Official Title:	**ATTAC-MCC**: Phase I/II study of Autologous CD8+ and CD4+ Transgenic T cells expressing high affinity MCPyV-specific TCRs combined with Avelumab and Class I MHC - upregulation in patients with metastatic MCC refractory to PD-1 axis blockade
NCT Number:	NCT03747484
Document Type:	Informed Consent Form
Date of the Document:	December 8, 2022

FRED HUTCHINSON CANCER CENTER
UNIVERSITY OF WASHINGTON SCHOOL OF MEDICINE

Consent to take part in a research study:

ATTAC-MCC: Phase I/II study of Autologous CD8+ and $CD4^+$ Transgenic T cells expressing high affinity MCPyV-specific TCRs combined with Avelumab and Class I MHC -upregulation in patients with metastatic MCC refractory to PD-1 axis blockade

Consent to undergo additional screening procedures, leukapheresis, investigational interferon gamma and T cell infusion and standard of care avelumab or pembrolizumab

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Important things to know about this study.

Your doctors are inviting you to participate in a research study. The purpose of this research is to find out the safe and appropriate dose of genetically modified T cells by infusion, and to see whether your cancer gets better after the infusion. We combine the T cell infusion with the use of another drug, interferon gamma, that is approved for another condition but is now being studied in combination with T cells to treat cancer.

If you agree to join the study, you will receive interferon gamma, genetically modified T cells by infusion and Avelumab or pembrolizumab. The avelumab and pembrolizumab are standard approaches, and will be billed to insurance. The T cell infusion and interferon gamma are investigational. You will not receive avelumab on this study if you had a severe immune side effect to that class of drug before, or if you could not be given that class of drug due to this history of an autoimmune disease.

We do not know if the interferon gamma and T cell infusion would help treat your cancer. The interferon gamma and T cell infusion and other study procedures could cause side effects.

You do not have to join this study. You could choose to receive standard methods to treat your cancer. We will give you details about the purposes, procedures, risks and possible benefits related to this study. We will explain other choices that you have. We will also give you any other information that you need in order to make an informed decision about joining this study.

Following is a more complete description of this study. Please read this description carefully. Afterwards, you can ask questions that will help you decide whether to join the study. If you join this study, we would give you a signed copy of this form to keep for future reference.

We invite you to join this research study.

You have metastatic Merkel cell carcinoma, a cancer of the skin that has spread to other organs. Metastatic Merkel cell carcinoma is rarely cured by current treatment. This protocol represents an investigational approach to treating patients with metastatic Merkel cell carcinoma.

Research is not the same as treatment or medical care. The purpose of a research study is to answer scientific questions. We will enroll up to 16 Merkel cell carcinoma patients for this research study.

You do not have to be in the study. You are free to say “yes” or “no”, or to drop out after joining. If you say “no,” you have no penalty or loss of benefits. Whatever you decide, your regular medical care would not change.

Why are we doing this study?

The purpose of this study is to test a new treatment for metastatic Merkel cell carcinoma (MCC). The treatment is for patients whose MCC is caused by the Merkel virus. Your blood or tumor will be tested to determine whether your MCC is caused by the Merkel virus. The new treatment consists of your own immune cells (autologous T cells) that are engineered (genetically modified) to be able to recognize (see) the Merkel virus. These T cells will be collected and then after engineering be reinfused into your bloodstream (given by IV). We hope that the interferon gamma will help the T cells to recognize and

kill the cancer cells. During this study, you will also continue with standard-of-care treatments for MCC including avelumab or pembrolizumab (which are T cell immune booster medications).

In this study, we want to learn:

- the best way to give genetically modified T cells,
- if experimental treatment with genetically modified T cells in combination with interferon gamma and standard avelumab or pembrolizumab is safe in Merkel cell patients
- if experimental treatment with genetically modified T cells in combination with interferon gamma and standard avelumab or pembrolizumab can shrink Merkel cell carcinoma tumors

To determine the safest dose for T cell infusions, we will first treat study participants, one at a time, starting at a low dose. Once a group of patients has been treated at a certain dose, we will look at the safety of that dose and decide if we should increase the T cell dose for the next group of patients. We will watch carefully for any side effects.

Patients will receive one infusion and in some circumstances two infusions (one or two cycles) approximately 12 weeks apart, followed by avelumab once every 2 weeks or pembrolizumab every 3 weeks for approximately 12 months or as long as your oncologist recommends.

What research tests, procedures and infusions are part of this study?

If you decide to join this study, we will do the following research tests and procedures, which are performed in addition to your usual care. Where possible we will try to schedule the times and locations of research tests at the same time as the tests done as part of your usual care. There are several parts to this study.

To determine if you are eligible for this study, a number of routine tests will be evaluated. This will include routine blood tests, including testing for blood grouping, viruses like hepatitis and HIV, complete blood counts, pregnancy test and metabolic function panels.

Your medical history at diagnosis and when enrolling for this study along with prior treatments and response to said treatments will also be reviewed to determine your eligibility to enroll on this study.

You will also undergo a restaging of your disease which may include the following tests:

Tumor imaging

You should have PET/CT or MRI scans to determine the amount and location of disease you have prior to starting therapy.

