A031501 Consent Form

Study Title for Study Participants:

Testing MK-3475 (pembrolizumab) after surgery for localized muscle-invasive bladder cancer and locally advanced urothelial cancer

Official Study Title for Internet Search on http://www.ClinicalTrials.gov:

Phase III randomized "**A**djuvant study of MK-3475 (pembrolizumab) in mu**S**cle inva**S**ive and locally **AD**vanced ur**O**thelial ca**R**cinoma" (**AMBASSADOR**) versus observation

This study is conducted by the Alliance for Clinical Trials in Oncology, a national clinical research group supported by the National Cancer Institute. The Alliance is made up of cancer doctors, health professionals, and laboratory researchers, whose goal is to develop better treatments for cancer, to prevent cancer, to reduce side effects from cancer, and to improve the quality of life of cancer patients.

WHAT IS THE USUAL APPROACH TO MY MUSCLE INVASIVE BLADDER OR LOCALLY ADVANCED UROTHELIAL CANCER?

You are being asked to take part in this study because you have had surgery to remove bladder cancer which is in the deep muscle of the bladder wall (called muscle-invasive bladder cancer) or urothelial cancer (in the urine collection area). Patients who are not in a study are usually followed with scans without treatment or are treated with chemotherapy with a combination of drugs. Cisplatin-combination chemotherapy before surgery is the standard of care if you have normal kidney function. It has been shown to improve survival in patients. If you did not get chemotherapy before surgery it can be given after surgery (also called adjuvant chemotherapy). Studies have shown adjuvant chemotherapy may lengthen the time it takes for the disease to come back but it does not improve survival in patients like yourself.
You should understand and have had an opportunity to discuss the risks and benefits of the standard of care for your disease and that you have declined the adjuvant cisplatin-based or other systemic chemotherapy based on an informed discussion with your doctor. If you have any questions please talk to your doctor.

WHAT ARE MY OTHER CHOICES IF I DO NOT TAKE PART IN THIS STUDY?

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

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

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to compare any good and bad effects of using a drug called MK-3475 (pembrolizumab) after the removal of your muscle invasive bladder cancer or urothelial cancer. MK-3475 is a drug that uses a person's own immune system to treat cancer. This study will allow researchers to know whether treatment with MK-3475 is better, the same, or worse than the usual approach. To be better, the MK-3475 should increase life by 9 months or more, compared to observation alone. The use of MK-3475 could

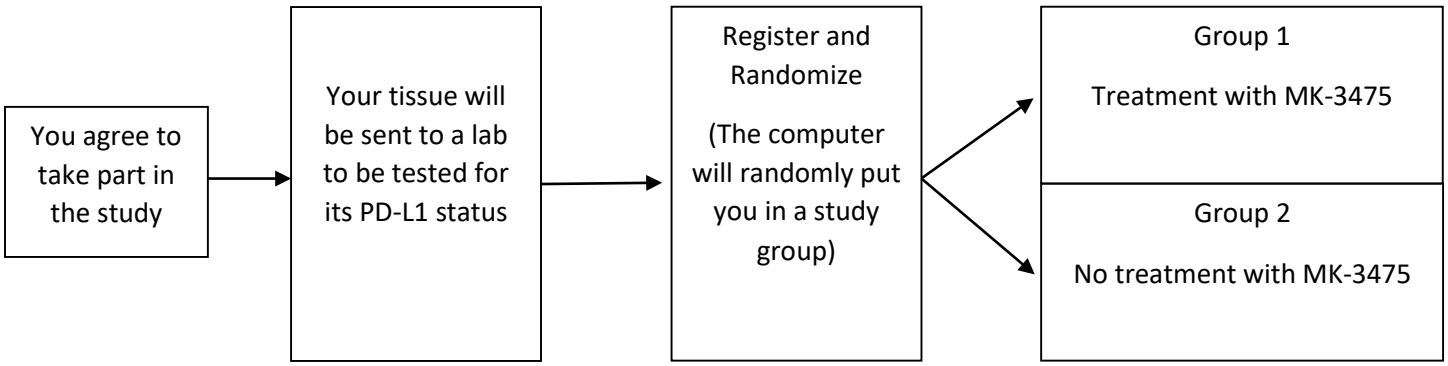
prevent your cancer from returning but it could also cause side effects. This immunotherapy drug, MK-3475, is already FDA-approved for use in other types of cancers, but for your type of cancer it is considered experimental. There will be about 739 people taking part in this study.

WHAT ARE THE STUDY GROUPS?

This study has two study groups. If you are in Group 1 you will receive treatment with MK-3475. The MK-3475 will be given through your vein over 30 minutes once every 3 weeks. If you are in Group 2 you will be followed with scans without treatment. You will not receive any treatment but you will be contacted every 3 weeks with a phone call from your doctor's office to see how you are feeling. You will also be asked to come back to the clinic every 6 weeks for a check-up for one year.
A computer will by chance assign you to one of the 2 groups in this study. This is called randomization. This is done by chance because no one knows if one study group is better or worse than the others. You will have an equal chance of being placed in either group.

