<<CF-Main Approval Stamp - Approved>>

ITL-019-CORK-CRYVAC
Madappa N. Kundranda, MD, PhD

RESEARCH SUBJECT INFORMATION AND CONSENT FORM

ITL-019-CORK-CRYOVAV
NCT: 02380443

[

INFORMED CONSENT AND HIPAA AUTHORIZATION DOCUMENT

TITLE:	IN-SITU CANCER VACCINE: PHASE I/IIB OPEN-LABEL STUDY TO ASSESS THE SAFETY OF ALLOSTIM® IN COMBINATION WITH CRYOABLATION AS THIRD LINE THERAPY FOR METASTATIC COLORECTAL CANCER
PROTOCOL NO.:	ITL-019-CORK-CRYVAC WIRB® Protocol #20152314
SPONSOR:	Immunovative Therapies, Ltd.
INVESTIGATOR:	Madappa N. Kundranda, MD, PhD 2940 E. Banner Gateway Drive, Suite 450 Gilbert, Arizona 85234 United States
SITE:	Banner MD Anderson Cancer Center 2946 E Banner Gateway Drive Gilbert, Arizona 85234 United States
STUDY-RELATED PHONE NUMBER(S):	Madappa N. Kundranda, MD, PhD +1-480-256-6444 (24 hours)

SUMMARY

You are being asked to participate in a research study because you have metastatic colorectal cancer that has spread to other parts of your body and is not responding to chemotherapy. The purpose of this consent form is to help you decide if you want to be in the research study.

You should not join this research study until all of your questions are answered. You should ask questions of your doctors, family, friends, clergy and others that you trust.

Things to know before deciding to take part in this research study:

- The main goal of a research study is to learn things to help patients in the future and not necessarily as a treatment for your disease.
- A decision not to join this research study will not cause you to lose any medical benefits. If you decide not to take part in this study, your doctor will continue to treat you.
- While participating in this study you will receive standard supportive medical care. Standard supportive medical care is the treatment normally given when you experience symptoms from your illness, such as pain, low blood cell counts, dehydration or metabolic disturbances.
- There are two FDA approved drugs called Regorafenib and Lonsurf for treatment of

metastatic colorectal cancer. You can choose to take these drugs instead of participating in the study.

- This study involves an experimental immunotherapy drug that is being investigated to determine if it is safe and if any potential benefit to patients with metastatic colorectal cancer.
- The investigational immunotherapy drug is used together with a medical procedure called cryoablation where a selected tumor lesion is killed by freezing. While cryoablation is an approved treatment for some cancers, the manner in which the procedure is used in this study may be considered experimental.
- The investigational immunotherapy drug ("Study Drug") being investigated has not been approved by the U.S. Food & Drug Administration (FDA) or any other regulatory authority worldwide. The name of the Study Drug is "AlloStim®".
- After reading the consent form and having a discussion with the study staff, you should know which parts of the study are experimental and which are standard medical care.
- Your medical records may become part of the research record. If that happens, your medical records may be looked at and/or copied by the sponsor of this study and government agencies or other groups associated with the study.
- Your medical insurance may be billed for any standard medical care you receive during the research study. If your insurance company is billed then it may have access to the research records. Insurance companies may not pay for treatment that is part of a research study. Taking part in a research study could affect your current or future insurance coverage.

If you take part in this research study, you will be given a copy of this signed and dated consent form.

PURPOSE OF THE STUDY

The study doctors want to learn if the Study Drug can help metastatic colorectal cancer patients. The purpose of this study is to evaluate two different dosing schedules of the Study Drug in order to find out what effects (good or bad) the Study Drug has on you and your cancer when administered with or without a procedure to freeze a selected tumor called cryoablation. This research study is designed to determine if any of these dosing schedules are able to safely stimulate your immune system to eliminate any of the tumors in your body or stop or slow the growth of your tumors and, if so, determine which schedule is optimal.

If you agree to participate in this research study, you will be assigned to either schedule A-1 (with cryoablation) or schedule A-2 (without cryoablation). You will be provided with experimental treatments over a period of 84 days (if you are in schedules A1) or 77 days (if you are in schedule A-2) with a follow-up period making for a total of 154 days. You will not be allowed to have any other treatments for your cancer during the first 154 days except supportive care treatments for pain, nausea, nutrition or radiation for pain or to prevent fractures in your bones.

Your study doctors also want to analyze the changes inside your tumors over time, and to compare the changes documented in your biopsy samples to changes that occur on your CT scans. These biopsies are mandatory. You will not be able to participate in this research study, including receiving any study-related intervention if you do not consent to these biopsies.

Therefore, as part of the trial, your study doctors would also like to perform biopsy procedures at the same time as your CT scans as follows:

1. Baseline visit
2. During intratumoral injection on day 21 (only if you are in Schedule A). The intratumoral procedures use a guide needle that will have already been inserted into the tumor to conduct the intratumoral injection and thus the injection into your tumor and biopsy of these lesions will not add an additional invasive needle insertion through your skin.
3. 7 days after the last IV booster infusion (day 91 if you are in Schedules A1) and day 84 if you are in Schedule A-2).

