INSTITUTE: National Cancer Institute

STUDY NUMBER: 13-C-0016 PRINCIPAL INVESTIGATOR: Hoyoung Maeng, M.D.

STUDY TITLE: A Phase I Study of an Adenoviral Transduced Autologous Dendritic Cell Vaccine Expressing Human HER2/neu ECTM in Adults with Tumors with 1-3+ HER2/neu Expression

Continuing Review Approved by the IRB on 11/05/18
Amendment Approved by the IRB on 08/19/19 (O) Date posted to web: 08/24/19
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 study is being conducted in patients with HER2/neu expressing tumors. HER2 stands for **H**uman **E**pidermal Growth Factor **R**eceptor **2**. HER2/neu (HER2) is a tumor protein over expressed in up to 25-30% of breast cancers and in other cancers such as ovarian, cervical, colon, gastric, non-small cell lung (NSCLC), renal cell, bladder, sarcoma, prostate and other cancers. Research has shown that tumors that over express HER2 can be associated with a more aggressive cancer, a higher recurrence rate and a reduced survival rate. If you have breast cancer that expresses HER2, you may have previously been treated with FDA approved agents such as Herceptin® (also known as trastuzumab), Tykerb (also known as lapatinib), Perjeta (also known as pertuzumab), Kadcyla (also known as ado-trastuzumab) or investigational agents such as MGAH22 that specifically target the HER2/neu tumor protein.

This research study involves the use of a cancer vaccine that expresses human HER2 and is designed to stimulate your immune system to recognize HER2. The vaccine is a custom-made vaccine using your own immune cells (dendritic cells). Dendritic cells (DCs) are derived from immune cells that circulate in the blood called monocytes. The monocytes are collected from your blood during a process called apheresis that you will undergo one time at the beginning of this study.

The autologous AdHER2 DC vaccine being used in this study is investigational and has not been approved by the U.S. Food and Drug Administration (FDA). The adenoviral vector and adenoviral DC vaccine has been studied in mouse models of breast cancer and was shown to shrink large established tumors. This is the first time that it is being tested in humans to see if it is safe and whether it may be a potential treatment for HER2 positive cancers.

The main purpose of this study is to determine the safety of autologous AdHER2 DC vaccination and to determine the risk, if any, for cardiac toxicity.

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

We invite you to participate in this research study because you have a recurrent, metastatic solid tumor such as breast, ovarian, cervical, colon, gastric or gastroesophageal, non-small cell lung, prostate or bladder cancer, malignant soft tissue and bone tumor or other cancer that over-expresses HER2 or you have HER2 positive bladder cancer and have received primary treatment for your cancer and you are at high risk of recurrence.

How many people will take part in this study?

The total number of patients we are seeking to enroll in this study is up to 65. There are two parts to this study. Part I seeks to enroll 30 subjects and Part II seeks to enroll another 30 subjects.

Description of Research Study

Study Design: This study is an open label (open-label means that both you and your study doctor know what investigational vaccine you are receiving), non-randomized, two-part, phase I study of 48 weeks duration for evaluation of your tumor's response to the vaccine with extended follow-up out to 30 months (a total of 124 weeks) to monitor your cardiac function. We will monitor your heart function by doing echocardiograms (echos) that will allow us to assess the pumping function of your heart. We will monitor your cardiac function at regular intervals for 2 years following the last dose of vaccine (delivered at Week 24) as mandated by the FDA. Everyone enrolled in this study will receive the investigational autologous AdHER2 DC vaccine.

Part I of the study involves vaccine dose escalation in subjects with recurrent or progressive, metastatic breast, ovarian, colon, non-small cell lung, renal cell, prostate or bladder cancer and malignant soft tissue and bone tumors whose tumors express HER2, that have failed standard therapies and ***who have not received treatment with any prior HER2-directed therapies.*** We want to determine that the vaccine is safe and rule out that there is any potential cardiac toxicity. Your heart function will be assessed by regular echocardiograms (echos) at study Weeks 4, 12, 20, 28, 32, 40 and 48 during the first year of the study and every 6 months (at Weeks 76, 100, and 124) until the end of the study. We also want to determine if the vaccine stimulates the immune system (is immunogenic) and whether or not it shrinks or stabilizes the growth of tumors (anti-tumor activity). In this part of the study, participants will receive five doses of the vaccine given intradermally (under the skin) at study Weeks 0, 4, 8, 16 and 24. The AdHER2 DC vaccine dose will not be increased until safety has first been established at lower doses. Following vaccination, re-staging CT scans for clinical evidence of tumor response will be assessed at Weeks 8, 16, 24, 36, 48, 76, 100 and 124 with confirmatory scan at least 4 weeks after the response is documented, if needed. Additional scans may be performed if clinically indicated. Re-staging bone scans will be performed at Weeks 8, 16, 24, 36,48, 76, 100 and 124 if bony metastatic disease was documented at baseline or as clinically indicated.

