PRINCIPAL INVESTIGATOR: Mark Gilbert, MD

STUDY TITLE: A Randomized, Double Blind Phase II Trial of Surgery, Radiation Therapy plus Temozolomide and Pembrolizumab with and without HSPPC-96 in Newly Diagnosed Glioblastoma (GBM)

STUDY SITE: NIH Clinical Center

Cohort: Standard

Consent Version: 06/30/2021

Who Do You Contact About This Study?

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This consent form describes a research study and is designed to help you decide if you would like to be a part of the research study.

The remaining document will now describe the research study in more detail. This information should be considered before you make your choice. Members of the study team will talk with you about the information described in this document. Some people have personal, religious, or ethical beliefs that may limit the kinds of medical or research interventions in which they would want to participate. Take the time you need to ask any questions and discuss this study with NIH staff, and with your family, friends, and personal health care providers.

If the individual being asked to participate in this research study is not able to give consent for themselves, you, as the legally authorized representative, will be their decision-maker and you are being asked to give permission for this person to be in this study. For the remainder of this document, the term "you" refers to you as the decision-maker and/or the individual being asked to participate in this research.

It Is Your Choice to Take Part in the Study

You may choose not to take part in this study for any reason. If you join this study, you may change your mind and stop participating in the study at any time and for any reason. In either case, you will not lose any benefits to which you are otherwise entitled. However, to be seen at the NIH, you must be taking part in a study or are being considered for a study. If you do choose to leave the study, please inform your study team to ensure a safe withdrawal from the research.

Why Is This Study Being Done?

This study is being done on a type of brain tumor called Glioblastoma (GBM). The purpose of this research is to find out if adding a chemotherapy drug called pembrolizumab and a vaccine to standard of care treatment for GBM improves survival. If a GBM patient is eligible for surgery, the standard of care treatment is to have surgery to remove as much of the tumor as possible. After surgery, you can continue on the study only if the GBM is a specific type and if sufficient tumor

tissue is removed. After the surgery, patients eligible to continue get radiation therapy and chemotherapy with a drug called Temozolomide (TMZ). In this study, there will be 3 different groups; patients who are not eligible for group 2 or 3 because we could not generate a vaccine from sufficient samples taken at surgery will be treated in group 1.

These groups will receive the following treatment after surgery:

Group 1: Radiation + TMZ +Pembrolizumab

Group 2: Radiation + TMZ +Pembrolizumab + Heat Shock Protein Peptide Complex -96 (HSPPC-96) Vaccine

Group 3: Radiation +TMZ + Pembrolizumab + Placebo vaccine

The experimental parts of this research are the addition of the drug pembrolizumab and HSPPC-96 vaccine to the standard of care therapy. Pembrolizumab is a drug that has been approved by the Food and Drug Administration (FDA) for use in certain types of cancers. It is referred to as investigational or experimental in this study because it has not yet been approved for use with GBM. Pembrolizumab is an antibody drug. An antibody is a type of protein produced by the immune system to kill bacteria or viruses that can cause disease. Much like a key can only fit into and open one lock, an antibody can only recognize one other protein. Pembrolizumab recognizes a protein that can turn off the immune response. When Pembrolizumab recognizes this protein, it binds, or holds on to it, so no other proteins can recognize it. This helps turn on an immune response. When this immune response is turned on, it may help the cells that are already in your body to fight the cancer in your body.

HSPPC-96 stands for “Heat Shock Protein Peptide Complex -96”. This is a type of protein that is found in your tumor. Researchers will create a HSPPC-96 vaccine from your tumor. When your tumor is removed during surgery, a portion of it will be used to create a HSPPC-96 vaccine. You may be familiar with vaccines such as the flu vaccine. Vaccines expose you to little portions of the virus or cancer to help your immune system respond to the flu or cancer. The HSPPC-96 vaccine contains small parts of your tumor to help your immune system recognize your tumor. Researchers hope this will help your own immune system fight your cancer, but they do not yet know if it is effective. The HSPPC-96 vaccine is investigational, and not approved by the FDA.

The research is being done to see if the addition of pembrolizumab with or without HSPPC-96 to standard treatment of radiation and TMZ improves the survival of newly diagnosed GBM patients. All patients on this trial will receive standard of care therapy plus Pembrolizumab. Some patients will receive a placebo instead of the HSPPC-96 vaccine. A placebo will be injected like the HSPPC-96 vaccine, but it does not contain any medication. The use of Pembrolizumab and HSPPC-96 together is investigational. The use of HSPPC-96 in combination with Pembrolizumab and Temozolomide is investigational, and the use of Pembrolizumab and Temozolomide together is investigational. Temozolomide is a drug that has been approved by the FDA for use in treatment of adult patients with newly diagnosed glioblastoma.

As of May 20, 2021, no more participants will be enrolled in the study. Enrollment has stopped early due to a decision by an internal committee that reviews the safety and progress of a study. The committee determined that the number of participants on the study is too low. Therefore, enrollment is this study has stopped permanently.

We will continue to provide study therapy as assigned if you choose/chose to remain on study therapy. If you received/are receiving a vaccine on the study, you will be informed whether it was the placebo or the HSPPC-96 vaccine. The placebo will be stopped for anyone still receiving it. Those still receiving the HSPPC-96 vaccine will continue to do so as planned in the study. You will not be able to switch to the other group. You will continue to complete the tests and procedures as described below in the sections titled **Study Tests** and **Additional Blood Collection**.