The reason for the need for taking biopsy samples at the same time as your CT scans is because after immunotherapy it is sometimes difficult for doctors to determine if you are responding to the immunotherapy. Sometimes immunotherapy will cause tumors to swell and look bigger on a CT scan. Normally if the tumors look bigger on a CT scan doctors will diagnosis "progressive disease". However, with immunotherapy the tumors may be bigger on CT scan because they are swollen with immune cells and the actual amount of tumor in the large lesion may actually be less than it was previously.

Up to 15 subjects are expected to participate in this study.

PROCEDURES

Baseline Visit

Your first visit to the clinic after being informed you may be eligible to participate in the study is called the Baseline Visit. During this visit, study staff will explain the study to you fully. You will be asked to sign this consent form before starting any study procedures. If you agree to volunteer for this study, after you sign this consent form, you will first be screened to determine your eligibility to participate in this study. You will need to have exams, tests, or procedures to find out if you can be in the study. The study doctors will exam you and take blood samples for laboratory analysis to determine your general health status and determine how well your internal organs function. The following procedures will take place during the baseline visit (it is possible that not all procedures will be completed in a single visit):

- Complete medical history, including disease history
- Comprehensive physical exam, including vital signs.
- Review of your current medicines and medication history.
- Blood draws will be taken for laboratory tests as necessary to determine if your organ function is adequate for participation in this study.
- Baseline CT scan of head, chest, abdomen, and pelvis.
- The Eastern Cooperative Oncology Group (ECOG) performance score will be calculated to assess how your disease is progressing and affecting your daily living abilities.
- You will have an EKG procedure to determine how well your heart functions.
- Biopsy procedure.

After you have completed all these baseline tests, your study doctors will review all the information to determine if you meet all the criteria to participate in this study. It is possible that you may not be allowed to continue if something was found to exclude you during these Baseline

examinations. If you are found to qualify after the Baseline examinations, you will be notified and scheduled for your first Study visit (Day 0).

Assigning to Treatment Schedules

The study will evaluate two different study drug dosing schedules, A-1 with cryoablation and A-2 without cryoablation. After signing this Informed Consent Form and completing the screening process, if the study doctor finds that you are eligible to participate in this study, you will be assigned to one of the experimental treatment schedules. The schedule you are assigned to will depend on what schedule is still open.

Schedule A-1

If you are assigned to Schedule A-1 on Days 0, 7, and 14 you will receive an intradermal (ID) injection of AlloStim® (0.5 ml). On Day 21, you will receive cryoablation of a selected tumor in your liver followed with an intratumor injection (IT) of AlloStim® (1ml). On Day 28 you will receive an Intravenous Infusion (IV) of AlloStim® (3 ml) and you will continue receiving IV Infusions of AlloStim® (3 ml) on Days 56 and 84. You will be scheduled for a biopsy at baseline and Day 91 and a CT scan at baseline and Day 91.

Schedule A-2

If you are assigned to Schedule A-2 on Days 0, 3, 7, 10 and 14 you will receive an ID injection of AlloStim® (0.5 ml). On Day 21, you will receive an IV infusion of AlloStim® (3 ml). You will continue receiving Intravenous Infusions of AlloStim® (3 ml) on Days 49 and 77. You will be scheduled for a biopsy at baseline and Day 91 and a CT scan at baseline and Day 91.

Study Drug (AlloStim®)

AlloStim® is the Study drug being tested in this study. AlloStim® is manufactured in Jerusalem, Israel and contains living, bioengineered, immune cells derived from normal blood donors. The living immune cells have microscopic beads coated with special proteins called monoclonal antibodies attached. The microbeads make the AlloStim appear to have a brown color. The donors for the cells are screened to be free from blood-borne diseases such as the viruses that cause AIDS and hepatitis, by an FDA licensed laboratory. Specialized immune cells are purified from the blood of these donors and grown outside the body for 9 days under conditions that cause them to develop unique inflammatory properties. The cells are then divided up and placed into individual dose size vials and stored frozen for a year or more. Prior to the day of a scheduled experimental treatment, a dose vial with frozen cells is thawed in Jerusalem and incubated with the microscopic beads for 4 hours. This causes the activation of the immune cells.

AlloStim® is packaged in a syringe and then shipped to the point of care in specialized packaging under carefully controlled environmental conditions. AlloStim® cells are stable for only 72 hours after being packaged in a syringe. Therefore, the study drug must be administered within 72 hours of being placed into a syringe in Jerusalem.

Each AlloStim® dose is tested to assure it meets pre-defined identity and functional characteristics, is sterile, and meets international regulatory requirements for safe levels of bacterial contaminants called endotoxins. While AlloStim® is screened for the presence of infectious agents, all blood products have a risk of transmitting unknown infectious agents such as viruses.

Since AlloStim® is manufactured from the blood of unrelated donors, it is unlikely that the tissue type of the donor will be a match to your tissue type. Because of this mismatch, it is expected that your immune system will recognize the AlloStim® cells as foreign and reject them within 24 hours. If you have an abnormally weak immune system, it is possible that your immune system may not reject the AlloStim® cells completely. If the cells are not completely rejected, there could be side-effects such as the development of graft versus host disease, which may be serious and life-threatening.