Prior to randomization, a sample of your tumor tissue will be sent to a laboratory to determine if it contains a protein called PD-L1. This test is required because they will help the investigators determine who will be most likely to respond to this treatment in the future. In addition, it will ensure that the 2 groups are equal. The results of the PD-L1 will not be shared with you or your physician.

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.



HOW LONG WILL I BE IN THIS STUDY?

If you are in Group 1 you will receive MK-3475 once every 3 weeks for one year. After you finish one year of treatment, your doctor will continue to watch you for side effects and follow your condition for a total of five years after you were registered to this study. Once you stop therapy you will need to be seen every 3 months for the first 2 years following the start of treatment and then yearly the next 3 years.
If you are in Group 2 you will not receive treatment and your doctor's office will call you every 3 weeks to check on you. You will also be asked to come into the clinic every 6 weeks for a check-up for the first year after you are put onto the study. After that first year you will be seen every 3 months for the second year after you are registered to the trial and then yearly for the next 3 years.

WHAT EXTRA TESTS AND PROCEDURES WILL I HAVE IF I TAKE PART IN THIS STUDY?

Before you begin the study, your doctor will review the results of your exams, tests and procedures to make sure it is safe for you to take part. If you join the study, there will be exams, tests, and procedures that will be done to closely monitor your safety and health. Most of these are included in the usual care you would receive even if you were not in a study.
If the exams, tests, and procedures show that you can take part in the study, and you choose to take part, then you will need the following extra test. It is not part of the usual approach for your type of cancer.

- **Tissue for the PD-L1 testing:** Some of the cancer tissue that was removed when you had surgery will be needed for this study. As discussed above, this tissue will be sent to a laboratory to look at a marker called PD-L1. This sample is required in order for you to take part in this study because the research on the sample is an important part of the study. Merck, the maker of MK-3475, will pay for the costs of the PD-L1 testing.

WHAT POSSIBLE RISKS CAN I EXPECT FROM TAKING PART IN THIS STUDY?

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

- You may lose time at work or home and spend more time in the hospital or doctor's office than usual
- You may be asked sensitive or private questions which you normally do not discuss
- The study drug may not be better, and could possibly be worse, than the usual approach for your cancer.
- There is a risk someone could get access to the personal information in your medical records or other information researchers have kept about you. Someone might be able to trace this information back to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information. In some cases, this information could be used to make it harder for you to get or keep a job. (For non-U.S. participants, please verify the existence of such laws before including the following sentence.) There are laws against misuse of genetic information, but they may not give full protection. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.
- There can also be a risk in finding out new genetic information about you. New health information about inherited traits that might affect you or your blood relatives could be found during a study.

For patients in Group 1, the drug 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 drug.

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.

Possible Side Effects of MK-3475

The table below show the most common and the most serious side effects that researchers know about. 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.

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 • Infection • 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
- Fluid in the joints
- Pain in chest
- 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 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
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Reaction during or following infusion of the drug 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.

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

Reproductive risks: You should not get pregnant, breastfeed, or father a baby while in this study. The drugs used in this study could be very damaging to an unborn baby. Women of child bearing potential and men must agree to use adequate contraception (barrier method of birth control or abstinence) before registering to this study and for the duration of study participation through 120 days after receiving the last dose of treatment. If you become pregnant while receiving treatment on this study, you should inform your doctor immediately and stop the MK-3475. Two birth control methods are required if you are on treatment with MK-3475 (barrier method plus hormonal method).

WHAT POSSIBLE BENEFITS CAN I EXPECT FROM TAKING PART IN THIS STUDY?

It is not possible to know at this time if the study drug/study approach is better than the usual approach so this study may or may not help you. This study will help researchers learn things that will help people in the future.

CAN I STOP TAKING PART IN THIS STUDY?

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

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

The study doctor may take you out of the study:

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

WHAT ARE MY RIGHTS IN THIS STUDY?

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

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

WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?

The MK-3475 will be supplied at no charge while you take part in this study. The cost of getting the MK-3475 ready and giving it to you is not paid by the study sponsor so you or your insurance company may have to pay for this. It is possible that MK-3475 may not continue to be supplied while you are on the study. Although not likely, if this occurs, your study doctor will talk to you about your options.

You and/or your health plan/insurance company will need to pay for all of the other costs of treating your cancer while in this study, including the cost of tests, procedures, or medicines to manage any side effects, unless you are told that certain tests are supplied at no charge. Before you decide to be in the study, you should check with your health plan or insurance company to find out exactly what they will pay for.

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

WHAT HAPPENS IF I AM INJURED OR HURT BECAUSE I TOOK PART IN THIS STUDY?

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

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

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

WHO WILL SEE MY MEDICAL INFORMATION?

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

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

- Montana Cancer Consortium
- The Alliance, Merck (and its designees), and any drug company supporting the study
- The Institutional Review Board, IRB, is a group of people who review the research with the goal of protecting the people who take part in the study.
- The Food and Drug Administration and the National Cancer Institute

WHERE CAN I GET MORE INFORMATION?

