UNIVERSITY OF PENNSYLVANIA
RESEARCH SUBJECT
INFORMED CONSENT FORM AND HIPAA AUTHORIZATION

Protocol Title:	A phase II study of the Anti- GITR agonist INCAGN01876 and the PD-1 inhibitor INCMGA00012 in combination with stereotactic radiosurgery in recurrent glioblastoma
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Research Study Summary for Potential Subjects

You are being invited to participate in a research study. Your participation is voluntary and you should only participate if you completely understand what the study requires and what the risks of participation are. You should ask the study team any questions you have related to participating before agreeing to join the study. If you have any questions about your rights as a human research participant at any time before, during or after participation, please contact the Institutional Review Board (IRB) at (215) 898-2614 for assistance.

This research study is being conducted to test how safely and effectively the combination of two investigational drugs (INCMGA00012 and INCAGN01876) and stereotactic radiosurgery (SRS, a type of radiation) works in treating recurrent glioblastoma (GBM). “Investigational” means that the FDA (the U.S. Food and Drug Administration) has not approved these drugs as treatment for this condition. The short name of “anti-PD-1” will be used for INCMGA00012 throughout this consent, and short name “anti-GITR” will be used for INCAGN01876. PD-1 and GITR are two molecules on T-cells, which are cells in the body’s immune system that can help to fight against tumors. The drugs used in this study (anti-PD1 and anti-GITR) are designed to target these molecules on T cells and help the T

cells fight the tumor. More information on the PD-1 and GITR molecules is listed in the purpose section of this consent form.

If you agree to join the study, you will be asked to complete the following research procedures:

- Screening Visit- Your medical history will be reviewed, and you will have assessments like a physical exam and lab work to confirm you are eligible and safe to take the study drugs.
- Once eligibility is confirmed,
    - if your physician determines that surgical removal of your tumor SHOULD NOT be part of your treatment plan at this time, you will receive one dose of IV anti-GITR and IV anti-PD-1, SRS within 3-7 days after this dose, and then IV anti-GITR every 2 weeks and IV anti-PD-1 every 4 weeks for 2 years, until your tumor grows back, you are unable to tolerate the side effects of the drugs, you desire to stop treatment, or the investigator, sponsor, or the FDA decide to stop the study.
    - if your physician determines that surgical removal of your tumor SHOULD be part of your treatment plan at this time, you will receive treatment with one of two possible combinations of immunotherapy (anti-PD-1 + anti-GITR + SRS or anti-PD-1 + anti-GITR) prior to surgery. Postoperatively, you will receive IV anti-GITR every 2 weeks and anti-PD-1 every 4 weeks for 2 years, until your tumor grows back, you are unable to tolerate the side effects of the drugs, you desire to stop treatment, or the investigator, sponsor, or the FDA decide to stop the study.
- While taking the study drugs, you will have an assessment of your tumor by MRI (or CT scan if MRI is contraindicated) once every 2 months
- Periodic visits to assess if you are having any side effects or symptoms.

Some of the most common side effects of the anti-GITR study drug:
(full list below in Risks section, page 12)

- Fatigue
- Cough
- Abdominal pain
- Dyspnea: shortness of breath
- Nausea

Some of the most common side effects of the anti-PD-1 study drug:
(full list below in Risks section)

- Fatigue
- Diarrhea
- Pyrexia: raised body temperature, fever
- Anemia
- Dehydration

Some of the risks of both of the anti-GITR and anti-PD-1 study drugs:
(full list below in Risks section, page 13)

- Your immune system attacks healthy organs, which can lead to:
    - Colitis (diarrhea)
    - Pneumonitis (cough, low oxygen, and shortness of breath)

- Hepatitis (inflammation of the liver)
- Thyroid and adrenal gland dysfunction
- Dermatitis (rash)
- Other immune-mediated side effects in other organs

If you choose not to participate, your other choices may include:

- Getting treatment or care for your brain cancer without being in a research study
- Taking part in another research study
- Getting no treatment

Please note that there are other factors to consider before agreeing to participate such as additional procedures, use of your personal information, costs, and other possible risks not discussed here. If you are interested in participating, a member of the study team will review the full information with you. You are free to decline or stop participation at any time during or after the initial consenting process.

Why am I being asked to volunteer?

You are being invited to participate in a research study because you have recurrent glioblastoma (GBM). Your participation is voluntary which means you can choose whether or not you want to participate. If you choose not to participate, there will be no loss of benefits to which you are otherwise entitled. Before you can make your decision, you will need to know what the study is about, what the possible risks and benefits of being in this study are, and what you will have to do in this study. The research team is going to talk to you about the research study, and they will give you this consent form to read. You may also decide to discuss it with your family, friends, or family doctor. You may find some of the medical language difficult to understand. Please ask the investigator and/or the research team about anything that is not clear. If you decide to participate, you will be asked to sign this form. Your doctor may be an investigator in this research study. As an investigator, your doctor is interested both in your clinical welfare and in the conduct of this study. Before entering this study or at any time during the research, you may want to ask for a second opinion about your care from another doctor who is not an investigator in this study. You do not have to participate in any research study offered by your doctor.

This research study that you are being asked to voluntarily participate in is studying the combination of the anti-GITR agonist monoclonal antibody INCAGN01876, the anti-PD1 monoclonal antibody INCMGA0012, and SRS for recurrent GBM as a possible treatment for this diagnosis.

How many people will participate in this study?

