MC1578 / 16-002518

Pilot Study to Test the Safety and Efficacy of the Combination of Imiquimod and Pembrolizumab for the Treatment of Metastatic Melanoma

NCT03276832

Document Date: 01/21/2021

MAYO CLINIC

Name and Clinic Number

Approval Date: January 21, 2021
Not to be used after: January 20, 2022

RESEARCH PARTICIPANT CONSENT AND PRIVACY AUTHORIZATION FORM

Study Title: MC1578: Pilot study to test the safety and efficacy of the combination of imiquimod and pembrolizumab for the treatment of metastatic melanoma

IRB#: 16-002518

Principal Investigator: Richard Joseph, M.D. and Colleagues

Please read this information carefully. It tells you important things about this research study. A member of our research team will talk to you about taking part in this research study. If you have questions at any time, please ask us.

Take your time to decide. Feel free to discuss the study with your family, friends, and healthcare provider before you make your decision.

To help you decide if you want to take part in this study, you should know:

- Taking part in this study is completely voluntary.
- You can choose not to participate.
- You are free to change your mind at any time if you choose to participate.
- Your decision won't cause any penalties or loss of benefits to which you're otherwise entitled.
- Your decision won't change the access to medical care you get at Mayo Clinic now or in the future if you choose not to participate or discontinue your participation.

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.

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 a copy of this form to keep. A copy of this form will be put in your medical record.

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CONTACT INFORMATION

You can contact …	At …	If you have questions about …
Principal Investigator: Richard Joseph, M.D.	**Phone:** (904) 953-2000 **Institution Name and Address:** Mayo Clinic 4500 San Pablo Road Jacksonville, FL 32224	▪ Study tests and procedures ▪ Research-related injuries or emergencies ▪ Any research-related concerns or complaints ▪ Withdrawing from the research study ▪ Materials you receive ▪ Research-related appointments
Mayo Clinic Institutional Review Board (IRB)	**Phone:** (507) 266-4000 **Toll-Free:** (866) 273-4681	▪ Rights of a research participant
Research Subject Advocate **(The RSA is independent of the Study Team)**	**Toll-Free:** (866) 273-4681 **E-mail:** researchsubjectadvocate@mayo.edu	▪ Rights of a research participant ▪ Any research-related concerns or complaints ▪ Use of your Protected Health Information ▪ Stopping your authorization to use your Protected Health Information ▪ Withdrawing from the research study
Patient Account Services	**Toll Free:** (844) 217-9591	▪ Billing or insurance related to this research study

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.

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

You are being asked to participate in this study because you have metastatic melanoma. About 10 people will take part in this study at Mayo Clinic.

2. Why is this research study being done?

The purpose of this study is to gain preliminary data of the anti-tumor activity and safety profile of the combination of imiquimod and pembrolizumab in patients with unresectable cutaneous (skin) melanoma.

3. Information you should know

Who is Funding the Study?

Merck is funding the study. Merck will pay the institution to cover costs related to running the study.

4. How long will you be in this research study?

You will be in the study for a maximum of 3 years.

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

Before you begin the study:

If you agree to be in the study, you will be asked to participate in the following:

Within 28 days of registration:
You will need to have the following exams, tests or procedures to find out if you are eligible to be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This decision will be up to your study doctor.

- Medical history and physical exam, including height and weight and rating of how well you perform activities of daily living.
- Adverse events assessment
- Your vital signs (blood pressure, respiratory and heart rates) will be measured
- Pregnancy test if you are a woman of childbearing potential
- Routine blood tests (blood counts, liver tests, a kidney test, and other tests your doctor thinks should be done). About 3 teaspoons of blood will be drawn from a vein in your arm for the blood tests.
- Disease evaluation (radiographic tumor imaging CT scan, PET/CT, or MRI of the chest, abdomen, and pelvis). CT scan or MRI of the brain with contrast will only be performed if symptoms or signs of CNS metastasis are present.
- Photograph of lesions

After registration but prior to start of treatment:

- Mandatory research tissue collection (tissue biopsy)
- Pregnancy test if you are a woman of childbearing potential.