If you choose/chose to stop study therapy, we would still like to check in on you to determine your health status as described in the section When you are finished taking the drugs (treatment):

Why are you being asked to take part in this study?

This is an investigational study. We are asking you to take part in this research study because you have been recently diagnosed with glioblastoma or have a suspected glioblastoma and are eligible for surgery.

How many people will take part in this study?

There will be 108 people who will receive study therapy in this study across the United States. About 60 people will take part at the NIH and up to 250 people at other study sites.

Description of Research Study

What will happen if you take part in this research study?

Before you begin study therapy

Once it has been decided that you might benefit from surgical removal of your tumor, and if you agree to have your tissue tested and agree to undergo standard radiation therapy and temozolomide, you will undergo a number of tests to be certain that you can have surgery and that you are healthy except for your tumor. These exams, tests or procedures are part of regular surgical care. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- Pre-surgery Brain CT or MRI (for surgical planning)
- Cancer history and demographic information review
- Standard blood tests (approximately 2 tablespoons will be drawn)
- Urine Test
- Serum pregnancy test, if applicable
- You will also complete a questionnaire about your quality of life.

You will also have the following exams, tests, and procedures done before you start the investigational and standard of care treatment for your GBM in this study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- Post-surgery Brain CT or MRI
- Full physical (including vital signs, height, and weight) and neurological examination

- Medical history, medication, and demographic information review
- Standard blood tests (approximately 2 tablespoons will be drawn)
- You will also have blood drawn for immune studies. These blood tests will be used, along with the tumor specimen, to help determine the status of your body's immune system.
- Urine Test
- Serum or urine pregnancy test, if applicable
- You will also complete a questionnaire about your quality of life.

Study Therapy

You will first have a surgery to remove the tumor. You may have your surgery at a participating site or at NCI for this study. If so, then some of the exams, tests, and procedures may have been done and may not need to be repeated. For any study exams, tests, procedures and treatments that have not yet been done, your study doctor will discuss with you which ones will be done at that participating site and which ones will be done at NCI.

Once you undergo surgery, the tissue removed from surgery will first be used to confirm the presence of tumor as part of your standard of care. This tissue will be stored at the participating site where it was collected or at NCI. If your tumor and the amount of tumor removed do not meet certain criteria, you will be removed from the study and not receive treatment.

If it is determined that your tissue meets certain criteria, then the participating site or NCI will send the tissue directly to Agenus to possibly create the vaccine. Agenus is the company that makes the vaccine in their laboratories. When Agenus receives the tissue from your tumor to create the vaccine, it will be labelled with your initials and date of birth.

If there is extra tumor tissue, then the extra tissue will be prepared for future testing in this trial and stored at the participating site where it was collected or at NCI. If you qualify to start treatment on this study, then your extra tissue will be shipped to laboratories for additional research testing for this study. When these laboratories receive the tissue from your tumor for additional research testing, it will be labelled with a unique number assigned to your tissue.

In the Agenus laboratory, scientists will try to make a vaccine from the tumor. The vaccine that is prepared is specific to your tumor. Vaccines are substances that stimulate the body's immune system and when injected into a patient, it may cause their body's immune system to attack cancer cells.

There is a small chance (10-15%) that vaccine will not be able to be made from your tumor specimen, or that there will be an insufficient amount of vaccine produced (not enough to treat you in the study). There is also a chance that the vaccine produced from your tumor will not meet the test specifications (called "release specifications") that are necessary. This happened in less than 5-10% of patients in a previous study. If we obtain enough tumor to make the vaccine and if enough of your tumor is removed but we still cannot generate the vaccine, you will receive radiation, temozolomide and pembrolizumab only (you will be in Group 1). You will not be randomized to receive HSPPC-96 vaccine or placebo vaccine.

If we were able to create the vaccine, you will be randomly assigned to either Group 2 or Group 3. A computer will assign you by chance to one of the treatment groups in the study. This is called randomization. This is done by chance because no one knows if one study group is better or worse than the others. If your vaccine is created, you will have a 50-50 chance of being assigned to either Group 2 or Group 3.

Group 2 will receive the pembrolizumab and HSPPC-96 vaccine and Group 3 will receive pembrolizumab and placebo, a vaccine that looks like the study drug but contains no medication.

Part 1:

You will receive radiation therapy for about 6 weeks. This is the same type of radiation used for patients who are not participating in the study.

You will receive temozolomide by mouth on day 1 (1-2 hours before) of radiation treatment or the night before each radiation treatment. You should take it on an empty stomach (no food 1 hour before or after). You will be given a medicine for nausea 30-40 minutes before temozolomide (or 1 hour and 30 minutes before radiation therapy). You will take temozolomide every day at the same time including weekends even when you are not getting radiation therapy.

You will receive pembrolizumab as a 30-minute IV infusion every 3 weeks during radiation therapy starting on day 1 and then every 3 weeks for a total of 3 doses (one cycle).

You will also have the following procedures:

- Full physical and neurological examination
- Blood tests will be performed weekly
- You will be asked to report any symptoms you experience

If we are unable to create the vaccine even though we were able to remove enough tumor, you will continue to receive temozolomide and pembrolizumab for up to 6 cycles (one cycle is 9 weeks long). You can continue to take pembrolizumab for up to an additional 12 months without temozolomide if your physician feels you are benefiting from the drug once you have completed the first 6 cycles.