It is expected that about 32 total participants will take part in this research study. 16 participants will be in Cohort A (participants who do not require surgical removal of the tumor as part of their treatment) and 16 participants will be in Cohort B (participants who do require surgical removal of the tumor as part of their treatment).

What is the purpose of this research study?

GBM is the most common primary malignant brain tumor in adults and is characterized by a tumor environment that prevents the body's immune system from recognizing the tumor. The tumor is therefore able to grow without being attacked by the patient's T cells (immune system).

This research study is a phase II clinical trial. Phase II clinical trials test the safety and effectiveness of an investigational therapy to learn whether the intervention works in treating a specific disease. The FDA (U.S. Food and Drug Administration) has not yet approved the study drug/ interventions that are being used in the study, which means that they are considered to be investigational.

The main purpose of the study is to determine the effectiveness of the combination of INCMGA00012 (anti-PD-1_, INCAGN01876 (anti-GITR), and stereotactic radiosurgery (SRS) in recurrent GBM.

INCMGA0012 (anti-PD-1)

INCMGA0012 is an antibody that targets cells expressing the protein PD-1, such as T cells, in order to restore the immune function of these cells.

INCAGN01876 (anti-GITR)

INCAGN01876 is an immune modulator that targets the protein GITR, which is also found on T cells, in order to restore an immune response to the tumor.

Stereotactic Radio Surgery (SRS)

Stereotactic Radio Surgery is a non-surgical radiation therapy that is used to help tumors of the brain. It brings precisely-targeted radiation in fewer high-dose treatments, which aids in preserving healthy tissue. There have been studies in animals that suggest that this type of radiation can activate the immune system.

How long will I be in the study?

You will continue to receive the study drug and be in the study for 2 years, unless your tumor grows, you have side effects that cause your condition to worsen, or you desire to stop treatment. After you stop the study drug, your doctor will continue to monitor you for side effects and follow your condition for 12 weeks.

You may be taken off the research study for many reasons, including the following possibilities:

- It is considered to be in your best interest
- The study treatment or procedures are found to be unsafe or ineffective

- There is any problem with following study treatments and procedures
- You are a female and become pregnant or plan to become pregnant
- Your condition worsens
- A decision is made to close the study
- Additional unforeseen reasons that require treatment to stop

If you are removed from the research study, the research doctor will explain to you why you were removed. The research doctor and research team will help arrange for your continued care.

In addition, you can stop participating in the research study at any time. However, the FDA requires that any information collected up to the point of your withdrawal cannot be removed from the study. If you decide to stop participating in this research study, we encourage you to speak with your research doctor and primary care doctor first.

What am I being asked to do?

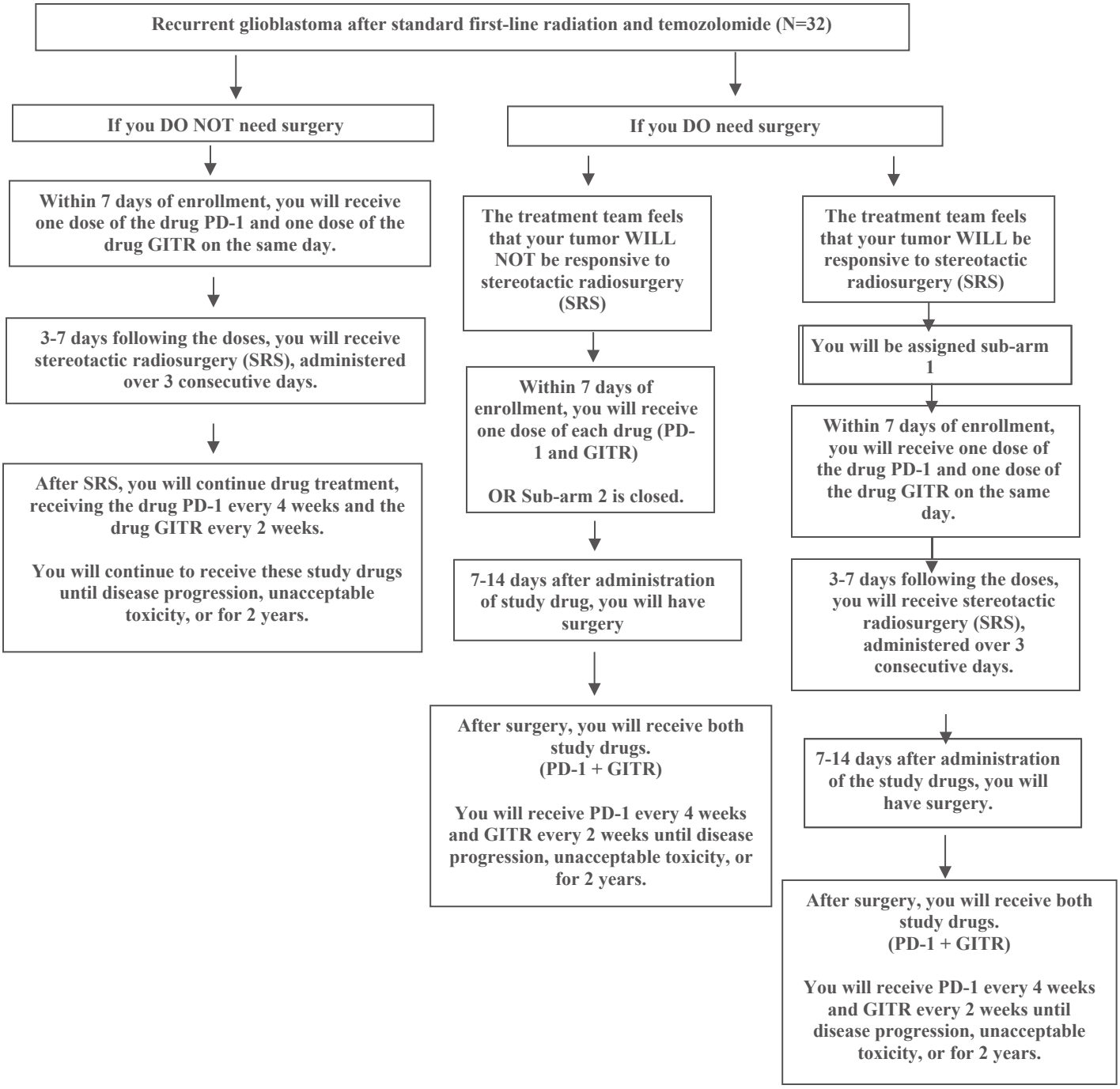
If you choose to participate in this research study, you will first complete a "screening visit," which consists of tests to determine whether you meet the study requirements. All tests performed will be for research purposes, with the exception of the following:

- If an MRI unrelated to the study is performed within a window that is needed for the study, it will be used instead of receiving an additional research MRI.

Additionally, this study requires routine blood draws, which will be drawn locally. If you decide to participate in this study, there are certain rules that you must follow before, during, and after the study period. Some are listed below, but there may be others that the study doctor will discuss with you:

- Keep your study appointments and complete all study assessments. If you cannot attend an appointment, please contact the study personnel (i.e., the study doctor or study nurse) as soon as possible to schedule a new appointment.
- You must not get someone pregnant or become pregnant during this study.
- It is very important that you tell your study doctors of all information you know about your health and the medications you may be taking throughout the study period. If you do not tell your study doctor everything you know, you may be putting your health at risk.
- You must follow all instructions given to you while you are participating in this study. If you do not follow all instructions given, you may be removed from the study. If you are unsure about what you are supposed to do, ask the study doctor or nurse.

Study Treatment Overview



Safety Lead- In: You will be placed either into Cohort A or Cohort B. Patients for whom surgical resection is not clinically indicated at the time of study screening will be placed into Cohort A (non- surgical cohort). Patients with a clinical indication for surgical resection at the time of study screening will be enrolled into Cohort B (surgical cohort). Enrollment will start in groups of 3 subjects as part of a safety run-in period.

Cohort A (non-surgical; N=16)
If you are enrolled into Cohort A, within 7 days of enrollment, youwill receive a single 500mg dose of anti-PD-1 Intravenously (IV) and a single 300mg dose of anti-GITR (IV) on the same day. Within 3 to 7 days following the doses, you will then receive stereotactic radiosurgery (SRS), administered over the course of 3 consecutive days. There will be a total dose of 24 Gy (8 Gy per day). After SRS, you will continue on combined drug treatment (anti-PD-1 500mg IV every 4 weeks and anti-GITR 300mg IV every 2 weeks) for 2 years, until disease progression, or until unacceptable adverse events occur.

Cohort B (surgical; N=16)

If you are enrolled into Cohort B, you will then be enrolled onto one of two surgical sub-arms (sub-arms 1 and 2; there are eight participants per sub-arm), depending on the tumor's amenability to SRS, in the oncology team's opinion. Each sub-arm will receive a different treatment regimen (referred to as "neoadjuvant" dosing) prior to surgical removal: the combination of anti-PD-1 + anti-GITR with SRS (sub-arm 1), the combination of anti-PD-1 + anti-GITR alone (sub-arm 2). In both surgical sub-arms, within 7 days of enrollment, you will receive a single dose of the investigational drugs. In sub-arm 1, within 3 to 7 days following the neoadjuvant doses of the study drugs, you will receive SRS which will be given over the course of 3 consecutive days.
If you are enrolled in sub-arm 2, within 7 -14 days following administration of the study drug(s), you will undergo maximal safe surgical removal of your tumor. If you are enrolled in sub-arm 1, you will undergo tumor removal 7-14 days following SRS. Following surgery, you will then resume therapy with both investigational agents. The investigational drug will be started as soon as the principal investigator feels that you have properly recovered from surgery, but the drug treatment must be restarted within 5 weeks of surgery. You will continue on combined drug treatment (anti-PD-1 500mg IV every 4 weeks and anti-GITR 300mg IV every 2 weeks) for 2 years, until disease progression or unacceptable adverse events.

Study Procedures
The following procedures will occur during your study visits while receiving the study drugs:

- A physical examination, vital signs (blood pressure, heart rate, respiratory rate, temperature and weight), and an evaluation of your ability to perform daily activities will be assessed every time you are seen in the office
- About 10 mLs (about 2 teaspoons) of blood will be taken for general health screening tests. These tests will measure how well your kidneys and liver are working, and whether your blood counts and chemistry are normal.
- About 50 mLs (about 3 tablespoons) of blood will be taken for future research use. These samples will be stored and used for future research studies to learn more about GBM and how immunotherapy affects GBM.

