INSTITUTE: National Cancer Institute

STUDY NUMBER: 15-C-0027 PRINCIPAL INVESTIGATOR: Tim Greten, M.D.

STUDY TITLE: A Pilot Study of Immune Checkpoint Inhibition (Durvalumab with or without Tremelimumab) in Combination with Radiation Therapy in Patients with Unresectable Pancreatic Cancer

Continuing Review Approved by the IRB on 05/20/19

Amendment Approved by the IRB on 08/29/18 (I) Date posted to web: 06/27/19

Arms A1 and A2

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 research is being done to study the safety and effectiveness of the combination of durvalumab (formerly known as MEDI4736) with or without tremelimumab with stereotactic body radiation therapy (SBRT). Stereotactic radiation treatment is a standard type of radiation therapy in which a few very high doses of radiation are delivered to small, well-defined tumors. The goal is to deliver a radiation dose that is high enough to kill the cancer while minimizing exposure to surrounding healthy organs.

As you are among the first group of ~ 20 subjects (Part A) enrolling on the study, you will be assigned to take durvalumab. The second group of 20 subjects will be will be assigned to take durvalumab and tremelimumab.
Durvalumab is an investigational drug designed to boost the body's immune system by targeting a protein on tumor cells called PDL-1. PDL-1 normally maintains the balance of the immune system. In cancer, PDL-1 helps tumors evade detection and elimination by the immune system. Durvalumab may increase the immune system's ability to identify and destroy cancer cells. "Investigational" means that durvalumab has not been approved by the Food and Drug Administration (FDA) as either a prescription or over-the-counter drug. It is possible that radiation therapy and durvalumab will work together to keep the cancer from blocking the immune response against the tumor. This research is being done to study if the effectiveness of the investigational drug durvalumab can be enhanced by combining it with either 1 or 5 days of stereotactic body radiation therapy (SBRT) directed to the pancreas.

This is the first study in which durvalumab will be tested in combination with SBRT.

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

You are being asked to take part in this study because you have pancreatic cancer that has not responded to other types of chemotherapy, and your doctor has determined that you are a candidate for radiation but not a candidate for resection.

How many people will take part in this study?

About 70 people will take part in this study with approximately 20 enrolled in Part A.

Description of Research Study

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

Before you begin the study

Before you begin this study, you will have several exams and tests to make sure you are eligible for this study. The exams and tests are part of regular cancer care and may be done even if you do not join the study. If you recently had some of the tests, they may not need to be repeated. The research team will explain these exams and tests to you. You will have:

- History and physical exam
- Review of current medications and past treatments
- Routine blood work
- Viral blood tests
- Tumor measurements using special x-rays called computerized tomography (CT or CAT scans) or magnetic resonance imaging (MRI) of your chest, stomach, and pelvis areas
- Urine or blood pregnancy test

During the study

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will begin treatment.

Before you begin treatment, you will have a biopsy of your tumor using a needle.

In this study, study therapy will be divided into cycles, each lasting 28 days. Treatment involves receiving durvalumab through an IV on days 1 and 15 of each cycle and, depending on what your study doctor decides, SBRT on day 1 of cycle 1 or for 5 consecutive days up to and including the day you receive durvalumab. After you have completed the first cycle of durvalumab, you will have another biopsy of your tumor. You will receive study therapy until your disease worsens or you experience intolerable side effects.

SBRT begins with a treatment planning session, which involves using imaging (4D computerized tomography) to precisely map the exact position of the tumor to be treated. These images are then used to create customized treatment plans in which sophisticated computerized devices direct several radiation beams of different intensities at different angles, so that the radiation is directed precisely to the tumor.

The dose of durvalumab is 10 milligrams per kilogram (a unit of body weight equal to about 2.2 pounds) durvalumab will be administered over approximately an hour.

One half of patients in Part A will receive one dose of radiation treatment (the SBRT) and durvalumab. The second half of patients in Part A will receive five doses of radiation treatment and durvalumab.

When you are finished taking the drugs (treatment)

You will be invited to clinical center approximately 30 and 90 days following the last dose of study drug. If you are unable to travel to the NIH, you will be contacted via phone to discuss your side effects. After your last visit to clinical center, you will be contacted via phone once a year to assess your status.

Re-treatment

If your treatment is stopped for any reason other than worsening of your cancer or intolerable side effects caused by durvalumab, the treatment with durvalumab only (once a month) can be re-started later if your doctor thinks it is in your best interest. Routine blood tests, physical exam and CT scan or MRI (every 8 weeks) will be done during re-treatment visits.

