INFORMED CONSENT FORM

PHASE I STUDY OF MK-3475 IN COMBINATION WITH BCG FOR PATIENTS WITH HIGH RISK SUPERFICIAL BLADDER CANCER

You are being asked to be a subject in a research study. The main goal of a research study is to gain knowledge that may help future patients, whereas routine care is based upon the best known treatment and is provided with the main goal of helping the individual patient.

If you agree to participate in this study, you will be asked to sign this informed consent document. Informed consent is a written agreement that you, or your authorized representative, sign indicating willingness to participate in this research. This informative document will tell you about the purpose, risks, and benefits of this research study. You should consent only after you have been given all the necessary information and have had enough time to decide whether you wish to participate. Your signature on this form is voluntary and does not waive any of your legal rights or make any institutions or persons involved in this research any less responsible for your well-being.

TITLE: Phase I Study of MK-3475 in Combination with BCG for Patients with High Risk Superficial Bladder Cancer

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who can choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

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 are being asked to take part in this study because you were diagnosed with superficial bladder cancer that has not responded to previous treatment with BCG. Superficial bladder cancer is a type of cancer found in the lining of the bladder and that has not invaded the muscle of the bladder wall. Typically, superficial bladder cancer is treated with medications that are placed inside the bladder through a catheter (tube inserted into the urethra) to decrease the possibility of the cancer returning. The urethra is the tube that carries urine from the bladder to the outside of the body.

You may take home an unsigned copy of this consent form to think about or discuss with your regular doctor, family, or friends before making your decision. Whether you take part in this study or not is entirely your decision. If you decide to take part in the study and sign this form, you may still end your participation at any time. In any case, your decision will not affect your regular medical care or any benefit to which you are otherwise entitled. If you decide to take part in this study, you will be asked to sign the consent form.

WHO IS THE PRINCIPAL INVESTIGATOR FOR THIS STUDY?

Krishna A. Rao, MD Telephone Number: 217-545-1129

WHY IS THIS STUDY BEING DONE?

This study is being conducted to test the safety of Pembrolizumab, also known as MK-3475 or Keytruda®, at different dose levels in combination with the current therapy (BCG) for superficial bladder cancer. We want to find out what effects, good and/or bad, it has on you and your bladder cancer.

Pembrolizumab (study drug) aids the body's immune system in fighting cancerous tumors and is approved by the Food and Drug Administration (FDA) for the treatment of various cancer types, including lung and melanoma. It is considered investigational in this study, which means it is not approved by the FDA for the treatment of superficial bladder cancer.

Bacillus Calmette-Guerin (BCG) is used to treat bladder cancer because it stimulates immune responses that can destroy cancer cells within the bladder. It is most often used after the cancer has been removed from the bladder using transurethral resection (TUR) surgery to prevent the recurrence of the cancer. This is an FDA approved and routine treatment for superficial bladder cancer and may occur even if you choose not to participate in this study.

BCG is also used in some countries as a vaccine to provide protection against tuberculosis (TB).

When it is used to treat bladder cancer, BCG is given through a urinary catheter (intravesically) into the bladder.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 15-24 people will take part in this study. This is a multi-site study which means there are other clinics, including the Simmons Cancer Institute, that will be enrolling these patients.

WHAT WILL HAPPEN IF I TAKE PART IN THIS RESEARCH STUDY?

Before you begin the study...

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- Obtain informed consent for participation in the treatment study.
- Obtain some of your personal and background information, such as your name, date of birth, race, etc.
- Review of your medical conditions and all medications you have taken recently or are currently taking.
- A review of your current symptoms and general activity level; how well you are doing in your daily life.
- A complete physical examination, including assessment of vital signs (temperature, height, weight, heart rate, blood pressure, and respirations or breathing rate).
- Cystoscopy - a procedure used to see inside your bladder. During a cystoscopy procedure, your doctor uses a hollow tube (cystoscope) equipped with a lens to carefully examine the lining of your bladder and your urethra. The cystoscope is inserted into your urethra and slowly advanced into your bladder.
- Trans-urethral removal of bladder tumor with a diagnosis of superficial bladder cancer (surgical removal of the tumor through the urethra rather than an incision on the abdomen). If you have had removal of your tumor at another institution and it is unclear if the tumor has advanced from the lining of your bladder into the muscle of the bladder you may need to have a second surgical procedure to ensure that you do not have more advanced disease. Bladder cancer that has crossed into the bladder muscle is treated differently than cancer that only remains in the lining of the bladder.
- Biopsy - A small amount of tissue will be removed from your bladder to determine if you have cancer. The biopsy may have been performed previously and, if so, will only be repeated if it is required to confirm that your cancer has not crossed into the bladder muscle.

In order to participate in the treatment portion of the study, a sample of your tumor is required in either the form of previously collected specimens or slides OR a new specimen or slides from a current biopsy.

Additional specimens, including blood, saliva and urine are requested at various time points throughout the study. These specimens are optional and you may decline them and still participate in the treatment study. You will be given the option to decline or accept these additional specimens later in this consent.