Effect of Technical Problems

Certain technical problems, such as failure of the AlloStim® to meet pre-determined quality control release characteristics, weather, ground transportation delays, manufacturing, quality control, or other circumstances not now known may prevent a particular dose from arriving to the point of care within the 72 hours window. This delay would require you to miss a scheduled experimental treatment. The missing of a scheduled experimental treatment may have an adverse effect on the potential efficacy of the study, and may also cause you inconvenience and increased expense for housing, travel and meals if you live far from the point of care.

Protocol

It is very important that you come to all your scheduled appointments over the protocol. If you miss protocol appointments, you may be removed from the study. You will be provided with a written schedule of appointments.

Intradermal (ID) Injections

The study drug can be injected ID (just under the upper layer of your skin) at any of various locations, such as your shoulder, forearm, abdomen and/or thigh. Intradermal injections are administered using a very thin needle. You may feel a slight burning sensation as the fluid is injected. When the 0.5ml of fluid is placed under the skin, a small blister or bubble is formed. The site may turn a little red after the injection, it is also possible you could get a minor rash on your chest or back and could feel some itching sensations after the injection site. Some patients report a slight amount of pain at the injection site. These symptoms, if they occur, usually reside within a few minutes to an hour after the injection. You will be observed for approximately 1 hour after each intradermal injection to make sure you are stable before being released from the clinic.

You may observe a "flare" at the injection site 24-48 hours after the injection. A flare is increased redness and hardness at the injection site. A flare may be accompanied by fever, chills and/or a feeling of fatigue. The injection site may feel warm and appear red and swollen. These symptoms are usually mild and tend to reside with 72 hours. After the symptoms reside, a small hard purple bump may remain at the injection site for several months after the injection or may never completely disappear. This purple mark is harmless, but you may not think it looks attractive. If you are concerned about the cosmetic look of the purple mark that occurs after the intradermal injections, make sure to tell your study nurse to select an injection site in a location where the mark will not be so obvious, such as on the abdomen under the pant or shirt line.

Cryoablation Procedures and Intratumor Injection

If you are assigned to Schedule A-1 on day 21 of the study, you will be referred to an

interventional radiologist for a medical procedure called cryoablation. Prior to being referred for the ablation procedure, a blood test will be conducted to check the thickness of your blood. If your blood is too thin, you may be at increased risk of bleeding and will not be able to undergo the ablation procedure. You should not take any aspirin or other non-steroid anti-inflammatory drugs (NSAID) drugs, such as ibuprofen, naproxen and indomethacin a week before the ablation procedure to make sure your blood does not become too thin.

The cryoablation is a medical procedure that is conducted in order to cause the death of some tumor cells in your body. The cryoablation procedure kills tumor cells using extreme cold. The killing of tumor cells by cold causes the release of the internal contents of the tumor cells into the surrounding environment. The internal tumor cell contents are believed to contain special proteins, called heat shock proteins, that are capable of educating your immune system that the tumor is a danger to the body.

The cryoablation procedure is a minimally-invasive out-patient procedure. You may be given sedation and other medicines through an Intravenous Infusions (IV) to lessen any pain or discomfort that you may have during the procedure and allow you to relax. Your doctor will use either CT or ultrasound to visualize your tumor. Your doctor will obtain a small sample of your tumor tissue for analysis under a microscope. You will be required to lie still for approximately 1-2 hours during the procedure. You may experience discomfort from having to be still for this long time during the procedure. Viewing the CT scan or ultrasound image, your study doctor will insert a guide needle through your skin and into the center of the selected tumor lesion. You will be given a numbing medication at the site where the needle will be inserted to lessen any pain of the needle placement.

A cryoprobe probe will then be inserted through the needle guide and ultra-cold gas will then be introduced through the probe that will freeze a portion of your tumor and cause some of the cancer cells to die.

After the cryoablation procedure, 1 ml of AlloStim® will be injected into the location of the ablated tumor.

During these procedures and two hours following the procedures, you will be connected to a machine to constantly monitor your pulse, blood pressure and blood oxygen levels. After the procedures, you will be observed for at least one hour to assure you do not experience any serious side-effects. If after the observation period, the study doctor determines you have recovered from the sedation and do not have any serious side-effects you will be allowed to leave the treatment facility with a responsible adult. If you experience any significant side-effects, you may be admitted to a hospital overnight for observation. Following cryoablation, you should be able to resume your usual activities within 24 hours.

While cryoablation is known to be a relatively safe procedure, the following risks are known:

- Like any percutaneous (through the skin) procedure, bleeding may result—both from the puncture and the freezing of tissues such as the liver, bone, lymph node or lung.
- Damage to normal structures may occur. During liver ablation, the bile ducts may be injured. Any treatment of the abdomen may result in damage to the bowel and cause a hole in the bowel, which may release bowel contents into the abdomen and can lead to

infection.
- If freezing occurs near the diaphragm, fluid can accumulate in the space around the lungs.
- If the procedure is in or near the lung, the lung may collapse.
- Nerve damage may result. Completely frozen nerves can cause motor weakness or numbness in the area supplied by the nerves.
- Complications related to medications, including anesthesia, administered during the procedure may occur.

Intravenous (IV) Infusions

Prior to the IV infusion, you may be given intravenous fluids and pre-study medications to lessen the possibility of side-effects during the infusion. Some of these medications may make you drowsy.