During the study:
The following will occur on day 1 of cycles 1-35 (Each Cycle is 21 days in length):

- Medical history and physical exam, including weight and rating of how well you perform activities of daily living.
- Adverse events assessment
- Routine blood tests (blood counts, liver tests, a kidney test, and other tests your doctor thinks should be done). About 3 teaspoons of blood will be drawn from a vein in your arm for the blood tests.

- Photograph of lesions

The following will occur at the end of cycle 2 (approximately week 6) and end of cycle 4 (approximately week 12):

- Mandatory research tissue collection (tissue biopsy)

The following will occur at the end of cycle 4 (approximately week 12) and then at the completion of every 4 cycles thereafter (every 12 weeks) until disease progression or end of the study:

- Disease evaluation (radiographic tumor imaging CT scan, PET/CT, or MRI of the chest, abdomen, and pelvis). CT scan or MRI of the brain with contrast will only be performed if symptoms or signs of CNS metastasis are present.

End of treatment:

- Medical history and physical exam, including weight and rating of how well you perform activities of daily living.
- Adverse events assessment
- Routine blood tests (blood counts, liver tests, a kidney test, and other tests your doctor thinks should be done). About 3 teaspoons of blood will be drawn from a vein in your arm for the blood tests.
- Disease evaluation (radiographic tumor imaging CT scan, PET/CT, or MRI of the chest, abdomen, and pelvis). CT scan or MRI of the brain with contrast will only be performed if symptoms or signs of CNS metastasis are present.
- Photograph of lesions

Pembrolizumab Treatment
Pembrolizumab will be administered by intravenous infusion over a 30-minute time interval. This infusion will take place at the clinic during your day 1 visit for every cycle.

Imiquimod Treatment
Imiquimod is a commercial product dispensed from the pharmacy and will be self-administered daily from Monday through Friday.

Regardless of what day of the week the cycle starts, Imiquimod is to be administered daily for the remaining weekdays up to and including Friday.

Imiquimod is not to be administered the day of the biopsy or for six days following biopsy. For example, if the biopsy is performed on Monday, Imiquimod treatment should be given the following Monday through Friday.

Follow up:
Every 12 weeks until 1 year after study completion or disease progression:

- Medical history and physical exam, including weight and rating of how well you perform activities of daily living.
- Adverse events assessment.
- Routine blood tests (blood counts, liver tests, a kidney test, and other tests your doctor thinks should be done). About 3 teaspoons of blood will be drawn from a vein in your arm for the blood tests.
- Disease evaluation (radiographic tumor imaging CT scan, PET/CT, or MRI of the chest, abdomen, and pelvis). CT scan or MRI of the brain with contrast will only be performed if symptoms or signs of CNS metastasis are present.
- Photograph of lesions.

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

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. In some cases, side effects can be serious, long lasting, or may never go away.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks and side effects related to Pembrolizumab (MK-3475) may include:

Very common side effects (>10%) seen in people taking MK-3475 include the following:

- Feeling tired
- Itching of the skin
- Rash
- Frequent or excessive bowel movements or diarrhea
- Fever
- Shortness of breath
- Decreased appetite
- Cough

- Nausea and vomiting
- Decrease in red blood cells that may result in patients feeling tired or short of breath
- Pain in a joint
- Headache
- Back Pain
- Swelling of the legs
- Muscle weakness or lack of energy
- Bowel movements occurring less often than usual (Constipation)

Common side effects (1-10%) seen in people taking MK-3475 include the following:

- Pain in a joint
- Headache
- Pain or cramping in a muscle or group of muscles
- Decreased release of thyroid hormone that may manifest as feeling tired, weight gain, feeling cold easily, or bowel movements occurring less often than usual
- Abnormal laboratory result of liver test by blood that occasionally indicates liver failure, manifesting as yellowing of the skin or whites of the eyes, fatigue, or leg swelling
- Feeling cold or sick
- Loss of skin color
- Pain or uncomfortable feeling in the belly
- Momentary feeling of whole-body warmth possibly accompanied by sweating
- Sweating extensively while sleeping such that clothes and sheets are wet
- Feeling dizzy or unsteady when walking or standing
- Loss of weight
- Pain in the back, arms, or legs
- Swelling of the legs
- Weakness
- Decreased platelets that may manifest as a tendency to bruise easily or bleed easily
- Dry eyes
- Blurred or changed vision
- Dry mouth
- Feeling of pain, pins & needles, or burning, usually in the fingers or toes
- Back pain
- Inflammation of the lungs (pneumonitis)
- Change of blood cholesterol or triglyceride level
- Change of blood sugar or albumin level
- Change of blood electrolytes, e.g. sodium, potassium, or magnesium
- Loss of body fluid may feel tired, confused, have a dry mouth or feel thirsty

