MC1376

Phase I Trial to Evaluate the Safety and Efficacy of Intratumoral and Intravenous Injection of Vesicular Stomatitis Virus Expressing Human Interferon Beta, and Tyrosinase Related Protein 1 (VSV-IFNb-TYRP1) in Patients with Metastatic Ocular Melanoma and Previously Treated Patients with Unresectable Stage III/IV Cutaneous Melanoma

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RESEARCH PARTICIPANT CONSENT AND PRIVACY AUTHORIZATION FORM

Study Title: MC1376 - Phase I Trial to Evaluate the Safety and Efficacy of Intratumoral and Intravenous Injection of Vesicular Stomatitis Virus Expressing Human Interferon Beta, and Tyrosinase Related Protein 1 (VSV-IFNb-TYRP1) in Patients with Metastatic Ocular Melanoma and Previously Treated Patients with Unresectable Stage III/IV Cutaneous Melanoma

IRB#: 18-000991

Principal Investigator: Roxana S. Dronca, Jose F. Pulido, Matthew S. Block, and Colleagues

Key Study Information

This section provides a brief summary of the study. This section provides a brief summary of the study. It is important for you to understand why the research is being done and what it will involve before you decide. **Please take the time to read the entire consent form carefully and talk to a member of the research team before making your decision.** You should not sign this form if you have any questions that have not been answered.

It's Your Choice	This is a research study. Being in this research study is your choice; you do not have to participate. If you decide to join, you can still stop at any time. You should only participate if you want to do so. You will not lose any services, benefits or rights you would normally have if you choose not to take part.
Research Purpose	The purpose of this research is to test the safety of a new "drug", a modified virus (VSV-hIFNβ-TYRP1), when given in your vein as well as being injected into your tumor or lesion, and to learn if this virus can produce responses in your tumor. We also want to determine the maximum tolerated dose of VSV-hIFNβ-TYRP1 to use in future studies (Phase I research study). You have been asked to take to take part in this research because you have been diagnosed with metastatic ocular or unresectable Stage III or metastatic Stage IV melanoma.

What's Involved	**For Group A (ocular or uveal melanoma patients) study participation involves:** • Screening visits including blood tests for pregnancy, HIV, hepatitis, and tuberculosis • A stay in the hospital to receive the study drug – you will receive two doses of study drug one directly into your tumor(s) and the second by intravenous (IV) infusion • You will be asked to stay within 30 miles of the hospital for up to 5 days after the IV infusion • Additional study visits on Days 4, 8, 15, 28, and 42 to monitor response and safety • Blood draws for safety and research and cheek swabs and urine collection for research and safety • Biopsy on Day 1 and optional on Day 8 • After the one cycle we will follow your health until you have disease progression, or you switch to another treatment for up to 5 years after you started this study **For Group B (cutaneous or lymphatic melanoma patients) study participation involves:** • Screening visits including blood tests for pregnancy, HIV, hepatitis, and tuberculosis • A stay in the hospital to receive the study drug for the first visit only – you will receive two doses of study drug one directly into your tumor(s) and the second by intravenous (IV) infusion • You will be asked to stay within 30 miles of the hospital for up to 5 days after the IV infusion • Additional visits on Days 4, 8, and 15 of Cycle 1 to monitor response and safety • Blood draws for safety and research and cheek swabs and urine collection for research and safety • Biopsies on Day 1, Day 3, and Day 8 of Cycle 1 only • Additional cycles of treatment with study drug by intratumoral (IT) injection only – these visits will be outpatient • Cycle 2 visits on Days 1, 2, and 8, with blood draws for safety and research and cheek swabs and urine collection for research and safety • Cycles 3, 4, and onward, visits on Day 1 and Day 2 with blood draws for safety and research

	• A visit when you stop treatment • After you have finished these steps, we will follow your health for up to 5 years after you start this study
Key Information	The biggest risks to consider are the risks of the injection of the virus and the risks of the biopsies. The virus drug may cause a reaction that could cause range from low grade fever, to severe low blood pressure, damage to the liver and possibly even death. Though the risks from biopsies are low, there is still a risk of infection, bleeding, and possibly even death. In addition, there is no guarantee that the drug will have any beneficial effect on your cancer. This study involves more time at the beginning, and about the same amount of time as any other treatment for cancer after the first cycle. The study drug will be provided for free and your stay in the hospital on the first cycle to receive the study drug will be covered by the study. The biopsies are paid for by the study. If you have ocular (uveal) melanoma, there are not a lot of other options for treatment. If you have cutaneous melanoma, there may be other kinds of treatment – be sure to discuss your options with your doctor.
Learn More	If you are interested in learning more about this study, read the rest of this form carefully. The information in this form will help you decide if you want to participate in this research or not. A member of our research team will talk with you about taking part in this study before you sign this form. If you have questions at any time, please ask us.

Making Your Decision

Taking part in research is your decision. Take your time to decide. Feel free to discuss the study with your family, friends, and healthcare provider before you make your decision. Taking part in this study is completely voluntary and you do not have to participate.

If you decide to take part in this research study, you will sign this consent form to show that you want to take part. We will give you either a printed or electronic copy of this form to keep. A copy of this form will be put in your medical record.

For purposes of this form, Mayo Clinic refers to Mayo Clinic in Arizona, Florida and Rochester, Minnesota; Mayo Clinic Health System; and all owned and affiliated clinics, hospitals, and entities.