Just prior to the infusion procedure and up to at least 1 hour after completing the procedure, you will be monitored on a machine that will continuously record your temperature, heart rate, blood oxygen level and blood pressure.

After completion of the IV administration, you will remain at the clinic facility for at least 1 hour for observation. You cannot drive for 8 hours after IV treatment.

After you receive the IV infusion, the study staff will call you by telephone to ask if you had experienced any side effects from the procedure. They will also ask you about any changes in your health.

You will be followed for survival monthly by telephonic contact for first 12 months and every three months thereafter.

Tumor Biopsy procedure

What is a tumor biopsy?

A tumor biopsy is a common procedure where a small sample of tumor tissue is removed using a needle passing through your skin. This is also called a Percutaneous Biopsy. Normally a biopsy procedure is conducted for diagnostic purposes. Additionally, normally only one biopsy is needed for diagnosis. However, your Study doctors are requesting that you consent to multiple biopsy procedures for research purposes. Since the biopsy is for research and not for treatment or diagnosis, only enough tissue will be removed to be analyzed, leaving the remaining tissue behind.

During this procedure, no incision is made. As the needle passes through the tumor, a small core of tissue is harvested. This small core is placed in a preservative and later processed into slides. The slides are prepared with various stains and dyes and examined under a microscope by a pathologist, an expert in making diagnoses from tissue samples in collaboration with study doctors with expertise in immunology and radiology.

Who will be doing the percutaneous biopsies?

A specially trained doctor called an Interventional Radiologist will be doing the percutaneous biopsies. Interventional Radiologists have special expertise in using x-ray and scanning

equipment, and also in interpreting the images produced. Your Interventional Radiologist will be viewing your tumor either by ultrasound and/or by CT scan.

Forbidden Medications

Your Interventional Radiologist will need to know all medications that you are taking, especially any anti-platelet drugs or anticoagulants. These are medicines that affect the way your blood clots. If your blood does not clot properly this increases the chances that you might bleed as a result of the biopsy. Listed below are some drugs that the doctor will need to be informed about if these have been prescribed to you:

- Abciximab
- Acenocoumarol
- Argatroban
- Aspirin
- Bemiparin
- Bivalirudin
- Clopidogrel
- Coumarins
- Dabigatran
- Dalteparin
- Danaparoid
- Dipyridamole
- Enoxaparin
- Eptifibatide
- Fondaparinux
- GP IIb/IIIa inhibitors
- Lepirudin
- Phenindione
- Plasugrel
- Rivaroxaban
- Tinzaparin
- Tirofiban
- Warfarin

The Interventional Radiologist will also need to know if you have a hereditary bleeding abnormality or abnormal bleeding history after minor procedures such as dental extraction and further tests to assess your blood may be needed.

What actually happens during a percutaneous biopsy?

During the percutaneous biopsy **y**ou will lie on the ultrasound or CT scanning table, in the position that the Interventional Radiologist has decided is most suitable. The Interventional Radiologist will keep everything as sterile as possible, and may wear a theatre gown and operating gloves. Your skin will be cleaned with antiseptic, and you may have some of your body covered with a theatre towel. The Interventional Radiologist will use the ultrasound machine or the CT scanner to decide on the most suitable point for inserting the biopsy needle. Then your skin will be anaesthetized with local anesthetic, and the biopsy needle inserted into the abnormal tissue. Actually doing the biopsy does not take very long at all, and the needle may be in and out so quickly that you barely notice it.

Will it hurt?

When the local anesthetic is injected, it will sting to start with, but this soon passes off, and the skin and deeper tissues should then feel numb. Later, you may be aware of the needle passing into your body, but this is generally done so quickly, that it does not cause any discomfort at all. There will be a nurse, or another member of clinical staff, standing next to you and looking after you. If the procedure does become painful for you, then they will be able to arrange for you to have painkillers through the needle in your arm.

How long will it take?

The biopsy procedure may be over in 30 minutes, although you may be in the x-ray department for about an hour altogether. Every subject's situation is different, and it is not always easy to predict how complex or how straightforward the procedure will be.

What happens afterwards?

You will be then taken to a recovery area where you will have to lie flat on the bed for 2 hours

after the procedure. Nurses will carry out routine observations, such as taking your pulse and blood pressure to make sure that there are no problems. They will do this every 15 minutes for a minimum of 2 hours. All being well, you will be allowed home either on the same day, or perhaps the next.

Biopsy Risks and Discomforts

There may be biopsy related complications, although these are uncommon. In a small number of cases there is some bleeding from the biopsy site. This is usually minor, and soon stops. Occasionally, the bleeding is more severe, and rarely a blood transfusion may be required. Very, very rarely, an operation or another radiological procedure is required to stop the bleeding. The main reason you are monitored for several hours after the biopsy is to check for bleeding. A rare complication for a liver biopsy is for bile to leak from the liver internally. There is also a small risk that the small wound will become infected after the biopsy. While biopsy procedures rarely have complications, the risk of complications does increase with each biopsy performed.