Part 2:

If we were able to create the vaccine, a minimum of 4 doses created, you will be randomly assigned to either Group 2 or Group 3. One week after radiation treatment has completed, you will receive a weekly dose of HSPPC-96 vaccine or placebo vaccine. You will be treated with a vaccination once a week for 4 treatments and then have a four-week break before having a 5th vaccination if you have more than 4 doses of vaccine made. It is possible that you may only have 4 vaccine vials available for administration. This means your treatment with vaccine will stop after the 4th vaccination and there will be no further vaccine treatments given with either HSPPC-96 or placebo.

You will continue to receive standard treatment with temozolomide.

You will also continue taking pembrolizumab once every 3 weeks of each cycle for a total of six cycles (one cycle is 9 weeks long). You can continue to take pembrolizumab for up to an additional 12 months without temozolomide if your physician feels you are benefiting from the

drug once you have completed the first 6 cycles.

Vaccine administration will be given twice during each cycle until it is used up or the 6 cycles are done. If that time your physician feels you are benefiting from the vaccine and not having serious side effects, you may continue on the vaccine (HSPPC-96 or placebo) for another 12 months or until it is used up.

If you are randomized to receive placebo or if there is any remaining vaccine after you have finished treatment, it will be deidentified and used by Agenus (the manufacturer of the vaccine) or other approved investigators for development and research purposes.

Standard of Care Treatment

Radiation therapy and temozolomide is standard treatment for your cancer. These treatments will not be experimental. Your doctors will describe your treatment plan to you in detail before asking you to sign this consent form. You may be asked to sign a separate consent form for any treatment procedures not outlined in this consent.

Study Tests

You will also complete the following tests and procedures that are part of regular cancer care, but they will be done more often because you are in this study:

- Physical Exam (including vital signs and weight) and neurological examination (every 3 weeks during radiation therapy and then every 4 weeks after radiation therapy)
- If you are in Group 1 (not randomized): MRI will be done pre surgery, post-surgery (within 72 hours) and then 4 weeks after radiation therapy is completed and then every 9 weeks. If you are in Group 2 or 3 (randomized): MRI will be done pre-surgery, post-surgery (within 72 hours) and within 7 days of last dose of vaccine or placebo, and then every 9 weeks.
- Blood tests will be done weekly during radiation therapy and then weekly after radiation therapy for the first year and then every 2 weeks for the year after if you remain on pembrolizumab.
- Serum or urine pregnancy test, if applicable, will be done before radiation therapy, TMZ, and pembrolizumab, before vaccine, and before the start of each cycle.
- You will complete a questionnaire about your quality of life whenever you have a MRI.

Additional Blood Collection

In addition to the blood draws identified above, we will collect immune research blood samples at the following time points:

- Before vaccine (This sample will not be collected if you are assigned to Group 1.)
- After vaccine (before Cycle 1) (If are assigned to Group 1, this sample will be collected before Cycle 1.)
- Day 1 of Cycle 2
- Day 1 of Cycle 4

- Day 1 of Cycle 6
- Day 1 of Cycle 8
- And then, at the discretion of the lead researchers, every other cycle*
- Time of tumor progression

* if you continue on pembrolizumab beyond 6 cycles

When you are finished taking the drugs (treatment):

You will complete the following at 12 months, after you have finished taking the drugs (treatment), or if you stop therapy:

- Full physical (including vital signs and weight) and neurological examination
- Blood Tests
- Questionnaire about your quality of life
- MRI

The study team would like to keep track of your medical condition every 8-16 weeks from when you stopped treatment. They will do this by contacting you to obtain information regarding the status of your health. Any anti-cancer treatment you may have undergone through this time will also be recorded.

Tumor Collection (at Progression)

If your tumor progresses while you are on the study and you need to undergo surgery, if you agree, we would like to collect a portion of the tumor so we can evaluate it for tumor markers. The research that may be done with your tissue at progression is not designed specifically to help you. It might help people who have cancer in the future.

Tissue and Blood Analysis

If there remains enough tumor tissue from surgery, then other research studies will be performed such as studying molecular pathways, biological and genetic characteristics or tumor markers to help us to better understand your disease. We are requesting your permission to perform exome sequencing on your blood and/or tissue samples and link this to your medical history. Your blood and tissue samples contain genes, which are made up of DNA (**d**eoxyribo**n**ucleic **a**cid) which serves as the "instruction book" for the cells that make up our bodies. Sequencing will determine the exact order of the base pairs (chemical letters) in [the tumor being studied, or blood]. Your sample(s), and medical information will help us study how genes are linked to your cancer.

The analyses that we perform in our laboratory are for research purposes only; they are not nearly as sensitive as the tests that are performed in a laboratory that is certified to perform genetic testing. Changes that we observe unrelated to our research may or may not be valid. Therefore, we do not plan to inform you of the results of testing on your specimens that is performed in our research lab. However, in the unlikely event that we discover a finding that is believed to be clinically important based on medical standards at the time we first analyze your results, we will contact

you. This could be many years in the future. We will ask you to have an additional tube of blood drawn to verify the findings we have seen in our lab. If the results are verified, you will be re-contacted and offered a referral to a genetic healthcare provider to discuss the results.