Contact Information

If you have questions about …	You can contact …
▪ Study tests and procedures ▪ Materials you receive ▪ Research-related appointments ▪ Research-related concern or complaint ▪ Research-related injuries or emergencies ▪ Withdrawing from the research study	**Principal Investigators:** Dr. Roxana Dronca (FL) Dr. Jose Pulido (MN) Dr. Matthew Block (MN) **Phone:** FL: (904) 953-2000 MN: (507) 284-2511 **Institution Name and Address:** Mayo Clinic 4500 San Pablo Road Jacksonville, FL 32224 Mayo Clinic 200 First St SW Rochester MN 55905
▪ Rights of a research participant	**Mayo Clinic Institutional Review Board (IRB)** **Phone:** (507) 266-4000 **Toll-Free:** (866) 273-4681
▪ Rights of a research participant ▪ Any research-related concern or complaint ▪ Use of your Protected Health Information ▪ Stopping your authorization to use your Protected Health Information ▪ Withdrawing from the research study	**Research Subject Advocate (RSA)** **(The RSA is independent of the Study Team)** **Phone:** (507) 266-9372 **Toll-Free:** (866) 273-4681 **E-mail:** researchsubjectadvocate@mayo.edu
▪ Billing or insurance related to this research study	**Patient Account Services** **Toll-Free:** (844) 217-9591

Other Information:
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.

A description of this research study will be available on http://clinicaltrials.mayo.edu. This website will not include information that can identify you. You can search this website at any time.

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

You have been asked to participate in this study because you have been diagnosed with metastatic ocular or unresectable Stage III or metastatic Stage IV melanoma.

Why is this research study being done?

The purpose of this study is to test the safety of a new "drug", a modified virus (VSV-hIFNβ-TYRP1), when given in your vein as well as being injected into your tumor or lesion, and to learn if this virus can produce responses in your tumor. We also want to determine the maximum tolerated dose of VSV-hIFNβ-TYRP1 to use in future studies (Phase I research study).

In this study (Phase I research study) we want to find out more about the side effects of VSV-hIFNβ-TYRP1and what doses of this drug are safe for people. Everyone in this study will receive VSV-hIFNβ-TYRP1, which is still experimental and isn't approved by the U.S. Food and Drug Administration (FDA). However, the FDA has allowed the use of this drug in this research study. We don't know all the ways that this drug may affect people. We hope the information from this study will help us develop a better treatment for unresectable Stage III or metastatic Stage IV melanoma.

The overall goal is to find new treatments that may be more effective in treating unresectable or metastatic melanoma, and to use this virus as an anti-cancer therapy.

The "drug" used in this trial is a modified version of the vesicular stomatitis virus (also called VSV). This virus can cause infection, and when it does it typically infects pigs, cattle, or horses. Most humans in the United States have not been exposed to the virus, although human infection is common in Central America. In the United States, adults that are infected typically work with

farm animals or are in the veterinary profession. Therefore, the vast majority of humans do not have immunity to the virus. The life span of VSV in a mammal's blood stream is short. The black fly and the sand fly can spread the virus, and mammal to mammal transmission occurs rarely in pigs due to direct contact with fluid filled sores containing the virus. However, human to human transmission, to our knowledge, does not occur. Hence the risk of spread of the virus from patients to their care providers or family is highly unlikely. Humans infected with VSV usually do not have any symptoms, or have a mild, flu-like illness that resolves without treatment within a few days.

The VSV used in this study and the one that will be administered to you has been altered by having two extra genes (pieces of DNA) added. The first gene is for human interferon β (hIFNβ). Interferon is a natural anti-viral protein, intended to protect your normal healthy cells from becoming infected with the virus. VSV is very sensitive to the effect of interferon. The anti-viral action of hIFNβ is possible because tumor cells have lost the capacity to either produce or respond to interferon. This permits VSV to multiply rapidly to high levels, and eventually leads to cancer cell death. Normal cells are safe because the virus will not multiply in them.

The second gene is for a protein TYRP1 (tyrosinase related protein 1) which is expressed mainly in melanocytes (specialized skin cell that produces the protective skin-darkening pigment melanin) and melanoma cells. By expressing this protein in conjunction with a virus we hope to elicit a strong immune response to the melanoma.

The VSV with these two extra pieces is referred to as VSV-hIFNβ-TRYP1 and was developed by Drs. Richard Vile and Jose Pulido.

VSV-IFN-TYRP1 is an oncolytic virus. An oncolytic virus preferentially infects and kills cancer cells. As the infected cancer cells are destroyed by oncolysis, they release new infectious virus particles that help destroy the remaining tumor. VSV-IFN-TYRP1 kills melanoma cancer cells and not liver cells, so it is safe to use for melanoma cancer that has spread to the liver. In patients with metastatic ocular melanoma VSV-IFN-TYRP1 will be injected into metastatic liver lesions because these patients do not commonly have injectable subcutaneous or lymph node disease. Preclinical studies in rodents, research beagles, pet dogs with spontaneous cancer and nonhuman primates have shown the safety of intratumoral, intrahepatic and intravenous administration of similar genetically altered VSV viruses (VSV-IFNβ and VSV-IFNβ-NIS).

Information you should know

Who is Funding the Study?

Awards from generous Mayo Clinic benefactors are funding the study. They will pay the institution to cover costs related to running the study.

Information Regarding Conflict of Interest:

This research has been reviewed by the Mayo Clinic Conflict of Interest Review Board and is being conducted in compliance with Mayo Clinic Conflict of Interest policies.

Both the Mayo Clinic Conflict of Interest Review Board and the Institutional Review Board have reviewed the Financial Conflict of Interest for one or more of the investigators and/or Mayo Clinic related to this research and they have determined that this Financial Conflict of Interest poses no additional significant risk to the welfare of participants in this research project or to the integrity of the research.

Additional information is available to any interested study participant regarding the details of this Financial Conflict of Interest and how it is being managed by contacting the study coordinator or the Office of Conflict of Interest Review at (507) 284-0075.

One or more of the investigators associated with this project and Mayo Clinic have a Financial Conflict of Interest in technology used in the research and that the investigator(s) and Mayo Clinic may stand to gain financially from the successful outcome of the research.

