Title of research study: A Study of Intravesical Bacillus Calmette-Guerin (BCG) in Combination with ALT-803 in Patients with Non-Muscle Invasive Bladder Cancer

Investigator: Stanley Yap, M.D and Marc Dall'Era, M.D.

Why am I being invited to take part in a research study?

We invite you to take part in a research study because you have been diagnosed with a type of non-muscle invasive bladder cancer (NMIBC) and are a potential candidate for Bacillus Calmette-Guerin (BCG), a standard therapy for NMIBC. To qualify you may not have received BCG before.

In this Phase II research Study, you will be selected by chance to receive either ALT-803 combined with BCG or BCG alone. ALT-803 is an investigational drug, which means that it has not been approved by the United States Food and Drug Administration (FDA), but the FDA has given its permission for ALT-803 to be tested in this Study. ALT-803 has been previously tested on animals, which showed effectiveness on their cancer/tumors. There is limited data on ALT-803 tested in humans.

ALT-803 is an immune therapy that creates a reaction that will affect cancer cells and their ability to progress. For this study, this drug will be given intravesically (instilled into the bladder). Once in the bladder, it is left in place to wash the bladder wall. ALT-803 causes a local reaction through its contact with the bladder tissue, potentially reducing the likelihood that the cancer will recur and/or invade more deeply.

Before you decide whether or not to take part in this Study, we would like to explain the purpose of the Study, how the Study is conducted, any risks to you, and what is expected of you.

What should I know about a research study?

(Experimental Subject's Bill of Rights)

- Someone will explain this research study to you, including:
  - The nature and purpose of the research study.
  - The procedures to be followed.
  - Any drug or device to be used.
  - Any common or important discomforts and risks.
  - Any benefits you might expect.
  - Other procedures, drugs, or devices that might be helpful, and their risks and benefits compared to this study.
  - Medical treatment, if any, that is available for complications.
- Whether or not you take part is up to you.
- You can choose without force, fraud, deceit, duress, coercion, or undue influence.
- You can choose not to take part.
- You can agree to take part now and later change your mind.
- Whatever you decide it will not be held against you.
- You can ask all the questions you want before you decide.
- If you agree to take part, you will be given a signed and dated copy of this document**.**
- If you agree to take part, you will be given a copy of this document.

For IRB Use

Who can I talk to?

If you have questions, concerns, or complaints, or think the research has hurt you, talk to the research team. Dr. Stanley Yap can be contacted by mail at UC Davis Medical Center, Department of Urology, 4860 Y Street Suite 3500, Sacramento, CA 95817 or by telephone at 916-734-5154.

In addition, there is a 24-hour emergency telephone number for the hospital which is able to contact Dr. Dall'Era or one of his associates at any time of the day or night. That number is 916-734-2011.

For non-emergency issues you can call the UCDMC Hospital Operator (916-734-2011), tell the Operator you are participating in a research study and you wish to talk to the Urology Resident on call. In the case of an emergency, dial 911 from any phone.

This research has been reviewed and approved by an Institutional Review Board ("IRB"). Information to help you understand research is on-line at http://www.research.ucdavis.edu/policiescompliance/irb-admin/.You may talk to a IRB staff member at (916) 703-9151, IRBAdmin@ucdmc.ucdavis.edu, or 2921 Stockton Blvd, Suite 1400, Room 1429, Sacramento, CA 95817 for any of the following:

- Your questions, concerns, or complaints are not being answered by the research team.
- You cannot reach the research team.
- You want to talk to someone besides the research team.
- You have questions about your rights as a research subject.
- You want to get information or provide input about this research.

Why is this research being done?

The purpose of this research Study is to find out the side effects of the Study drug, ALT-803, plus BCG in NMIBC. In this study, we wish to find out how safe the Study drug is and how well it is tolerated. We also wish to find out if the Study drug plus BCG can stop the growth of your tumor. In addition, we wish to collect other information about the Study drug which will help us improve the way the Study drug is given to patients.

If you were to receive this treatment outside of the Study, through your own doctor, the standard of care would involve the administration of BCG by itself once a week, for 6 weeks. The treatment for bladder cancer is the same as it is outlined in the Study Calendar below. Typically urinalysis, lab work, cystoscopy and biopsy are completed prior to treatment, as well as after to gauge treatment effectiveness. The administration of BCG alone is built into this Study itself and serves as the control group. This will then compare the action of BCG by itself, to BCG and ALT-803 in combination as a treatment for bladder cancer.

For IRB Use

STANDARD OF CARE TREATMENT CALENDAR

STANDARD OF CARE TREATMENT PROCEDURE	Induction Study Treatment					
Treatment Month	1				2	
Treatment Week	1	2	3	4	5	6
Study Day	1	8	15	22	29	36
BCG administration	X	X	X	X	X	X

How long will the research last?

We expect that you will be in this research study for up to two (2) years.