Birth Control

If you are a woman who is breast feeding or pregnant, you may not take part in the study because we don't know how this medicine would affect your baby or your unborn child. If you are a woman who can become pregnant, or are the partner of a woman who can become pregnant, you will need to practice an effective form of birth control and refrain from egg or sperm donation during study treatment, and for 4 months after you finish study treatment. If you think that you or your partner is pregnant, you should tell your study doctor or nurse at once.

Effective forms of birth control include:

- abstinence
- intrauterine device (IUD)
- tubal ligation
- vasectomy
- hormonal [birth control pills, injections, or implants] plus a condom or diaphragm with spermicide

Risks or Discomforts of Participation

Pembrolizumab side effects

Pembrolizumab can cause your immune system to attack normal organs and tissues in your body and can affect the way they work, which can result in side effects. These side effects may be serious (i.e. causing hospitalization or be life-threatening), may result in death, and/or may occur after you stop taking pembrolizumab.

In a small number of people (approximately 1-4% of patients treated with pembrolizumab) some of the common and less common adverse effects can be very serious and could possibly lead to death.

Common side effects (more than 10%) seen in people taking pembrolizumab include the following:

- Feeling tired, lack of energy
- Itching of the skin
- Rash
- Frequent or excessive bowel movements
- Pain in a joint, back pain
- Nausea
- Diarrhea
- Cough that may or may not bring up mucous
- Fever (may be serious)
- Low levels of salt in the blood that may cause you to feel tired, confused, have a headache, muscle cramps and/or feel sick to your stomach

Less Common side effects (between 2% to 10%) seen in people taking pembrolizumab include the following:

- Cough that may or may not bring up mucous
- Pain or cramping in a muscle or group of muscles
- Headache
- Loss of appetite
- Loss of skin color
- Decreased release of thyroid hormone that may manifest as feeling tired, weight gain, feeling cold easily, or bowel movements occurring less often than usual.
- Increased release of thyroid hormone which may manifest as anxiety, anger, confusion, irritability, or trouble sleeping, weakness, trembling, sweating, feeling uncomfortable in warm weather, fast or uneven heartbeats, feeling tired, weight loss, and frequent or excessive bowel movements.
- Shortness of breath while at rest or while performing physical activity (may be serious)
- Fever
- Feeling cold
- Abnormal laboratory result of liver test by blood that occasionally indicates liver failure, manifesting as yellowing of the skin or whites of the eyes, fatigue, or leg swelling
- Nausea
- Vomiting
- Bowel movements occurring less often than usual
- Red rash
- Decrease in red blood cells that may result in feeling tired or shortness of breath
- Loss of weight
- Weight gain
- Swelling of the legs
- Pain or uncomfortable feeling in the belly
- Inflammation of the lungs, manifesting as shortness of breath
- Sweating excessively while sleeping such that clothes and sheets are wet
- Pain in the back, arms, or legs
- Flu or flu-like illness which may include fever, chills, body aches, and feeling tired
- Change in how you see or change in how your eye(s) function
- Skin Changes (peeling, changes in color)

Serious Adverse Events (serious side effects)

No event occurred in ≥ 1% of everyone treated. Please note that some of these events have been previously stated above, so some have occurred more frequently but with less severity. Serious adverse events seen in people taking pembrolizumab include:

- Fever
- Vomiting
- Nausea
- Dizziness or fainting

- Few to no menstrual cycles
- Hair loss
- Rashes that can be itchy, red, blistering, shedding, bumpy, and acne-like
- Flushing, pain at the site of IV infusion
- Diabetes, resulting in the need for regular insulin shots
- Inflammation of the kidneys or kidney damage (less urine, cloudy or bloody urine, low back pain with swelling of the legs and possibly needing dialysis)
- Adrenal glands (glands on top of the kidneys) that may not make enough hormone, which could cause tiredness, weight loss, muscle weakness, feeling faint, joint, muscle and belly aches, nausea, vomiting, loose or watery stools, fever, salt craving, and sometimes darkening of the skin like a suntan
- Loss of body fluid manifesting as feeling tired, confused, having a dry mouth, or feeling thirsty
- Trouble thinking clearly or confused easily
- Inflammation of the eye (iritis, uveitis, iridocyclitis) causing symptoms such as redness in your eye/s, blurred vision, eye pain, headaches and you may be sensitive to light or see floaters
- Inflammation of the lungs, manifesting as shortness of breath
- Increased release of thyroid hormone which may manifest as anxiety, irritability, or trouble sleeping, weakness, trembling, sweating, feeling uncomfortable in warm weather, fast or uneven heartbeats, feeling tired, weight loss, and frequent or excessive bowel movements.
- Inflammation of the large intestine (colon) and small intestines that may manifest as frequent or excessive watery bowel movements, bleeding and severe pain in your belly
- Ulcers in your stomach and/or intestines which may cause bleeding
- Inflammation of the pituitary gland, which may manifest as headache, nausea, a sensation of the room spinning around you, changes in behavior, double vision, or weakness
- Infection throughout the body by a fungus that may manifest as fever, feeling tired, feeling cold, and not responding to most antibiotics
- Inflammation of the heart which may cause your heart to have difficulty pumping blood throughout your body, which can cause sharp chest pain and/or a fever difficulty breathing, swelling in your legs. You may also experience a fast or irregular heartbeat that can cause dizziness or fainting. Sometimes this condition can lead to death.
- Inflammation of the muscles that may manifest as weakness or pain in the muscles
- Inflammation of the nerves (pain, weakness or tingling in your hands and feet, and may spread to your legs, arms, and upper body leading to severe muscle weakness and possible temporary paralysis)
- Inflammation of the spinal cord with pain, numbness, tingling, or weakness in the arms or legs, bladder or bowel problems including needing to urinate more frequently, urinary incontinence, difficulty urinating, and constipation (myelitis)
- Decreased white blood cells, red blood cells, and/or platelets which may manifest with fever, feeling cold, infections, shortness of breath, feeling tired, a tendency to bruise easily, or a tendency to bleed easily