How long will you be in this research study?

You will be in the study for up to 5 years after you receive the VSV-hIFNβ-TYRP1 or until your disease gets worse.

The plan is to have between 24 and 72 people take part in this study at Mayo Clinic in Jacksonville, Florida, and Rochester, Minnesota.

What will happen to you while you are in this research study?

Before you start any research activities, you will be asked to sign this consent form.

If you agree to take part in this study, routine tests for your cancer will be done. Additional research tests (see below) will also be done both before and after the drug is given.

These tests will be done for safety and to understand where the VSV-hIFNβ-TYRP1 virus is going in your body. You will not be billed for the research tests. Details of what will occur if you participate are listed below.

Screening
Prior to starting treatment on this trial, you will have specific procedures and tests to make sure you are eligible to be in this study. They include:

- Medical history (including any medications that you are taking now or have taken in the past)
- Review of your current medical condition(s)
- Physical examination (including height and weight)
- Vital signs (blood pressure, heart rate, temperature)
- Routine imaging scans by CT, MRI, PET/CT, ultrasound, or other imaging methods for tumor measurement/evaluation
- Routine blood tests
- Pregnancy test if you are able to become pregnant

These tests are part of regular care for your cancer. If some of these tests have been done recently, you may not need to repeat them.

In addition, blood tests for HIV, hepatitis B and C, and tuberculosis tests will need to be done for participation in this research study. These are research tests and you will not have to pay for them.

If any of these test results is positive you will need to have a second test done to make sure the results are the same. If you are infected with HIV, hepatitis, or tuberculosis, the researcher will tell you how to find medical help and counseling as needed, and you will not be able to take part in the study. Your health insurer or you will have to pay for the cost of the repeat test, any follow-up medical care, or counseling. If any of the second test results are positive, it is state law that they be reported to the State Department of Health and the U. S. Centers for Disease Control and Prevention (CDC). The test results will also be put in your medical record.

If you are eligible and choose to take part in the study, you will have the following:

Day 1 of Cycle 1Virus administration
Just prior to virus administration you will have the following tests:

- Routine blood tests
- Pregnancy test if you are able to become pregnant and your most recent pregnancy test was more than 7 days ago
- Review of your current medical condition(s)
- Review of current medications, including over-the-counter (OTC) medications
- Physical examination (including weight)
- Vital signs (blood pressure, heart rate, temperature)
- Mandatory research blood, buccal swabs (swabs done on the inside of your mouth (cheek)), and urine specimens collected before the drug is given
- Tissue specimens will be collected at the same time as the tumor injections

Drug administration by tumor injection(s) and intravenous (into your vein) infusion
You will be admitted to Mayo Clinic Hospital in Jacksonville, FL, or Rochester, MN, on the day of virus administration.

VSV-IFN-ß- TYRP1 will first be injected into your tumor.

If you have metastatic melanoma other than ocular melanoma, VSV-IFN-ß- TYRP1 will only be injected into safely accessible cutaneous, subcutaneous, and lymph node tumors with or without ultrasound and/or computed tomography (CT) guidance as needed. VSV-IFN-ß- TYRP1 cannot be administered into internal organs in the chest or abdomen where the cancer has metastasized.

If you have metastatic ocular melanoma that has spread to your liver, VSV-IFN-ß- TYRP1 will be injected in liver lesions considered to be most easily accessible and safest for injection.

The tumor injections will be performed by an interventional radiologist with expertise in this procedure. If you have tumors on your skin or close to the surface of the skin, another trained health professional may administer the injections.

You will be given sedation and monitored closely during the procedure. Additionally, local anesthetic will be used. The injection will occur slowly. If the tumor is large it may require multiple injections which are apart from one another. Depending on the size and location of the tumor, it is estimated that the procedure will take anywhere from 30 to 60 minutes to complete.

You will be observed in the recovery area for up to two hours afterwards.

You will then be hospitalized in a private room as an inpatient in Florida, or in the Clinical Research and Trials Unit (CRTU) in Rochester to receive the IV virus. You will stay in the hospital for at least 24 hours. You will need to stay in the hospital until any effects from the virus, such as fever or nausea and vomiting, are under control.

Mandatory research blood samples will be drawn before the virus is given, and at the end of the infusion, then about 30 minutes, 60 minutes, 2 hours, 4 hours, and 24 hours after the end of the virus infusion.

Patient observation following injection (Cycle 1, Days 1-2)
After injection of the study virus at Mayo Clinic Hospital, you will be monitored for at least 24 hours in the hospital.

If there are signs of VSV infection, you will be placed in an isolation room. Supportive care for the viral infection will be given.

After 24 hours (on Day 2) you may be discharged if there have been no side effects from the virus administration. If you have had side effects from the virus, you may need to stay in the hospital for a longer time. After you are discharged from the hospital, you will be encouraged to stay with a family or other caregiver less than 30 miles from the Mayo Clinic campus for the first 5 days. Your caregiver will be instructed on signs of fever. If needed, the caregiver will be instructed to take your temperature and pulse, and if there is any concern to report these findings to the clinic. A board-certified Oncologist or Ophthalmologist is available at Mayo Clinic 24-hours a day, 7 days a week, and may be contacted by calling (507) 284-2511 in Rochester or (904) 953-2000 in Florida

Mandatory research blood samples will be drawn at the end of the infusion then about 30 minutes, 60 minutes, 2 hours, 4 hours, and 24 hours (on Day 2) after the virus injection.

Mandatory research mouth rinse, cheek swabs, and urine specimens will be collected on Day 2.

If you experience any side effects within the first 24 hours, you will remain hospitalized for continued observation until your symptoms resolve.