- You will also be asked whether there have been any changes in your health. This would include any new illnesses or health problems, medications, and/or side effects since your most recent visit.
- If you are a woman and can have children, your blood or urine will be tested to see if you are pregnant before receiving the first dose of study drugs. The results of the pregnancy test must come back negative for you to be in the study.
- Study drug(s) will be administered to you through an IV: anti-PD-1 is administered once every 4 weeks, and anti-GITR is administered every 2 weeks
- An MRI scan will be performed approximately once every 8 weeks
- One course of radiation (SRS) will be administered during cycle 1 and will be done for 3 consecutive days. This will start between 3 and 7 days after first dose of study drugs
- A piece of your original tumor from your initial surgery when you were first diagnosed with GBM will be requested for research use
- If you are assigned to Cohort B (the surgical arm of the trial), part of the tumor tissue that is removed during the surgery will be stored for research use

The following procedures will occur during the end of treatment visit:

- A physical examination, vital signs (blood pressure, heart rate, respiratory rate, temperature and weight), and an evaluation of your ability to perform daily activities will be assessed
- If you are a woman and can have children, your blood or urine will be tested to see if you are pregnant.
- You will also be asked whether there have been any changes in your health. This would include any new illnesses or health problems, medications, and/or side effects since your most recent visit.
- A urine sample will be collected for analysis.
- About 10 mLs (about 2 teaspoons) of blood will be taken for general health screening tests. These tests will measure how well your kidneys and liver are working, and whether your blood counts and chemistry are normal.
- About 50 mLs (about 3 tablespoons) of blood will be taken for future research use. These samples will be stored and used for future research studies to learn more about GBM and how immunotherapy affects GBM.

The following procedures will occur during the follow up visit (after you have completed the study):

- A physical examination, vital signs (blood pressure, heart rate, respiratory rate, temperature and weight), and an evaluation of your ability to perform daily activities will be assessed
- If you are a woman and can have children, your blood or urine will be tested to see if you are pregnant.

- You will also be asked whether there have been any changes in your health. This would include any new illnesses or health problems, medications, and/or side effects since your most recent visit.
- A urine sample will be collected for analysis.
- About 10 mLs (about 2 teaspoons) of blood will be taken for general health screening tests. These tests will measure how well your kidneys and liver are working, and whether your blood counts and chemistry are normal.
- About 50 mLs (about 3 tablespoons) of blood will be taken for future research use. These samples will be stored and used for future research studies to learn more about GBM and how immunotherapy affects GBM.
- On every 12th week following your 30 day after treatment visit, you will also get an MRI of your brain to assess the tumor (this would occur anyway as part of your routine care for GBM).
- Following this scheduled safety follow-up visit, you will be contacted by telephone, e-mail or visit one additional time 12 weeks (+/- 14 days) from the end of treatment visit to capture additional changes in your health, such as any new illnesses or health problems, medications, and/or side effects.

Tissue Collection for Research Purposes:

- By consenting for this clinical trial, you will also be consenting for the study to collect a preserved component of your tumor tissue from your initial surgery (both cohorts). This sample will be analyzed for research purposes.
- For subjects on cohort B, both a fresh and preserved sample from your surgery that you will undergo during this trial will also be collected.
- If you transition off study, and your care in the future involves an additional surgery, a tissue sample from this procedure will also be collected, if possible. This will occur if your most recent therapy prior to the scheduled surgery was trial therapy.

The following table is a sample schedule of what to expect during your standard treatment for Cohort A (only first 2 cycles and end of treatment are shown). Each cycle is 28 days in length.

	Visit 1 (Screening)	Cycle 1 Day 1	Cycle 1 Day 5	Cycle 1 Day 8	Cycle 1 Day 15	Cycle 2 Day 1	Cycle 2 Day 15	End of treatment
Informed Consent	X							
Medical History	X							
Physical Exam	X	X			X	X	X	X

Evaluation of daily activities	X	X			X	X	X	X
Vitals	X	X			X	X	X	X
Medication/ Reaction Updates	X	X				X	X	X
Pregnancy test	X							X
Blood work	X	X			X	X	X	X
Research Blood work		X		X	X	X	X	X
Urine Test	X							X
Adverse Event	X	X			X	X	X	X
Anti-PD-1		X				X		
Anti-GITR		X			X	X	X	
MRI	X							X
SRS delivery			X					

The following table is a sample schedule of what to expect during your standard treatment for Cohort B (only first 2 cycles and end of treatment are shown). Each cycle is 28 days in length.

	Visit 1 Screening	Neoadjuvant cycle	Day of surgery	Cycle 1 Day 1	Cycle 1 Day 5	Cycle 1 Day 8	Cycle 1 Day 15	Cycle 2 Day 1	Cycle 2 Day 15	End of treatment
Informed Consent	X									
Medical History	X									
Physical Exam	X	X	X	X			X	X	X	X
Evaluation of daily activities	X	X	X	X			X	X	X	X
Vitals	X	X	X	X			X	X	X	X
Medication / Reaction Updates	X	X	X	X				X	X	X
Pregnancy test	X									X
Blood work	X	X	X	X			X	X		X
Research Blood work		X		X			X	X	X	X

Urine Test	X									X
ECG	X									
Adverse Event	X	X	X	X			X	X	X	X
Anti-PD-1		X**		X				X		
Anti-GITR		X**		X			X	X	X	
MRI	X									X
SRS delivery					X					

The following table is a sample schedule of what to expect during the follow-up phase of the study for both cohorts.