As long as you do not have any unacceptable side effects, you will receive the induction Study treatment for up to 6 weeks and have evaluations of your disease for up to 24 weeks. Your health condition will be followed for up to 2 years. Your study doctor may decide to stop your Study treatment if:

- Your cancer worsens
- You have serious side effects
- Your health otherwise worsens
- New information on treating your cancer becomes available

You can decide to stop participating in this Study at any time. However, if you decide to stop participating in the Study, we encourage you to talk to your cancer doctor first.

How many people will be studied?

We expect about 5-10 people here will be in this research study out of around 81 people in the entire study national.

What happens if I say yes, I want to be in this research?

The treatment you get will be chosen by chance, like flipping a coin. Neither you nor the study doctor will choose what treatment you get. You will have an equal chance of being given each treatment.

Consent, Screening and Enrollment

This consent form will allow us to do tests to make sure that you are eligible for the Study. You will be asked to give personal information, such as your name, date of birth, etc.

You will be asked about your medical history, your current disease status and any medications you are currently taking.

You will have a complete physical exam and your vital signs including height, weight, heart and breathing rate, blood pressure and temperature will be checked.

We will collect about two teaspoons of blood for testing the functions of your kidneys, liver and other

organs and for blood cell counts. If any sample remains, it will be retained at either Altor Biosciences or the University of Hawaii and used for future biomarker research.

We will also collect urine for routine urine tests. If any sample remains, it will be retained by the Sponsor and used for future biomarker research.

An electrocardiogram (EKG) will be run to test electrical activity of your heart. Your lung functions will be examined.

If you have had a bladder biopsy within 3 months of starting the Study, these tissue samples can be used to help determine if you qualify for the Study. If you have not had a recent (within 3 months) biopsy, one will be performed during your screening process.

You will have a cystoscopy (a scope/lens with tubing that will be inserted into your bladder) within 4 weeks of you starting the Study to check the status of the disease. If a mass is noted during this procedure, then a bladder biopsy will be necessary regardless of when your last biopsy occurred. The bladder biopsy is necessary to check the status of the disease and the cystoscopy and bladder biopsy procedures *may* be completed again at your Week 12 or Week 24 Study visit

The Study will need to collect some tissue from these biopsies. The tissue may be analyzed for genes, gene products, proteins, or markers involved in cancer, immune response or cell death. The tissue from your biopsies that are collected for testing will be analyzed and stored at either Altor Biosciences or the University of Hawaii for possible future analysis.

You will also have your disease assessed by urine tests.

Results from these screening tests will be used by the Study doctor to find out if you qualify for the research Study. If you are a woman who can have children, we will collect another teaspoon of blood for a pregnancy test. The study doctor or Study staff will tell you if the pregnancy test results are positive. The results of the pregnancy test must be negative in order for you to be in the Study. We will enroll you and schedule your visits to receive the Study treatment within 14 days. If the screening tests show that you are not eligible to continue in the research Study, then you may *not* take part.

Study Treatment & Monitoring

Your participation in the Study will include one cycle of induction Study treatment consisting of up to six (6) weekly doses of BCG plus ALT-803 Study drug or BCG alone. Your Study doctor will inform you which treatment you are assigned to receive and if blood samples will be collected for Study related tests. You will have up to two response visits to evaluate your response to the Study treatment.

STUDY CALENDAR

TESTS & PROCEDURES	Screen/ Baseline	Induction Study Treatment						Initial Assessment	Confirmatory Assessment	Follow-Ups					
Study Month		1				2		3	6	9	12	15	18	21	24
Study Week		1	2	3	4	5	6	12	24	39	52	65	78	91	104
Study Day		1	8	15	22	29	36								
Study Visits	X	X	X	X	X	X	X	X	X	X					
Bloodwork & Urinalysis	X	X	X	X	X	X	X	X	X						
EKG	X	X													
Pulmonary Function Test (PFT)	X														
Urinalysis	X	X	X	X	X	X	X	X	X						
Cystoscopy & bladder biopsies	X							X	X	X					
Molecular response measurements	X							X	X						
Urine cytology	X							X	X	X					
Urine Immune cell and biomarker tests**		X		X		X	X								
Immunogenicity tests *		X		X		X	X	X							
BCG+ALT-803 administration		X	X	X	X	X	X								
BCG administration (control group)		X	X	X	X	X	X								

**Collected only if receiving BCG+ALT-803 treatment*

***Collection of urine will occur on multiple time points on these days. See below for further details.*

Maintenance Treatments

You may also be eligible to receive maintenance treatment with the same treatment (BCG plus ALT-803 or BCG alone) as assigned in the induction Study treatment. The maintenance treatment consists of BCG plus ALT-803 or BCG alone for three consecutive weeks at around 3, 6 and 12 months. You will be closely monitored during the entire treatment period. After you complete the Study treatment period, if you received at least one dose of Study treatment, we will continue to monitor and follow your disease and health status every 3 months during years 1 and 2 by scheduled office visits.

For IRB Use

Due to scheduling conflicts, Maintenance scheduling can be discussed on a patient by patient basis. All attempts will be made to stay within the allotted windows although altering the schedule may occur.