Blood tests

In addition to the blood tests mentioned above, 80 ml of your blood will be collected and stored for research purposes (this will happen before your T cells are collected). If there is a delay between your initial screening tests and your leukapheresis (a standard medical procedure that separates out

your white blood cells) or blood draw for T cell collection, we may need to repeat the screening blood tests closer to the time of T cell collection to help us plan the procedure.

Tumor biopsy

Tumor biopsies will be requested to evaluate your treatment and to provide tumor tissue samples for research studies. If you have a tumor that your doctor thinks can be safely biopsied, we would like to perform a biopsy procedure. Your doctor will explain the process and risks to you and tell you which tumor they feel is best to biopsy.

A minimum of 4 biopsies will be performed: before the interferon gamma starts, before your T cell infusion, 2 weeks after and 12 weeks after your T cell infusion; an additional biopsy will be recommended if the cancer comes back. The biopsies performed before treatment, at 12 weeks, and if the cancer comes back are for both clinical (to determine whether there is residual Merkel cell cancer) and research reasons; the biopsy after interferon gamma but before T cell infusion and at 2 weeks is for research only. If you do not wish to undergo the tumor biopsy you do not have to give a reason and your medical care will not change. You are free to say no to the biopsy procedures, even if you sign this consent form.

The study team may also request some tissue from a previously collected biopsy for research.

Blood or tumor samples will be stored and can be used for future research to study merkel cell carcinoma and its treatment. Information about your medical care and testing on your samples that does not include identifying information can be shared with other researchers at our institution and elsewhere.

Your tissue contains DNA. DNA makes up the genes that serve as the "instruction book" for the cells in our bodies. By studying genes, researchers can learn more about diseases such as cancer. There are many different types of genetic tests. The testing on your tissue samples might include genetic testing such as whole genome sequencing, which looks at all the known genes in your cells. This type of testing can provide useful information to researchers. It can also present risks if the test results became known to others, for example you could have problems with family members or insurance companies. There is also a risk that these test results could be combined with other genetic information to identify you. We will do our best to keep your personal health information confidential.

Several genetic databases are available to help researchers understand diseases such as cancer. These databases contain DNA information and other data helpful to study diseases. DNA comes from cells in your body and contains all your genetic information. As part of this study, we might obtain genetic information about your tumor and immune cells, which we may wish to add to these anonymous databases. This information may benefit future research. All of your personal information would be removed. Your name, address, etc will not be in the database. Only genetic information and information about your condition will be sent to the database.

There is a small risk that your genetic information could be matched against other genetic databases to get your name. Once we release your data to a central database, we would no longer be in control

of the information. However, we will do everything possible before that to protect your personal health information.

Collection of T cells

T cells will be collected from your blood by a procedure called leukapheresis, a standard medical procedure in which needles are inserted into both arms and your blood is circulated through a machine before being returned to you. You will be hooked up to the machine for 1-4 hours. While you are on it, some white blood cells will be removed from your blood and collected in a sterile bag. You will be monitored carefully during the procedure.

If you are not able to undergo leukapheresis because your veins are difficult to access, you may have a temporary percutaneous central venous catheter inserted to support this collection.

If you are not eligible to undergo a leukapheresis procedure and you have adequate blood counts, we may be able to collect 400 ml (about 2 cups) of blood by a standard blood draw procedure to obtain the necessary numbers of T cells.

After T cells have been collected from your blood, they will be taken to our laboratory where we will insert a new gene into their DNA to make them kill cancer cells. These genetically modified T cells will then be grown in the laboratory. This process may take several weeks and may be difficult or impossible depending on how much prior chemotherapy you have had. If the genetically modified T cells can be made and grown in sufficient numbers, then we will schedule the T cell infusion to take place when clinically appropriate.

Should a technical issue arise during the leukapheresis procedure or in the processing of the product, or if manufactured T cells are insufficient for the prescribed cell dose, a second leukapheresis procedure may need to be performed.

It is possible that we will not be able to produce a sufficient number of T cells and in that case, we would not be able to administer the manufactured cell product to you as part of this study. This risk could also apply to a second collection of your blood cells.

Blood samples in excess of those required for cell selections may be archived for research.

You will receive interferon gamma prior to the T cell infusion

Prior to each T cell infusion you are will receive interferon gamma treatment. This durg is FDA approved for use in a rare condition called chronic granulomatous disease, but its use in cancer is investigational. The goal of this treatment is something called MHC up-regulation (MHC class I up-regulation). Up-regulation increases the amount of the Merkel Cell Polyoma Viral proteins on the surface of your tumor(s) so that white blood cells can better attack your tumor. We will start this treatment 4-8 days before the T cell infusion, and it is given as an injection under the skin three times per week.