Procedure	Safety Visit (30 days after End of Treatment)	Safety Follow-Up (12 Weeks after End of Treatment)	Disease Status and Survival (Every 12 Weeks after End of Treatment)
Physical Exam	X		
Medical History	X		
Vitals	X		
Evaluation of daily activities	X		
Medication/Reaction Updates	X	X	
Adverse Event	X	X	
Blood Test	X		
Urine Test	X		
Pregnancy Test	X		
MRI			X
Vital Status			X

What are the possible risks or discomforts?

All cancer treatments can have side effects. These side effects can range from mild to severe and from reversible to permanent. In a research study, all of the risks or side effects may not be known before you start the study. Research may involve risks that are currently unforeseeable. There are several kinds of risks and discomforts involved in a research study. These possible risks and discomforts will be discussed in this section. A significant risk to taking part in this research study is the possibility of receiving a drug or a dose of drug that is not effective in treating your disease. This means that you could spend time taking the investigational drug, but that drug does not provide you with health related benefits.

The other main risks of this research study are the side effects. You need to tell your doctor or a member of the study team immediately if you experience any side effects. Since the effect of the study drug(s) taken with the other medication may not be known, it is important that you tell your research doctor about all prescription and non-prescription drugs, herbal preparation and nutritional supplements that you are taking or plan on taking. There is also a possibility of some foods that you should avoid while participating in this research study. Please ask your research doctor of examples of food items that should be avoided while participating in this study. Your research doctor will review this information with you.

These side effects include but are not limited to the following:

Risks Associated with anti-PD-1 (INCMGA00012)

Common (occurred in ≥10%) side effects may include:

- Fatigue
- Diarrhea
- Pyrexia: raised body temperature, fever
- Anemia
- Dehydration
- Vomiting
- Blood alkaline phosphatase increased
- Cough
- Decreased appetite
- Arthralgia: joint pain
- Hypertension: high blood pressure
- Pruritus: irritation of the skin
- Tumor flare
- Tumor pain
- Urinary tract infection

Frequent (occurred in ≥5%) side effects may include:

- Nausea
- Hypothyroidism: the thyroid gland is not able to produce enough hormone which results in a slow metabolism
- Dyspnea: shortness of breath
- Weight decreased
- Hypokalemia: low potassium levels
- Asthenia: weakness or lack of energy
- Pain in extremity
- Constipation
- Blood creatinine increase
- Hyperthyroidism: the over activity of the thyroid gland, which will result in a rapid heartbeat and an increased rate of metabolism

Potentially serious immune- related side effects may include

- Pneumonitis: inflammation of the walls of the alveoli in the lungs
- Hepatitis
- Colitis: inflammation of the lining of the colon
- Nephritis: inflammation of the kidneys
- Endocrinopathies: disease of the endocrine gland
- Encephalitis: inflammation of the brain
- Myocarditis: inflammation of the heart muscle
- Skin reactions
- Rejection of organ transplants
- Other reactions (including arthritis, uveitis, myositis, Guillain- Barre syndrome, myasthenia gravis, vasculitis, pancreatitis and hemolytic anemia)

Risks Associated with anti-GITR (INCAGN01876)

Common (occurred in >10% of participants) side effects may include:

- Fatigue
- Cough
- Abdominal pain
- Dyspnea: shortness of breath
- Nausea
- Pyrexia: raised body temperature, fever
- Vomiting
- Dehydration
- Hypokalemia: increased potassium
- Influenza like illness
- Chills
- Dizziness
- Gastroesophageal reflux disease
- Hyponatremia: low sodium
- Hypotension: low blood pressure
- Muscular weakness
- Pain in extremity
- Paranesthesia: an abnormal sensation, typically the “pins and needles”
- Decreased Appetite
- Pruritus: irritation of the skin
- Diarrhea
- Upper respiratory tract infection
- Anemia
- Headache
- Peripheral Edema: swelling which usually occurs in the lower limbs
- Constipation
- Cough

- Back pain
- Blood alkaline phosphatase increase
- Aspartate aminotransferase increase
- Alanine aminotransferase increase

Not as common (occurred in >5% of participants)

- Rash
- Arthralgia: pain in a joint
- Ascites: buildup of fluid in the belly area
- Asthenia: weakness or lack of energy
- Dysphagia: difficulty in swallowing
- Hypercalcemia: high calcium levels
- Insomnia
- Pneumonia
- Pruritus generalized
- Tachycardia: abnormally rapid heart rate

There are additional risks associated with radiation therapy such as:

Likely risks include:

- Scalp redness or soreness
- Hair loss, which may be temporary or permanent
- Ear/canal reactions such as dryness of ear canal, hardening of the wax in the ear canal, or redness of the external ear, possibly causing temporary hearing loss
- Fatigue
- Temporary worsening of brain tumor symptoms such as headaches, seizures or weakness

Occasional risks include:

- Problems with mental function (neurocognitive problems), including memory deficits, which may be permanent
- Permanent hearing loss
- Condition in which the lens of the eye becomes cloudy, cataracts. This could possibly require surgery to repair.
- Behavioral change, which can be due to physical effects of radiation therapy such as fatigue or headaches
- Nausea
- Vomiting
- Temporary worsening of existing neurological problems, such as decreased vision, drowsiness, and weakens of your arms and legs
- Endocrine problems related to changes to the pituitary gland, a gland that produces hormones that control other glands. Symptoms can include problems with your thyroid gland, sugar metabolism, fertility, or decrease in ability to regulate water, which may lead to excessive urination

- Dry mouth or altered taste

Rare but serious risks include:

- Severe local damage to normal brain tissue, a condition called necrosis. Radiation necrosis can mimic recurrent brain tumor and may require surgery for diagnosis and treatment

If you become injured during the study, you should inform the physician treating you that you are participating in a research study.

