INSTITUTE: National Cancer Institute

STUDY NUMBER: 17-C-0061 PRINCIPAL INVESTIGATOR: Ravi A. Madan, M.D.

STUDY TITLE: Phase II Trial of Pembrolizumab in Recurrent or Metastatic Medullary Thyroid Cancer

Continuing Review Approved by the IRB on 12/31/18

Amendment Approved by the IRB on 04/18/18 (D) Date posted to web: 01/03/19

Standard

INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary**.**

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

Why is this study being done?

This is an investigational study of a drug called pembrolizumab (MK-3475). Pembrolizumab is in a class of drugs called monoclonal antibodies, which include some relatively new types of cancer therapies. This drug works through its effect on the immune system, and is therefore considered an "Immunotherapy". The purpose of this clinical research study is to evaluate how

the study drug affects you and if it can offer you clinical benefit. Pembrolizumab has been approved to treat melanoma and lung cancer, and may be effective in treating other types tumors.

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

You are being asked to take part in this study because you have been diagnosed with Metastatic Medullary Thyroid cancer.

How many people will take part in this study?

Approximately 30 people will be enrolled in this study.

Description of Research Study

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

Before you begin the study

You will need to have the following exams, tests or procedures to find out if you can 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. However, there are some extra exams, tests and procedures that you will need to have if you take part in this study. If you have had some of them recently, they may not need to be repeated.

These tests include:

- History and physical evaluation including vital signs
- Routine blood tests
- Urine tests
- Pregnancy test (if you are female and can have children)
- CT scan of neck/chest/abdomen/pelvis or MRI
- Bone scan
- Electrocardiogram (EKG) to assess your heart.
- Hepatitis B and C
- HIV Testing: As part of this study, we will test you for infection with the human immunodeficiency virus (HIV), the virus that causes AIDS. If you are infected with HIV you will not be able to participate in this study. We will tell you what the results mean, how to find care, how to avoid infecting others, how we report HIV infection, and the importance of informing your partners at possible risk because of your HIV infection.

During the study

Once it has been determined that you are eligible and agree to participate in the study, you will be assigned to one of two cohorts (groups) based on your treatment history. You may also need to have some of the tests that were done at screening repeated depending on how much time has passed. Your study team will let you know if any of the above tests need to be repeated.

You will be assigned to Cohort 1 (if you have had previous treatment with an immune stimulating therapeutic cancer vaccine) or Cohort 2 (no previous vaccine).

You will receive pembrolizumab as a 30-minute IV infusion every 3 weeks for up to 2 years, as long as you are willing to participate in this study, and you tolerate treatment without evidence of disease getting worse based on symptoms or follow-up studies. The infusion can be given in the outpatient clinic. You will be monitored for 30 minutes after the infusion for the first 3 infusions. You will be evaluated by a physician, with history, physical exams and standard blood tests. Restaging CT and bone scans will be obtained every 3 months or earlier if your doctor suspects your cancer get worse.

Research blood samples:
Research tests will be done on blood taken at various times during your participation in this study: at baseline and before pembrolizumab dose on each cycle. Each of these blood draws will take about 6-8 tablespoons of blood, which is within the limit that the NIH has set for the amount of blood that can be taken for research.

Tissue collection:
Optional biopsies may be requested at baseline and after treatment has been initiated. A separate consent form will be provided to you at the time of the biopsy for you to grant permission to that procedure if you agree to the biopsies.

When you are finished taking the study drug

We would like to see you again within 3 to 4 weeks after you have stopped taking the study drug in order to perform the following tests:

- History and physical evaluation including vital signs
- Standard blood tests including a complete blood count, chemistry panel
- Research blood will be obtained at baseline, then at 3 month intervals thereafter, with possibility of blood collection post-treatment, if feasible.
- Electrocardiogram (EKG)

At the end of this study, we would still like to follow you for any late side effects and to see how you do on other treatments. We would request that at that time you enroll onto our Long Term Follow-up Study 04-C-0274 which the study team can go over with you.