- Inflammation of the pancreas that may manifest as severe upper abdominal pain that may move to the back, nausea and vomiting that is worsened with eating.
- Inflammation of the liver or liver damage that may manifest as poor appetite, yellowing of the skin and whites of the eyes, dark urine, fever and belly pain
- Severe pain in the top part of your belly that may move to the back
- Skin changes (More severe skin reactions may involve the inside of your mouth, the surface of your eye and genital areas, and/or may cause the top layer of your skin to peel from all over your body which can cause severe infection. Rarely can lead to death.)
- Inflammation of the brain which can cause a headache, confusion and fever or more severe symptoms (disorientation, seizures, loss of consciousness)
- A condition that may make you feel weak and tired and might have drooping of the eyelids, blurred or double vision, difficulty swallowing, slurred speech, weakness in your arms and legs, or difficulty breathing
- The formation of small clusters of immune cells (called granulomas) in parts of your body such as your lymph nodes, eyes, skin or lungs
- Cytokine release syndrome (a generalized inflammatory response of the body which can result in fever, fatigue, loss of appetite, muscle and joint pain, nausea, vomiting, diarrhea, rashes, fast breathing, rapid heartbeat, low blood pressure, seizures, headache, confusion, delirium, hallucinations, tremor, and loss of coordination and death)
- Serum sickness, a type of delayed allergic response causing skin rash, fever, joint pain and swollen lymph nodes and other allergic reactions.
- Inflammation of the blood vessels.
- Inflammation of the bile ducts.

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

- Inflammation of the joints which may include joint pain, stiffness and/or swelling
- Changes in eyesight, eye pain, whitish patches on the skin and hearing loss (Vogt-Koyanagi-Harada syndrome)

In addition to the above, the following side effect(s) have been seen in patients on pembrolizumab, but are still being evaluated to determine if they are related to the drug:

- Weakness and fatigue in your hip and thigh muscles, and an aching back. This is caused by your body's immune system attacking your healthy cells and tissues.

Temozolomide side effects

Most common (seen in 20 or more out of 100 people taking temozolomide):

- Fatigue
- Swelling

- Fever
- Dizziness
- Hair loss
- Rash
- Nausea or vomiting
- Constipation or diarrhea
- Loss of appetite
- Muscle weakness, paralysis, or difficulty walking
- Trouble with memory
- Difficulty sleeping

Less Likely (seen in 4-20 out of 100 people taking temozolomide):

- Headache
- Seizure
- Infection, especially when white blood cell count is low
- Depression
- Anxiety
- Mouth sores
- Weight gain
- Cough
- Blurry vision
- Shortness of breath
- Anemia (low red blood cell count) which may cause tiredness
- Thrombocytopenia (low platelet count)
- Bruising and/or bleeding
- Damage to the bone marrow (which is not reversible) and may cause infection, bleeding, or require blood transfusions

Rare but Serious (seen in 3 or fewer out of 100 people taking temozolomide)

- Severe rash, including skin rash with blisters; can involve inside of the mouth and other parts of the body
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, and/or swelling of the face or throat
- Cancer of bone marrow caused by chemotherapy
- Interstitial lung disease (lung injury) which can cause respiratory failure
- Numbness or tingling of fingers or toes
- Liver damage which may cause yellowing of eyes and skin, swelling, and may result in liver failure.

Risk of pembrolizumab used in combination with temozolomide plus radiation therapy

There is a small chance that addition of pembrolizumab to temozolomide and radiation therapy for brain cancers could cause swelling in the brain. This could be life-threatening or can lead to serious

effects such as paralysis, or the risk of not being able to receive the full doses of radiation therapy and temozolomide, which can otherwise prolong survival in patients with newly diagnosed glioblastoma. Swelling can be treated with steroids. You will be closely monitored for this side effect.

HSPPC-96 side effects

The most common adverse events (between **10% and 22%** of total occurrences) in the HSPPC-96 treated patient population (all Agenus sponsored completed clinical studies) reported by incidence were:

- Fatigue (lethargy)
- Nausea
- Constipation
- Fever
- Headache
- Back pain
- Joint pain
- Injection site reaction with tenderness and redness and possible infection
- Malignant Neoplasm Progression (Cancer Progression)

Less Likely (between **5% and 10%** of total occurrences**):**

- General weakness
- Anorexia (loss of appetite)
- Insomnia (difficulty sleeping)
- Vomiting
- Diarrhea
- Edema (organ/tissue swelling due to excess fluids)
- Leg pain
- Abdominal/stomach pain
- Difficulty breathing or shortness of breath
- High blood pressure
- Decrease in red blood cells and platelets (which can lead to anemia and bleeding)
- Dizziness
- Cold symptoms
- Incision site reaction
- Cough

Rare, but serious toxicities in less than 1% of patients were:

- Rash (usually facial)
- Excessive sweating
- An immune reaction where the patient's immune system attacked normal cells
- Respiratory failure
- Kidney failure

- Abnormal liver function levels
- Thyroid function abnormality
- Capillary leak syndrome (fluid and proteins leak out of tiny blood vessels and flow into the surrounding tissues, resulting in dangerously low blood pressure)
- Acidosis (increase in acid production)
- Unequal size of pupils in your eyes
- Collection of fluid between the thin layers of tissue (pleura) lining the lung and the wall of the chest cavity
- Groin pain
- Swelling
- Mental status changes
- Depression
- Muscle Pain
- Cancer Pain
- Paraneoplastic syndrome (secretion of hormones from one's own tumor, which can cause respiratory disorder)
- Cellulitis (infection in the skin)
- Left Sided Weakness

Other Risks

Local brain tissue damage (necrosis) may occur after vaccine therapy, pembrolizumab or radiation therapy, which could result in worsening neurological symptoms. This damaged tissue can look like brain tumor that has grown back or a stroke. This might require treatment with drugs called steroids or a surgery to make a diagnosis. In some cases, a surgery may be necessary to remove damaged tissue if it is causing a lot of brain swelling and making the symptoms worse.

Blood draws may cause pain, bleeding, and/or bruising. You may faint and/or develop an infection with redness and irritation of the vein at the site where blood is drawn. Frequent blood collection may cause anemia (low red blood cell count), which may create a need for blood transfusions.

Questionnaires may contain questions that are sensitive in nature. You may refuse to answer any question that makes you feel uncomfortable. The primary use of the information you provide is to assess the severity of your symptoms. Submission of this information is voluntary. If you have concerns about completing the questionnaire, you are encouraged to contact your doctor or the Principal Investigator.

MRIs - People are at risk for injury from the MRI magnet if they have some kinds of metal in their body. It may be unsafe for you to have an MRI scan if you have pacemakers or other implanted electrical devices, brain stimulators, some types of dental implants, aneurysm clips (metal clips on the wall of a large artery), metal prostheses (including metal pins and rods, heart valves, and cochlear implants), permanent eyeliner, tattoos, an implanted delivery pump, or shrapnel fragments. Welders and metal workers may have small metal fragments in the eye. You will be screened for these conditions before having any MRI scan. If you have a question about metal in your body, you should inform the staff. You will be asked to complete an MRI screening form before each MRI scan you have.

In addition, all magnetic objects (like watches, coins, jewelry, and credit cards) must be removed before entering the MRI scan room.

People with fear of confined spaces may become anxious during an MRI. Those with back problems may have back pain or discomfort from lying in the scanner. The noise from the scanner is loud enough to damage hearing, especially in people who already have hearing loss. Everyone having a research MRI scan will be fitted with hearing protection. If the hearing protection comes loose during the scan, you should let us know right away.

There are no known long-term risks of MRI scans.

Risks for gadolinium enhanced MRI scans:

Procedure

During part of the MRI you will receive gadolinium, a contrast agent, through an intravenous (iv) catheter. It will be done for medical purposes.

It is not known if MRI with contrast is completely safe for a developing fetus. Therefore, all women of childbearing potential will have a pregnancy test performed no more than 24 hours before each MRI scan with contrast. The scan will not be done if the pregnancy test is positive.

MRI Risks:

The risks of an IV catheter include bleeding, infection, or inflammation of the skin and vein with pain and swelling.

Mild symptoms from gadolinium infusion occur in fewer than 1% of those who receive it and usually go away quickly. Mild symptoms that may occur include: coldness in the arm at injection, a metallic taste, headache, and nausea. In an extremely small number of patients, fewer than one in 300,000 people, more severe symptoms have been reported including: shortness of breath, wheezing, lowering of blood pressure. You should not receive gadolinium if you previously had an allergic reaction to it. You will be asked about such allergic reactions before gadolinium is given.

People with kidney disease are at risk for a serious reaction to gadolinium contrast called "nephrogenic systemic fibrosis (NSF)". This condition always involves the skin and can also involve the muscles, joints and internal organs. NSF has resulted in a very small number of deaths. A blood test of your kidney function may be done within the month before an MRI scan with gadolinium contrast. You will not receive gadolinium for a research MRI scan if your kidney function is below the safe level.

Most of the gadolinium contrast leaves the body in the urine. However, the FDA has issued a safety alert that indicates small amounts of gadolinium may remain in the body for months to years. The effects of the retained gadolinium are not clear. At this time, retained gadolinium has not been linked to health risks in people whose kidneys work well. Some types of gadolinium contrast drugs are less likely to remain in the body than others. In this study, we will use the gadolinium contrast drugs that are less likely to remain in the body, whenever possible. We will also give you additional information called a "Medication Guide." Upon request, we will give you individual information about retained gadolinium we see on your studies.

This study may involve unpredictable risks to the participants including death.

Genetic Testing

Psychological or Social Risks Associated with Return of Incidental or Secondary Findings

As part of the research study, it is possible that you could learn that you have genetic risks for another disease or disability. This may be upsetting and, depending on what you learn, might create a need to make challenging decisions about how to respond.

Although your genomic information is unique to you, you share some genomic similarities with your children, parents, brothers, sisters, and other blood relatives. Therefore, learning your research results could mean something about your family members and might cause you or your family distress. Before joining the study, it may be beneficial to talk with your family members about whether and how they want you to share your results with them.