Cycle 1, Days 3, 4, and 5
Then you will need to come back to the clinic every day for the next 3 days (Days 3-5) for a quick check. These checks are very important for your safety. You may have any of the following once or more than once depending on how you are doing:

- Routine blood tests to see how your body is handling the virus
- Review of your current medical condition(s)

- Physical examination (including weight)
- Vital signs (blood pressure, heart rate, temperature, etc.)
- Mandatory research blood samples will be collected on Day 3
- Mandatory research mouth rinse, cheek swabs, and urine specimens will be collected on Day 3
- Tissue specimens collected (Day 3) if feasible (only for cutaneous melanoma patients)

You must tell the study team of any new symptoms each time you come for a visit.

Cycle 1, Days 8 and 15
You will have the following:

- Routine blood tests
- Review of your current medical condition(s)
- Physical examination (including weight)
- Vital signs (blood pressure, heart rate, temperature)
- Mandatory research blood samples will be collected on Days 8, and 15
- Mandatory mouth rinse, cheek swabs, and urine specimens will be collected on Days 8 and 15
- Optional tissue specimens collected (Day 8) if feasible (all patients)

If you have ocular melanoma, you will only receive one cycle of treatment including both intratumoral (IT) and intravenous (IV) VSV-hIFNb-TYRP1.

If you have any other type of melanoma (cutaneous/subcutaneous or nodal disease) you will have both IV and IT VSV-hIFNb-TYRP1 on Cycle 1, Day 1. Then you will continue to receive the study drug injected into your tumors (IT) every 3 weeks until your disease gets worse, or you have intolerable side effects. This three-week schedule is called a "cycle."

Cycle 1, Day 28 (Ocular melanoma patients only)

- Routine blood tests
- Review of your current medical condition(s)
- Physical examination (including weight)
- Vital signs (blood pressure, heart rate, temperature)
- Mandatory research blood samples
- Mandatory mouth rinse, cheek swabs, and urine specimens will be collected

Cycle 1, Day 42 (Ocular melanoma patients only)
This is the end of the study for ocular melanoma patients.

You will have routine scans with CT, ultrasound, MRI or other methods, to see how your cancer is doing. You will have research samples taken. You will meet with the study team to decide on next steps.

Cycle 2, Day 1 Prior to virus administration (Cutaneous melanoma patients only)
Just prior to virus administration you will have the following tests:

- Routine blood tests
- Pregnancy test if you are able to become pregnant
- Review of your current medical condition(s)
- Review of current medications, including over the counter (OTC) medications
- Physical examination (including weight)
- Vital signs (blood pressure, heart rate, temperature)
- Mandatory research blood, mouth rinse, buccal swabs (swabs done on the inside of your mouth (cheek)), and urine specimens collected before the drug is given

Cycle 2, Day 1 Drug administration, tumor injection(s) only
If you have metastatic melanoma other than ocular melanoma, VSV-IFN-ß- TYRP1 will only be injected into easily accessible cutaneous, subcutaneous, or lymph node tumors. These injections may be given with or without ultrasound (US) and/or computed tomography (CT) guidance. VSV-IFN-ß- TYRP1 cannot be administered into internal organs in the chest or abdomen where the cancer has metastasized.

The tumor injections will be performed by an interventional radiologist with expertise in this procedure. If you have tumors on your skin or close to the surface of the skin, another trained health professional may administer the injections.

If needed, you will be given minimal sedation during the procedure. Additionally, local anesthetic will be used. The tumor injection will occur slowly. If the tumor is large it may require multiple injections which are apart from one another. Depending on the size and location of the tumor, it is estimated that the procedure will take anywhere from 30 to 60 minutes to complete.

Cycle 2, Day 2
You will have blood drawn for routine testing to make sure you are not having bleeding or other issues from the virus.

Mandatory research blood samples will be drawn on Day 2, about 24 hours after the virus injection.

Cycle 2, Day 8
You will have blood drawn for routine testing to make sure you are not having bleeding or other issues from the virus.

Mandatory research mouth rinse, cheek swabs, and urine specimens will be collected on Day 8.

If you experience any side effects within the first 24 hours, you may be hospitalized for continued observation.

End of Cycle 2
At the end of Cycle 2, you will have routine scans with CT, ultrasound, MRI or other methods, to see how your cancer is doing.

V**irus administration visit, Day1 of each subsequent 21-day cycle until End of Treatment**

Cycle 3 and beyond, Day 1 just prior to virus administration:

- Routine blood tests
- Pregnancy test if you are able to become pregnant
- Review of your current medical condition(s)
- Review of current medications, including over the counter (OTC) medications
- Physical examination (including weight)
- Vital signs (blood pressure, heart rate, temperature)

Drug administration, tumor injection(s) only
If you have metastatic melanoma other than ocular melanoma, VSV-IFN-ß- TYRP1 will only be injected into easily accessible cutaneous, subcutaneous, or lymph node tumors. The tumor injections can be done with or without ultrasound and/or computed tomography (CT) guidance. VSV-IFN-ß- TYRP1 cannot be administered into internal organs in the chest or abdomen where the cancer has metastasized.

The tumor injections will be performed by an interventional radiologist with expertise in this procedure. If you have tumors on your skin or close to the surface of the skin, another trained health professional may administer the injections.

You will be given minimal sedation during the procedure. Additionally, local anesthetic will be used. The injection will occur slowly. If the tumor is large it may require multiple injections which are apart from one another. Depending on the size and location of the tumor, it is estimated that the procedure will take anywhere from 30 to 60 minutes to complete.

Cycle 3 and up, Day 2 of each subsequent 21-day cycle until End of Treatment
You will be asked to return to Mayo Clinic the morning following the injection into your tumor for blood tests to assure you are not having bleeding or other issues.

At the end of every even numbered cycle (Cycle, 4, Cycle, 6, Cycle 8, etc.) you will have:

- Routine imaging scans for tumor measurement/evaluation

End of Treatment
For patients with ocular melanoma, study drug treatment will stop after Cycle 1.