- Lung Infection
- Fluid around the lung
- Blood clot developed in lung
- Inflammation of the large intestine (colon) that may lead to frequent or excessive watery bowel movements

Serious Adverse Events (No event occurred in > 2% of everyone treated)
Please note that some of these events have been previously stated above, so some have occurred more frequently but with less severity. Serious adverse events seen in people taking MK-3475 include:

- Trouble thinking clearly or confused easily
- Decreased white blood cells, red blood cells, and platelets which may manifest with fever, feeling cold, infections, shortness of breath, feeling tired, a tendency to bruise easily, or a tendency to bleed easily
- Increased release of thyroid hormone which may manifest as anxiety, irritability, or trouble sleeping, weakness, trembling, sweating, feeling uncomfortable in warm weather, fast or uneven heartbeats, feeling tired, weight loss, and frequent or excessive bowel movements.
- Infection throughout the body by a fungus or bacteria or others that may manifest as fever, feeling tired, feeling cold, and not responding to most antibiotics
- Inflammation of the lining around the heart which may manifest as sharp chest pain and/or a fever
- Inflammation of the pancreas
- Inflammation of the muscles that may manifest as weakness or pain in the muscles
- Inflammation of the kidneys causing them not to work as well, which may manifest as swelling of the legs and possibly needing dialysis.
- Inflammation of the pituitary gland, which may manifest as headache, nausea, a sensation of the room spinning around you, changes in behavior, double vision, or weakness
- Change of blood pressure or body fluid level as a result of inflammation of the body status
- Failure of liver or lung function
- Damage of the peripheral nerves to cause weakness of muscle
- Cancer of the skin
- Inflammation of the heart muscle which can cause shortness of breath or heart rhythm problems or may be serious and require hospitalization, in rare case can cause sudden death (Immune-mediated myocarditis)
- Severe skin and digestive tract reaction that may include rash and sloughing or breakdown of tissue. This may manifest as various blisters, hives, and other lesions in

various locations on the body including palms and soles, face, and other extremities. This is serious and maybe be life threatening. (Stevens-Johnson Syndrome (SJS))

- Toxic Epidermal Necrolysis (TEN) is a rare, life-threatening skin condition that is usually caused by a reaction to a drug. The top layer of skin detaches from the lower layers of skin all over the body. This is similar to the skin damage from a severe burn and is serious and life threatening
- Myasthenic Syndrome (muscle weakness)
- Guillain-Barre Syndrome (damage to the nervous system (causing numbness and/or paralysis)

Other less common side effects have been reported. The study doctor or staff can discuss these with you.

There may be other side effects or risks that are not known at this time.

Risks and side effects related to Imiquimod may include:

Local skin reactions have been reported with Imiquimod as used for genital warts. Erythema, excoriation/flaking, and edema are described as "common" in the package insert. Itching, burning, pain, and soreness occur at the treatment site. Remote skin reactions can occur in less than 5% of patients. Ulceration, scabbing, and vesicles occur in 3 to 5%. Fungal infections are reported in 11% of women using Imiquimod. Examination prior to each application will be the primary means of protecting patients from cumulative local toxicities.

Systemic Reactions:

Systemic reactions have not been a major problem with topical use of Imiquimod. When systemic symptoms are reported, they are suggestive of a viral syndrome. Headaches, myalgias, and flu-like symptoms have been reported. The frequency of these symptoms with vulvar application appears to be elevated no more than 1% over the frequency in the placebo group. The frequency of systemic symptoms with repeated application will be monitored in this trial.