Privacy Risks Associated with Genetic Testing

It may be possible that genetic information from you could be used by law enforcement agencies or other entities to identify you or your blood relatives.

Protections against misuse of genetic information

This study involves genetic testing on samples. Some genetic information can help predict future health problems of you and your family and this information might be of interest to your employers or insurers. The Genetic Information Nondiscrimination Act (GINA) is a federal law that prohibits plans and health insurers from requesting genetic information or using genetic information. It also prohibits employment discrimination based on your health information. However, GINA does not address discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. GINA also does not protect you against discrimination based on an already-diagnosed condition or disease that has a genetic component.

Potential Benefits of Participation

Are there benefits to taking part in this study?

The aim of this study is to see if this experimental treatment of pembrolizumab, temozolomide and HSPPC-96 vaccine or placebo will cause your tumor to shrink. We do not know if you will receive personal, medical benefit from taking part in this study. These potential benefits could include shrinking of your tumor or lessening of your symptoms, such as pain, that are caused by the cancer. Because there is not much information about the drug or vaccine's effects on your cancer, we do not know if you will benefit from taking part in this study, although the knowledge gained from this study may help others in the future who have cancer.

Alternative Approaches or Treatments

What other choices do I have if I do not take part in this study?

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

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- 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. Instead, it tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Please talk to your doctor about these and other options.

Stopping Therapy

Your doctor may decide to stop your therapy for the following reasons:

- If your tumor is not large enough or does not meet the criteria to make the vaccine
- if he/she believes that it is in your best interest
- if your disease comes back during treatment
- if you have side effects from the treatment that your doctor thinks are too severe
- if new information shows that another treatment would be better for you
- In this case, you will be informed of the reason therapy is being stopped.

You can stop taking part in the study at any time. However, if you decide to stop taking part in the study, we would like you to talk to the study doctor and your regular doctor first.

If you decide at any time to withdraw your consent to participate in the trial, we will not collect any additional medical information about you. However, according to FDA guidelines, information collected on you up to that point may still be provided to Merck, Agenus or designated representatives. If you withdraw your consent and leave the trial, any samples of yours that have been obtained for the study and stored at the NCI can be destroyed upon request. However, any samples and data generated from the samples that have already been distributed to other researchers or placed in the research databases cannot be recalled and destroyed.

New Information

During the course of the study, if we receive any important new information about the study drug that might change your mind about continuing in the study, the study doctor or study staff will tell you about it. You are free to withdraw your consent from the study at any time.

Conflict of Interest

The National Institutes of Health (NIH) reviews NIH staff researchers at least yearly for conflicts of interest. This process is detailed in a Protocol Review Guide. You may ask your research team for a copy of the Protocol Review Guide or for more information. Members of the research team who do not work for NIH are expected to follow these guidelines, but they do not need to report their personal finances to the NIH.

Members of the research team working on this study may have up to $15,000 of stock in the companies that make products used in this study. This is allowed under federal rules and is not a conflict of interest.

The National Institutes of Health and the research team for this study are using pembrolizumab developed by Merck through a joint study with your researchers and the company. NIH and the research team for this study are also using HSPPC-96 developed by Agenus through a joint study

with your researchers and the company. Both companies also provide financial support for this study.

Use of Specimens and Data for Future Research

To advance science, it is helpful for researchers to share information they get from studying human samples. They do this by putting it into one or more scientific databases, where it is stored along with information from other studies. A researcher who wants to study the information must apply to the database and be approved. Researchers use specimens and data stored in scientific databases to advance science and learn about health and disease.

We plan to keep some of your specimens and data that we collect and use them for future research and share them with other researchers. We will not contact you to ask about each of these future uses. These specimens and data will be stripped of identifiers such as name, address or account number, so that they may be used for future research on any topic and shared broadly for research purposes. Your specimens and data will be used for research purposes only and will not benefit you. It is also possible that the stored specimens and data may never be used. Results of research done on your specimens and data will not be available to you or your doctor. It might help people who have cancer and other diseases in the future.

Agenus and Merck, the companies that supply the study drug and vaccine, will use study results for further research, development and commercialization of their products, and will process and transfer data in their discretion with identifying information about you removed. By signing this form, you consent to such use of the study results.

If you do not want your stored specimens and data used for future research, please contact us in writing and let us know that you do not want us to use your specimens and/or data. Then any specimens that have not already been used or shared will be destroyed and your data will not be used for future research. However, it may not be possible to withdraw or delete materials or data once they have been shared with other researchers.

Genomic Data Sharing

As part of this research study, we will put your genomic data in a large database for broad sharing with the research community. These databases are commonly called data repositories. The information in this database will include but is not limited to genetic information, race and ethnicity, and sex. If your individual data are placed in one of these repositories, they will be labeled with a code and not with your name or other information that could be used to easily identify you, and only qualified researchers will be able to access them. These researchers must receive prior approval from individuals or committees with authority to determine whether these researchers can access the data.

Summary information about all of the participants included in this study (including you) is being placed in a database and will be available through open access. That means that researchers and non-researchers will be able to access summary information about all the participants included in the study, or summary information combined from multiple studies, without applying for permission. The risk of anyone identifying you with this information is very low.

NIH policies require that genomic data be placed in a repository for sharing. Therefore, we cannot offer you a choice of whether your data will be shared. If you do not wish to have your data placed in a repository, you should not enroll in this study.