Optional Additional Tumor Biopsies

In order to obtain more information on the changes over time in the immune cell patterns of tumors as well changes in tumor size, your study doctors may ask you to volunteer for two or three additional biopsies to the two mandatory biopsies and two or three additional CT scans procedures. The additional biopsies will occur at the same time as the additional CT scan procedures because they believe these procedures will provide more information about how your immune system is interacting with your cancer. If you elect not to consent to these additional biopsy procedures, your status in the clinical trial will not be affected and you will still be able to participate in the clinical trial. If you consent now to these additional procedures, you can withdraw your consent at any time also without affecting your status in the clinical trial.

Please initial for your selection below for the Optional Tumor Biopsies

I give consent for the optional two or three additional biopsies

_____ (Participant initials)

I do **NOT** give consent for the optional two or three additional biopsies of my tumor tissue

_____ (Participant initials)

Research Blood Sample Collection

You will be asked to provide a sample of blood for research analysis of your immune response. Between approximately 5-65 milliliters (1-13 teaspoons) of whole blood will be collected each time research blood is collected. Research blood is scheduled between 7-8 times during the protocol depending on the treatment schedule. The blood will be taken at the same time you are having blood drawn for your standard clinic visit.

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

RISKS AND DISCOMFORTS

You may have side effects while on the study. You will be watched carefully for any side effects during and after receiving the study drugs. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects that might occur. Some possible side effects such as fever, rash, swollen lymph nodes, mild pain, nausea, headache, muscle aches and/or chills are expected to lessen and go away soon after you receive the Study Drug. However, in some cases, it is possible that unexpected side effects could be serious, long lasting, or may never go away.

When medicines are infused through a vein, they can be associated with hypersensitivity reactions. These reactions range in severity from mild flushing and itching to a severe allergic type reaction that can result in shortness of breath, high fever, sudden drop in blood pressure and in some rare cases, can lead to death. The risk of a severe reaction to immunotherapy increases with each exposure to the study drug.

The study drugs contain very small microscopic beads. While these beads were not found to cause any toxic effects in monkeys or mice in pre-clinical testing, there is a risk that these beads could cause clumps in your blood that could block circulation in small capillaries. This could lead to a possible heart attack, stroke or difficulty in breathing. The very small beads do not naturally degrade in your body, so they may remain in your tissues (especially your kidneys, liver, and/or spleen) for an extended period of time. The long term effects of these beads in your organs are not known. There is a risk that these beads could cause tissue damage in these organs that could adversely affect their function.

Most patients experience flu-like symptoms (fever, chills, swollen lymph nodes, muscle pains) within 24 hours of receiving AlloStim®. Flu-like symptoms are more likely to be experienced after intravenous AlloStim® infusion than intradermal or intratumoral injections. Intradermal injections will cause swelling and redness at the injection site for a few days. After the swelling goes away, there may be a dark purple mark on your skin. This mark is not harmful but may remain for a long time. The flu-like symptoms can include high fever, chills, swollen lymph nodes, nausea, diarrhea, fatigue and shaking (rigors). These symptoms usually subside after 24-48 hours. Medications can be administered to lessen the symptoms.

AlloStim® can cause swelling of tumors. When the tumors are near vital organs or major blood vessels or are in the brain, this swelling could cause serious and possibly life-threatening side effects. Your study doctor will monitor you closely for any evidence of swelling in your brain or other vital areas such as your liver and pancreas. If swelling occurs, your study doctor may have to provide you with medications to control or reduce the swelling. Some medications that reduce swelling also suppress the immune system. Suppression of the immune system could make the study drug less effective. There also is no guarantee that any medication will be able to control the swelling if it occurs. If medication does not control the swelling, you may have to have surgery or undergo other interventional procedures in order to attempt to drain or otherwise remove the swollen tissue.

It is possible that AlloStim® may over-stimulate your immune system. This could create acute or chronic inflammatory conditions, including autoimmune conditions where your immune system attacks normal tissues. These could cause pain and/or restrict movement, diarrhea and/or vomiting, adversely affect organ function such as your liver or pancreas. These side-effects could

adversely affect your quality of life and could become serious and even lethal. Chronic inflammation may also make you more susceptible to abnormal blood clot formation. Blood clots can cause severe pain and can have potentially life-threatening and/or disabling effects. Drugs can be given to control overstimulation and to treat and prevent blood clots. However, there is no assurance that medical intervention could reverse these conditions.

Severe fatigue is known to occur in patients with metastatic colon cancer. These fatigue symptoms could become worse after immunotherapy and after cryoablation. Notify your study doctor if you are feeling symptoms of fatigue, such as a deep tiredness not relieved by rest.

AlloStim® could cause your immune system to attack your tumors too quickly. This could cause metabolic changes requiring treatment. Some metabolic changes require emergency treatment to correct. In addition, chronic inflammation and/or immune-mediated tumor killing could cause fluid accumulation in areas where you had tumors, such as your abdomen or lungs. Fluid accumulation in the abdomen may cause nausea, changes in bowel patterns, cramps and/or pain. Fluid in your lungs could cause difficulty in breathing. Excess fluid may have to be drained in an attempt to relieve symptoms. Fluid accumulation in the body may continue despite medical intervention and continuous fluid accumulation could be life threatening.