You will receive genetically modified T cells by infusion (FH-MCVA2TCR)

Approximately one to three days after MHC class I up-regulation, you will receive an infusion of your Merkel Cell Polyoma Virus-specific T cells. You will receive up to *two* T cell infusions according to the following schedule, and with the following doses:

	Infusion #1	**Infusion #2 (if indicated)**
Timing	Day 0	≥ 12 weeks later
Cell Dose - phase I	One billion CD8+ T cells ('killer' T cells) plus CD4+ T cells; up to one billion virus-specific cells total	five billion CD8+ T cells ('killer' T cells) plus CD4+ T cells; up to ten billion virus-specific cells total
Cell Dose - phase II	five billion CD8+ T cells ('killer' T cells) plus CD4+ T cells; up to ten billion virus-specific cells total	five billion CD8+ T cells ('killer' T cells) plus CD4+ T cells; up to ten billion virus-specific cells total

Infusions will occur at the Fred Hutch Cancer Center (or at the University of Washington Medical Center if you are hospitalized) where you will be monitored for two hours after your T cells infusion.

Approximately 12 weeks after the first infusion, you will have scans to evaluate your cancer. This can be done earlier if you have symptoms that raise concern that the cancer is growing. If your cancer is still there or returns at a later point, this treatment regimen may be repeated. If the cancer grows after the first infusion, you might be able to receive other treatments like chemotherapy before getting a second infusion.

You will receive anti-PD-1/PD-L1 drug (avelumab or pembrolizumab**) after the T cell infusion:**

Approximately 2 weeks after the T-cell infusion, you will receive an IV infusion of either avelumab every 2 weeks or pembrolizumab every 3 weeks for approximately 12 months. For the first infusion of avelumab or pembrolizumab after each T cell infusion, you will be observed for one hour post infusion for potential infusion-related reactions and receive this infusion at Fred Hutch or UW. Avelumab or pembrolizumab therapy will be given as a standard of care treatment for palliation of advanced MCC, and as such will be billed to your insurance. Avelumab (Bavencio) and pembrolizumab (Keytruda) have been recently FDA-approved and carry an indication for the treatment of metastatic Merkel cell carcinoma. Subsequent infusions can be prescribed by your primary oncologist, as long as he or she is comfortable with prescribing avelumab or

pembrolizumab. Because avelumab or pembrolizumab are given as standard-of-care, if you or your doctor think it is in your best interest to do avelumab or pembrolizumab for a shorter or longer period of time (more or less than 12 months), this is acceptable. If you have a history of severe immune side effects with avelumab, pembrolizumab, or similar drugs, you will receive the other treatments on this trial, but without the Avelumab or pembrolizumab to minimize your risk of these side effects returning. If you have a history of an autoimmune disease that prevented you from getting a PD-1/PD-L1 inhibitor, you will also not receive pembrolizumab or avelumab on this study, but will receive the other treatments.

After you have finished the T cell infusion, you will enter the active follow-up part of the study. In active follow-up, we will run the below tests and procedures:

- **Tumor imaging studies.** CT scans with or without PET scans will be performed at approximately 12 weeks after the T cell infusion and again at 6, 9 and 12 months. These tests are performed to restage your disease and to determine the effect of the T cell infusions.

  The PET/CT and MUGA scans that you will have in this research study will expose you to radiation. Everyone receives a small amount of radiation every day called "background radiation". This radiation is natural and comes from space, air, water, soil, and the food you eat. Each year you are exposed to about 3 milliSieverts (mSv) of this background radiation. A milliSievert is a unit of radiation dose. There is minimal risk to your health from the amount of radiation you will receive in this study. The usual lifetime risk of getting cancer is 42%. For every 10 mSv you receive, your risk may increase 0.1%. If you have more procedures that expose you to radiation, your risk will go up. For comparison, the estimated radiation dose from each of these tests is listed below:

  · FDG PET/CT: 19 mSv

  · MUGA: 9.4

- **History and Physical Exams.** One day post and at least weekly for up to 6 weeks post each T-cell infusion.

- **Blood tests.** After the T cell infusion, we would like to take blood samples to study the T cells. We plan to collect samples at the following approximate times and amounts after your T cell infusion. These samples will be used to monitor the effects of the T cell infusion. We may collect additional samples, up to 40 ml (almost 3 tablespoons), at other times to evaluate your medical condition after the treatment. Some of the samples may be analyzed by the research labs and may be stored for analysis later.

  - At enrollment - 80 ml, 5.5 tablespoons
  - The day of the infusion- 50 ml, 3.5 tablespoons
  - Day 1 – 50 ml, 3.5 tablespoons
  - Day 3 - 50 ml, 2.5 tablespoons
  - Day 7 - 70 ml, 2.5 tablespoons
  - Day 14 - 80 ml, 5.5 tablespoons
  - Day 21 – 30 ml, 2.5 tablespoons

- Day 28 – 50 ml, 3.5 tablespoons
- Day 56 – 50 ml, 3.5 tablespoons
- Day 84 – 80 ml, 5.5 tablespoons
- If second infusion:
    - Day 0, 1, 3, 7, 14, 28, and 56 after second infusion – up to 70 mL (3.5 tablespoons) each
- Day 180 – 80 ml, 5.5 tablespoons
- Day 270 – 80 ml, 5.5 tablespoons
- Day 365 - 80 ml, 5.5 tablespoons

How long will you stay in this study?

You will be actively participating in the study for approximately 15 months. The total time includes the time for the T cells to be made, the T cell infusion, and for approximately 12 months after the T cell infusion is given.