If these tests and procedures show that you have superficial bladder cancer, then you will need the following tests and procedures required by the study before you begin treatment:

- Electrocardiogram (ECG) - a tracing of the electrical activity of the heart. This procedure may be done at other times during the study, if deemed appropriate by your study doctor.
- Chest X-ray - a painless test that creates pictures of the structures inside your chest, such as your heart, lungs, and blood vessels.
- Pulmonary function tests - a group of tests that measure how well the lungs take in and release air and how well they move gases, such as oxygen from the air into the body's blood stream.

  If you currently have, or have had in the past, an inflammation of the lungs not caused by an infection that required treatment with steroids you may not be eligible to participate in this study. Please inform the study team if you have any lung related conditions.
- Blood tests to determine your blood count and chemistry, to check your overall health, and to see how well your blood clots.
- Urine analysis - an examination of your urine to check for disease and kidney health.
- Thyroid function - a blood test to determine the levels of hormones produced by the thyroid gland.
- Hepatitis Panel - a blood test for viral infections of the liver.
- Pregnancy test, if you are a woman of child bearing potential.
- Blood, saliva, urine and tissue samples collected for additional research.
- American Urologic Association symptom index and quality of life questionnaire.

During the study...

If the exams, tests and procedures show you can be in the study, and you choose to take part, you will then receive the following treatment.

BCG

BCG is a bacterial strain called Bacillus Calmette-Guerin. It contains live, attenuated (weak) bacteria. In order for BCG to work it must come in direct contact with the tumor cells. In order to do so the BCG is instilled (administered directly into the bladder). You will receive treatment once a week for 6 weeks as part of this study treatment. BCG treatment will begin on Day 1 of Week 7. Depending on your response after Week 19, you may have additional treatments beyond the 6 scheduled, but they will be outside of your participation in this study.

Below is a description of the procedure:

It is suggested that you limit your fluid intake for 4 hours before the procedure, so you will be able to hold the medicine in your bladder during the treatment. Upon arrival, you will be asked to provide a

urine specimen to ensure that it is safe to administer your BCG treatment. It is important that you be on time to your appointment as your BCG is mixed specifically for you and can only be kept for a short time.

BCG is given through a urinary catheter (a tube inserted through your urethra). Treatment may be uncomfortable, but generally is not painful. The actual placement of the BCG into your bladder only takes a few minutes. The BCG will be instilled into the bladder according to this site's institutional standards based on FDA approved indications for treatment of bladder cancer. If you have any questions, please ask the study staff.

Once outside the body, BCG fluid may be unsafe for you and others to come in contact with it. Simple safety measures will help keep you and others safe. This includes sitting down while urinating, adding bleach to the toilet, closing the toilet lid before flushing, and washing your hands and genital areas carefully with soap after every urination.

You will also be asked to drink plenty of fluids to help wash out the BCG from your bladder after treatment has finished.

You should report any unusual symptoms to your study doctor while undergoing BCG treatment. This includes: noticing blood in your urine, urgent or frequent need to urinate, flu-like symptoms or a fever of 101.3ºF or higher.

Pembrolizumab (study drug)
Pembrolizumab will be given to you through intravenous (needle inserted into your vein) infusion. You will be given study drug once every 21 days (one cycle) for a total of 6 cycles. It will take 30 minutes for the infusion of the study drug. If you develop side effects as a result of the study drug or its infusion you may be given pre-medications prior to your treatment to lessen the side effects. This may lengthen your treatment time.

Pembrolizumab will be given on Day 1 of weeks 1, 4, 7, 10, 13, and 16 while BCG will be given on Day 1 of weeks 7-12.

The first three patients enrolled in the study were given a dose of 100mg of pembrolizumab. The data safety committee approved the escalation of the dose to 200mg of pembrolizumab in combination with BCG. You will be in the group treated with 200mg of pembrolizumab in combination with BCG.

While being treated…

You will need these tests and procedures that are part of regular care, but may be done more often because you are in this study. Additional tests may also be done as part of your regular care, if your doctor requests them.

- Physical examination and reporting of adverse events (side effects) will be performed before each administration of study drug.
- Review of your medications and any changes that may have occurred.
- Review of how you are performing in your daily activities.
- Urinalysis will occur at weeks 7-12 prior to each BCG treatment.

You will need these tests and procedures that are being done to see how the study is affecting your body.

- You will be asked to complete questionnaires about your urination habits (frequency, urgency, etc.) and quality of life on Day 1 of weeks 1, 10 and 19.
- Blood counts will be obtained on Day 1 of every 21 day cycle.
- Blood chemistries will be performed on Day 1 of weeks 1, 7, 10, 13 and at the end of therapy (Week 19).
- Blood tests will be performed to evaluate your blood clotting function (may be done more frequently when clinically indicated).
- You will be called on Days 2 through 4 of each BCG treatment (Weeks 7-12) to inquire about any symptoms you may be having and to see if you have a fever.
- You will be given a thermometer and a diary to fill out during the weeks of your BCG treatment. You will be asked to take your temperature in the morning and evening every day and record it on the diary as well as any symptoms you are having. This will occur every day for the full 6 weeks of BCG treatment or a total of 42 days.
- Blood, urine and tissue samples will be collected for additional research.