Payment

Will you receive any type of payment for taking part in this study?

You will not receive any payment for taking part in this study.

REIMBURSEMENT

Will you receive reimbursement or direct payment by NIH as part of your participation?

On this study, the NCI will reimburse the cost for some of your expenses such as those for hotel, travel, and meals. Some of these costs may be paid directly by the NIH and some may be reimbursed after you have paid. The amount and form of these payments are determined by the NCI Travel and Lodging Reimbursement Policy. You will be given a summary of the policy which provides more information.

COSTS

Will taking part in this research study cost you anything?

NIH does not bill health insurance companies or participants for any research or related clinical care that you receive at the NIH Clinical Center.

- If some tests and procedures are performed outside the NIH Clinical Center, you may have to pay for these costs if they are not covered by your insurance company.
- Medicines that are not part of the study treatment will not be provided or paid for by the NIH Clinical Center.
- Once you have completed taking part in the study, medical care will no longer be provided by the NIH Clinical Center.
- You will receive study treatment at no charge to you. This may include surgery, medicines, laboratory testing, x-rays or scans done at the Clinical Center, National Institutes of Health (NIH), or arranged for you by the research team to be done outside the Clinical Center, NIH if the study related treatment is not available at the NIH.

Clinical Trial Registration and Results Reporting

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.

Confidentiality Protections Provided in This Study

Will your medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The NIH and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- National Institutes of Health Intramural Institutional Review Board
- The study Sponsor, NCI Center for Cancer Research (CCR) or their agent(s).
- Qualified representatives from Merck, the pharmaceutical company who produces pembrolizumab.
- Qualified representatives from Agenus, the pharmaceutical company who produces the vaccine. When Agenus receives the tissue from your tumor to create the vaccine, it will be labelled with your initials and date of birth, but no direct identifiers.

The researchers conducting this study and the NIH follow applicable laws and policies to keep your identifying information private to the extent possible. However, there is always a chance that, despite our best efforts, your identity and/or information about your participation in this research may be inadvertently released or improperly accessed by unauthorized persons.

In most cases, the NIH will not release any identifiable information collected about you without your written permission. However, your information may be shared as described in the section of this document on sharing of specimens and data, and as further outlined in the following sections.

Further, the information collected for this study is protected by NIH under a Certificate of Confidentiality and the Privacy Act.

Certificate of Confidentiality

To help us protect your privacy, the NIH Intramural Program has received a Certificate of Confidentiality (Certificate). With this certificate, researchers may not release or use data or information about you except in certain circumstances.

NIH researchers must not share information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if requested by a court.

The Certificate does not protect your information when it:

1. is disclosed to people connected with the research, for example, information may be used for auditing or program evaluation internally by the NIH; or
2. is required to be disclosed by Federal, State, or local laws, for example, when information must be disclosed to meet the legal requirements of the federal Food and Drug Administration (FDA);
3. is for other research;
4. is disclosed with your consent.

The Certificate does not prevent you from voluntarily releasing information about yourself or your involvement in this research.

The Certificate will not be used to prevent disclosure to state or local authorities of harm to self or others including, for example, child abuse and neglect, and by signing below you consent to those disclosures. Other permissions for release may be made by signing NIH forms, such as the Notice and Acknowledgement of Information Practices consent.

Privacy Act

The Federal Privacy Act generally protects the confidentiality of your NIH medical records we collect under the authority of the Public Health Service Act. In some cases, the Privacy Act protections differ from the Certificate of Confidentiality. For example, sometimes the Privacy Act allows release of information from your medical record without your permission, for example, if it is requested by Congress. Information may also be released for certain research purposes with due consideration and protection, to those engaged by the agency for research purposes, to certain federal and state agencies, for HIV partner notification, for infectious disease or abuse or neglect reporting, to tumor registries, for quality assessment and medical audits, or when the NIH is involved in a lawsuit. However, NIH will only release information from your medical record if it is permitted by both the Certificate of Confidentiality and the Privacy Act.

Policy Regarding Research-Related Injuries

The NIH Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the NIH, the NIH Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

Problems or Questions

If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Dr. Mark Gilbert, email: mark.gilbert@nih.gov, Tel: 2407-60-6023. You may also call the NIH Clinical Center Patient Representative at 301-496-2626, or the NIH Office of IRB Operations at 301-402-3713, if you have a research-related complaint or concern.

Consent Document

Please keep a copy of this document in case you want to read it again.

Adult Research Participant: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I consent to participate in this study.

Signature of Research Participant	Print Name of Research Participant	Date

Legally Authorized Representative (LAR) for an Adult Unable to Consent: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I am legally authorized to make research decisions on behalf of the adult participant unable to consent and have the authority to provide consent to this study. As applicable, the information in the above consent was described to the adult participant unable to consent who agrees to participate in the study.

Signature of LAR	Print Name of LAR	Date

Investigator:

Signature of Investigator	Print Name of Investigator	Date

Witness should sign below if either:

1. **A short form consent process has been used to enroll a non-English speaking subject or**
2. **An oral presentation of the full consent has been used to enroll a blind or illiterate subject**

Signature of Witness*	Print Name of Witness	Date

***NIH ADMINISTRATIVE SECTION TO BE COMPLETED REGARDING THE USE OF AN INTERPRETER:**

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent and served as a witness. The investigator obtaining consent may not also serve as the witness.

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent but did not serve as a witness. The name or ID code of the person