The study doctor or your doctor may take you out of this study at any time, whether you want to leave the study or not. This would happen if:

- They think it is not in your best interest to continue in the study.
- You are not able or willing to follow study procedures.
- The whole study is stopped.

If you are thinking about dropping out of this study, please tell the study doctor. The doctor can tell you about the effects of stopping. You and the doctor can talk about what follow-up care and testing would help you the most.

If you withdraw from the study for any reason, previously collected information would remain in the study records and would be included in the analysis of results. This information could not be removed from the study records.

We would like to do long-term follow-up.

Long-term follow-up means keeping track of your medical condition for the rest of your life. Long-term follow-up is not the same as the one-year period for this research study. It begins when your active participation in this research study ends, one year after you received your T cell infusion.

The FDA requests that people who receive an infusion of genetically modified T cells be asked if they will participate in long-term follow-up for 15 years after they receive the genetically modified T cells.

Although we would like you to do long-term follow-up, you do not have to agree to be in long-term follow-up. You can say yes or no. Either way, you can still join this study. If you drop out of the study, we will ask again if we may contact you once a year.

If you choose not to join long-term follow-up, we will not contact you regularly after the study has finished, but we may still need to contact you for some other reason.

If you agree to do long-term follow-up we will call you and/or your provider on the telephone or send you or your provider a letter or survey once a year to see how you are doing. We may ask you to see your physician for a complete exam and to have a blood test twice a year for the first 5 years then once a year after that. This will help us learn about the long-term effects of the T cell infusions. It will also help us let you know about health information that is related to this study and might be important to you. It is important that you notify us of any change in your or your provider's contact information.

If you have questions during long-term follow-up, contact information is as follows:

imtxltfu@fredhutch.org	(206) 667-5811

What are the side effects (risks)?

In this part of the consent form, we tell you the side effects we expect from the tests, interferon gamma, and infusion of T cells in this study.

The procedures used to get T cells from the blood, to genetically modify them with lentivirus, and to give them to people are experimental. The FDA will only allow these procedures to be used in research studies and they are not part of standard treatment.

With any new treatment or combination of treatments, there may be side effects that we do not know about and cannot predict.

If we learn about other side effects, we will tell you. We carefully watch everyone in the study for side effects. If you want more information about side effects and risks, ask the doctor or nurse.

You should talk to your doctor about any side effects that you have while you are in this study.

If they occur, side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after the T cell infusion stops. However, sometimes side effects can last a long time or never go away. There is a risk of death.

Risks of study procedures

Where possible, we will schedule study blood tests and bone marrow procedures to take place at the same times as your regular clinical tests to minimize any risks and discomfort. If you have the tests done separately, the extra risks are as follows.

Blood tests

The risks of blood tests depend on whether the blood is taken by needle directly from a vein or from a device, such as a Port or Hickman catheter, that stays in place for blood tests. If blood is taken from a Hickman catheter, there is usually no pain or bruising.

Likely side effects (≥ 20%) of blood tests are:

- Temporary discomfort if blood is taken straight from a vein.
- A small bruise or redness at the site from which the blood was taken.

Less likely side effects (3-20%) of blood tests are:

- Fainting, sweating, or feeling sick in the stomach that gets better when you lie down and rest.
- Bruising larger than a "quarter" coin.

Rare but serious side effects (< 3%) of blood tests are:

- Infection from the blood draw.
- Injury to blood vessels, nerves, or other structures near the blood draw site.

Risks of leukapheresis

Likely side effects (≥ 20%) of leukapheresis are:

- Discomfort associated with the needle puncturing the skin and vein.
- A small bruise or redness at the needle stick.
- Temporary (1-2 days) decrease in your red blood cell count.
- Temporary (up to 4 hours) decrease in the clotting ability of your blood.

Less likely side effects (3-20%) of leukapheresis are:

- Fainting, sweating, or feeling sick in the stomach that gets better when you lie down and rest.
- Bruising larger than a "quarter" coin at the needle stick site.
- During the collection, you may experience stiff arms, chilling sensations, faintness, and muscle cramping in the jaw or fingers and/or tingling around the mouth.

Rare but serious side effects (< 3%) of leukapheresis are:

- Infection from the blood collection.
- Blood vessel disturbances from the needle irritating the vein.
- Injury to blood vessels, nerves, or other structures near the needle stick site.
- Rarely, the muscle cramping during the collection may be severe.
- Symptoms from the procedure can be reduced or eliminated by slowing the procedure or giving a calcium supplement, either by mouth or as an infusion.
- If catheters cannot be placed in the blood veins in your arms to perform a leukapheresis, a central venous catheter will be needed. A separate consent form for the placement of that catheter will be required and will include a complete list of risks.

- In general, while the central line is in place you have an increased risk of a local infection around the catheter, which sometimes leads to a generalized infection in the blood. If this happens you will be treated with antibiotics. Clotting in the catheter could also occur and may require the catheter to be removed or treatment with medicines that dissolve blood clots.