Adjuvant HER2 positive bladder cancer patients will not be enrolled in Part I of the study until AdHER2 DC vaccine safety has been demonstrated out to 12 weeks in at least 10 patients. Enrollment in Part II of the study has begun since vaccine safety has been demonstrated in Part I of the study. Part II of the study examines use of the vaccine in patients with breast or gastric/gastroesophageal or other cancers with 1+ to 3+ HER2 expression or FISH $\geq$ 2.2 that have progressed on HER2-targeted therapies.

Patients determined to have poor cardiac function (LVEF <53%) or who have a history of prior cardiac toxicity associated with trastuzumab or any HER2-targeted therapy or chemotherapy will not be allowed to enroll in this study. In this part of the study, participants will also receive five doses of the vaccine given intradermally (under the skin) at study Weeks 0, 4, 8, 16 and 24. The AdHER2 DC vaccine dose will not be increased until safety has first been established at lower doses. Following vaccination, re-staging CT scans for clinical evidence of tumor response will be assessed at Weeks 8, 16, 24, 36, 48, 76, 100 and 124 with confirmatory scan atleast 4 weeks after the response is documented, if needed. Additional scans may be performed if clinically

indicated. Re-staging bone scans will be performed at Weeks 8, 16, 24, 36,48, 76, 100 and 124 if bony metastatic disease was documented at baseline or as clinically indicated.

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

Before you begin the study

You will need to have the screening examinations, tests or procedures to find out if you can take part in the study. Some of these examinations, test or procedures will be repeated during the study to assure your safety and to assess your response to AdHER2 DC vaccination.

Screening tests and scans must be done within 2 weeks before enrolling in the study. The tests will check your medical history and overall health, determine if your tumor is HER2 positive, and measure the extent of your disease with a CT scan and bone scan. If you are a female with the ability to get pregnant, the study doctors must also confirm that you are not pregnant. We will also request medical information from your local doctor.

Your heart will be tested before you receive the AdHER2 DC vaccine and regularly throughout the study. If you have a heart problem that would put you at risk for cardiac side effects you will not be able to join the study. The AdHER2DC vaccine will be stopped if you develop a heart problem during the study.

A screening visit will include:

- Complete medical history and physical exam
- Blood tests
- Pregnancy test for women
- CT scan of the brain, chest, abdomen and pelvis and a bone scan
  2D Echocardiogram (echo)

During the Study

After you have been found eligible for this study you will be scheduled for apheresis. During the apheresis procedure circulating peripheral blood cells will be collected; these cells will be processed and used to make your own custom made AdHER2 DC vaccine. A large number of cells are required to ensure that we have sufficient cells to make at least 5 vaccines; that is why we use the apheresis procedure. Apheresis is explained below.

Apheresis:

The procedure for obtaining certain types of blood cells through apheresis is a very common procedure that is done routinely here in the Clinical Center with very few risks. Apheresis requires you to have a needle placed in your arm where the blood can be removed from you and circulated through a cell separator machine (a machine that divides whole blood into red cells, plasma (the serum part) and circulating cells (that includes lymphocytes and monocytes). The circulating blood cells are removed and the plasma and red cells are returned to you through another needle in your other arm. The procedure takes approximately 1 to 3 hours to complete. The primary purpose of apheresis is to collect a sufficient number of cells in order to make all the vaccines you will be given during the study. However, if not enough cells are collected to make a

minimum of 5 vaccines, apheresis may be repeated if the investigator thinks it's necessary. Another purpose of apheresis is to allow the investigator to collect a sufficient amount of immune cells to measure the immune response to the vaccine. This testing will provide no benefit to you and is part of the experimental portion of this research study. Patients do not need to be hospitalized for the apheresis procedure. The apheresis will be done in the apheresis clinic in the Department of Transfusion Medicine (Blood Bank) in the NIH Clinical Center and is carried out by trained nurses supervised by Blood Bank physicians.

Vitamin D testing:

The exact role that Vitamin D deficiency plays in cancer has been controversial; but we do know that Vitamin D plays a critical role in cellular and immune functions within the body. Included in your blood work will be a Vitamin D level; if your Vitamin D levels are found to be deficient (low) you will be asked to start an oral supplement of Vitamin D. Your Vitamin D levels will be monitored throughout the study.