Study Chart

Arm A1 (~ 10 patients in part A)

Cycle 1	
Day 1	• History and physical exam • Review of current medications and treatments • Routine and research blood tests • Stereotactic body radiation therapy • durvalumab infusion
Day 8	• Routine and research blood tests
Day 15	• Routine and research blood tests • durvalumab infusion
Day 22	• Routine blood tests
Cycle 2	
Day 1	• Physical exam • Review of current medications and treatments • Routine and research blood tests • Tumor Biopsy • durvalumab infusion
Day 8	• Routine blood tests
Day 15	• Routine blood tests • durvalumab infusion
Day 22	• Routine blood tests
Cycle 3	
Day 1	• Physical exam • Review of current medications and treatments • Routine and research blood tests • durvalumab infusion • CT Scan or MRI
Day 8	• Routine blood tests
Day 15	• Routine blood tests • durvalumab infusion
Day 22	• Routine blood tests
Subsequent Cycles	
Day 1	• Physical exam • Review of current medications and treatments • Routine and research blood tests • durvalumab infusion • CT scan or MRI (every 8 weeks)

Day 15	• durvalumab infusion

Arm A2 (the other ~ 10 patients part A)

Cycle 1	
Days -3, -2, -1 and 0	• Stereotactic body radiation therapy
Day 1	• History and physical exam • Review of current medications and treatments • Routine and research blood tests • Stereotactic body radiation therapy • Durvalumab infusion
Day 8	• Routine and research blood tests
Day 15	• Routine and research blood tests • Durvalumab infusion
Day 22	• Routine blood tests
Cycle 2	
Day 1	• Physical exam • Review of current medications and treatments • Routine and research blood tests • Tumor Biopsy • Durvalumab infusion
Day 8	• Routine blood tests
Day 15	• Routine blood tests • Durvalumab infusion
Day 22	• Routine blood tests
Cycle 3	
Day 1	• Physical exam • Review of current medications and treatments • Routine and research blood tests • Durvalumab infusion • CT Scan or MRI
Day 8	• Routine blood tests
Day 15	• Routine blood tests • Durvalumab infusion
Day 22	• Routine blood tests
Subsequent Cycles	

Day 1	• Physical exam • Review of current medications and treatments • Routine and research blood tests • Durvalumab infusion • CT Scan or MRI (every 8 weeks)
Day 15	• Durvalumab infusion

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, you will need to practice an effective form of birth control before starting study treatment, during study treatment, and for 6 months after you finish study treatment. If you are the male 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 3 months after you finish study treatment. You also should not donate sperm before, during and for 3 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)
- hormonal [birth control pills, injections, or implants]
- tubal ligation
- vasectomy

Risks or Discomforts of Participation

<u>What side effects or risks can I expect from being in this study?</u>

Durvalumab

Likely

- Fatigue
- Difficulty breathing
- Nausea
- Constipation
- Decreased appetite

- Diarrhea
- Vomiting
- Rash/dry itchy skin
- Increased liver enzymes
- Cough
- Fever
- Pain in muscles and joints

Less Likely

- Inflammation in the lungs (pneumonitis). Preliminary data suggested that there may be the tendency of higher frequency and severity in Japanese patients compared with non-Japanese patients.
- Sensitivity to cold
- Unexplained loss or gain in weight
- Puffy face
- Muscle weakness
- Slow heart rate
- Thinning hair
- Impaired memory
- Anxiety or nervousness
- Feeling hot and possibly having heart palpitations.
- Decreased kidney function
- Weakness of legs, arms, or face, numbness or tingling in hands or feet
- During or after drug infusion having fever, chills, change in blood pressure or difficulty in breathing which might be serious
- Inflammation of the colon which can lead to abdominal pain and diarrhea with or without blood. If left untreated, this may lead to a tear in the wall of the intestine which can be serious and life threatening.
- Inflammation of the heart muscle (myocarditis). Symptoms can include chest pain, rapid or abnormal heart beat, shortness of breath and swelling of your legs. Tell your study doctor right away if you experience any of these symptoms.

Rare

- Depression, changes in mood and personality
- Change in blood pressure

- Increased pancreas enzymes: lipase and amylase.
- Type 1 Diabetes mellitus (high blood sugar)
- Allergic reactions, causing:
  - swelling of the face, lips and throat
  - breathing difficulties
  - hives or nettle like rash
- Headaches
- Thirstiness
- Trouble seeing or double vision
- Leakage of breast milk or irregular periods in women.
- Inflammation of the liver called hepatitis, however this is uncommon
- Problems swallowing
- New allergies to previously exposed substances, other than Durvalumab. For example, it is possible that you could develop an allergy to shellfish or IV contrast while taking Durvalumab. These allergies may be severe and life threatening.