Tumor Biopsy

Likely side effects (≥ 20%) of tumor biopsy procedures are:

- Pain or discomfort from where the incision is made or where the needle punctures the skin.
- Bruising

Less likely side effects (3-20%) of tumor biopsy procedures are:

- Infection from the biopsy.
- Injury to blood vessels, nerves, or other structures.
- Bleeding

Rare but serious side effects (< 3%) of tumor biopsy procedures are:

- Serious reaction to the anesthesia drugs.

There will be a separate consent form for this procedure, and the health care provider who will perform the biopsy will discuss the risks of your specific procedure in more detail at that time**.**

Interferon Gamma

In a study like this one, every risk or side effect cannot be predicted. Each person's reaction to a study drug, device or procedure may be different. You may have a side effect or be at risk for symptoms, illnesses and/or complications that could not be predicted by your study doctor or the sponsor of this study. If such side effects occur, you must inform your study doctor immediately.

Likely side effects (≥ 10%) of interferon gamma are:

- Fever (52%)
- Headache (33%)
- Chills (14%)
- Fatigue (14%)
- Rash (17%)
- Diarrhea (14%)
- Vomiting (13%)
- Injection site redness or tenderness (14%)

Less likely side effects (1-10%) of interferon gamma are:

- Depression (3%)
- Nausea (10%)

- Abdominal pain (8%)
- Muscle aches (6%)
- Joint pain (2%)
- Back pain (2%)

Rare but serious side effects (< 1%) of interferon gamma are:

- Liver damage or enlargement
- Severe rash
- Allergic reaction
- Low potassium in the blood
- Decreased blood counts
- Intestinal inflammation

Anti-PD-L1/PD-1 (avelumab or pembrolizumab) Infusions

Likely side effects (≥ 20%) of anti-PD-L1/PD-1 infusions are:

- Fatigue
- Fevers
- Chills
- Flu-like symptoms
- Mild drop in white blood cell counts
- Increased liver enzymes
- Mild to moderate allergic reactions with the presence of hives

Less likely side effects (3-20%) of anti-PD-L1/PD-1 infusions are:

- Infusion related reactions
- Diarrhea
- Joint pains
- Skin redness or rash
- Nausea
- Itching
- Headaches
- Allergic reactions not requiring advanced cardiac life support

Rare but serious side effects (< 3%) of anti-PD-L1/PD-1 infusions are:

- Inflammation of the bowel
- Inflammation of the lung
- Inflammation of the kidney
- Abnormal function or inflammation of the thyroid gland (hypo- or hyper-thyroiditis)
- Inflammation of the liver (hepatitis)

- Inflammation of the pancreas
- Abnormal collections of chronic inflammatory cells forming nodules in multiple organs (sarcoidosis)
- Inflammation of the skin leading to itching, blisters and peeling (exfoliative dermatitis and toxic epidermal necrolysis)
- Inflammation of the muscles leading to muscle weakness (myasthenia gravis)
- Inflammation of the eyes (endophthalmitis)
- High blood sugar levels (diabetes)
- Inflammation of the pituitary gland (hypophysitis)
- Breakdown and release of cancer cells contents (tumor lysis syndrome)
- Decreased function of the adrenal glands (adrenal insufficiency)
- Severe allergic reactions requiring advanced cardiac life support, potentially including low blood pressure or difficulty breathing
- Inflammation of the heart muscle (myocarditis) resulting in death
- Death

T-cell Infusion

Risks of T cell preparation: The T cells are cultured in the laboratory under sterile conditions using human serum and irradiated blood cells to ensure optimal growth. There is a risk of transmitting bacterial infection from the cultured T cells. There is a very rare risk of transmission of hepatitis B, hepatitis C, and HIV.

Risks of virus used to make a T cells: A virus is used to generate the T cells. The virus used is a 'broken' version of a laboratory virus. However, there is a risk that the virus will be able to divide/replicate. There is also a risk of having false positive HIV test in the future, and if you ever have a positive HIV test you should let your health care provider know that you have had TCR-T therapy so additional testing can be performed to determine whether or not you have HIV.

Side effects and risks of T cell infusion:
The frequency of side effects to the ATTAC-MCC T cells are unknown, and one of the goals of the study is to determine how safe the T cells are. Therefore, estimates for frequency are based on other T cell therapies including small studies of other T cell therapies for MCC. There is a chance of hospitalization, prolonged hospitalization, need for intensive care unit care, permanent morbidity (organ damage), brain injury, or death from T cell therapy.
If you have significant side effects associated with T cell infusion, you may need to be treated with medications to reduce the effect of or eliminate the T cells

- Likely (>50%) Drop in blood counts: We anticipate mild temporary drops in blood counts to result after T cell infusion. There can be more significant drops in a certain type of blood count called a lymphocyte count. You may be at increased risk for infections during this period of time.
- Likely (>50%) Fatigue/tiredness