For patients with cutaneous/subcutaneous or nodal melanoma, study drug treatment will continue until:

- You have no evidence of a tumor
- Your tumor increases in size
- You are unable to tolerate the study drug
- You choose not to continue study drug treatment

At the end of treatment, you will have:

- Routine blood tests
- Pregnancy test if you are able to become pregnant
- Review of your current medical condition(s)
- Physical examination (including weight)
- Vital signs (blood pressure, heart rate, temperature)
- Optional research blood

At this time, you will begin the observation period.

Observation period (every 3-4 months up to 3 years)
You will be monitored about every 3-4 months for up to 3 years to evaluate you for possible long-term side-effects of the virus, as well as the possible improvement of your cancer from the therapy. If your disease has progressed and you are being monitored for long term side-effects, these tests may be done by your local doctor.

- Routine blood tests
- Review of your current medical condition(s)
- Physical examination (including weight)
- Vital signs (blood pressure, heart rate, temperature)
- Routine imaging scans for tumor measurement/evaluation

If you participate in this study you cannot join any other study involving a drugs or gene therapy, even if it is for symptom control and not to treat your disease. (NOTE: If your disease progresses, you will work with your doctor to determine your next steps).

Optional tumor biopsy
You are being asked to provide a tumor tissue sample for research testing which will require you to have a biopsy after you receive treatment. The optional biopsy is on Cycle 1 Day 8 for all patients. You must provide your permission to undergo a tumor biopsy procedure to obtain this sample. You can say yes or no to this procedure. We will only do this biopsy if the doctors think it is safe for you.

This **optional** tumor tissue biopsy is not required, and your study participation will not be affected whether or not you agree to the biopsy. The cost for the optional biopsy and resulting testing will be paid for by the study.

Consent for Optional Tumor Biopsy
I agree to have an optional tumor biopsy on Cycle 1, Day 8.

☐ Yes ☐ No Please initial here: _____Date: _____

Special Considerations
Because we need to understand how the virus affects the cancer and your body, we are requesting two additional items as a condition of participation in this Phase I study. **Please note: Responding "No" to either question will prevent you from taking part in this study.**

We ask that you be willing to have life supportive care measures (such as dialysis) taken if you have a reaction to the virus within 30 days after administration.

1. I understand and agree to this request.

   ☐ Yes ☐ No Please initial here: _____Date: _____

In addition, should you pass away during the 12 months following virus administration; we ask that you be willing to have an autopsy.

2. I understand and agree to this request.

   ☐ Yes ☐ No Please initial here: _____Date: _____

You will be informed of any clinically relevant research results. Any results reported to you individually, will also be placed in your medical record. Study results will be reported on ClinicalTrials.gov after the study is completed.

What are the possible risks or discomforts from being in this research study?

Risks from the Study Virus Itself
Vesicular Stomatitis Virus Genetically Engineered to Express Human Interferon beta (hIFNβ) and Tyrosinase Related Protein 1 (VSV-hIFNβ-TYRP1) is a new viral agent which is currently being used for the first time in humans through this trial. The risk of death from receiving an investigational drug is 0.49%, based on a study that reviewed 11,935 participants in 460 different Phase I trials. The risk of dying from cancer despite participation in such trials is much higher (>90%). As such, the risk-to-benefit ratio favors participation in studies for patients with advanced cancer.

Potential Risks
Risks of the giving the virus to humans are unknown because it has not been done before. However, some data regarding potential adverse effects are available.

Neurological side effects are serious harmful events seen in pre-clinical studies in rats. The dose used in the study you participate in will be much lower than the lowest safe dose used in the rat studies to ensure your safety. A comprehensive neurological examination is part of the baseline and ongoing assessments to also ensure your safety. The chance of a neurological side effect is thought to be <10%. If you experience such an event, it is expected to be mild-to-moderate in severity and probably will not be permanent.

Cytokine release syndrome (CRS), which consist of fever, chills, muscle aches and pains, loss of appetite, low blood pressure and higher than normal heartbeat rate are typical reactions with this type of treatment. These side effects are generally easily managed, and the staff treating you has extensive experience managing these side effects while treating patients during their routine clinical care. (The treatment of CRS is similar to the treatment of shock.) The risk of CRS is unknown because it was not seen in pre-clinical studies, but the chances are felt to be low. If you experience CRS it is expected to be mild to moderate in severity and probably will not be permanent.

You may experience mouth sores (stomatitis) from VSV-hIFNβ-TYRP1. (The VSV virus is known to cause mouth sores in animals.) The mouth sores can be treated with mouth rinses and acetaminophen (Tylenol®) for pain.

Based on experience using high-doses of a similar virus, you may expect the following side-effects: fever, chills, headache, nausea, fatigue, drop in blood pressure, and a drop in the white blood cells (also known as leukopenia, lymphopenia, and neutropenia), which can increase your risk for other infections. A reduction of the clotting blood cells called platelets may also occur, which could increase your chance of bleeding. A reduction in red blood cells, anemia, may happen, which may make you feel tired or weak.

Since the virus is derived from the VSV strain, it is considered unlikely that serious complications will occur after administration of the virus, but they cannot be excluded.

A similar virus strain, Vesicular Stomatitis Virus Genetically Engineered to Express Human Interferon beta (hIFNβ) (VSV-hIFNβ), is currently being tested as an injection directly into tumors in humans with cancer involving the liver. After 11 patients were treated without major side effects, the 12th patient experienced rapid virus replication, liver dysfunction, kidney failure, and died. It is not known what role the virus played in the liver effects because at the start of the trial the patient's liver was filled with tumor and very little normal liver remained. This death may have also been due to tumor lysis syndrome and high levels of IFNβ in the blood.