When you finish your treatment (Week 19)...

You will need the following tests and procedures. They are part of regular care.

- Physical examination with vital signs and weight.
- Review of your medications, symptoms and any adverse effects you may be having.
- Review of how you are performing in your daily activities.
- Blood tests to evaluate your blood clotting function.
- Tests for blood counts and chemistries.
- Urine analysis, cystoscopy and possible bladder biopsy.

You will need these tests and procedures that are being done to see how the study is affecting your body. (All done once at the 30 day follow up after the end of treatment, unless otherwise indicated.)

- Collection of blood and urine samples for additional research studies (Week 19 only), if you agree to the optional collection for future research.
- Collection of bladder tissue taken (required), only if you have a biopsy during your cystoscopy at Week 19.
- You will be asked to answer the American Urologic Association symptom index and quality of life questionnaire (and also at 90 days after your cystoscopy).
- Review of your medications, symptoms and any adverse effects you may be having.
- Tests for blood counts and chemistries, as well as thyroid function.
- Review of the status of your disease (has it recurred and if any new therapies have occurred) at 90 days after your cystoscopy.

WHAT HAPPENS DURING LONG TERM FOLLOW UP?

The study wants to monitor your cancer status following your treatment. Subjects who complete all study treatment or discontinue study treatment for any reason other than disease progression will move into the Follow-Up Phase of the study.

Information about your cancer (if it has returned) and any new treatments will be monitored at about 3, 6, 9, 12, 18 and 24 months after completion of study treatment/cystoscopy. We expect this to somewhat follow your usual routine care. Usual care will include cystoscopy and possible biopsy or resection, if indicated by your urologist. We will collect information through routine visits, calls or from public sources, such as obituaries. If a clinic visit is required, it may be done at another clinic if you do not live locally.

If you agreed to the collection of research specimens, you will also be asked to provide urine, blood and tissue (only if a biopsy or resection is required medically) at these visits if you are being seen at the study site.

You will also be asked to complete a set of final questionnaires about your urination habits (frequency, urgency, etc.) and quality of life during the study Follow-up Phase. These questionnaires can be completed at a clinic visit, by mail or at the time of a telephone contact.

HOW LONG WILL I BE IN THIS STUDY?

You will be in this study for approximately ***28 months*** from the time of consent until final follow up for the study.

CAN I STOP BEING IN THIS STUDY?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the Pembrolizumab can be evaluated by your study doctor. Another reason to tell your study doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow study instructions; or if the study is stopped.

WHAT SIDE EFFECTS OR RISKS CAN I EXPECT FROM BEING IN THIS STUDY?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors do not know all the side effects that may happen. Side effects may be mild to very serious. Your health care team may give you medicines to help lessen side effects.

Many side effects go away after you stop taking the Pembrolizumab. In some cases, side effects can be serious or long-lasting or may never go away. Serious side effects are those that may require hospitalization or may be irreversible, long-term, life threatening or fatal. To identify the “serious” risks, a double asterisk (**) has been placed next to the risk below.

Pembrolizumab works by helping your immune system 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.

It is also possible to experience a serious allergic reaction, which could become life-threatening or fatal. Symptoms of an allergic reaction include rash, hives, itching, swelling of the mouth, face, lips, tongue or throat, dizziness, tightness in the chest, coughing or trouble breathing. If you believe you are having a serious allergic reaction, you should seek emergency medical assistance immediately.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks and side effects related to the <u>Pembrolizumab</u> include the following:

<u>VERY COMMON, SOME MAY BE SERIOUS</u> (i.e. causing hospitalization, life-threatening or where noted, may cause death)

Out of 100 people who receive pembrolizumab, 20 or more people may have the following:

- Itching of the skin
- Loose or watery stools
- Cough

<u>COMMON, SOME MAY BE SERIOUS</u> (i.e. causing hospitalization, life-threatening or where noted, may cause death)

Out of 100 people who receive pembrolizumab, at least 5, but less than 20 people, may have the following:

- Joint pain
- Rash
- Fever
- Back pain
- Pain in your belly
- Loss of skin color
- Not enough thyroid hormone so you may feel tired, gain weight, feel cold, have infrequent or hard stools
- Low levels of salt in the blood that may cause you to feel tired, confused, have a headache, muscle cramps and/or feel sick to your stomach

LIKELY CHANGES IN LABORATORY RESULTS

- Hyperglycemia (increase in glucose levels in blood)
- Hyponatremia (low sodium levels in blood)

- Hypoalbuminemia (low levels of albumin in blood)
- Hypertriglyceridemia (high triglyceride levels in blood)
- Increased liver enzymes
- Hypocalcemia (low levels of calcium in the blood)

UNCOMMON, SOME MAY BE SERIOUS (i.e. causing hospitalization, life-threatening, or where noted, may cause death)

Out of 100 people who receive pembrolizumab, at least 1, but less than 5 people, may have the following:

- **Inflammation of the lungs so you may feel short of breath and cough. Sometimes this might lead to death.
- Too much thyroid hormone so you may feel anxious, angry, have trouble sleeping, feel weak, tremble, sweat, feel tired, have loose and watery stools.
- **Infusion reaction, where you may feel dizzy or faint, flushed, get a rash, have a fever, feel short of breath, experience a decrease in blood pressure at the time of receiving your infusion (IV) or just after, or pain at the site of infusion.
- **Inflammation of the bowels/gut, which may cause severe pain in your belly with loose or watery stools, and black, tarry, sticky stools or stools with blood or mucus.
- **Inflammation of the skin so you may have peeling of the skin, itchiness, and/or skin redness. The skin inflammation (i.e. peeling, itching and redness) could also be widespread throughout your body. More severe skin reactions may involve the inside of your mouth, the surface of your eye and genital areas, and/or may cause the top layer of your skin to peel from all over your body which can cause severe infection. These severe conditions can sometimes lead to death.

RARE, SOME MAY BE SERIOUS (i.e. causing hospitalization, life-threatening, or where noted, may cause death)

Out of 100 people who receive pembrolizumab, less than 1 person may have the following:

- **Inflammation of the nerves that may cause pain, weakness or tingling in your hands and feet, and may spread to your legs, arms and upper body leading to severe muscle weakness and possible temporary paralysis.
- **Inflammation of the muscles so you may feel weak or have pain in your muscles.
- **Inflammation of the pancreas (a gland in your abdomen that controls sugar levels) so you may have severe pain in the top part of your belly that may move to your back, feel sick to your stomach, and vomiting that gets worse when you eat.
- **Inflammation of the eye so you may have eye redness, blurred vision, sensitivity to light, eye pain, see floaters or have headaches.
- **Inflammation of the liver that may make you feel sick to your stomach and vomit, feel like not eating, feel tired, have a mild fever, have a pain in the right side of your belly, yellow eyes and skin, and dark urine.

- **Inflammation of the pituitary gland (a gland in the head), which may cause you to feel sick to your stomach or have headaches, changes in your behavior, double vision, few to no menstrual cycles, weakness, vomiting and dizziness or fainting.
- **Adrenal glands (glands on top of the kidneys) that may not make enough hormone (secondary adrenal insufficiency), which could cause tiredness, weight loss, muscle weakness, feeling faint, joint, muscle and belly aches, nausea, vomiting, loose or watery stools, fever, salt craving, and sometimes darkening of the skin like a suntan.

  **A more serious form of adrenal insufficiency (primary adrenal insufficiency, also called Addison's disease) has been identified with the use of pembrolizumab. Primary adrenal insufficiency has similar side effects as secondary adrenal insufficiency, but can be life-threatening. Primary adrenal insufficiency is an irreversible condition.
- **Type 1 Diabetes, a condition that can cause too much sugar in your blood, feeling thirstier than usual, frequent urination and weight loss. You are likely to need regular insulin shots.
- **Inflammation of the kidney so you may pass less urine or have cloudy or bloody urine, swelling and low back pain.
- **Inflammation of the middle layer of your heart wall that may cause your heart to have difficulty pumping blood throughout your body, which can cause chest pain, shortness of breath and swelling of the legs. You may experience a fast or irregular heartbeat that may cause dizziness or fainting. Sometimes this condition can lead to death.
- **Inflammation of the thyroid gland, an organ that makes and stores thyroid hormones. This condition may lead to a change in your heart rate, blood pressure, body temperature, and the rate at which food is converted into energy.
- **A condition that may make you feel weak and tired and might have drooping of the eyelids, blurred or double vision, difficulty swallowing, slurred speech, weakness in your arms and legs, or difficulty breathing.
- **The formation of small clusters of immune cells (called granulomas) in parts of your body such as your lymph nodes, eyes, skin, or lungs.
- **Inflammation of the brain with confusion and fever. This may also include: disorientation, memory problems, seizures (fits), changes in personality and behavior, difficulty speaking, weakness or loss of movement in some parts of your body, and loss of consciousness.
- **Pulmonary Embolism (blood clot in the lung that presents with symptoms of chest pain/discomfort and shortness of breath)

Additionally, since pembrolizumab was approved in September 2014, side effects have been reported by people receiving pembrolizumab. These side effects were voluntarily reported from a group of people of unknown size. It is not possible to estimate the frequency of these side effects:

- Inflammation of the joints (arthritis) which may include joint pain, stiffness and/or swelling.
- **Severe responses of the immune system that cause the body to attack its own blood cells, spleen, liver, lymph nodes, skin and brain. This may include fever, rash, inflammation of the liver, yellowing of the skin, an enlarged liver and spleen, low blood

counts, and enlarged lymph nodes. The nervous system may also be affected and cause confusion, seizures, and even coma.

- ****If you have had** an allogeneic stem cell transplant (a procedure in which a person receives blood-forming stem cells from a donor), you may experience graft versus host disease (GvHD), which may include diarrhea, skin rashes, and liver damage, **after receiving pembrolizumab**. Sometimes this condition can lead to death.
- ******If you have had a solid organ transplant (for example, if you received a kidney or heart transplant), you may experience rejection of the transplanted organ. Your doctor will monitor you and should tell you what signs and symptoms you should report depending on the type of organ transplant you have had.