Biopsy

Having biopsies performed may cause pain, bruising, bleeding, redness, low blood pressure, swelling and/or infection at the site of the biopsy. An allergic reaction to the anesthetic may occur. A scar may form at the biopsy site. Other potential risks will be described to you and discussed with you by physicians who conduct these biopsies.

Standard of care risks

Your doctor will discuss the risks of these tests and procedures, which are part of your standard clinical care:

- CT scan or MRI of chest, abdomen and pelvis
- Surgery to remove the cancer

Genetic Testing

This study involves testing your DNA, which is the genetic information you inherited from your parents (also known as genetic testing). 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.

Reproductive risks

You should not become pregnant or father a baby while on this study, because the drug used in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study.

Female patients of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication. Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for >1year. Male patients should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.

7. Are there reasons you might leave this research study early?

Taking part in this research study is voluntary. You may decide to stop at any time. You should tell the Principal Investigator 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 clinical interest,
- if you do not follow the study procedures,
- if the study is stopped.

If you leave this research study early, or are withdrawn from the study, you will be asked if the study team can follow your disease status for a maximum of 2 years post-registration in this study.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

8. 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. The study will not offer free medical care or payment for any bad side effects from taking part in this study.

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

This study may or may not make your health better. We do know that the information from this study will help doctors learn more about metastatic melanoma. This information could help future cancer patients with a similar condition to yours.

10. 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:

- Taking part in another study
- Getting treatment or care for your cancer without being in a study
- Getting 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.

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

You won't need to pay for tests and procedures which are done just for this research study. These tests and procedures are:

- Research tissue biopsies
- Blood tests that are not considered standard of care
- Study Drug Pembrolizumab

However, you and/or your insurance will need to pay for all other tests and procedures that you would have as part of your clinical care, including co-payments and deductibles. These tests and procedures are:

- Pembrolizumab administration costs
- Imiquimod
- Pregnancy tests
- Other drugs or treatments given to help control side effects
- Office visits
- Standard of care CT, MRI and/or PET scans
- Blood work as this is part of your standard clinical care.

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

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

You will not be paid for taking part in this study.

13. What will happen to your samples?

We would like to keep your sample for future research. You can still take part in this current study even if you don't want your sample used for future research. If you agree to give your sample, it will be the property of Mayo Clinic.

Other researchers at Mayo Clinic who aren't involved with this study may ask to use your sample for future research. Researchers at other institutions may also ask for a part of your sample for future studies. If you approve release of your sample by checking 'yes' below, Mayo may send the sample(s) and some information about you 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 sample. Your sample will be sent to researchers in a coded format, which protects your identity.

Some future studies may examine your DNA, which is the genetic information you inherited from your parents (genetic testing). The Principal Investigator may contact you if there are findings which may be useful for your health care. You would be given general information on the potential risks, benefits, and costs of choosing to learn about the findings.

Please read the following statements and mark your choices:

1. I permit my sample to be stored and used in future research of metastatic melanoma at Mayo Clinic:

☐ Yes ☐ No Please initial here: _____Date: _____

2. I permit my sample 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 sample to researchers at other institutions:

☐ Yes ☐ No Please initial here: _____Date: _____

There is a very small chance that some commercial value may result from the use of your donated sample. If that happens, you won't be offered a share in any profits.

You may request to have your sample destroyed by writing to the Principal Investigator. The address is found in the "Contact Information" section of this consent form.

Because we cannot predict how your sample will be used in the future, we cannot promise that samples can be retrieved and destroyed.

14. 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 your 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.
- Photographs of the skin lesions to document changes to lesions during the study.

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.
- Merck & Co., Inc.

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. Researchers involved in this study at other institutions.
- 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, or 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 Privacy Rights

You do not have to sign this form, but if you do not, you cannot take part in this research study.

If you cancel your permission 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.

If you choose not to take part or if you withdraw from this study, it will not harm your relationship with your own doctors or with Mayo Clinic.

You can cancel your permission 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
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 lasts forever, unless you cancel it.

MAYO CLINIC

Name and Clinic Number

Approval Date: January 21, 2021
Not to be used after: January 20, 2022

ENROLLMENT AND PERMISSION SIGNATURES

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

	/ /	: AM/PM
Printed Name	Date	Time

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.

	/ /	: AM/PM
Printed Name	Date	Time

Signature