Tumor lysis syndrome (TLS), which can cause salt imbalances in the blood and even kidney failure and is caused by the dead tumor cells breaking apart and releasing their contents into the body. TLS can happen if the virus kills cancer cells too rapidly.

IFNβ is a signaling protein that is made and released by your body when tumor cells are present. This release triggers a defense to cancer cells and causes nearby cells to increase their anti-tumor defenses. Additional precautions to watch for and treat liver dysfunction, tumor lysis syndrome, or any other life-threatening side effect, if it occurs have been built into the trial you are considering. However, liver dysfunction, tumor lysis syndrome, and other side effects due to the virus's activity on cancer cells remain possible risks of this trial.

Other potential side effects include: bleeding, allergic reaction, hepatic failure, kidney injury, blood clots throughout the body, bleeding tendencies, infusion related reactions, injection site reactions (pain, tenderness, redness, a hardened lump), headache, altered mental states, sleepiness, nausea, vomiting, oral ulcers or blisters, fatigue, and joint pain.

Other adverse effects at this time are unknown and a comprehensive safety monitoring plan is in place to ensure that any adverse events that may be a threat to your safety are quickly dealt with. Other potential risks include serious side effects that could result in hospitalizations or death.

Rarely, patients can develop life-threatening toxicity caused by the interferon beta in the virus itself. Symptoms of this toxicity include not recovering from the early reaction to the VSV

infusion, feeling very tired with low blood pressure or low oxygen, feeling confused and signs in your lab tests that your liver is not working properly and your blood platelets are dropping. This toxicity can be fatal.

The interferon beta toxicity can also be associated with another type of toxicity called tumor lysis syndrome, where your tumor cells burst and cause problems throughout the body. This event in itself can also be life-threatening, but if diagnosed early can be treated with IV fluids and drugs.

For this reason, you will have daily blood tests and your doctor may keep you in hospital for longer than expected. If you show signs of the serious interferon beta toxicity, you will be given a drug to block the toxicity, called ruxolitinib.

The most common risks of ruxolitinib include low platelet count; dizziness; low red blood cell counts (anemia); headache; and bruising.

Risks of Transmission of Virus to Others
The risk of transmission of the virus to individuals other than the patient is unknown but is felt to be very low (less than 0.1%).

Risks of Biopsy
The optional needle biopsy of a tumor may cause local pain, infection at the biopsy site, or prolonged bleeding from the site, but these are all uncommon. Most biopsies will be done using ultrasound guidance. If a biopsy is performed using CT guidance, you will be exposed to radiation. The amount of radiation you will be exposed to has a low risk of harmful effects.

Risks of Blood Draw
The risks of drawing blood include pain, bruising, lightheadedness, and/or fainting, or rarely, infection at the site of the needle stick.

Birth Control and Pregnancy
The effect of VSV-hIFNβ-TYRP1 on a fetus (developing baby still in the womb), or on a breastfeeding infant is unknown and may be harmful. You should not become pregnant or father a child while on this study. Because of these risks, patients cannot take part in this study if they are pregnant or breastfeeding.

If you are able to become pregnant, you must have a negative pregnancy test in order to participate in this study. For the pregnancy test, you will give a blood sample taken from a vein in your arm with a needle before the study and starting the study drug. You will be told the results of the pregnancy test. If the pregnancy test is positive, you will not be able to take part in the study.

Your study doctor will discuss prohibited and acceptable birth control methods for use during your participation in this study. You should notify your study doctor if birth control methods other than those specified below are started during the course of this study or if you start any prescription drug or other medication (including herbal and over-the-counter medications) not prescribed by the study doctor.

All patients: If you are sexually active and able to become pregnant or father a child, you and your partner must agree to use two of the birth control methods listed in the table below. **One of the two forms of birth control must be highly effective,** and the second method may also be highly effective or selected from the list of other contraceptive methods. See the table on the next page for options.

<table>
<tr><td rowspan="6">Highly Effective Methods of Contraception</td><td colspan="2">Progestogen only hormonal contraception associated with inhibition of ovulation (oral, injectable or implantable)</td></tr>
<tr><td colspan="2">Hormonal methods of contraception including
• combined oral contraceptive pills (that is, those that contain both estrogen and progestogen)
• vaginal ring
• injectables, implants and intrauterine devices (IUDs)
Sometimes, hormonal levels of birth control can be affected by the study drug. Your doctor will tell you whether hormonal forms of birth control are allowed for this study.</td></tr>
<tr><td colspan="2">Non-hormonal IUDs</td></tr>
<tr><td colspan="2">Bilateral tubal occlusion</td></tr>
<tr><td colspan="2">Vasectomized partner</td></tr>
<tr><td colspan="2">Complete abstinence</td></tr>
<tr><td rowspan="6">Less than Highly Effective Methods of Contraception</td><td colspan="2">Diaphragm with spermicide</td></tr>
<tr><td colspan="2">Cervical cap with spermicide</td></tr>
<tr><td colspan="2">Vaginal sponge with spermicide</td></tr>
<tr><td colspan="2">Progestin only pills</td></tr>
<tr><td>Male condoms with or without spermicide*</td><td rowspan="2">*A male and a female condom must not be used together</td></tr>
<tr><td>Female Condoms*</td></tr>
<tr><td rowspan="4">Unacceptable Methods for Contraception</td><td colspan="2">Periodic abstinence (calendar, symptothermal, post-ovulation methods)</td></tr>
<tr><td colspan="2">Withdrawal (coitus interruptus)</td></tr>
<tr><td colspan="2">Spermicide only</td></tr>
<tr><td colspan="2">Lactation amenorrhea method (LAM)</td></tr>
</table>

If you choose abstinence as a method of contraception, your doctor will discuss other methods of contraception with you in the case you choose not to continue abstinence. Pregnancy testing remains mandatory even if you do choose abstinence as your method of contraception.