Risks and side effects related to the <u>BCG</u> treatment include the following:

<u>Likely (Greater than 20 out of 100 patients experienced these side effects)</u>

- Painful urination
- Urinary frequency
- Flu-like symptoms
- Hematuria (blood in urine)
- Fever

<u>Less Likely (Between 4 and 20 out of every 100 patients experienced these side effects)</u>

- Malaise/fatigue
- **Cystitis (inflammation of the bladder)
- Urgency (the feeling of the need to urinate)
- Nocturia (frequent urination throughout nighttime)
- Cramping or pain in bladder
- Chills
- Nausea
- Incontinence (loss of bladder control)

<u>Rare, but serious (Less than 4 out of every 100 patients experienced these side effects)</u>

- **Anemia - decrease in the number of red blood cells which may cause tiredness
- **BCG sepsis – whole body inflammation caused by severe infection
- **BCG infection in other organs
- **Coagulopathy - impaired clotting of blood
- **Contracted Bladder (spasms of the bladder)
- **Epididymitis/prostatitis - inflammation of the prostate or epididymis, the tube which carries sperm from the testicle
- **Hepatic Granuloma –a collection of immune cells in the liver
- **Hepatitis-Inflammation of the liver
- **Leukopenia - decreased number of blood cells which help fight infection

- **Orchitis - inflammation of the testis
- **Pneumonitis - inflammation of the lung
- **Urinary obstruction-blockage of the flow of urine from the body

REPRODUCTIVE RISKS

The effects of the investigational drug on an unborn child are unknown. You should not become pregnant or father a baby while on this study. It is very important that you practice birth control to prevent pregnancy during this study.

If you are sexually active, you and your partner must use adequate and acceptable methods of birth control to avoid pregnancy from the time the consent form is signed and for 120 days after your last dose of study drug. Acceptable methods include use of an IUD, contraceptive rod implant, vasectomy of the male partner or a combination of two of any of the following: diaphragm with spermicide, cervical cap with spermicide, contraceptive sponge, male or female condom (cannot be used together), and hormonal contraceptive pill/patch/subcutaneous injection. If you or your partner do become pregnant, you should notify the study doctor as soon as possible.

Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle.

Female participants must not be pregnant at the time of study entry. This must be confirmed by a pregnancy test taken within 96 hours before the first dose of the study drugs. Women should not breast feed a baby while on this study because the study drugs may affect an infant.

If you do become pregnant, you will stop taking study drugs, but will be followed for safety reasons. You will be followed by the study doctor until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the study doctor will notify the sponsor of the research. At the completion of the pregnancy, the study doctor will document the outcome of the pregnancy.

For men, if your spouse or partner thinks she is pregnant during the study, tell your study doctor immediately. The study doctor will ask to follow the pregnancy until completion. If the pregnancy ends for any reason before the anticipated date, the study doctor will notify the sponsor of the research. At the completion of the pregnancy, the study doctor will document the outcome of the pregnancy.

The effects of the study drugs on male fertility are unknown.

If you are a patient at St. John's Hospital, you should be aware that St. John's (an Affiliate of Hospital Sisters Health System), a Catholic health care facility, adheres to the Ethical and Religious Directives for Catholic Health Care Services. St. John's is not endorsing birth control; however, in order to maintain compliance with the study, we are required to provide this information to participants, as a matter of public safety. Please note that no method of birth control besides complete abstinence provides 100% protection from pregnancy. If you are concerned about the morality of methods of birth control, please consult your religious advisor before agreeing to participate in this study.

For more information about risks and side effects, ask the study doctor.

There are risks to taking part in any research study. Participation in this study may involve some risks or discomforts. These may be related to the procedure itself or to the study drugs. There may be some unanticipated risks.

The anticipated risks and discomforts related to the procedures include, but are not limited to, the following:

Intravenous (IV) Infusions: A method of delivering drugs directly into a vein (intravenous) using a needle or tube. A thin plastic tube called an IV catheter is inserted into the vein. While delivery of drugs by IV is generally safe, it can cause side effects. Examples of IV side effects include:

- Infection at the infusion site which can also travel into the bloodstream causing a severe infection throughout the body; symptoms can include fever and chills, as well as redness, pain, and swelling at the infusion site.
- Damage to blood vessels and infusion site which can cause infiltration (causing the drug to leak into surrounding tissue instead of going into the bloodstream). Infiltration can cause tissue damage. Phlebitis, or inflammation of the veins is also possible; symptoms of both infiltration and phlebitis include warmth, pain, and swelling at the infusion site.
- Air embolism which can cause air bubbles to travel to the heart or lungs and block blood flow; an air embolism can cause severe problems, such as heart attack or stroke.
- Blood clots can form which can block important blood vessels and cause problems such as tissue damage or death; deep vein thrombosis (DVT) is a type of dangerous blood clot that IV treatment can cause.