Birth Control

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

Effective forms of birth control include:

- abstinence
- intrauterine device (IUD)
- contraceptive rod implanted into the skin
- tubal ligation
- vasectomy
- combination method (requires use of two of the following):
    - diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
    - cervical cap with spermicide (nulliparous women only)
    - contraceptive sponge (nulliparous women only)
    - male condom or female condom (cannot be used together)
    - hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

Risks or Discomforts of Participation

What side effects or risks can I expect from being in this study?

Pembrolizumab is a cancer therapy that inhibits (blocks) "immune checkpoints," and allows the immune system to detect and kill tumor cells. This may result in serious and possibly fatal immune-related side effects. These side effects are probably due to activation and growth of immune cells (T-cells). Immune-related side effects have been reported in patients receiving pembrolizumab. In clinical trials, most immune-related side effects were reversible and managed by stopping pembrolizumab temporarily, administering corticosteroids, and receiving supportive care.

COMMON, SOME MAY BE SERIOUS
In 100 people receiving pembrolizumab, more than 20 and up to 100 may have:

- Tiredness

OCCASIONAL, SOME MAY BE SERIOUS
In 100 people receiving pembrolizumab, from 4 to 20 may have:

- Anemia which may require blood transfusion
- Pain
- Pain and swelling of thyroid
- Diarrhea, nausea
- Sores in the mouth which may cause difficulty swallowing
- Chills, fever
- Swelling of the body which may cause shortness of breath
- Infection
- Loss of appetite
- Damage to the bone which may loss of motion
- Fluid in the joints
- Joint stiffness
- Blisters on the skin, itching, acne, rash, skin changes, hives
- Swelling and redness of the skin
- The body's reaction to the drug can occur during treatment or weeks to months later: multiple organs may be involved but primarily bowels, liver, skin, nerves and glands that make hormones; symptoms may include diarrhea, rash and numbness/tingling of hands and feet

RARE, AND SERIOUS In 100 people receiving pembrolizumab, 3 or fewer may have:
• Heart failure which may cause shortness of breath, swelling of ankles, cough or tiredness • Swelling and redness of the eye • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Reaction during or following a drug infusion which may cause fever, chills, rash • Weakness and paralysis • Muscle weakness • Feeling of "pins and needles" in arms and legs • Kidney damage which may require dialysis • Severe skin rash with blisters and can involve inside of mouth and other parts of the body

There have been additional side effects seen in patients who have participated in trials using Pembrolizumab. Some of these have been serious. We do not know for certain whether these side effects were caused by pembrolizumab. These additional side effects have included:

- Damage to the bone marrow (irreversible) which may cause bleeding, may require blood transfusions
- Fluid around heart which can stop the heart from beating
- Constipation
- Cough
- Headache
- Shortness of breath
- Vomiting
- Weight loss
- Tinnitus

Other Risks

The study treatment may involve risks to you that are currently unknown. Your cancer may not get better or may become worse while you are in this study.

Risks from X-rays and / or Scans: Radiological testing, such as CT scans, MRIs, X-rays and/or radioactive drugs may be used to assess the treatment of your disease at various times during therapy. The cumulative radiation exposure from these tests is considered very small and is unlikely to adversely affect you or your disease. Because some of these tests require administration of contrast you could experience pain, bruising, and/or infection at the site of

injection, or an allergic reaction to the contrast agent. Please notify the investigator if you know or suspect you are allergic to contrast dye.

EKG: There are no significant risks or discomforts associated with an EKG. Some patches will be adhered to your skin that may cause some reddening or slight itching.

Blood draws: There may be some side effects associated with the procedures for drawing blood in this study, but the person drawing your blood will attempt to minimize this discomfort. Side effects include pain and bruising in the area where the needle is inserted, lightheadedness, and rarely, fainting. When large amounts of blood are collected, low red blood cell count (anemia) is a risk.

Tissue biopsy: The optional biopsy will be performed by physicians specially trained in the necessary procedures. We will only ask you to undergo the biopsies if we feel that the tumor can be easily accessed and there are no major risks associated with the procedure. The biopsy procedure usually causes only brief discomfort at the site from which the biopsy is taken. Rarely, infection or bleeding may occur at the needle site.