You must use birth control for the entire study and for at least 120 days after your last dose of study drug.

A pregnancy test can be wrong. If you or your partner become pregnant or think you or your partner may be pregnant during the study, contact the study doctor's office immediately. The study doctor must follow up and document the course and the outcome of all pregnancies, even if you withdraw from the study or if the study has finished.

You must not breast-feed an infant during the study. The study drug may cause unforeseeable risk to a breastfed baby.

You must NOT be a sperm/ovum or blood donor while you are being treated with VSV-hIFNβ-TYRP1 and for up to one year after your last dose.

Risk Summary
Many side effects go away shortly after the VSV-hIFNβ-TYRP1 is stopped, but in some cases side effects can be serious, long lasting, or may never go away. There may be other risks that are unknown at this time. There may be a risk of death. Side effects may range from mild to life-threatening. Other drugs may be given to make side effects less serious and less uncomfortable. Talk to the researcher and/or your healthcare provider about side effects and ask any other questions.

Should death occur, irrespective of the cause, permission for an autopsy will be requested of your family. This is important so that the researchers can further document the safety and effectiveness of this treatment. The researchers encourage you to talk to your family regarding this issue.

This study involves testing your DNA, which is the genetic information you inherited from your parents (also known as genetic testing). This testing may include whole genome sequencing (mapping your entire genetic code). You will not be notified of the genetic test results and they will not be put into your medical record.

A Federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information when making a decision to hire, promote, or fire you or when setting the terms of your employment.

All health insurance companies and group health plans must follow this law.

Be aware that this new Federal law doesn't protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

Are there reasons you might leave this research study early?

You may decide to stop at any time. You should tell the researchers if you decide to stop and you will be advised whether any additional tests may need to be done for your safety.

In addition, the Principal Investigator or Mayo Clinic may stop you from taking part in this study at any time:

- If it is in your best interest
- If you don't follow the study procedures
- If the study is stopped

If you leave this research study early, or are withdrawn from the study, no more information about you will be collected; however, information already collected about you in the study may continue to be used.

We will tell you about any new information that may affect your willingness to stay in the research study.

What if you are injured from your participation in this research study?

Where to get help:

If you think you have suffered a research-related injury, you should promptly notify the Principal Investigator listed in the Contact Information at the beginning of this form. Mayo Clinic will offer care for research-related injuries, including first aid, emergency treatment and follow-up care as needed.

Who will pay for the treatment of research related injuries?

Care for such research-related injuries will be billed in the ordinary manner, to you or your insurance. You will be responsible for all treatment costs not covered by your insurance, including deductibles, co-payments and coinsurance.

What are the possible benefits from being in this research study?

This study may not make your health better. However, the information learned from the results of this study may help benefit others.

What alternative do you have if you choose not to participate in this research study?

You do not have to be in this study to receive treatment for your condition. Your other choices may include:

- Other standard chemotherapy or targeted medications such as pembrolizumab
- Enrollment in a study using different investigational drugs
- No treatment

You should talk to the researcher and your regular physician about each of your choices before you decide if you will take part in this study.

What tests or procedures will you need to pay for if you take part in this research study?

You will not need to pay for any tests and procedures which are done just for this research study. These tests and procedures are:

- HIV, hepatitis, and TB testing prior to taking part in this study
- Research blood draws, urine collection, and mouth swabs to check levels of VSV-hIFNβ-TYRP1
- Testing of research samples
- Pregnancy testing while you are receiving treatment on this study (only for persons able to become pregnant)
- The study drug, VSV-hIFNβ-TYRP1, and administration of the virus
- Biopsies done just for this study - prior to treatment (all patients); Cycle 1, Day 3 (for cutaneous patients only); and Cycle 1, Day 8 (optional for all patients)
- Your stay at the hospital to receive the VSV-hIFNβ-TYRP1 (Cycle 1 only)

However, you and/or your health plan will need to pay for all other tests and procedures that you would normally have as part of your regular medical care including routine blood and urine testing, routine monitoring of your cancer by imaging, etc. NOTE: For ocular patients this includes clinical laboratory studies, imaging, and visits on Days 4, 5, 8, 15, 28 and 42. For cutaneous melanoma patients this timeframe includes Cycle 1: Days 4, 5. 8, 15; Cycle 2: Days 2 and 8; and Cycles 3 and onward Day 2.

You may also be billed for other expenses such as medication prescribed at the time of discharge after receiving the virus.

If you have billing or insurance questions call Patient Account Services at the telephone number provided in the Contact Information section of this form.

Will you be paid for taking part in this research study?

You won't be paid for taking part in this study. However, travel reimbursement is provided. The maximum *per diem* for food and hotel will be $300. Itemized receipts are required. In addition, you will be reimbursed for travel to and from your local address to the study site for any study visit that you attend. For ground travel, your reimbursement for travel is calculated based on the

round-trip number of miles you travel from your local address (lodging) to the site address and back as determined by a web-based mileage calculator (e.g., MapQuest). This distance (miles) will be documented in your study file. You will receive automobile reimbursement per mile at the current IRS mileage rate.

There is a very small chance that some commercial value may result from the use of your donated samples. This could include new products like a drug or a test to diagnose a disease. If that happens, you won't be offered a share in any profits.

Will your information or samples be used for future research?

We would like to keep your study information and samples for future research. You can still take part in this study without giving permission to use your data and samples for future research. If you agree to give your sample, it will be the property of Mayo Clinic.

Researchers at Mayo Clinic who aren't involved with this study may ask to use your information and samples for future research. Researchers at other institutions may also ask for a part of your sample for future studies. Your sample will be sent to researchers in a coded format, which protects your identity. Unless you indicate otherwise, the future research may be on any topic. No direct benefits to you are expected from the future research. Your information and/or samples will only be shared consistent with your consent, and with all applicable laws and regulations.