Urinary Catheter Insertion: A procedure using a thin plastic tube inserted through the urethra to deliver BCG to the bladder. Side effects include:

- Discomfort and/or pain during the catheter insertion; numbing medication may be used to reduce the discomfort.
- Infection in the urethra, bladder or, less commonly, kidneys; symptoms include pain in the bladder or urethra, offensive-smelling discharge from the urethra, passing foul-smelling, cloudy urine, general symptoms of an infection, such as a high temperature (100.4°F or above), a feeling of being generally unwell, tired and lethargic (lacking in energy).
- Bladder spasm, which feels like abdominal cramps.
- Leakage around the catheter causing incomplete delivery of the BCG dose.
- Injury to the urethra caused by inserting the catheter.
- Injury to the bladder or rectum (back passage) caused by incorrectly inserting the catheter.

Blood Sampling: Obtaining blood may sometimes cause local pain or discomfort at the site where the blood is drawn, bruising, occasional light headedness and, rarely, fainting.

Approximately 30 - 45 ml (2 - 3 tablespoons) of blood will be collected during your screening visit and then approximately 10 ml (2 teaspoons) each cycle of treatment.

ECG: You may experience some discomfort, skin redness or irritation when the ECG electrodes are removed from the skin.

Chest X-ray: There is low radiation exposure. X-rays are monitored and regulated to provide the minimum amount of radiation exposure needed to produce the image. Most experts feel that the risk is very low compared with the benefits. Pregnant women and children are more sensitive to the risks of X-rays.

Transurethral Bladder Resection: There is a risk of bleeding, infection of the bladder, perforation (or hole) of the bladder wall, blood in the urine or blockage of the urethra by blood clots in the bladder.

Cystoscopy: There is a risk of bleeding, infection of the bladder, and complications from the anesthesia. There are also risks of perforation of the bladder or anywhere along the urinary tract, development of scar tissue which can cause difficulties in urination, and the inability to urinate or obstruction of the flow of urine. The bladder can also become distended during the procedure, which temporarily weakens the voiding muscles.

- Men can sometimes experience pain and swelling in the testicles after an extensive procedure.

Biopsy: All medical procedures that involve removing tissue run the risk of bleeding and infection. There is also a risk of blood or blood clots in your urine, as well as a burning sensation when you urinate.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

If you agree to take part in this study, there may or may not be medical benefit to you. We hope the information learned from this study will benefit other patients with superficial bladder cancer in the future.

WHAT OTHER OPTIONS ARE THERE?

Instead of being in this study, you have these options:

- You could choose not to participate in this study.
- You could choose to receive only treatment with BCG and follow up with cystoscopy to treat recurrence if it happens.

Please talk to your regular doctor or the study doctor about these and other options.

WILL MY MEDICAL INFORMATION BE KEPT PRIVATE?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

A federal law called the Genetic Information Nondiscrimination Act (GINA) generally makes it illegal for health insurance companies, group health plans, and employers with 15 or more employees to discriminate against you based on your genetic information. GINA does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. GINA also does not protect you against discrimination based on an already-diagnosed genetic condition or disease.

State law may require that you sign a separate consent form for HIV, Sexually Transmitted Diseases (STD) or communicable diseases testing. Test results may be reportable to the Illinois Department of Public Health (IDPH). For more information please visit http://www.idph.state.il.us/.

WHAT ARE THE COSTS?

The following tests and/or procedures are required solely for the purposes of this research study and will be paid for by the sponsor of the study. (They will be provided at no cost to you or your insurance company.):

- All blood tests (blood counts and chemistries, thyroid function tests, hepatitis panel, sample collection), pulmonary function tests, electrocardiogram, and chest X-ray required to make sure you could enter the study, and that are performed to monitor for side effects of the investigational therapy.
- The pembrolizumab will be provided at no cost as well as the cost for intravenous treatment once every 3 weeks for the total of 6 treatments.
- The BCG will be provided at no cost. However, you or your insurance company will be charged the cost associated with the BCG instillation (delivery through a urinary catheter).

You or your insurance company will be charged for routine care (i.e., cystoscopy, urinalysis, resection) and continuing medical care and/or hospitalization at the usual rate.

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

INSTITUTION AND INVESTIGATOR INTERESTS

SIU School of Medicine and the Principal Investigator, Krishna A. Rao, MD, received a grant from Merck & Co. to support the costs of conducting this clinical trial. Merck & Co. is the manufacturer of the drug (Keytruda®/MK-3475/pembrolizumab) being used in this study. Merck & Co. is also providing the drug free of charge to subjects while participating in this study.

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

If you are injured during your participation in this study, you should contact the study doctor as soon as possible in person or at the telephone number listed on page 2 of this consent form. If you have a medical emergency during the study, you should go to the nearest hospital emergency room. Be sure to tell the hospital staff that you are in a research study being conducted at this study clinic. Ask them to call the study doctor at the telephone number on the second page of this consent form for further instructions or information about your care.

In the event of any injury resulting from study procedures, immediate medical treatment for injuries is available at usual and customary fees at Memorial Medical Center or St. John's Hospital, Springfield, Illinois or your local hospital.

Your medical expenses will be your responsibility or that of your third-party payer, although you are not precluded from seeking compensation for injury related to your participation in the research study.