If you have pre-existing inflammation in your body, AlloStim® could make this condition worse, causing increased pain or discomfort. If you had prior radiation or surgery in an area, AlloStim® could cause inflammation in the affected areas, causing increased swelling and pain in those areas. If you have had prior radiation in your lungs or chest, inflammation could make it more difficult for you to breath. Inflammatory side effects can cause pain and discomfort which may be severe. The pain may require medications, such as narcotics. There is no assurance that pain caused by chronic inflammation can be controlled adequately even with narcotics.

If medical interventions for treatment of inflammation are necessary, these interventions may reduce the chance for a beneficial immune effect against your tumors. Steroids such as solumedrol or prednisolone that may be used to suppress excess inflammation are preferred because they may allow a beneficial immune response to return after stopping the drugs. However, some drugs for immune suppression have irreversible effects on your experimental therapy, eliminating any potential benefit. You should avoid taking the drug called Dexamethasone (Decadron) while on experimental immunotherapy, as this drug will irreversibly suppress any potentially beneficial immune response against your tumors.

It is possible that AlloStim® may elicit a beneficial immune response to decrease the amount of tumor in your body, but your body may replace the killed tumor with scar tissue. Small amounts of scar tissue usually do not have any serious long lasting adverse effects. However, if you have a large amount of tumor in a vital organ, such as the liver or the lung, replacement of the tumor with scar tissue may adversely affect the function of the organ. This could be a serious, life-threatening and irreversible condition.

AlloStim® can cause changes in your CT, PET, X-ray and MRI ("Scans") images that will make it difficult for your doctor to determine if your disease is progressing or regressing. Generally, the appearance of larger tumors or new tumors on Scans is interpreted as progressing disease. However, an immune response in the tumor can cause swelling which will make the tumor

appear larger on Scans, even if there is actually less tumor. In addition, AlloStim® can cause swelling of tumors that previously were too small to be seen on Scans. This could be misinterpreted as new disease. Additionally, the immune response may be slow and you may in fact progress for several months before a beneficial immune response is evident. Your study doctor will discuss your Scan results with you. You should have any Scans after immunotherapy sent to your study doctor for interpretation, as most radiologists will not have experience in interpreting Scans of patients that have received immunotherapy and may erroneously report progressive disease. In addition, X-rays CT /PET and MRI procedures may be done. The risks of these procedures are minimal but there is the radiation risk. Radiation is believed to be related to the total lifetime exposure. You should think about your own history of radiation exposure from tests (like x-rays or CT scans) in deciding about the radiation in this study. If you have questions about the total amount of radiation you will be receiving, you should ask your doctor.

In order to better determine the status of your disease after immunotherapy, it is possible that your study doctor may recommend additional laboratory tests or procedures in order to obtain additional information about your disease status.

The following are possible side effects of AlloStim® that have not been observed to date but are considered possible, and if they occur, are serious, life-threatening risks:

- Blood clot in the heart, lung, brain or other critical area;
- Liver granuloma formation (growth on the liver);
- Hypovolemic Shock, which can be a life-threatening decrease in blood volume;
- Septic Shock, which can include fever, rash, low blood pressure, and multiorgan failure;
- Transfusion Related Acute Lung Injury (TRALI), which can include difficulty breathing, low blood pressure, fever, and fluid in the lungs;
- Tumor Lysis Syndrome (TLS), which includes metabolic changes from the rapid killing of tumor cells. This can lead to excess potassium in the blood and life threatening irregular heartbeats, heart attack, or kidney failure.

Depression and suicide have been associated with other immunotherapies. You should notify the study investigator if you have any suicidal thoughts during the trial.

There may be additional risks to you that are currently unforeseeable, including risks that may be fatal.

Women who are pregnant or nursing a child may not take part in this study. Before entering the study, you and your study doctor must agree on the method of birth control you will use during the entire study. If you think that you have gotten pregnant during the study, you must tell your study doctor immediately. Pregnant women will be taken out of the study.

Other Risks

Your condition may not get better or may get worse during this study.

NEW INFORMATION

You will be told about any new information that might change your decision to be in this study. You may be asked to sign a new consent form if this occurs.

BENEFITS
It cannot be promised that you will receive any medical benefits from being in this study. Your participation in this study may contribute information about the immune responses to cancer that may benefit research knowledge and other patients in the future.

CONFIDENTIALITY
We may share your health information with your primary care physician or specialist taking care of your health.

COSTS
Immunovative Therapies, Ltd. will provide the study drug, AlloStim®, free of charge during this study. Tests and procedures that are done only for the study will not be billed to you or your insurance company.

You or your insurance company may be billed for any standard medical care procedures given during this research study.

You may want to talk with your insurance company about its payment policy for standard medical care given during a research study. If your insurance company does not pay, you may be billed for those charges.

You might have unexpected expenses from being in this study. Ask your study doctor to discuss the costs that will or will not be covered by the sponsor. This discussion should include who will pay the costs of treating possible side effects.

PLEASE NOTE: To ensure payment, all study-related procedures/tests must be conducted at a Banner Health facility. If you have any questions, please ask your physician or the study staff.

PAYMENT FOR PARTICIPATION
You will not be paid for your participation in this study.