MAINTENANCE SCHEDULE:

	Maintenance #1			Maintenance #2			Maintenance #3		
Treatment Month*	3			6			12		
Treatment Week*	13	14	15	26	27	28	50	51	52
Treatment Day	1	8	15	1	8	15	1	8	15
Dose#	7	8	9	10	11	12	13	14	15
BCG only arm	X	X	X	X	X	X	X	X	X
BCG+ALT-803 arm	X	X	X	X	X	X	X	X	X

*estimated if schedule is followed exactly, otherwise may vary

Treatment Center: On each day you receive the Study treatment, you will be treated as an outpatient in a treatment Infusion Center. After the BCG plus ALT-803 is placed within your bladder, you will be asked to stay in the treatment center for up to 4 hours, so that we can carefully monitor your body's functions and closely watch for potential side effects of the Study drug on your body. If you experience certain side effects, you may be asked by your Study doctor to be admitted to the hospital overnight for observation and/or treatment of the side effects. Otherwise, you will be discharged from the center and asked to come back for the next treatment the following week.

After you receive the first and last induction treatment, you may be asked to return to the treatment center the next day for blood draws to do a Study drug related test. A urine sample for Study drug related tests will also be collected the day after you receive the last induction treatment.

Urinary Catheter: If you do not already have a permanent catheter placed to assist with urination, before starting treatment, you will have a minor surgical procedure to insert a temporary plastic urinary catheter (plastic tube) to deliver the treatment to your bladder, but this is not permanent.

Placing a catheter during instillation is the standard practice regardless of which medication is received. The Study catheter will be removed before you leave, after your treatment is received. Certain patients who rely on a catheter to assist with urination will have the Study drug instilled through their already existing catheter. Subjects will not go home with any tubes additional to what they usually have.

How are the study drugs given? Each dose of BCG plus ALT-803 is given through the tube (catheter) and the treatment will stay in your bladder for about two (2) hours. For those who receive BCG alone, administration of the Study drug will be the same as with BCG plus ALT-803.

Treatment Regimen: Your induction treatment plan includes one cycle of Study treatment over six (6) weeks with dosing on Days 1, 8, 15, 22, 29 and 36. Your maintenance treatment plan includes Study treatment over three (3) weeks at around 3, 6 and 12 months. If you did not

have severe side effects after each dose of study treatment, your treatment will continue. Study treatment continues unless your disease grows or spreads, or you develop unacceptable side effects, or you choose to discontinue treatment. At the completion of the induction Study treatment cycle, you will have received a total of six doses of study treatment. If you receive at least one Study treatment dose, you will have response visits at around Week 12 and Week 24 (or 12 weeks from the start of maintenance) to evaluate your response to the Study treatment.

Dose Level: You will be assigned by chance to receive either 50 mg of BCG alone for each dose or 50 mg of BCG plus 400 μg of ALT-803 for each dose.

Side effects monitoring & management: You will be closely watched for any side effects you might have while in the Study. At the beginning of the induction study treatment cycle, if you are receiving BCG plus ALT-803 we will give you a complete physical exam and an EKG will be run. Also for each visit, we will check your vital signs including weight, heart and breathing rate, blood pressure, temperature, lung and heart function monitoring. We will collect urine for routine tests and blood for tests to check the functions of your kidneys, liver and other organs and to monitor your blood cell counts. ALT-803 is similar to two other drugs. One is called Proleukin® (IL-2) and the other is rhIL-15. There is limited information on managing side effects from giving rhIL-15 to humans. Your study doctor will manage any side effects of the study drug ALT-803 following the guidelines for the use of IL-2. You may receive some medications to help prevent or treat side effects. You should ask the Study doctor about these medications. Your study doctor will inform you of what to expect if you receive BCG alone.

Blood draws and urine collection for clinical tests (Chemistries & Hematology): Blood samples (up to two teaspoons each time) will be drawn and a urine sample will be collected before you receive each BCG plus ALT-803 Study treatment and on each of the study visit days.

Routine urine tests and blood tests including complete blood count and blood chemistry will be performed to make sure that you do not have any unacceptable side effects from the Study treatment. Your Study doctor will inform you of what to expect if you receive BCG alone.

Urine collections for disease related tests: Urine samples will be collected at screening and on each of the response visits for tests to evaluate your disease.

Urine collections for study drug related tests: Urine samples will be collected to test the level of substances that may predict the effectiveness of the treatment (biomarkers) and to check your immune cell levels and types. The schedule of obtaining these urine samples is: Two samples on Day 1 (before treatment start and 4 hours after treatment start); 4 hours after treatment start on Days 15, 29, 36; and 24 hours after Day 36 treatment start. Left over urine may be used by the Sponsor for additional biomarker studies following rules set by the FDA.

If you receive BCG+ALT-803, blood samples will be collected before treatment start on Day 1, Day 36 and at the Week 12 response visit to find out whether your body's immune system reacts against the study drug.

Left over blood collected for research may be used by the Sponsor for additional biomarker research studies or other tests.