We will repeat a CT scan immediately before you are scheduled to receive your first dose of AdHER2 DC vaccine to make sure you do not have rapidly progressive disease. Patients documented to have rapidly progressive disease at Week 0 will be removed from the study and not be eligible to receive the AdHER2 DC vaccine.

With each visit you will have blood draws and a physical exam, you will be asked about any side effects or illnesses you may have had. You will also be asked if you took any medicine at each visit. You will be given a study calendar with the visits and test or exams listed.

You will receive your last vaccine at week 24 but you will continue to have monitoring visits with blood draws, physical exams, cardiac examinations, scans, and clinic visits.

Study Visit and Procedure Calendar

Study Procedures	**Screen/ Baseline**	**Wk 0**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24**	**Wk 28**	**Wk 32**	**Wk 36**	**Wk 40**	**Wk 48**	**Wk 60**	**Wk 76**	**Wk 100**	**Wk 124**
Clinic Visit for Medical History, Physical Exam, Vital Signs, Lab Draws for Monitoring and Research	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Informed Consent	x																
HER2/neu Path Confirm	x																
Urinalysis	x				x			x						x			x
Apheresis	x																
AdHER2 DC		x	x	x		x		x									

VACCINE																	
AdHER2 DC Vaccine Report Card		x	x	x		x		x									
CT Brain (Screening only) CT Torso	x			x		x		x			x		x		x	x	x
Bone Scan[1]	x			x		x		x			x		x		x	x	x
2-D ECHO[2]	x		x		x		x		x	x		x	x		x	x	x

[1] Bone scans after you complete the treatment are optional and may be repeated only if clinically indicated

[2] after you complete your treatment, we will ask your doctor for ECHO reports to make sure your heart is properly working.

Birth Control

If you are a woman who is breast feeding or pregnant, you cannot take part in the study because we don't know how this investigational vaccine 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 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

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

Because this is the first study of the AdHER2 DC vaccine in people, it is not known what the side effects will be. Since this is a vaccine, it is highly likely that you will have a reaction at the site where the vaccine is injected under the skin. Because trastuzumab targets HER2 and is known to be associated with cardiac toxicity, we are monitoring patients in this study very closely since we are giving them a vaccine that will induce their own immune system to make antibodies that target HER2. There have been many studies investigating different types of HER2 therapeutic cancer vaccines and there have been no known reports of cardiac toxicity to date with these agents. Nevertheless, your heart will be tested before you receive the investigational AdHER2 DC and at regular intervals during the study as described previously. If you have a heart problem that would put you at risk for these side effects, you will not be able to join the study. The test drug will be stopped if you develop a heart problem during the study.

Likely

- Injection site reaction, possible pain or soreness, swelling, itching and/or redness at the injection site.
- Inflammation or swelling at and around sites of tumor that could lead to discomfort and/or possibly build up of fluid around your lungs (a pleural effusion) or in your abdomen (ascites). If this fluid build up occurs, the fluid may need to be withdrawn through a needle (a standard procedure) in interventional radiology.

Rare but Serious

- Change in heart function.

Potential Benefits of Participation

Are there benefits to taking part in this study?

The aim of this study is to see if this experimental AdHER2 DC vaccine will stimulate your immune system and cause your tumor to shrink. We do not know if you will receive personal, medical benefit from taking part in this study. Your tumor may shrink, stay the same or get larger. From pre-clinical animal studies, we know that mice treated with the AdHER2 vaccine had tumors get larger for a brief period of time before they subsequently shrunk and disappeared. Because we have no information about this vaccine in humans, we are unable to predict whether the autologous AdHER2 DC vaccine will have an effect on your cancer and 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 and are receiving immune-based therapies and cancer vaccines.

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 and maximize your quality of life. Comfort care tries to keep you as active and comfortable as possible.

Please talk to your doctor about these and other options.

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 Institutes of Health Intramural Institutional Review Board
- The study Sponsor, NCI Center for Cancer Research, or their agent(s)

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.

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 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
- if you develop another cancer

- if your doctor decides to end the study

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 the Study Sponsor 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.

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 have developed a vaccine being used in this study. This means it is possible that the results of this study could lead to payments to NIH scientists and to the NIH. By law, government scientists are required to receive such payments for their inventions. You will not receive any money from the development of AdHER2 DC vaccine.

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, Hoyoung Maeng, M.D., Building 10, Room B2L312, Telephone: 301-250-5161, Santhana Webb, RN, 240-760-6123. 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 NOVEMBER 05, 2018 THROUGH NOVEMBER 12, 2019.

Signature of Investigator _____ Date _____

Print Name _____

Signature of Witness _____ Date _____

Print Name _____