If you suffer any physical injury as a result of participation in this study, you should contact the Chairperson of the Springfield Committee for Research Involving Human Subjects (which is a group of people who review the study to protect your rights) at:

Southern Illinois University School of Medicine
201 East Madison
P.O. 19664
Springfield, IL 62794-9664
Telephone number: (217) 545-7602

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or may leave this study at any time. Leaving this study will not result in any penalty or loss of benefits to which you are entitled.

We will tell you about new information that may affect your willingness to stay in this study.

WHO WILL USE AND SHARE INFORMATION ABOUT MY PARTICIPATION IN THE STUDY?

This section explains who will use and share your study-related health information if you agree to participate in this study.

A federal privacy law, the Health Insurance Portability & Accountability Act (HIPAA), protects your individually identifiable health information (protected health information). The privacy law requires the researchers to get your agreement to allow them to use and/or disclose your protected health information for research purposes in this study. Your agreement will be documented when you sign this consent. This authorization to use and share your information expires in 50 years.

During the study, the researchers will use, collect, and record health information about you. This can include any information about you that the study doctor needs to conduct this study.

The protected health information that may be used and/or disclosed includes:

- Name
- Address
- Telephone number
- Social security number
- Medical record number
- Race
- Gender
- Date of birth
- History and diagnosis of allergies
- Family medical history
- Current and past medical records
- Prior medical history
- Current and past medications
- Current and past therapies
- Information from a physical examination that generally also includes blood pressure reading, heart rate, breathing rate, temperature, height and weight

- Medical data, including blood and urine test results, pathology reports, and scan results (MRI, CT, ECHO, MUGA, EKG, etc.)
- Information on side effects (adverse events) you may experience, and how these were treated.

If you sign this consent, you agree to allow the study doctor and research team to use and/or disclose your protected health information described above with:

- SIU HealthCare
- SIU School of Medicine
- Memorial Medical Center
- St. John's Hospital
- Merck Sharp, & Dohme Corporation, any laboratories, individuals, and organizations that use your health information in connection with this study, including the researchers at other sites.
- The study sponsor, SIU School of Medicine, including representatives, collaborators, assignees, licensees or designees and their affiliates, agents, employees, its current or future research partners, collaborators and other individual organizations that analyze or use the information for research activities (e.g. laboratories, etc.)
- Southern Illinois University School of Medicine's Institutional Review Board: The Springfield Committee for Research Involving Human Subjects (SCRIHS)
- Government representatives, when required by law
- U.S. Food and Drug Administration (If an FDA regulated clinical trial)
- Office for Human Research Protections (OHRP)

There are national and state laws that require the study doctor to protect the privacy of your records. However, you do not have a guarantee of absolute privacy. Some information may be subject to re-disclosure. If this should occur, your information may no longer be covered/protected by the federal privacy protections.

If you would like to know how the sponsor would protect the privacy of your records, ask the study doctor how to get this information.

You have the right to see and copy your records. However, if you sign this consent form, you may not be able to see or copy some records until all subjects complete the study. Once the study has ended, you will be able to see and copy your records.

You can withdraw your consent to use and share your records at any time. **If you choose to withdraw your authorization, you must submit this request in writing** to Dr. Krishna A. Rao to inform him of your decision at the following address:

Krishna A. Rao, MD
Associate Professor of Clinical Medicine
Department of Internal Medicine, Division of Hematology/Oncology
Southern Illinois University School of Medicine
Attention: Clinical Trials Office, Room 3000
315 West Carpenter Street, Springfield, Illinois 62702
Telephone: 217-545-1129

If you decide to withdraw from this study, federal regulations may allow the data collected about you to continue to be used for the purposes of the study. Please be sure to ask the study doctor about your options for removing your data should you withdraw from this study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study or a study-related injury, contact the study doctor Krishna A. Rao, MD at 217-545-1129.

For questions about your rights as a study participant, contact the Springfield Committee for Research Involving Human Subjects (which is a group of people who review the study to protect your rights) at:

Southern Illinois University School of Medicine
201 East Madison
P.O. 19664
Springfield, IL 62794-9664
Telephone number: (217) 545-7602

The Chairperson of this committee will review the matter with you.

THE REMAINDER OF THIS PAGE IS INTENTIONALLY LEFT BLANK.

Permission for Future Research

SIU School of Medicine, the study sponsor, would like to keep any unused portion of your tumor and saliva, blood and urine samples in a tissue bank for future research. The main goal of a Tissue Bank is to collect biological specimens (tissue, hair, blood, etc.) for use by researchers to gain knowledge about human disease that may help other people in the future. The specimens will be stored until your specimens are used up or for 50 years, whichever occurs first.

At this time, it is impossible to name all the different types of studies that researchers may want to perform using your specimens, including studies on the genetics of your disease. However, studies performed using these specimens can help researchers understand how the human body works and can be helpful in the development of new tests and treatments for diseases. In the future, this research may help to develop new products, such as drugs or tests to detect disease. Some of the possible goals of the research involving human specimens might include determining whether a particular gene (material that is passed from parents to child that determines the makeup of the body) is associated with a certain type of disease. You should be aware that new products might be developed and commercially sold as a result of research done on your specimens. You should understand that you will receive no economic benefit from this commercial development. You will not be offered any compensation for your tumor, saliva, blood and urine samples.