Tumor tissue: Tumor tissue from the biopsy done prior to Study entry and tumor tissue, if collected at each of the response visits, will be tested to confirm tumor type, to determine if

immune cells are present and to determine if there are changes in tumor cell activity. Tumor tissue, if collected at each of the response visits, will also be tested to evaluate your response to the Study treatment. The tissue from your biopsies may also be used for additional biomarker studies following rules set by the FDA.

Response Evaluation & Follow-Up

After the Study treatment period, if you received at least one dose of induction Study treatment you will be asked to return for a response visit at around Week 12 and Week 24 (or 12 weeks from the start of maintenance). The Study Doctor or Coordinator will tell you exactly what dates to return for these visits. If you receive BCG+ALT-803, a blood sample (about one teaspoon) will be collected at the Week 12 response visit to find out how your body's immune system reacts against the Study drug.

If you receive BCG+ALT-803 the following will be done at each response visit:

- Urinalysis
- Blood draw (about two teaspoons of blood will be collected for routine tests)
- Complete physical examination
- Vital signs
- Weight

At each response visit, you will be asked how you feel to find out if you have recovered from any side effects that may have occurred during the period in which you received the study treatment. At each response visit, urine samples will be collected and you will be asked to return to the study center for a cystoscopy. You will receive a local anesthetic (medicated lubricant that will numb your urethra) and your doctor will look in your bladder. If a mass or abnormality is seen inside your bladder, then your doctor may schedule you to go to the operating room to remove small pieces (biopsies) of the bladder wall for testing. Tumor tissue, if collected at the Week 12 and Week 24 (or 12 weeks from the start of maintenance) response visits, will be tested to evaluate your response to the Study treatment and to confirm tumor type, to determine if immune cells are present and to determine if there are changes in tumor cell activity.

You will return for a visit at 9, 12, 15, 18, 21 and 24 months after the start of your treatment to find out the status of your disease and to collect information on what other treatment you may have received or are receiving for your disease. If you are receiving maintenance treatment, the data may be collected during some of these visits

Laboratory Tests & Procedures

The Study will involve the following tests and procedures. Some of these tests would be done even if you do not take part in the Study. The detailed schedule for these tests and procedures is included in the *Laboratory Tests and Procedures* Schedule.

- **Medical history**
- **Complete physical exam**: Examination of head, eyes, ears, nose, throat, neck, heart, lungs, abdomen, arms and legs, and nervous system (for example, level of consciousness, pupils, responses, and motor reflexes).

- **Vital signs:** Body temperature, heart rate, breathing rate, blood pressure, weight, and height.
- **Pregnancy blood test:** For women of childbearing potential.
- **Heart function tests:** Your cardiac function will be closely monitored during the entire study. You will also have an EKG to check the electrical activity of your heart to find out if you qualify for the research study and at the beginning of the study treatment cycle.
- **Lung functions:** Your lung function will be closely monitored during the entire study. Your lung function will be examined to determine whether you can enter the study. A lung test may be done.
- **Clinical blood tests:** Complete blood count and blood chemistry.
- **Side effects assessment & current medications**
- **Routine urine tests.**
- **Specific urine tests to assess the disease.**
- **Urine biomarker tests:** To test some substances produced by your immune cells that may predict the effectiveness of the treatment (*i.e.* including but not limited to IL-2, IL-4, IL-6, IL-10, IFN-γ and TNF-α) in urine.
- **Immunogenicity test:** To determine if your body has had an immune response against the study drug ALT-803.
- **Urine immune cell tests:** To find out the different types and amounts of immune cells you have.
- **Tumor response tests:** To confirm tumor type, to determine if immune cells are present and to determine if there are changes in tumor cell activity.
- **Cystoscopy and bladder biopsy:** To evaluate your response to the study treatment, you will receive an anesthetic (you will be put to sleep or the lower part of your body will be numbed with an injection into your spine). Your doctor will look into your bladder and if needed will remove small pieces (biopsies) of the bladder wall for testing in the lab.

Each blood sample drawn on any given day during the study period will take a maximum of 3 tablespoons of blood.

Research on left-over urine, blood and tissue

Any remaining samples may be used by Altor Bioscience Corporation for research studies or other tests following rules set by the FDA.

What are my responsibilities if I take part in this research?

If you take part in this research, you will be responsible for following certain rules before, during, and after the Study period. Some are listed below, but there could be others that the study doctor will discuss with you:

• You must be able to provide written consent to be in this Study.
• You must tell your Study doctor all of the medications that you have been taking for at least 30 days before you take part in the study. This includes vitamins, minerals, and medications that do

not require a doctor's prescription. Some medications may not be allowed. Your Study doctor will discuss these with you in detail.
• You must ask your study doctor before you take any new medications during the Study.
• If you decide to take part in this Study, it is very important that you attend all visits as scheduled, including all of the follow-up visits.
• You must not be pregnant, become pregnant, or in the case of male subjects, get your partner pregnant during this study.
• You must not breastfeed during the study.
• You must return all of the used and unused study drug materials
• You must follow all instructions given to you while you are participating in this Study. If you do not, you may be removed from the Study. If you are unsure about what you are supposed to do, ask the Study doctor.
• Some insurance companies require people who are renewing a policy or getting a new policy to tell them about participating in a clinical study. You should check with your insurer to determine if taking part in this study will affect your existing insurance policy.
• If you are a woman that can have children and are sexually active, you and your partner must use two effective methods of birth control during the Study.