Risks Associated with MRI Scans:

When having an MRI (Magnetic Resonance Imaging) scan, you will lie still on a table that slides into a tunnel slightly wider than your body. People who feel uncomfortable in small spaces may feel uncomfortable in the narrow cylinder. If you do feel uncomfortable in confined spaces, please tell your research doctor. Your doctor may give you medication to make you feel more comfortable. As the images are being taken, a loud banging noise will be produced. Earplugs or headphones will be available if needed. The MRI can be stopped at any time at your request. There are no known health risks associated with exposure to magnetic fields during an MRI.

Flying Objects: The known risk associated with an MRI is minimal. Implanted medical devices and metallic foreign fragments inside your body may pose a risk if you were to enter the MRI magnet room. Therefore, questions regarding medical and work history will be asked prior to your exam. The greatest risk is a magnetic object flying toward the magnet and hitting you. To reduce this risk, we require that all people involved with the study remove all magnetic metal from their clothing and all magnetic metal objects from their pockets. No magnetic metal objects can be brought into the magnet room at any time except by approved personnel. In addition, once you are in the magnet, the door to the room will be closed so that no one inadvertently walks into the room.

IV Contrast Risks: Part of the MRI study will require the injection of a gadolinium contrast agent into the blood stream. There is a rare possibility that you could have an adverse reaction to the contrast agent such as rash, hives, itching, mild headache and nausea. You may also experience some minor discomfort and low risk of bleeding, infection and bruising associated with Intravenous catheter placement. Recently, FDA has also required a new class warning for all gadolinium-based contrast agents (GBCAs) for MRI concerning gadolinium remaining in patients' bodies, including the brain, for months to years after receiving these drugs.

Retention: Traces of gadolinium may remain in the body long-term after contrast administration. This risk increases with the number of administrations, but reviews to date have not identified adverse health effects from gadolinium retained in the brain or bodily tissues after MRI ([Gadolinium agents administered in this study are thought to minimize or eliminate this risk]). The long-term risks of this retention are not well elucidated; Gadolinium retention has not been directly linked to adverse health effects in patients with normal kidney function, and the FDA has concluded that the benefit of all approved GBCAs continues to outweigh any potential risks.

Reproductive risks: Because of the effects of this drug/device, there could be serious harm to unborn children or children who are breast-feeding. These effects could also harm the mother. It is also possible that harmful side effects that are not yet known could happen to both the mother and unborn or breast-feeding child. If you are currently pregnant, it is important that you inform the investigator because you will not be able participate in the study. If you are able to become pregnant, you will be given a serum pregnancy test before entry into the study. You are asked to use a medically accepted method of birth control while you participate in the study. You should not become pregnant while you are taking this drug/device. If you do become pregnant, you must tell the investigator and consult an obstetrician or maternal-fetal specialist.

Reproductive Risks for studies involving MRIs

There is no know health risks related to MRI on pregnant women or a fetus. However, there is a possibility of yet undiscovered pregnancy related risk. Since there is no possible benefit from participating in this protocol for a pregnant woman, we will exclude pregnant woman.

Non –Physical Risks

Because of side effects or the time required for tests and clinical visits while you are on this research study, you may be unable to keep up with your normal daily activities.

What if new information becomes available about the study?

During the course of this study, we may find more information that could be important to you. This includes information that, once learned, might cause you to change your mind about being in the study. We will notify you as soon as possible if such information becomes available.

What are the possible benefits of the study?

You might not obtain any benefit from being in this research study. No benefit can be granted as a result of enrolling in this trial. Your participation in this research study may benefit future patients with your disease or condition. Your condition may get better, worse, or stay the same.

What other choices do I have if I do not participate?

Your participation in this research study is voluntary. Instead of being in this research study, you have other options. This may include the following:

- Receive standard treatment including surgery and chemotherapy.
- Receive some of the same therapies as offered on this trial, but not as part of the research study. This applies specifically to SRS and not to the study drugs.
- Take part in another research study.
- Receive no therapy specific to your cancer.

- Comfort care, also known as palliative care, may help to reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat cancer directly, but it attempts to treat the symptoms.

Please discuss your options with the research doctor before you decide whether you will take part in this research study.

Will I be paid for being in this study?

There will be no compensation for participation in this study.

Will I have to pay for anything?

Taking part in this research study might lead to added costs to you or your insurance company. You are still responsible for any deductibles or applicable co-pays for routine office visits, scans, and blood work. Please talk to your doctor and study team about putting you in touch with a financial counselor to determine exactly what the deductible and co-pay will be for you; this is highly variable depending on your type of insurance.

You will not be charged for the investigational drugs, anti-GITR and anti-PD-1. It is possible that anti-GITR and anti-PD-1 may not continue to be supplied free for an unknown reason. If this would occur, your research doctor will talk with you about your options.

The National Cancer Institute provides an online resource to help people participating in cancer clinical trials understand which services their insurance company is required by law to pay. This can be found at the website below or can be provided by the study team:

www.cancer.gov or 1-800-4-CANCER (1-800-422-6237)

What happens if I am injured from being in the study?

If you think you have been injured as a result of taking part in this research study tell the study doctor immediately. Contact information is listed in this consent form.

