally get better with treatment. The chances of developing any side effects, and the severity of the effect when taking pembrolizumab and tazemetostat together is unknown. However, there is a chance the overlapping side effects, such as fatigue, nausea, and diarrhea could be worse when combined.

Side Effects or Risks of Special Interest
The following side effects or risks have been identified, requiring additional monitoring, or tests, to potentially minimize the occurrence of these events.

T-cell lymphoblastic lymphoma or T-cell acute lymphoblastic leukemia (T-LBL/T-ALL)
- A 9-year-old subject treated with tazemetostat in a study being conducted in children developed a type of non-Hodgkin lymphoma, which is also called T-cell lymphoblastic lymphoma (T-LBL), after receiving tazemetostat for 14 months.

During pre-clinical animal testing, T-LBL, including lymphoid hyperplasia in the thymus, was observed in one model, rats, but not in other animal models. It was noted by the company that in rats, these events were observed at the highest doses, doses higher than have been used in humans.

B-cell acute lymphoblastic leukemia

- A patient with diffuse large B-cell lymphoma developed B-cell ALL after approximately 46 months of treatment with tazemetostat. The observed development of with B-cell ALL may be due to the underlying diffuse large B-cell lymphoma or prior therapy for the lymphoma.

As per the tazemetostat Investigator Brochure, V10.0, this is the only case of T-cell lymphoma that has occurred out of a total of 90 children enrolled in tazemetostat clinical trials. In addition, there have been no cases of T-LBL/T-ALL or B-cell ALL in the 725 adult patients treated across multiple studies conducted in different types of cancer. The company will continue to monitor all patients treated with tazemetostat very carefully for the development of secondary malignancies.

As of 1 May 2018, this is the only case of T-cell lymphoma that has occurred out of a total of 79 children enrolled in tazemetostat clinical trials. In addition, there have been no cases of T-LBL/T-ALL in the 702 adult patients treated across multiple studies conducted in different types of cancer. The company will continue to monitor all patients treated with tazemetostat very carefully for the development of secondary malignancies.

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.

Additional Drug Risks
The study drug pembrolizumab (MK-3475) could interact with other drugs. 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.

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

Genetic Testing Risk
The genetic test used in this study will test for any genetic markers and information about your tumor. This change also may 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.

Since this study is only testing tumor tissue, we will not know if a genetic change in your tumor is also in your normal tissue. If you want to find out if the change is in your normal tissue, then you will need to get other tests done outside of this study.

Genetic tests of normal tissue can reveal information about you and also about your relatives. Your study doctor will talk with you about what testing your normal tissue may mean for you and your family. He or she also may suggest that you talk with a genetics counselor to learn more. You or your insurance plan would have to pay for any genetic tests and visits to a genetic counselor done outside of this study.

What are my responsibilities in this study?

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

- Keep your study appointment.
- Tell your doctor about:
  - all medications and supplements you are taking
  - any side effects
  - any doctors' visits or hospital stays outside of this study
  - if you have been or are currently in another research study
- Write down in your medication diary when you take the study drug at home

For women: Do not get pregnant while taking part in this study and for 6 months after the last dose of tazemetostat. Do not breastfeed while taking part in this study and for 1 week after the last dose of tazemetostat. **For men:** Do not father a baby (or donate sperm) while taking part in this study and for 3 months after the last dose of tazemetostat. **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 (3 months for males) after your last dose of study drug. Treatments used in this study could be very harmful to an unborn or newborn baby.

Female and male patients of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug and for 6 months for females, or 3 months for males, after the last dose of study drug by complying with one of the following:

1. Practice abstinence[†] from heterosexual activity;

OR

2. Use (or have their partner use) acceptable contraception during heterosexual activity.

Acceptable methods of contraception are: intrauterine device (IUD), vasectomy of a female patient's male partner, or a combination of 2 of the following:

- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (women who have not had children only)
- contraceptive sponge (women who have not had children only)
- male condom or female condom (cannot be used together)
- hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection
- contraceptive rod implanted into the skin

Female subjects that use hormonal contraceptives should also use an additional barrier method.

Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the patient's preferred and usual lifestyle. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

What are the costs of taking part in this study?

You and/or your health plan/insurance company 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 urothelial carcinoma. This includes:

- the cost of tests, procedures, or medicines that you get during the study to monitor your safety, and prevent and treat side effects.
- the costs of getting the pembrolizumab (MK-3475) ready and giving it to you intravenously.
- 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 this 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 blood samples collected for research purposes
- the required biopsy at the beginning of the study if there isn't enough tissue available
- the optional biopsies and tissue collection after 2 treatment cycles and disease progression

You or your insurance provider will not have to pay for pembrolizumab (MK-3475) or tazemetostat 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 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 drug company supporting the study now or in the future. This would include any organization helping the company with the study.
- The NCI Central IRB, which is a group of people who review the research with the goal of protecting the people who take part in the study.
- The FDA and the groups it works with to review research
- The NCI and the groups it works with to review research
- The NCI's National Clinical Trials Network and the groups it works with to conduct research.

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 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. You will not get health benefits from any of these studies. The researchers leading these optional studies hope the results will help other people with cancer in the future.

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

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. You can still take part in the main study even if you say “no” to any or all of these studies. If you sign up for but cannot complete any of the studies for any reason, you can still take part in the main study.

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

Optional sample collections for known laboratory studies (translational endpoints)

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

If you choose to take part in this study, researchers will collect tissue for research on information about your tumor.

If you choose to take part, a sample of tissue from a previous or new biopsy will be collected. The researchers ask your permission to use your samples and related health information (for example, your response to cancer treatment, results of study tests and medicines you are given) for medical research. Research samples will be stored at a lab/repository at Northwestern University until they have been completely used up or they are no longer needed. If the study doctor determines that the samples are no longer needed, all stored sample material will be destroyed.

What is involved in this optional sample collection?

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

1) If you do not have tissue left over from your biopsy at diagnosis, a sample of tissue will be collected from an optional extra biopsy at baseline. .
2) A sample of tissue will be collected from an optional biopsy after 2 cycles of treatment.
3) If your disease becomes worse, you may have a biopsy as part of your standard care. A sample from the tissue will be collected at this biopsy. If there is not sufficient tissue, you may need to have another biopsy.
4) Your sample(s) and some related health information will be sent to a researcher for use in the study described above. The samples will be kept until they are used for research or destroyed.

What are the risks in this optional sample collection?

1) The most common risks related to a tissue biopsy are a small amount of bleeding at the time of the procedure, bruising, and pain at the biopsy site. Rarely, infection may occur.
2) 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.

How will information about me be kept private?

Your privacy is very important to the study researchers. 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 likning the code numbers to names, but they will keep it separate from the samples and information.

2) Researchers who study your sample and information will not know who you are. They also must agree that they will not try to find out who you are.
3) Your personal information will not be given to anyone unless it is required by law.
4) If research results are published, your name and other personal information will not be used.

What are the benefits to taking part in this optional sample collection?
You will not benefit from taking part.

The researchers, using the samples from you and others, might make discoveries that could help people in the future.

Are there any costs or payments to this optional sample collection?
There are no costs to you or your insurance. You will not be paid for taking part in this study. If any of the research leads to new tests, drugs, or other commercial products, you will not share in any profits.

What if i change my mind about 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 researchers 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 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:

TISSUE SAMPLES FOR THE LABORATORY STUDIES:

If there is not enough tissue from my previous biopsy for diagnosis, I agree to have tissue collected for laboratory studies before starting study treatment.

YES _____ NO _____

I agree to have my tissue collected after two (2) cycles of study treatment and I agree that my tissue samples and related information may be used for the laboratory studies described above.

YES _____ NO _____

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

YES _____ NO _____

I agree that my study doctor, or their representative, may contact me or my physician to see if I wish to learn about results from these studies.