- Likely (5-20% mild; <5% moderate or severe) Cytokine release syndrome: Cytokine release syndrome, or CRS, means immune activation as a result of the T cell therapy. This results in symptoms like the body has an infection. In mild cases, this can be muscle aches, fatigue (tiredness), chills. In more significant cases, fevers, difficulty breathing, low blood pressure can develop. Other symptoms can include rashes and inflammation of organs such as kidney, liver, lungs, heart and eyes. In rare severe cases, medications to support blood pressure and respiratory support (life support) can be required
- Rare (<5%) Allergic or other reaction to T cell infusion: There is a risk of allergic reaction to T cell infusion to the T cells or one of the components used in the T cell culture. This could be manifested by facial swelling, hives or other rashes, difficulty breathing, low blood pressure, fever, or other reaction during the infusion. In rare cases, this could be life-threatening or even fatal.
- Rare (<5%) Neurotoxicity/ICANS: Neurotoxicity (also called ICANS) means inflammation of the brain associated with T cell therapy. This has not been observed in cases of T cell therapy for Merkel cell cancer, but has been observed in other T cell therapies given for other diseases. Symptoms of neurotoxicity can be headaches, confusion, 'fogginess', weakness, numbness, difficulty writing, difficulty with speech, or poor focus. In severe cases, seizure, stroke, and coma can develop. If you develop signs or symptoms of neurotoxicity, you will be treated with medications to reduce your chance of seizure, and may receive other treatments to quiet the T cells. In most reported cases, neurotoxicity improves/resolves. However, there is a chance for permanent brain damage, coma, or death to result
- Rare (<5%) Tumor lysis syndrome: T cell infusion may be associated with tumor lysis syndrome, which is where large numbers of cancer cells die off at once. Tumor lysis syndrome can cause levels of certain electrolytes in the blood to be too high, which can cause problems with the kidneys and heart, and can also result in gout (joint inflammation). If you develop tumor lysis syndrome you may need hospitalization to monitor for abnormal heart rhythms, IV fluids, and/or medicines to help with treatment. Severe cases of tumor lysis syndrome can require dialysis (short or long term), cause long term kidney damage, and/or cause significant heart arrhythmias. Very rarely, tumor lysis syndrome is associated with death.
- Rare (<5%) Uncontrolled T cell proliferation: There is a chance that the infused T cells could grow more rapidly than expected and cause problems related to overgrowth or even become cancerous. If this were to happen, you would be treated with immune suppressing medications to stop the T cell growth.
- In addition, there is a risk that transferred T cells could be activated by the first infusion of the avelumab or pembrolizumab, and that this could lead to any of the above side effects including cytokine release syndrome, neurotoxicity, allergic reactions, tumor lysis syndrome, and tumor inflammation or pain.

We will monitor you carefully for any of the above complications and treat them accordingly.

It is possible that the T cells will last in your body for months or for years after infusion. The long term effects of T cell therapy are unknown.

Non-physical risks

If you join this study, non-physical risks are:

- You might not be able to work.

- Results of genetic tests or other medical records and data might be released by accident. This risk is very low, because we keep personal information private. If these results became known, you could have problems with family members or insurance coverage.

- This study involves growing T cells in a laboratory. Sometimes T cells do not grow well, which could mean that you might not be able to receive the T cell infusion even if you received the interferon gamma. Your regular medical care would not be affected. Additionally, if you develop serious medical problems shortly before the T cell infusion you may not be able to receive the T cells.

Risks Related to Pregnancy

You must be on some method of birth control during this study. You should ask for more information about how to prevent pregnancy if you are having sex and are able to have children.

Because the treatment you are receiving in this study may affect an unborn baby, **you should not become pregnant or father a baby while taking part in this study.**

These treatments may also cause sterility (make you unable to have children in the future).

Are there benefits to taking part in this study?

Anti-PD-L1 may be able to slow or reverse the progression of cancer. Immunotherapy is effective therapy for tumors in some animal models and has been shown in small studies to have some effect on melanoma and Merkel cell carcinoma patients. Since this is unproven therapy, it is not known whether adoptive immunotherapy will be effective for treating Merkel cell cancer.

You may not personally benefit from the study, but the medical knowledge gained from participating in this study may be helpful in the development of T cell therapy studies for Merkel cell carcinoma that may benefit others.

What other choices are there if i do not take part in this study?

There are other approved and investigational therapies available at many medical centers for patients with Merkel cell carcinoma. In a small percentage of patients, conventional therapy may result in durable disease remission.

You do not have to join this study. You are free to say yes or no. Your regular medical care will not change. Each of these choices has risks and benefits. Talk to your doctor about your choices.

Are there circumstances where I may be taken off the study?

Your doctor may take you off the study whether you want to or not, if one of the following happens:

- The study treatment does not work for Merkel cell carcinoma.

- You have a serious side effect that cannot be controlled.
- Your health gets worse.
- You are not able to take the medicine as directed.

Any significant new information that develop during the course of this study about the treatment of Merkel cell carcinoma will be given to you, even if it may affect your willingness to continue to participate in the study.

Can I change my mind about taking part in this study?

Yes, you can change your mind. You have the right to choose whether or not you want to take part in this research study. You may decide to stop taking part in the study once you have started. Leaving the study will not result in any loss of benefits that you already have.

Your decision to participate in this study is voluntary. You may choose to take part or not to take part in this research study.

It is very important to let your doctor (attending physician) know right away if you want to stop taking part in this study. Your doctor will talk with you about your choices.