We will offer you the care needed to treat injuries directly resulting from taking part in this research. We may bill your insurance company or other third parties, if appropriate, for the costs of the care you get for the injury, but you may also be responsible for some of them. You will be responsible for deductibles and co-payments.

There are no plans for the University of Pennsylvania to pay you or give you other compensation for the injury. You do not give up your legal rights by signing this form.

If you think you have been injured as a result of taking part in this research study, tell the person in charge of the research study as soon as possible. The researcher's name and phone number are listed in the consent form.

For more information on clinical trials and insurance coverage, visit the National Cancer Institute's website at https://www.cancer.gov and type "paying for clinical trials" into the website's search bar. Another way to get this information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

When is the Study over? Can I leave the Study before it ends?

This study is expected to end after all participants have completed all visits, and all information has been collected. This study may also be stopped at any time by your physician, the study Sponsor, or the Food and Drug Administration (FDA) without your consent because:

- The Primary Investigator feels it is necessary for your health or safety. Such an action would not require your consent, but you will be informed if such a decision is made and the reason for this decision.
- You have not followed study instructions.
- The Sponsor, the study Principal Investigator, or the Food and Drug Administration (FDA) has decided to stop the study.

If you decide to participate, you are free to leave the study at any time. Tell your research doctor if you are thinking about stopping or decide to stop. Your research doctor will tell you how to stop. Withdrawal will not interfere with your future care.

It is important to tell your research doctor if you are thinking about stopping. Your research doctor can then evaluate the risk of stopping the study drugs. In some cases, the sudden stopping of a drug can have a risk in itself. Also, another reason to tell your research doctor that you are thinking about stopping is to discuss what follow-up care could be the most beneficial for you.

How will my personal information be protected during the study?

We will do our best to make sure that the personal information obtained during the course of this research study will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used. The Institutional Review Board (IRB) at the University of Pennsylvania will have access to your records. If this study is being overseen by the Food and Drug Administration (FDA), they may review your research records.

Medical information created by this research study may become party of your hospital medical record and may be forwarded to your primary care doctor. Information that does not become part of your medical record will be stored in your study file.

The study team plans on publishing the results of this research study. When we do so, we may be asked to make the data we collected available to other researches. We will not include information that identifies you in any publication or to the researchers who request the data to do additional research.

How Your Data Will Appear:

Your identity and contact details will not be disclosed except as described in this form, unless required by law. Rather, your identity and contact details will be replaced by a code, such as numbers, which will be used for future research concerning GBM or other cancers.

Who Will See Your Data:

The only people with access to your personal health information in identifiable form will be Stephen Bagley, MD, MSCE, personnel helping with Stephen Bagley, MD, MSCE conduct the study at the facility, sponsor representatives who are checking that the study is conducted properly, Institutional Review Board (IRB) and regulatory authorities when required by law. However, the sponsor, The University of Pennsylvania, will take reasonable measures to keep your personal health information confidential. Please refer to “Who, Outside the School of Medicine, might receive my information?” section for more information.

Will information about this study be available to the public?

A description of this clinical trial will be available on www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. This website will not include any information that can identify you. The website may include a summary of the results. You can search this website at any time.

What may happen to my information and samples collected on this study?

Your blood and tumor tissue samples obtained during this study may be used to create products, including some that may be sold and/or make money for others. If this happens, there are no plans to tell you, pay you, or give any compensation to you or your family. Most uses of bio specimens or information do not lead to commercial products or to profit for anyone.

- Whole genome sequencing may be conducted on your samples. Whole genome sequencing involves analyzing your entire personal genetic code.

Your information and samples will be de-identified. De-identified means that all identifiers have been removed. The information and samples could be stored and shared for future research in this de-identified fashion. It would not be possible for future researchers to identify you as we would not share any identifiable information about you with future researchers. This can be done without seeking your consent in the future, as

permitted by law. The future use of your information and samples only applies to the information and samples collected on this study.

If you have questions about the storage of your information and samples, or have changed your mind, you can contact the study doctor.

The biological samples collected from you during this study (tumor tissue and blood) may be shared with industry partners (private companies) that may assist the Penn Investigators with research on these samples. If this occurs, the samples will be provided to the companies in de-identified format and without any of your private health information.

Electronic Record and Release of Study Related Information

What is an Electronic Medical Record and/or a Clinical Trial Management System?
An Electronic Medical Record (EMR) is an electronic version of your medical chart within a health system. An EMR is simply a computerized version of a paper medical record.

If you have never received care within Penn Medicine and are participating in a University of Pennsylvania research study that uses Penn Medicine healthcare related services, an EMR will be created for you for the purpose of maintaining any information produced from your participation in this research study. The creation of this EMR is a requirement of participation in this study. In order to create your EMR, the study team will need to obtain basic information about you that would be similar to the information you would provide the first time you visit a hospital or medical facility (i.e. your name, the name of your primary doctor, the type of insurance you have). If you have been a patient at Penn Medicine in the past, information from your research participation will be added to your existing medical record.

What may be placed in the EMR?
Information related to your participation in the research (e.g., laboratory tests, notes from your physician, imaging studies, and clinical procedures, etc.) will be placed in your EMR maintained by Penn Medicine.

Once placed in your EMR your information may be accessible to appropriate Penn Medicine workforce members that are not part of the research team. Information within your EMR may also be shared with others who are determined by Penn Medicine to be appropriate to have access to your EMR (e.g. Health Insurance Company, disability provider, etc.).