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

_____

Appendix A. Study Calendar

Study Procedures Table (1 cycle = 21 days / 3 weeks)									
	Pre-Study[1]	C1	C2	C3	C4	C5	C6+	Off Study[9]	Follow-Up[10]
Pembrolizumab (MK-3475)[A, C]		X	X	X	X	X	X		
Tazemetostat[B,C]		X----------					----------X		
Informed consent	X								
Demographics	X								
Medical history	X								
Concurrent meds	X	X----------					----------X		
Physical exam	X	X[12]	X[12]	X[12]	X[12]	X[12]	X[12]	X	X
Vital signs	X	X	X	X	X	X	X	X	
Height	X								
Weight	X	X[12]	X[12]	X[12]	X[12]	X[12]	X[12]	X	
Performance status	X								
CBC w/diff, plts[11]	X	X[12]	X[12]	X[12]	X[12]	X[12]	X[12]	X	
Serum chemistry[2]	X	X[12]	X[12]	X[12]	X[12]	X[12]	X[12]	X	
TFTs (TSH, T3, T4)[3]	X	X[12]		X[12]		X[12]	X[3, 12]	X	
PT/INR and aPTT	X								
CD4 testing (only required for known HIV- positive patients)	X								
EKG	X								
Adverse event evaluation	X	X----------					----------X	X	
Tumor measurements	X				X		X	X	
Radiologic evaluation	X[5]				X[5]		X[5]	X	X
B-HCG	X[4]	X[4]							
PDL1 testing	X[6]								
Other Correlative tissue[7]	X[7]			X[7]				X[7]	
Correlative blood sample[8]		X[8]	X	X				X[8]	

A: Pembrolizumab (MK-3475): Given intravenously at 200 mg once every 3 weeks
B: Tazemetostat: Given by mouth twice daily at the assigned dose
C: Combination treatment will continue for up to 2 years in the absence of progression, until progressive disease, unacceptable toxicity, or discontinuation for any of the criteria in section 5.11.

1: Screening procedures are required within 14 days prior to registration unless listed otherwise.

2: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.

3: Patients receiving pembrolizumab (MK-3475) should be monitored for changes in thyroid function (at screening, periodically during treatment every odd cycle (C1, C3, C5, C7 etc.), post-treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.
4: Serum or urine pregnancy test (women of childbearing/reproductive potential) ≤72 hours prior to registration. Pregnancy test must be repeated on C1D1 if performed >72 hours prior to first treatment.
5: CT scan or MRI is required at screening, within 28 days prior to full patient registration. Patients will have radiographic evaluation (CT scan or MRI as appropriate) of disease response every 12 weeks (4 cycles, ± 7 days) for 6 months then every 15 weeks (5 cycles, ±7 days) up to one year, and every 18 weeks (6 cycles, ±10 days) for year 2. See also footnote 10 and Section 11.1.
6: It is highly desirable for patients to provide baseline tissue, but tissue may be sent any time.
7: Tissue will be collected for correlative studies at baseline (mandatory if available; if not available, a new biopsy is optional), prior to or during Cycle 3 (optional and recommended if patient agrees), and at the time of disease progression (optional if patient agrees). See section 9 and separate lab manual for further details.
8: Blood will be collected for correlative studies at C1D1 (pre-dose), C2D1, C3D1, and one year or the time of progression or removal from protocol (whichever occurs first). See separate lab manual for details.
9: Off-study evaluation 30 days (±10 days) after treatment discontinuation.
10: Patients will be followed for up to 1 year after treatment discontinuation with routine clinic visits every 3 months (± 10 days). For patients who discontinue for any reason other than progression, scans must be completed for up to 1 year or until confirmed progression (whichever occurs first), according to the schedule described in Section 11.1.
11: CBC with platelets and differential is required during screening, each cycle, and at the off study evaluation visit. 12: Assessments may be conducted within 48 hours prior to the initiation of the next cycle of therapy.

APPENDIX B: CLINICAL TRIAL WALLET CARD (TAZEMETOSTAT)

NIH NATIONAL CANCER INSTITUTE

CLINICAL TRIAL WALLET CARD

Show this card to all of your healthcare providers and keep it with you in case you go to the emergency room.

Patient Name:
Diagnosis:
Study Doctor:
Study Doctor Phone #:
NCI Trial #:
Study Drug(s):

For more information: 1-800-4-CANCER

cancer.gov | clinicaltrials.gov