The biopsy may be done under CT guidance. If that is the case, then this research study involves exposure to radiation from up to 2 CT scans, at baseline prior to starting treatment and at the end of treatment (at 2 years). This radiation exposure is not required for your medical care and is for research purposes only. The amount of radiation you will receive per one CT scan in this study is 0.77 rem which is below the guideline of 5 rem (or 0.5 rem in children) per year allowed for research subjects by the NIH Radiation Safety Committee. The average person in the United States receives a radiation exposure of 0.3 rem per year from natural sources, such as the sun, outer space, and the earth's air and soil. If you would like more information about radiation, please ask the investigator for a copy of the pamphlet, An Introduction to Radiation for NIH Research Subjects.

While there is no direct evidence that the amount of exposure received from participating in this study is harmful, there is indirect evidence it may not be completely safe. There may be a very slight increase in the risk of cancer.

Please tell your doctor if you have had any radiation exposure in the past year, either from other research studies or from medical tests or care, so we can make sure that you will not receive too much radiation. Radiation exposure includes x-rays taken in radiology departments, cardiac catheterization, and fluoroscopy as well as nuclear medicine scans in which radioactive materials were injected into your body.

If you are pregnant you will not be permitted to participate in this research study. If you are breast feeding and the protocol involves injection of radioactive material, you will not be

permitted to participate. It is best to avoid radiation exposure to unborn or nursing infants since they are more sensitive to radiation than adults.

Potential Benefits of Participation

Are there benefits to taking part in this study?

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

Alternative Approaches or Treatments

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

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

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly. Instead, it tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Please talk to your doctor about these and other options.

Stopping Therapy

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

- if he/she believes that it is in your best interest
- if your disease comes back during treatment
- if you become pregnant
- if you have side effects from the treatment that your doctor thinks are too severe
- if new information shows that another treatment would be better for you

In this case, you will be informed of the reason therapy is being stopped.

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

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

Research Subject's Rights

What are the costs of taking part in this study?

If you choose to take part in the study, the following will apply, in keeping with the NIH policy:

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

Will your medical information be kept private?

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

- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- National Cancer Institute Institutional Review Board
- Qualified representatives from Merck, the pharmaceutical company who produces pembrolizumab.

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.

Certificate of Confidentiality

To help us protect your privacy, we have obtained a Certificate of Confidentiality. The researchers can use this Certificate to legally refuse to disclose information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if there is a court subpoena. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

You should also know that there are several circumstances in which the Certificate does not provide coverage. These include when information:

- will be used for auditing or program evaluation internally by the NIH; or
- must be disclosed to meet the legal requirements of the federal Food and Drug Administration (FDA).
- is necessary for your medical treatment and you have consented to this disclosure;
- is for other research.

In addition, identifiable, sensitive information protected by this Certificate cannot be admissible as evidence or used for any purpose in any action, suit, or proceeding without your consent.

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers will not use the Certificate to withhold that information.

The Certificate of Confidentiality will not protect against the required reporting by hospital staff of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.

Conflict of Interest

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

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

Merck is providing the drug for this study to NIH without charge. No NIH investigator involved in this study receives payments or other benefits from Merck. However, there are some non-NIH collaborators on this study who may receive payments or benefits, limited by the rules of their workplace.

Use of Specimens and Data for Future Research

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

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

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

OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or authorized hospital accreditation organizations.

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

3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health. Reimbursement of travel and subsistence will be offered consistent with NIH guidelines.

4. Problems or Questions. If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Ravi Madan, M.D., Building 10, Room 13N240, Telephone: 301-480-7168. You may also call the Clinical Center Patient Representative at 301-496-2626. If you have any questions about the use of your specimens or data for future research studies, you may also contact the Office of the Clinical Director, Telephone: 240-760-6070.

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

COMPLETE APPROPRIATE ITEM(S) BELOW:

A. Adult Patient's Consent

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

Signature of Adult Patient/ Legal Representative | Date

Print Name

B. Parent's Permission for Minor Patient.

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study.

(Attach NIH 2514-2, Minor's Assent, if applicable.)

Signature of Parent(s)/ Guardian | Date

Print Name

C. Child's Verbal Assent (If Applicable)

The information in the above consent was described to my child and my child agrees to participate in the study.

Signature of Parent(s)/Guardian | Date | Print Name

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM DECEMBER 31, 2018 THROUGH JUNE 18, 2019.

Signature of Investigator | Date | Signature of Witness | Date

Print Name | Print Name