These symptoms might or might not be caused by problems with your liver, kidneys, colon, pancreas, nervous system, thyroid, adrenal or pituitary gland, affected by Durvalumab.

Some of these complications may be permanent and may require hormone replacement.

Tell your study doctor right away if you have any of these symptoms as they may need to be treated urgently.

A new drug may show an increase in side effects or unexpected effects as more studies are conducted. For your safety, you will be followed closely by your Study Doctor and the study staff for any undesirable or unexpected side effects during your participation in this study and each time you receive durvalumab.

There may be other side effects of durvalumab that are unknown. Other immune-mediated side effects are possible that have not been observed and can result in inflammatory side effects in any organ or tissue. You will be told about any new findings that develop during the course of this study that may affect your decision to stay in the study.

Stereotactic body radiation therapy (SBRT)

In general, radiation can cause the following side effects regardless of the site that is being treated.

- Tiredness
- Lowered blood counts
- Skin reddening

- Mild ache at the site that received radiation

These side effects tend to go away after the radiation therapy is completed. However, there are some long-term or chronic side effects that primarily affect the small bowel, liver, kidneys, and spinal cord. Many of these side effects take months to years to develop. Rarely, treatment with radiation may also lead to developing other types of cancer, usually years after receiving the treatment. It is possible that you may experience some, all, or none of the side effects described above. It is also possible that your specific treatment may cause some side effects that we cannot anticipate. For that reason, you will be watched closely while you are receiving treatment for any signs that might signal the earliest stage of toxicity so that we can treat them early.

Specific symptoms that have been associated with SBRT to the liver area are the following:

- Nausea, vomiting
- Diarrhea
- Abdominal pain
- Feelings of claustrophobia
- Skin irritation
- Fatigue
- Sore throat and trouble swallowing
- Late or delayed side effects (the side effects noted above but they occur after the radiation has completed)

Blood Sampling

Bruising or bleeding at the needle site; rarely infection. This is treated with bandages, pressure and, if infection, antibiotic medicines. For more information about risks and side effects, ask your study team.

Tumor Biopsy

If your doctor determines it is safe we will obtain a piece of your tumor (biopsy) before you begin any study therapy and on day 1 of cycle 2 using a needle with minimal risk to you. You will be given local anesthesia (numbing medicine) and a sedative prior to the biopsy. The biopsy will be taken through a needle put through the skin into your tumor. After the procedure the nurses will watch your blood pressure and other vital signs. This biopsy is mandatory and you cannot participate in this study if you do not agree to the biopsies. If the first biopsy is too difficult or if you experience too much discomfort as a result of it you will be able to continue on the protocol without undergoing the second biopsy. However, an attempt at the first biopsy is needed to enter this study. There are other studies at NIH which may also be options for you and which do not involve biopsies. While we are performing some genetic analysis on the tumor biopsy, this analysis

will be very focused and limited and is highly unlikely to provide any relevant information for you or your family.

Risk of Radiation

This research study involves exposure to radiation the CT used during your tumor biopsies**.** This radiation exposure is not required for your medical care and is for research purposes only. The amount of radiation you will receive in this study is 1.6 rem which is below the guideline of 5 rem 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. 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 is safe and if it 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 you become or intend to become pregnant during the study
- if you have an illness that prevents you from being treated
- if your disease comes back during treatment
- if you have side effects from the treatment that your doctor thinks are too severe
- if you begin another treatment for your cancer
- if he/she decides to close the protocol

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 MedImmune, Inc. and The Center for Cancer Research 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 MedImmune, Inc., the pharmaceutical company who produces tremelimumab and durvalumab.

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.

The National Institutes of Health and the research team for this study are using a drug developed by MedImmune, Inc. through a joint study with your researchers and the company. The company also provides financial support for this study.

Use of Specimens and Data for Future Research

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

We plan to keep some of your specimens and data we are collected 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, Tim Greten, M.D., Building 10, Room 12-N228, Telephone: 240-760-6114. 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 MAY 20, 2019 THROUGH JUNE 24, 2020.

Signature of Investigator _____ Date _____

Print Name _____

Signature of Witness _____ Date _____

Print Name _____