If you approve release of your information and/or samples by checking ‘yes’ below, Mayo may send the information and/or samples to researchers who request them, but Mayo will not send your name, address, phone number, social security number, or any other identifying information with the information and/or samples. Your information and/or samples may be sent with a code, and only the researchers for this study at Mayo Clinic would be able to link the code to you.

Some future studies may examine your DNA, which is the genetic information you inherited from your parents (genetic testing). If there are findings which may be useful for your health care, the researchers may contact Mayo Clinic, so Mayo Clinic can give you the option of learning the results. You would be given general information on the potential risks, benefits, and costs of choosing to learn about the findings.

To support future research, de-identified genetic information may be placed in databases accessible by the internet. Some of the information may be available to anyone using the internet, and some will be released only to approved researchers. Combined study information (including genomic summary results) may be published, but the information will not identify you.

Even though information traditionally used to identify you will not be shared, people may develop ways in the future to allow someone to link your genetic information back to you. For this reason, confidentiality cannot be guaranteed. It is also possible that re-identified information could be used in discriminating ways, and there could be additional unknown risks. We will make every effort to protect your confidentiality.

Please read the following statements and mark your choices:

1. I permit my information and samples to be stored and used in future research on cancer at Mayo Clinic:

   ☐ Yes ☐ No Please initial here: _____Date: _____

2. I permit my information and samples to be stored and used in future research at Mayo Clinic to learn about, prevent, or treat any other health problems:

   ☐ Yes ☐ No Please initial here: _____Date: _____

3. I permit Mayo Clinic to give my information and samples to researchers at other institutions:

   ☐ Yes ☐ No Please initial here: _____Date: _____

You may withdraw your consent for future use of your information and/or samples at any time, by writing to the Principal Investigator at the address provided in the "Contact Information" section of this consent form.

Your information and/or samples would be removed from any repository where they are stored, if possible. Information and/or samples already distributed for research use will not be retrieved.

It is possible that information identifying your samples or your data could be removed. These samples and data will no longer be linked to you. If that were to happen, the samples and data could be used for future research studies or given to another researcher without asking for your permission.

How will your privacy and the confidentiality of your records be protected?

Mayo Clinic is committed to protecting the confidentiality of information obtained about you in connection with this research study.

Various methods are used to safeguard confidentiality. Some or all of the following may be used in this study: assigning a specific code or registration number to each participant's data and samples, research materials stored in locked areas, password protected data stored on a computer.

During this research, information about your health will be collected. Under Federal law called the Privacy Rule, health information is private. However, there are exceptions to this rule, and you should know who may be able to see, use and share your health information for research and why they may need to do so. Information about you and your health cannot be used in this research study without your written permission. If you sign this form, it will provide that permission (or "authorization") to Mayo Clinic.

Health information may be collected about you from:

- Past, present and future medical records.
- Research procedures, including research office visits, tests, interviews and questionnaires.

Why will this information be used and/or given to others?

- To do the research.
- To report the results.
- To see if the research was done correctly.

If the results of this study are made public, information that identifies you will not be used.

Who may use or share your health information?

- Mayo Clinic research staff involved in this study

With whom may your health information be shared?

- The Mayo Clinic Institutional Review Board that oversees the research.
- Other Mayo Clinic physicians involved in your clinical care.
- Federal and State agencies (such as the Food and Drug Administration, the Department of Health and Human Services, the National Institutes of Health and other United States agencies) or government agencies in other countries that oversee or review research.

- The sponsor(s) of this study and the people or groups it hires to help perform this research.
- A group that oversees the data (study information) and safety of this research.

In addition, individuals involved in study oversight and not employed by Mayo Clinic may be allowed to review your health information included in past, present, and future medical and/or research records. This review may be done on-site at Mayo Clinic or remotely (from an off-site location). These records contain information that directly identifies you. However, the individuals will not be allowed to record, print, copy (using paper, digital, photographic or other methods), or remove your identifying information from Mayo Clinic.

Is your health information protected after it has been shared with others?

Mayo Clinic asks anyone who receives your health information from us to protect your privacy; however, once your information is shared outside Mayo Clinic, we cannot promise that it will remain private and it may no longer be protected by the Privacy Rule.

Your Rights and Permissions

Participation in this study is completely voluntary. You have the right not to participate at all. Even if you decide to be part of the study now, you may change your mind and stop at any time. You do not have to sign this form, but if you do not, you cannot take part in this research study.

Deciding not to participate or choosing to leave the study will not result in any penalty. Saying 'no' will not harm your relationship with your own doctors or with Mayo Clinic.

If you cancel your permission for Mayo Clinic to use or share your health information, your participation in this study will end and no more information about you will be collected; however, information already collected about you in the study may continue to be used.

You can cancel your permission for Mayo Clinic to use or share your health information at any time by sending a letter to the address below:

Mayo Clinic
Office for Human Research Protection
ATTN: Notice of Revocation of Authorization
201 Building 4-60
200 1st Street SW
Rochester, MN 55905

Alternatively, you may cancel your permission by emailing the Mayo Clinic Research Subject Advocate at: researchsubjectadvocate@mayo.edu.

Please be sure to include in your letter or email:

- The name of the Principal Investigator,
- The study IRB number and /or study name, and
- Your contact information.

Your permission for Mayo Clinic to use and share your health information lasts forever, unless you cancel it.

Enrollment and Permission Signatures

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

Printed Name Date (mm/dd/yyyy) Time (hh:mm am/pm)

Signature

Person Obtaining Consent

- I have explained the research study to the participant.
- I have answered all questions about this research study to the best of my ability.

Printed Name Date (mm/dd/yyyy) Time (hh:mm am/pm)

Signature