What happens if I do not want to be in this research?

You may decide not to take part in the research and it will not be held against you.

Instead of being in this research study, your choices may include:

• Treatment with other immune-based or chemotherapy drugs.

• Surgery to remove your bladder (cystectomy)

• Treatment with other investigational drugs.

• No therapy at all, but with comfort care only. In comfort care only, treatments are not directed at curing, slowing, or reversing your disease. The treatments are directed only at reducing symptoms, controlling pain, relieving suffering, maximizing comfort and maintaining the dignity of you and your family.

Talk to your cancer doctor about these and other options. Please ask any questions you may have and take as much time as you need to make your decision.

What happens if I say yes, but I change my mind later?

You can leave the research at any time and it will not be held against you.

Taking part in this clinical research Study is voluntary and you can refuse to take part or stop at any time without stating a reason. Your withdrawal will not affect your access to other medical care to which you would otherwise be entitled. If you decide to leave the research Study, you are strongly urged to:

- Tell your Study doctor.
- Return to the Study doctor for one more visit to remove you from the Study. You will have an exam and plan for your cancer treatment care.
- Return any unused Study supplies to the Study doctor.

If you leave the study for any reason you will be asked to complete the required procedures for the final visit.

If you decide to leave the research, you would transition into standard of care treatments if/when they become available. This will be decided by your current doctor managing your care.

If you stop being in the research, already collected data may not be removed from the study database. You will be asked whether the Investigator can collect data from your routine medical care. If you agree, this data will be handled the same as research data.

Is there any way being in this study could be bad for me?

While on this Study, you are at risk for the side effects listed below. Not everyone will get these side effects. You may not have any or you may have several. Most people do not experience all of the side effects listed. A side effect may get worse through your course of treatment, or more side effects may develop as the treatment goes on. This depends on your general health and the amount of the Study drug you receive (the dose). Many side effects are inconvenient but not damaging to your health. They are almost always reversible and usually go away shortly after treatment is complete. However, some side effects are serious medical conditions that may cause death or cause your condition to worsen. Your Study doctor will closely monitor, treat and/or prevent the side effects you might have during the Study period. Other drugs and procedures may be given to make side effects less serious and less uncomfortable.

On the days you receive the study treatment, you will be asked to stay in the treatment center for up to four (4) hours after starting the BCG plus ALT-803 dose. This will allow the Study doctor or Study staff at the treatment center to carefully monitor your body's functions and to watch you closely for any side effects. If any severe side effects occur you may be admitted to the hospital for observation and/or treatment at your Study doctor's discretion. If severe side effects occur, or if your condition worsens while you are on this Study, the Study treatment may be discontinued at your Study doctor's discretion without your consent. You should discuss this with your cancer doctor, the Study doctor and/or the Study staff. There may also be other side effects that we cannot predict. While on the Study, we want you to talk to your Study doctor or Study staff about all your side effects so that they can help you manage them.

Tell your Study doctor about any other medicines you are taking, including vitamins, herbal supplements and other over the counter remedies. Drugs can interact or react together.

Risks/Side effects from the Study Treatment

I. ALT-803: The study drug ALT-803 can cause many side effects which may be similar to the side effects of Proleukin® (IL-2).

Most likely (greater than 10% - 1 in 10 patients):

• Weight gain may occur which could be as much as 20 pounds of fluid over the course of receiving the study drug. This weight gain results in swelling in the arms and legs. This swelling can be treated with a medicine called a diuretic, which will cause you to have increased urination to remove the excess fluid.

• ALT-803 can cause fluid to collect in the lungs, which can cause shortness of breath. Shortness of breath is common and you may require oxygen during some portion of your treatment. Some subjects who have received this therapy have rarely required intubation (the insertion of a tube into the air passage) and the temporary aid of a breathing machine to assist breathing.

• Anemia - This is due to a drop in the number of red blood cells made by your bone marrow, which is called anemia. Tiredness often continues after treatment has ended, but most people find that their energy levels are back to normal from 6 months to a year after their treatment finishes. Blood transfusions may be used to correct the anemia, which can produce allergic reactions and carry a very small risk of transmitting viral infections, such as hepatitis and HIV. A medicine called Aranesp, which is injected under the skin every other week, can also be used to reverse the anemia.