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

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

WHO CAN ANSWER MY QUESTIONS ABOUT THIS STUDY?

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

ADDITIONAL STUDIES SECTION:

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

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

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

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

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

1. OPTIONAL QUALITY OF LIFE STUDY

If you choose to take part in this study, you will be asked to fill out 3 forms with questions about your physical and emotional well-being as a cancer patient and specific to your bladder cancer. Researchers will use this information to learn more about how cancer and cancer treatment affects people.

You will be asked to fill out these forms at 4 times during normal study clinic visits or completing them at home and sending them back by mail:

- Before starting treatment
- 6 months after you are registered to the study
- 12 months after you are registered to the study
- 24 months after you are registered to the study

Each form will take about 10 minutes to complete. The forms will ask about things like fatigue, pain, insomnia, urinary function, bowel symptoms, sexual function, and overall quality of life. You may feel uncomfortable answering some of the questions, and you can skip any you do not want to answer.

1) Please circle your answer: I choose to take part in the Quality of Life study and will fill out the forms:
YES NO

2. OPTIONAL SAMPLE COLLECTIONS FOR LABORATORY STUDIES AND/OR BIOBANKING FOR POSSIBLE FUTURE STUDIES

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

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

If you choose to take part in this study, the study doctor for the main study would like to collect blood and a sample of your tumor tissue for research on heritable changes in your DNA and how you respond to study treatment. This tumor and blood collection would be in addition to what is already being collected in order to participate in this study.

If you choose to take part, tissue and blood will be collected. The researchers ask your permission to store and 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. The research that may be done is unknown at this time. Storing samples for future studies is called “biobanking”. The Biobank is being run by the Alliance and supported by the National Cancer Institute.”

WHAT IS INVOLVED?

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

1) About 2 tablespoons of blood will be collected from a vein in your arm before any treatment is given, before you receive treatment on weeks 15, 27, 39 and 51 of treatment. Also, a sample from the tissue that was collected at the time of your surgery will be sent to the Biobank.
2) Your sample and some related health information will be sent to a researcher for use in the study described above. Remaining samples may be stored in the Biobank, along with samples from other people who take part. The samples will be kept until they are used up.
3) Qualified researchers can submit a request to use the materials stored in the Biobanks. A science committee at the clinical trials organization, and/or the National Cancer Institute, will review each

request. There will also be an ethics review to ensure that the request is necessary and proper. Researchers will not be given your name or any other information that could directly identify you.

4) Neither you nor your study doctor will be notified when research will be conducted or given reports or other information about any research that is done using your samples.
5) Some of your genetic and health information may be placed in central databases that may be public, along with information from many other people. Information that could directly identify you will not be included.

WHAT ARE THE POSSIBLE RISKS?

1) The most common risks related to drawing blood from your arm are brief pain and possibly a bruise.
2) There is a risk that someone could get access to the personal information in your medical records or other information researchers have stored about you.
3) There is a risk that someone could trace the information in a central database back to you. Even without your name or other identifiers, your genetic information is unique to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information.
4) In some cases, this information could be used to make it harder for you to get or keep a job or insurance. There are laws against the misuse of genetic information, but they may not give full protection. There can also be a risk in knowing genetic information. New health information about inherited traits that might affect you or your blood relatives could be found during a study. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.

HOW WILL INFORMATION ABOUT ME BE KEPT PRIVATE?

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

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

WHAT ARE THE POSSIBLE BENEFITS?

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?

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

WHAT IF I CHANGE MY MIND?
If you decide you no longer want your samples to be used, you can call the study doctor, who will let the researchers know. Contact information for your study doctor is listed on the consent cover page. Then, any sample that remains in the bank will no longer be used and related health information will no longer be collected. Samples or related information that have already been given to or used by researchers will not be returned. Any remaining samples will either be destroyed, or if it is a tumor block, will be returned to the site.

WHAT IF I HAVE MORE QUESTIONS?
If you have questions about the use of your samples for research, contact the study doctor. Contact information for your study doctor is listed on the consent cover page.

Please circle your answer to show whether or not you would like to take part in each option (*include only applicable questions)*:

SAMPLES FOR THE LABORATORY STUDIES:

2) I agree to have my specimen collected and I agree that my specimen sample(s) and related information may be used for the laboratory study(ies) described above.

YES NO

SAMPLES FOR FUTURE RESEARCH STUDIES:

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

YES NO

4) I agree that my study doctor, or their representative, may contact me or my physician to see if I wish to participate in other research in the future.

YES NO

This is the end of the section about optional studies.

My Signature Agreeing to Take Part in the Main 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 copy of this form. I agree to take part in the main study and any additional studies where I circled 'yes'.

Participant Signature: _____

Date: _____

Signature of Person Obtaining Consent: _____

Date: _____

Time of consent: _____ (AM) (PM)

(Required for initial consent only)