The research that may be conducted with your specimens is not designed to provide direct benefit to you. You will not be notified of any results of the research conducted using your specimens. However, others may be helped through the knowledge gained from these studies regarding diseases or conditions and how to detect, prevent or treat them.

Information from your medical records may be stored along with your specimens. The results of research, including genetic testing, not described in this informed consent document will not be provided to you or your healthcare provider. Any information obtained for the Tissue Bank that may identify you will remain confidential within the limits of the law or will be disclosed only with your permission and the approval of the Springfield Committee for Research Involving Human Subjects.

A federal law called the Genetic Information Nondiscrimination Act (GINA) generally makes it illegal for health insurance companies, group health plans, and employers with 15 or more employees to discriminate against you based on your genetic information. GINA does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. GINA also does not protect you against discrimination based on an already-diagnosed genetic condition or disease.

The study sponsor may share your specimens with researchers or collaborators at other institutions. Information that could be linked to you or allow your specimens to be identified will not be released with your specimens. Should any publication or public presentation result from this research, your identity will not be revealed.

CONSENT/AUTHORIZATION FOR ADDITONAL RESEARCH ON SPECIMENS

We would like to request your consent to use your tumor tissue samples, and saliva, blood and urine samples collected during the study to perform additional research on superficial bladder cancer. You are free to change your mind at any time. If you wish to withdraw consent for use of the samples, you

will need to contact the study center and inform them of your decision. The sponsor can keep and use any information from the samples which is obtained prior to your decision to withdraw consent.

Please indicate below whether you agree to allow for the following:

1. **If I am unable to participate in the TREATMENT STUDY, I would like my specimens destroyed**.

   ☐ YES

   ☐ NO (If no, please see question 2 below)

   Participant's Initials _____

2. I agree to the storage of and additional analysis of the sample taken from the **tumor and surrounding tissue** after my trans-urethral resection of my bladder:

   ☐ YES, I give permission for my tumor and surrounding tissue sample to be stored and used for additional research.

   ☐ NO, I do not give my permission for my tumor tissue and surrounding tissue sample to be stored and used for additional research.

   Participant's Initials _____

3. Collection of **blood** for storage and analysis for future research.

   ☐ YES, I give permission for the collection of about 13 tablespoons, over the course of the study, of blood to be collected for additional research, including that related to bladder cancer and its treatment.

   ☐ NO, I do not give permission for the collection of about 13 tablespoons, over the course of the study, of blood to be collected for additional research, including that related to bladder cancer and its treatment.

   Participant's Initials _____

4. Collection of **urine** for storage and analysis for future research.

   ☐ YES, I give permission for the collection of urine specimens to be collected for additional research, including that related to bladder cancer and its treatment.

   ☐ NO, I do not give permission for the collection of urine specimens to be collected for additional research, including that related to bladder cancer and its treatment.

   Participant's Initials _____

5. Collection of **saliva** for storage and analysis for future research.

   ☐ YES, I give permission for the collection of a saliva specimen at baseline to be collected for additional research, including that related to bladder cancer and its treatment.

   ☐ NO, I do not give permission for the collection of a saliva specimen at baseline to be collected for additional research, including that related to bladder cancer and its treatment.

   Participant's Initials _____

DOCUMENTATION OF INFORMED CONSENT

AFTER SIGNATURES ARE OBTAINED FROM YOU AND AUTHORIZED STUDY PERSONNEL LISTED BELOW, A SIGNED COPY OF THIS CONSENT WILL BE GIVEN TO YOU.

You are voluntarily making a decision whether to participate in this study. Your signature means that you have read and understood the information presented and have decided to participate. Your signature also means that the information on this consent form has been fully explained to you and all your questions have been answered to your satisfaction. If you think of any additional questions during this study, you should contact the study doctor(s).

I agree to take part in this study.

Signature of Participant, Legal Guardian, or Power of Attorney **Date**

Printed Name

I certify that all the elements of informed consent described on this consent form have been explained fully to the participant. In my judgment, the participant has voluntarily and knowingly given informed consent and possesses the legal capacity to give informed consent to participate in this study.

Signature of Authorized Study Personnel **Date**

Printed Name

AUTHORIZED STUDY PERSONNEL CAPABLE OF OBTAINING INFORMED CONSENT FROM PARTICIPANTS

Participating Physician(s) and Participating Health Care Personnel

Principal Investigator

Krishna A. Rao, MD	(217) 545-1129

Co-Investigator(s)

Bradley Schwartz, DO	(217) 545-7362
Aziz-Ur-Rehman Khan, MD	(217) 545-1129
Swati Pathak, MD	(217) 545-1129
Edem Agamah, MD	(217) 545-1129
Dodie Gazda, ANP-BC	(217) 545-8124

Participating Health Care Personnel

Smitha Abraham, RN, BSN	(217) 545-7929
Rebecca Wolf, RN, BSN	(217) 545-7489
Kathy Robinson, PhD	(217) 545-1946