• ALT-803 may cause your blood pressure to fall to low levels. You may be given fluids before, during and after receiving ALT-803 to help prevent this from occurring. This may also require the use of medicines called pressors to raise your blood pressure to a safe level. If the use of fluids cannot keep your blood pressure at a safe level at the time of the next scheduled treatment of BCG plus ALT-803, that treatment will be skipped. If the symptom persists for more than 24 hours, you may not continue to receive the study drug ALT-803. In previous studies with IL-2, this side-effect of low blood pressure was temporary and returned to normal after the IL-2 was stopped. The drop in blood pressure may decrease the amount of urine you make. Very rarely there may be a need for hemodialysis, in which a machine substitutes for the kidneys because of decreased kidney function. On rare occasions, the drop in blood pressure may cause swelling or decreased blood supply to the bowel, which may result in bowel death or rupture. Due to a possible drop in blood pressure, some subjects have developed heart attacks during or shortly after receiving IL-2. In at least one case the heart attack was fatal with IL-2 treatment. The heart troubles are felt to be related to the added stress placed on the heart during the IL-2 treatment. Therefore, if you have any history of heart problems, be sure to tell your study doctor.

• Flu-like symptoms - You may experience fever, chills, shaking, headache, stiffness, aching muscles and joints. These symptoms usually get better as your course of treatment continues. The symptoms usually begin 2 - 4 hours after treatment and last for about 12 hours. Rarely, some people have experienced high fevers. The fevers and flu-like symptoms can be controlled with acetaminophen and indomethacin, which are medicines given by mouth.

• You may also develop nausea, diarrhea, skin rash with itching, nasal congestion, and abnormalities in kidney and liver function. The fever, chills, shaking, nausea, diarrhea, and itching may be controlled with medicines given before, during and after receiving ALT-803.

• Increased risk of getting an infection - This is due to a temporary drop in the number of white blood cells produced by the bone marrow. Having a low white blood count means that you are less able to fight infections. You may have headaches, aching muscles, cough, sore throat, pain passing urine or feel cold and have chills. During the study you will require a catheter or tube placed into a large vein in your chest or arm. In previous studies, there has been a 1 in 4 chance that infection will develop at that site, which would require removal of the catheter and treatment with antibiotics. Such infections can cause additional side effects leading to prolonged hospitalization, and at least 2 cases with IL-2 treatment has been fatal. The use of antibiotics in

all people receiving IL-2 have reduced the chance of infection to about 1 in 20. You will receive antibiotics if you have a fever.

Infections can sometimes be life-threatening. You should urgently contact your study doctor if you think you have an infection.

• Getting bruises more easily - This is due to a drop in the number of blood clotting platelet cells produced by your bone marrow. You may have lots of tiny red spots or bruises on your arms or legs. You may have nosebleeds or notice your gums bleed when you brush your teeth. If that happens you will receive a platelet transfusion.

• Skin rash - You may have red, dry and itchy skin. Your skin may peel or you may have small blisters.

• Weakness, headache, dizziness.

• Vomiting, nausea, loss of appetite.

• ALT-803 may lower the levels of electrolytes (magnesium, potassium, phosphate, sodium and calcium) in your blood. These levels will be monitored by the study doctor and replacement drugs will be given if necessary.

Less likely (3% to 10% - 1 in 30 to 1 in 10 patients):

• Heart problems - Sometimes the study drug ALT-803 can affect the way your heart works, causing low blood pressure, dizziness, chest pain or changes in heart rhythm (heart beat). These are quite uncommon and nearly always get better when treatment has stopped. If the abnormal heart rhythms continue, you will be treated with anti-arrhythmia medicines. You should tell your study doctor if you have had heart problems before or if you have any of these side effects.

• Altered blood tests - The study drug ALT-803 can raise the amount of chemicals called bilirubin and creatinine in your blood. Your study doctor will take regular blood tests to monitor this.

• Cough and breathlessness.

• Mouth sores.

• Confusion, depression and extreme sleepiness - this is more common in older people or those who have had depression before. Tell your study doctor if you have these symptoms.

Rarely (< 3% - 1 in 30 patients):

• Allergic reaction (rash, itching or scaling of the skin).

• A very small number of people may temporarily have hair thinning.

II. BCG: Common Risks/Side Effects of intravesical BCG therapy.

Most likely:

• Burning or pain with urination, a sense of needing to urinate often, or urinating small amounts often.

• Fatigue, joint aches, skin rash, or fever of less than 101^0F (38^0C).

• Nausea, vomiting, or loss of appetite.

For IRB Use

Less likely:

• A whole body inflammatory response to an infection, also known as sepsis. Common signs include fever, increased heart rate, increased breathing rate and confusion.

• Hepatitis or abscess.

• Inflammation of the lung tissue.

• For men, inflammation and infection of the prostate, testicles, or epididymis.

• Contraction of the bladder or obstruction of the ureters.

• Allergic reaction to BCG or disseminated tuberculosis (a bacterial infection in where tuberculosis, from the lungs, has spread to other parts of the body).

Risks/Side Effects from Cystoscopy/Biopsy

Risks associated with cystoscopy and/or bladder biopsy are rare but may occur. These risks include profuse bleeding, a damaged urethra, a punctured bladder, a urinary tract infection, or an injured penis.