ALTERNATIVE TREATMENTS
You do not have to take part in this research study. Patients with advanced metastatic cancers that do not respond to current treatments do not have many treatment options. Your other choices may include:

- Getting the FDA approved drugs 'Regorafenib' and 'Lonsurf' which have survival benefit demonstrated for metastatic colorectal cancer patients.
- Getting chemotherapy or radiation treatments for your cancer without being in a study. Some of these treatments may prolong your life
- Taking part in another study
- Getting no treatment
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

You should consult with your oncologist about your choices. Make sure you understand all of

your choices before you decide to take part in this study. You may leave this study and still have these other choices available to you.

COMPENSATION FOR INJURY

If you are injured or get sick as a result of being in this study, call the study doctor immediately. The study doctor will provide emergency medical treatment. Your insurance will be billed for this treatment. The sponsor will pay any charges that your insurance does not cover. No other payment is routinely available from the study doctor or study sponsor.

VOLUNTARY PARTICIPATION AND WITHDRAWAL

Your participation in this study is voluntary. You may decide not to participate or you may leave the study at any time. Your decision will not result in any penalty or loss of benefits to which you are entitled.

Your participation in this study may be stopped at any time by the study doctor or the sponsor without your consent for any reason, including:

- if it is in your best interest;
- you do not consent to continue in the study after being told of changes in the research that may affect you;
- Protocol violation;
- Protocol non-compliance;
- Subject becomes pregnant.

If you leave the study before the planned final visit, you may be asked by the study doctor to have some tests or procedures done so that you leave the study safely.

SOURCE OF FUNDING FOR THE STUDY

Banner Health may receive compensation to cover costs associated with conducting this study and for your participation in this study. If you have any questions about this compensation, please discuss this with your study doctor.

QUESTIONS

Contact Dr. Madappa Kundranda at (480) 256-6444 (24 hours) for any of the following reasons:

- if you have any questions about your participation in this study,
- if you feel you have had a research-related injury or a reaction to the study drug, or
- if you have questions, concerns or complaints about the research.

If you have questions about your rights as a research subject or if you have questions, concerns or complaints about the research, you may contact:

Western Institutional Review Board® (WIRB®)
1019 39th Avenue SE Suite 120
Puyallup, Washington 98374-2115
Telephone: 1-800-562-4789 or 360-252-2500
E-mail: Help@wirb.com

WIRB is a group of people who perform independent review of research.

WIRB will not be able to answer some study-specific questions, such as questions about appointment times. However, you may contact the study WIRB if the study staff cannot be reached or if you wish to talk to someone other than the study staff.

Do not sign this consent form unless you have had a chance to ask questions and have gotten satisfactory answers.

If you agree to be in this study, you will receive a signed and dated copy of this consent form for your records.

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.

By signing this consent form, you have not given up any of your legal rights.

Authorization to Use Your Health Information for Research Purposes

What is the purpose of this form?
The federal medical HIPAA Privacy Rule protects your personal health information (PHI). The purpose of this form is to let you know how your PHI will be used or disclosed (shared) in this research study. In order for the study doctor and study staff to use and share your PHI for this study, your written permission, called your "authorization", is needed.

If you have any questions or concerns about this authorization you should contact Sue Colvin, Banner Research Regulatory Affairs Director, at (602) 839-4583 or sue.colvin@bannerhealth.com. You may also request and will be provided a copy of the Notice of Privacy Practices.

By signing this form, you voluntarily give permission for the use and/or sharing of your PHI. Please consider the important information in this form prior to making your decision.

What PHI will be obtained, used or shared?
Information related to this study that identifies you and your PHI will be collected from your past, present, and future hospital and/or other health care provider medical records. The PHI you are permitting to be used and/or shared includes:

☒ Entire Official Medical/Clinical Record (**including all boxes in this table**)				
☐ Assessments	☐ Discharge Summaries	☐ Interviews	☐ Operative Reports	☐ Primary Care Physician Records
☐ Audiology Records	☐ EEG Reports	☐ Laboratory Reports	☐ Outpatient Clinic Records	☐ Problem List (electronic medical record)

☐ Autopsy Reports	☐ EKG Reports	☐ Medicare Records	☐ Ophthalmology Records	☐ Progress Notes
☐ Consultation Reports	☐ Emergency Medicine Reports	☐ Medication Lists	☐ Pathology Reports	☐ Questionnaire
☐ Demographic Information	☐ Genetic Testing	☐ Neuropsych Test Results	☐ Pathology Slides	☐ Recordings (Audio/Video) / Photographs
☐ Dental Records	☐ Health Care Billing Records	☐ Nursing Notes	☐ Pathology Specimens	☐ Survey
☐ Diagnostic Imaging Reports/Films/ CDs/Scans	☐ History & Physical Exams	☐ Occupational Therapy Records	☐ Physical Therapy Records	☐ Vocational Test Results
☐ Other:				

Demographic information to be shared may include, but is not limited to, your name, address, and phone number.

By signing this form you are also giving permission to the study staff to collect, use and/or share PHI related to the diagnosis or treatment of sexually transmitted disease (STD), acquired immunodeficiency syndrome (AIDS), human immunodeficiency virus (HIV), other communicable diseases, genetic information (for example, genetic testing), alcohol abuse, and/or drug abuse. Your information will only be used and/or shared for this study.