Penn Medicine also participates in automated information sharing through Health Information Exchanges (HIEs). HIEs securely share parts of your electronic health record, including research information, with other healthcare organizations involved in your care. This information is shared to improve the quality, safety and efficiency of your

healthcare. To request that your health information not be shared through HIEs, please call 215-662-4484.

Will I, as a subject, have access to research related information within the EMR/?
The 21st Century Cures Act requires healthcare institutions to allow patients increased access to their electronic medical record. As part of your participation in this research, you will have access to research related information within your EMR through Penn Medicine's patient portal – called MyPennMedicine (MPM).

Will I receive the results of research testing that may be relevant to my health?

Many of tests done in research studies are only for research and have no clear impact on your healthcare. Research results for this study will not be returned to you because they would not be relevant to your healthcare.

Results that may be relevant to your healthcare may be released to you.

What information about me may be collected, used or shared with others?

The following personal health information will be collected and used for the purpose of this study:

- Name, date of birth, telephone number, address, medical record number
- The history and diagnosis of your disease
- Specific information about the treatments you have received, including previous treatment(s) you may have had and your response to them
- Information related to study visits and other tests/ procedures performed while you are participating in this study
- Information on adverse events (side effects) you may experience, and how these were treated
- Information about other medical conditions that may affect your treatment
- Medical data generated during this study
    - Physical exams
    - Laboratory test results
    - CT/MRI scans
    - Results of any other tests/ procedures performed during the study

Why is my information being used?

Your information is used by the research team to contact you during the study. Your information and results of tests and procedures are used to:

- Perform the research
- Oversee the research
- Ensure the research was done correctly
- Evaluate and manage research functions.

Where may my information be stored?
Information related to your participation in clinical research will be contained in a clinical trial management system (CTMS). A clinical trial management system (CTMS) is used to register your information as a participant in a study. This allows for your research data to be entered and stored for the purposes of study operational and financial applications and other activities required as part of the conduct of the research. Once placed in the CTMS your information may be accessible to other authorized personnel at Penn Medicine that support research operations. Your information may be held in other research databases.

Who may use and share information about me?

The following individuals may use or share your information for this research study:

- The investigator for the study and the study team
- Other authorized personnel at Penn, including offices that support research operations
- Other research personnel with access to the databases for research and/or study coordination, and with approval by the IRB

Who, outside of the Penn Medicine, might receive my information?

As part of the study, the Principal Investigator, the study team and others listed above, may disclose your personal health information, including the results of the research study tests and procedures. This information may be disclosed to those listed below

- Outside individuals or entities that have a need to access this information to perform functions relating to the conduct of this research such as analysis by outside laboratories on behalf of Incyte and its affiliates (for example, data storage companies, insures or legal advisors)
- The study's sponsor (University of Pennsylvania)
- Safety Oversight organizations:
    - The Food and Drug Administration
    - The Office of Human Research Protections
    - The Office of Biotechnology Activities and their committees overseeing gene therapy research
    - DHHS- Department of Health and Human Services, DSS- Department of Social Services, and other state and federal agencies as required by law.

Once your personal health information is disclosed to others outside the School of Medicine, it may no longer be covered by federal privacy protection regulations.

The Principal Investigator or study staff will inform you if there are any additions to the list above during your active participation in the trial. Any additions will be subject to University of Pennsylvania procedures developed to protect your privacy.

How long may the Penn Medicine use or disclose my personal health information?

Your authorization for use of your personal health information for this specific study does not expire.

Your information may be held in a research database. However, the Penn Medicine may not re-use or re-disclose information collected in this study for a purpose other than this study unless:

- You have given written authorization
- The University of Pennsylvania's Institutional Review Board grants permission, as permitted by law

Can I change my mind about giving permission for use of my information?

Yes. You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the investigator for the study. If you withdraw your permission, you will not be able to stay in this study.

What if I decide not to give permission to use and give out my health information?

If you decide not to give permission to use and give out your health information, you will not be able to be in this research study.

You will be given a copy of this Research Subject HIPAA Authorization describing your confidentiality and privacy rights for this study.
By signing this document, you are permitting the Penn Medicine to use and disclose personal health information collected about you for research purposes as described above.

Who can I call with questions, complaints or if I'm concerned about my rights as a research subject?

If you have questions, concerns or complaints regarding your participation in this research study or if you have any questions about your rights as a research subject, you should speak with the Principal Investigator listed on page one of this form. If a member of the research team cannot be reached or you want to talk to someone other than those working on the study, you may contact the Office of Regulatory Affairs with any question, concerns or complaints at the University of Pennsylvania by calling (215) 898-2614.

When you sign this form, you are agreeing to take part in this research study. This means that you have read the consent form, your questions have been answered, and you have decided to volunteer. Your signature also means that you are permitting the University of Pennsylvania to use your personal health information collected about you for research purposes within our institution. You are also allowing the University of Pennsylvania to disclose that personal health information to outside organizations or people involved with the operations of this study.

A copy of this consent form will be given to you.

Name of Subject (Please Print)	Signature of Subject	Date

Name of Person Obtaining Consent (Please Print)	Signature	Date

For subjects unable to give authorization, the authorization is given by the following authorized subject representative:

Authorized subject representative **[print]**	Authorized subject representative Signature	Date

Provide a brief description of above person authority to serve as the subject's authorized representative.