Factors that may increase the risk of complications include: active infection, diabetes, and bleeding disorder. Be sure to discuss these risks with your study doctor before the procedure.

You should contact your study doctor if you experience any of the following symptoms after the procedure, including pain, redness, swelling, drainage, or bleeding from the surgical site; signs of generalized infection, which may include headache, muscle aches, dizziness, or an overall ill feeling and fever; nausea or vomiting; or difficult or painful urination.

If anesthesia is required, there is additional risk, particularly for people who are obese, smoke, or are in poor health. If you are undergoing anesthesia, you must inform the study doctor of any medications you are taking.

Common Risks/Side Effects from Insertion of a Urinary Catheter

Risks associated with urinary catheters are not likely but may occur. These risks include infection and bleeding. Rarely, injury of the urethra may occur. The risks associated with this procedure will be reviewed in detail with patients by the individual who places the catheter.

Risks/Side Effects from ECG

For the ECG, you will lie down and have adhesive patches (similar to Band-Aids®) placed on your chest, arms and legs. In some areas, it may be necessary to shave a small spot of body hair so the adhesive patches can be properly placed on your body. Wires from the machine are then attached to the adhesive patches. These wires record your heart's electrical activity. After you have an ECG, you may have mild irritation, slight redness, and itching at the places on your skin where the recording patches are placed**.**

Reproductive Risks

The Study drug ALT-803 may pass the placenta and be secreted in breast milk, and may be harmful to fetal and infant development. If you are a woman of childbearing potential, a blood pregnancy test will be done, and it must be negative before you can enter this Study. You should not nurse your baby while on this Study. There have been no Studies conducted assessing the

effect of the Study drug on fertility. If sexually active, you, either male or female, **must agree to use two forms of birth control for the duration of the Study**.

Acceptable birth control methods **(in addition to a male partner who correctly uses a condom)** include:

- an intrauterine device (IUD) with a failure rate of <1% per year
- female barrier method: cervical cap or diaphragm with spermicidal agent
- tubal sterilization (having your tubes tied)
- vasectomy in male partner
- implants of progestin
- injectable progestin
- oral contraceptives (either combined or progestin only)
- contraceptive vaginal ring
- transdermal contraceptive patch

Ask the study doctor about counseling and more information about preventing pregnancy. If you or your partner does become pregnant during this Study *and for a minimum of 30 days after stopping Study drug*, you must inform your study doctor immediately.

Risks/Side Effects from Blood Draws

Risks associated with blood draws are slight but may include: excessive bleeding, fainting or feeling light-headed, hematoma (blood accumulating under the skin), and infection (a slight risk any time the skin is broken).

Risks/Side Effects from Pulmonary Function Test (PFT)

Pulmonary function tests (PFTs) are a group of tests that measure how well your lungs work. This includes how well you're able to breathe and how effective your lungs are able to bring oxygen to the rest of your body. Side effects could include dizziness and/or shortness of breath.

Randomization Risk

You will be assigned to a treatment program by chance, and the treatment you receive may prove to be less effective or to have more side effects than the other study treatments(s) or other available treatments.

Recovery from the Side Effects

- You will typically be discharged from the treatment center on the same day you are treated. You may be required to stay longer depending on your condition.

- You may feel very fatigued (tired) after receiving the study treatment but your energy should return in the days following treatment. Any water weight gained during your treatment will be quickly lost. At first your appetite may be poor, and nausea may alternate with hunger but expect this to improve within a few days.

- You should feel much better overall within seven to ten days after the last study treatment and you should be back to normal within a few weeks after the study treatment. If you experience

itching and peeling, this may be one of the last things to improve, along with the gradual fading of fatigue.

Unkown/Unexpected Risks and Discomforts
In addition to the risks listed above, there are risks that are not known or do not happen often when subjects take these study drugs, including severe or life-threatening allergic reactions, interactions between study drugs, or interactions with another medication. You will be informed in a timely manner, both verbally and in writing of any new information, findings or changes to the way the research will be done that might influence your willingness to continue to take part in this study.

In addition to these risks, this research may hurt you in ways that are unknown. These may be a minor inconvenience or may be so severe as to cause death.

The research may also hurt a pregnancy or fetus in ways that are unknown. These may be a minor inconvenience or may be so severe as to cause death. You should not be or become pregnant or father a baby while on this research Study.

Will being in this study help me in any way?

We cannot promise any benefits to you or others from your taking part in this research. If you agree to take part in this Study, there may or may not be direct medical benefit to you. Your participation in this Study may provide important information regarding the Study drug which may lead to future clinical Studies. Other patients with cancer may benefit in the future.

What happens to the information collected for the research?

Efforts will be made to limit use or disclosure of your personal information, including research study and medical records, to people who have a need to review this information. We cannot promise complete confidentiality. Organizations that may inspect and copy your information include the IRB and other University of California representatives responsible for the management or oversight of this study.