Who will use and/or share your PHI?
The following parties are authorized to use and/or disclose your PHI for the research described in the attached consent form:

a. Study doctor and study staff
b. Banner Health

Who may receive your PHI?
The parties listed in the preceding paragraph may disclose your health information to the following persons and organizations for their use in connection with this research study:

a. The study sponsor, Immunovative Therapies, Ltd., and their representatives
b. Banner Health
c. Central laboratories and companies working with the sponsor
d. Local laboratory at Banner Gateway Medical Center
e. Western Institutional Review Board
f. U.S. Department of Health and Human Services (HHS); HHS Office for Human Research Protections (OHRP); HHS Office of Research Integrity (ORI); and the U.S. Food and Drug Administration (FDA), or other regulatory agency as required.

Your PHI may no longer be protected under the HIPAA privacy rule once it is disclosed by the

research team to these other parties, and it may be further shared without your permission.

For what purposes are you giving permission to use and/or share of your PHI?

a. To conduct the study described earlier in this document
b. Oversight, audit and monitoring of the study

When will your permission expire?

There is no expiration date or event for your permission to use and/or share your PHI. Therefore, unless you cancel this permission (as instructed below) it will continue to be effect.

Do you have to sign this form?

You do not have to sign this form. However, if you decide not to sign, you will not be able to take part in this study, including receiving any study-related intervention. If you do not sign, it will not affect any non-study Banner Health medical treatment or health care, payment, enrollment in any health plans, or benefits.

What do you need to know if you decide to cancel your permission?

After signing this form, you may decide to cancel your permission to use your PHI. If you cancel your permission, you will no longer be able to stay in the study.

Please note that any PHI collected before you canceled your permission may still be used as described above. The study staff is required by law to report any bad side effect you have even if you have canceled your permission.

How do you cancel your permission?

To cancel your permission you must notify the study doctor/study staff in writing at the following address:

Dr. Madappa N. Kundranda/ Research
2940 E Banner Gateway Drive, Suite 450
Gilbert, AZ 85234

Will access be limited to your research study record during the study?

You may not have access to the research information developed as part of this study until it is completed.

Optional Research Activity

Optional research activity is part of this study. If you choose to take part in this optional activity your PHI will be used and/or shared for the activity. You can still be in the main part of the study even if you do not give permission to the use and/or sharing of your PHI. However, if you agree to take part in the optional research activity you must also give your permission to the use and/or sharing of your information below.

By initialing the line below, you agree to allow your PHI to be used and/or shared for the optional study described above.

Future Use of PHI

If you choose to provide the authorization you are authorizing us to use and/or disclose of your PHI for future research purposes (e.g., future studies). The following information includes a description of the future research purposes (e.g., future studies) so that you understand and expect the future use and disclosure of your PHI for such purposes.

Immunovative Therapies, Ltd. research, Target Health Inc., and other researchers may use my medical data and may patent or commercialize discoveries or inventions that result from this research.

Sponsor may use electronic pictures or other images of your body for the benefit of the study medical objective, science or for educational purposes without identifying or providing any descriptive information of your identity.

If you have any questions or concerns about this authorization you should contact Sue Colvin, Banner Research Regulatory Affairs Director, at (602) 839-4583 or sue.colvin@bannerhealth.com. You may also request and will be provided a copy of the Notice of Privacy Practices.

CONSENT AND HIPAA AUTHORIZATION

Before signing the Informed Consent Form and HIPAA Authorization, I confirm that the study information and procedures have been explained to me in details during the consent process, including the study objective, methodology, risks and benefits and I have understood it.

I confirm that I have had the opportunity to ask questions about this study and HIPAA Authorization and I am satisfied with the answers and explanations that have been provided by the investigator.

I have been given an adequate time and opportunity to read the information carefully, to discuss it with others if I wished to and to decide whether or not to take part in this study.

I have had all alternative treatments discussed with me.

I consent voluntarily to participate as a participant in this research and understand that I have the right to withdraw from the research at any time without in any way affecting my medical care.

It is clear to me that there is no guarantee that I will benefit from being in this research and that there are no expected study results. I understand that I may suffer side-effects as a result of participating in the study.

Should I be injured from participating in the study, I will receive medical care from the Investigator without charging me.

I agree that Immunovative Therapies, Ltd. research and other researchers may use my medical data and may patent or commercialize discoveries or inventions that result from this research.

Neither Immunovative Therapies, Ltd. nor other participants in this research will compensate me if this happens.

I authorize the use and disclosure of my health information to the parties as outlined in this consent form for the purposes described above.

I agree to use electronic pictures or other images of my body for the benefit of the study medical objective, science or for educational purposes without identifying or providing any descriptive information of my identity.

If I have questions, I can contact Dr. Madappa Kundranda, who is in charge of the study at the Banner MD Anderson Cancer Center at (480) 256-6444 (24 hours) at any time.

I have read all above information form (or it has been read to me) and fully understood and voluntary signed this informed consent form and HIPAA Authorization and have been given a copy of signed informed consent form and HIPAA Authorization.

By signing this consent form and HIPAA Authorization, I have not given up any of my legal rights.

SIGNATURE SECTION

_____
Subject Name (printed)

_____ _____
Signature of Subject Date

_____
Person Obtaining Consent (printed)

_____ _____
Signature of Person Obtaining Consent Date