Protecting your Privacy as an Individual and the Confidentiality of Your Personal Information

At the start of the study, this research is covered by a Certificate of Confidentiality from the U.S. government. This Certificate means that generally we would not have to give out identifying information about you even if we were asked to by a court of law. We would use the Certificate to resist any demands for identifying information. The Certificate may not last the duration of the research. Talk to the study doctor if you have questions about this.

We could not use the Certificate to withhold research information if you give written consent to give it to an insurer, employer, or other person.

This protection has some limits. We would voluntarily provide the information:

- To a member of the federal government who needs it in order to audit or evaluate the research.
- To individuals at the University of Washington, the funding agency and other groups involved in the research, if they need the information to make sure the research is being done correctly.
- To the federal Food and Drug Administration (FDA), if required by the FDA.
- To someone who is accused of a crime, if he or she believes that our research records could be used for defense.
- To authorities, if we learn of child abuse, elder abuse, or if participants might harm themselves or others.

Some people or organizations may need to look at your research records for quality assurance or data analysis. They include:

- Researchers involved with this study.

- Institutional Review Boards (IRB), including the Fred Hutchinson Cancer Center IRB. An IRB is a group that reviews the study to protect your rights as a research participant.
- The study sponsor, Fred Hutchinson Cancer Center, and its agents carrying out the study on its behalf and the University of Washington.
- Office for Human Research Protections, Food and Drug Administration, and other agencies as legally required.
- Affini-T Therapeutics, who is providing partial financial support for this trial.

These people are interested in study data, not your personal information that can identify you such as your name, date of birth, social security number, phone number, or other information. Such directly indentifying information will be removed before the study data are provided to these people, unless otherwise required by law.

We will do our best to keep your personal information confidential. But we cannot guarantee total confidentiality. Your personal information may be given out if required by law. For example, workplace safety rules may require health workers to contact you about lab tests or a court may order information to be disclosed. In addition, there could be unauthorized access to, or security breaches of, the systems used to store your study data. Such cases are rare.

We will not use your personal information in any reports about this study, such as journal articles or presentations at scientific meetings. In some cases, government agencies and medical journals may require us to make information about this study available to researchers outside of Fred Hutch in order to use or publish the results of this study. In that case we will remove your personal information before making the study information available.

A description of this clinical trial will be available on a national government sponsored website, *http://www.clinicaltrials.gov*, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

If you join this study, information about participation would be made part of your permanent medical record. This information would include a copy of this consent form. If an insurance company or employer or anyone else were authorized to see your medical record, they would see a copy of this consent form.

How is my genetic information protected?

A federal law called the Genetic Information Nondiscrimination Act (GINA) helps protect genetic information about people who join research studies.
GINA restricts access to genetic information so that it cannot be used for health insurance coverage decisions. GINA prevent health insurance companies or group health plans from

- Asking for genetic information obtained in research studies, or
- Using genetic information when making decisions regarding your eligibility or premiums

GINA *does not* help or protect against genetic discrimination by companies that sell life, disability or long term care insurance.

Financial interests of the Center and certain Center employees

Fred Hutchinson Cancer Center ("Fred Hutch") has filed a patent on a part of the process for preparing the T cells used in this study, and will receive royalty and other payments. Fred Hutch will pay the scientists at Fred Hutch who were involved in the development of this process a share of the payments received by Fred Hutch. These payments are required by the Fred Hutch Patents and Invention Policy.

No individual Fred Hutch employee that will receive payments as described in this section is or will be, allowed to be directly involved in the conduct or oversight of this study**.** It is possible that some Fred Hutch employees who are entitled to receive these payments will provide expert clinical or scientific advice to the study team if requested.

What will my information and/or tissue samples be used for?

Your information and tissue samples (such as blood and tumor cells) will be used for the purposes of this study.

Your tissue samples might help researchers develop new products. This research could be done by for-profit companies. There is no plan to share with you any revenue generated from products developed using your tissue samples.

During this study, if the researchers learn new information that may be important to your general health or to your disease or condition, they will share that information with you.

In addition, be aware that by agreeing to participate in this study, your information or tissue samples and FH-MCVA2TCR product made from your T cells but not used in the study, could be used for future research studies or sent to other investigators for future research studies without additional consent from you. These future research studies will be reviewed by an oversight group known as an institutional review board (IRB) if required by law. The information that identifies you will first be removed from your information or tissue samples. If you do not want your information or tissue samples to be used for future research studies without your additional consent, you should not participate in this study.

Samples may be sent to Affini-T Therapeutics or other institutions for research testing, analysis, and other immunotherapy research related to this study and for product development related to the FH-MCVA2TCR and similar products. Prior to sending any of these samples, personal information that could easily identify you, such as your name, age, date of birth and medical record number will be removed. These samples will be identified to the recipient by your study identification code.

There will be no cost to you for any of the independent testing and analyses of these samples. Data from this testing and analyses will not be part of your medical record and will not be provided to you.

How much will this study cost me?

You or your insurer will have to pay for the routine costs of treating your cancer in this study. Check with your insurer before you join this study as some insurers will not pay for research. Taking part in

the study may lead to extra costs for you or your insurance company because of the possibility of additional hospitalizations, procedures and blood tests.