During your participation in this research, data will be collected about you. The de-identified data and any specimens, such as blood or tissue that are taken from you for this Study, will become the property of the University of California. There is no exact time-line to 'use-up' the samples. The samples will be used for the lab testing per Protocol and any remaining samples will be used for future biomarker research. The specimens may be used in this research, may be used in other research, and may be shared with other organizations, including, but not limited to, Altor designated personnel and designated personnel at the University of Hawaii Cancer Research. The specimens will be de-identified (containing only your Study ID# and initials) and will be stored at Altor Biosciences and/or at the University of Hawaii Cancer Center. These specimens could lead to discoveries or inventions that may be of value to the University of California or to other organizations. Under state law you do not have any right to money or other compensation stemming from products that may be developed from the specimens.

You will NOT receive the results of the Biomarker testing.

The sponsor, monitors, auditors, the Institutional Review Board (IRB), the Food and Drug Administration will be granted direct access to your research records to conduct and oversee the study.

We may publish the results of this research. However, we will keep your name and other identifying information confidential.

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.

If we access protected health information (e.g., your medical record), you will be asked to sign a separate form to give your permission. Your medical records may become part of the research record. If that happens, your research records may be looked at by the sponsor of this study and government agencies or other groups associated with the study. They may not copy or take your personal health information from your medical records unless permitted or required by law.

Federal law provides additional protections of your medical records and related health information. These are described in the UC Davis Health System Notice of Privacy Practices (http://www.ucdmc.ucdavis.edu/compliance/pdf/notice.pdf) and in an attached document.

Can I be removed from the research without my OK?

The person in charge of the research study or the Sponsor can remove you from the research study without your approval. Your Study doctor may withdraw you from the study if it is considered important for your medical safety. Possible reasons for removal include include but are not limited to: the judgment that any condition or circumstance may jeopardize your welfare or the integrity of the study, you did not give an accurate medical history, your failure to follow the instructions of the study doctor, you need additional medication, you become pregnant or begin breastfeeding, you do not consent to continue in the study after being told of changes in the research that may affect you, the study is stopped by the sponsor and/or study doctors participating in the Study, or for any other reason. Your study doctor will explain the reasons for doing so and will help arrange for your continued care by your own doctor, if needed.

Special care will need to be taken when determining if you need to stop study drug. Your study doctor will supervise any discontinuation of the study drug with your health as the first priority. Your taking part in this Study may be terminated at any time by a) your Study doctor, b) Altor BioSciences Corporation, c) FDA, or d) the Institutional Review Board (IRB) which is a review group that gives approval to your Study doctor to conduct this Study, and other appropriate regulatory agencies.

If you are taken off the study, you will no longer receive the study drug.

We will tell you about any new information that may affect your health, welfare, or choice to stay in the research.

What else do I need to know?

This research is being funded by Altor Bioscience Corporation, also called the Sponsor. Sponsors may change or be added.

UC Davis is being paid to conduct this study, but the study doctor and research staff have not received any direct income from the sponsor.

For IRB Use

There are portions of this Study that are no charge to you for your involvement in this study. The Sponsor, Altor Bioscience Corporation, will provide you with the Study drug, ALT-803, free of charge while you are participating in this study.

Other portions of this Study will be billed to you or your health plan for the costs of routine medical care you receive during the Study. Certain tests and examinations will need to be done regularly to monitor your safety and to measure the effects of the study drugs. These tests include physical examinations, cystoscopy, bladder biopsy, urine tests, and blood tests. Costs for these tests and examinations will be billed to you and/or your health care plan or insurer. The use of medications or other types of treatment to help control side effects you might have, could also result in added costs to your and/or your health care plan or insurer. You will be expected to pay for the usual deductibles and co-payments, and for any routine care that is not covered. *Only the costs of research or experimental procedures will be paid by the Study.*

For more information about possible costs, please contact the research team. The research team can follow UC Davis Uninsured Non-Emergency Estimate Policy (Policy ID 1883) to work with their department and Decision Support Services to get you a cost estimate.

It is important that you promptly tell the person in charge of the research if you believe that you have been injured because of taking part in this study. If you are injured as a result of being in this study, the University of California will provide necessary medical treatment. Depending on the circumstances, the costs of the treatment may be covered by University or the study sponsor or may be billed to your insurance company just like other medical costs. The University and the study sponsor do not normally provide any other form of compensation for injury. For more information about compensation, you may call the IRB Administration at (916) 703-9151 or email at IRBAdmin@ucdmc.ucdavis.edu.

If the sponsor pays any of your medical expenses, we may be required to give the sponsor your name, date of birth, and Medicare ID or social security number.

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

The results of this study, including specimens collected, may have commercial value to the sponsors, UC Davis, and/or the researchers. You will have no legal or financial interest in any commercial development resulting from the research or from the information or materials collected.

For IRB Use

Signature Block for Capable Adult

Your signature documents your permission to take part in this research.

Signature of subject	Date
Printed name of subject	
Signature of person obtaining consent	Date
Printed name of person obtaining consent	

For IRB Use