The collection and production of the investigational T cells, interferon gamma and research biopsies are paid for by Affini-T Therapeutics and research grant funding.

If you have any questions concerning your costs, financial responsibilities, and or medical insurance coverage for this activity, please contact the Fred Hutch Patient Financial Services Department at (206) 606-6226.

Will I be paid to take part in this study?

You will not be paid for being in this study.

You and/or your caregiver are eligible for reimbursement of up to $3500 for travel expenses (i.e. airfare, mileage, parking, overnight accommodations and food) related to your participation in this study from the time of your consent to 30 days post your immunotherapy infusion.

Please discuss this with the study staff to better understand your reimbursement options and the process for reimbursement.

Fred Hutch has no plans to share potential future royalty or other payments it receives from Affini-T Therapeutics or anyone else with study participants. Affini-T Therapeutics has no plans to share with you any profits or other compensation that come from any of its research or development activities related to this study.

What if I get sick or hurt while taking part in this study?

For a life threatening problem, call 911 right away or seek help immediately. Contact your study doctor when the medical emergency is over or as soon as you can.

For all other medical problems or illness related to this research, immediately contact the IMTX clinic by calling (206) 606-6000. They will treat you or refer you for treatment. You or your health insurance will have to pay for the treatment. There are no funds to pay you for a research-related injury, added medical costs, loss of a job, or other costs to you or your family. State or national law may give you rights to seek payment for some of these expenses. You do not waive any right to seek payment by signing this consent form.

You or your insurer will be billed for treatment of problems or complications that result from your condition or from standard clinical care.

You would not lose any legal right to seek payment for treatment if you sign this form.

Your rights

- You do not have to join this study. You are free to say “yes” or “no”.

- If you get sick or hurt in this study, you do not lose any of your legal rights to seek payment by signing this form.
- During the study, we might learn new information that you need to know. For example, some information may affect your health or well-being. Other information might make you change your mind about being in this study. If we learn these kinds of information, we would tell you.
- If you join this study, you would not have to stay in it. You could stop at any time (even before you start). Your regular medical care would not change. You would have no penalty for stopping, but it would be better not to join the study if you think that you would change your mind later.

For more information

If you have questions or concerns about this study, you may talk to your doctor anytime. Other people you may talk to are listed below.

If you have questions about:	**Call:**
This study (including complaints and requests for information)	206-667-5108 (Joshua Veatch, MD, Principal Investigator
If you get sick or hurt in this study	206-606-6000 (IMTX clinic)
Your rights as a research participant	206-667-5900 or email irodirector@fredhutch.org (Director of Institutional Review Office, Fred Hutchinson Cancer Center)
Your bills and health insurance coverage	206-606-6226 (Fred Hutch Patient Financial Services)

Emergency number (24 hours): 206-598-8902

Will my information and/or tissue samples ever be use for future research?

After we do tests on your tissue in this study, some tissue may be left over. We would like you to donate this leftover tissue for future research. This may include genetic research.

You do not have to donate your tissue for research. You are free to say yes or no. Your regular medical care will not change. If we want to use your tissue for other research or share it with other scientists for research, an ethics review committee (IRB) will review the request. The IRB will decide if we need to ask for your consent to do the research.

Your donated tissue will be stored in a secure location. It will be used for research only. This research may be done by for profit companies. Researchers will not report their results to you or your doctor. The research results will not appear in your health record. They will not affect your care.

Research on your tissue may help develop new products. If these products make money, there is no plan to share the money with you.

If you donate your tissue for research, you can change your mind anytime. Just call Dr. Joshua Veatch at 206-667-5108 and tell us you do not want us to use your tissue. There is no penalty for changing your mind. Your regular medical care will not change. However, if you do change your mind, we cannot return donated tissue. We may be able to destroy tissue we know is yours. But if it is stored or shared anonymously (without any label saying who it belongs to), we cannot destroy it. In this case it would still be used for research, but no one would know it was yours.

Read each question and think about your choice. When you decide on each question, please circle **YES** or **NO**.

Do you agree to donate your tissue to study cancer? (initial one) **YES** **NO**

Do you agree to donate your tissue to study other health problems, such as diabetes, Alzheimer's disease, or heart disease? (initial one) **YES** **NO**

Is it OK if someone contacts you in the future to ask you to donate more tissue for research? (initial one) **YES** **NO**

Signature

If you have read this form (or had it read to you), asked any questions, and agree to participate, please sign:

Participant printed name (18 years or older) Date

Participant signature

If you served as an interpreter or witness during the consent process, sign below to indicate you attest to the accuracy of the presentation to the participant and the apparent understanding of the research by the participant.

Witness or Interpreter / Printed Name, Signature, and Date

Researcher's Statement

I have discussed the research study, including procedures and risks, with the person signing above. A copy of the signed consent form will be given to the participant.

Person obtaining consent printed name Date

Person obtaining consent signature

Protocol: 9845A
Current version date: 11/01/2022
Previous version date: 07/19/2022
Copies to: Copies to: Patient, Medical Records, Research File