INSTITUTE: National Cancer Institute

STUDY NUMBER: 14-C-0036 PRINCIPAL INVESTIGATOR: Piyush Agarwal, M.D.

STUDY TITLE: A Randomized, Prospective, Phase II Study to Determine the Efficacy of Bacillus Calmette-Guerin (BCG) Given in Combination with PANVAC™ versus BCG Given Alone in Adults with High Grade Non-Muscle Invasive Bladder Cancer (NMIBC) Who Failed at Least 1 Induction Course of BCG

Continuing Review Approved by the IRB on 05/07/18

Amendment Approved by the IRB on 05/08/18 (F) Date posted to web:05/18/18

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?

PANVAC™ is a poxvirus-based cancer vaccine that has been tested in a variety of cancers. Two proteins in particular are usually produced by many cancers and may be used as a target for your immune system to attack the cancer. The PANVAC™ vaccine places the genes for these two proteins inside a virus vaccine in order for your body to recognize these proteins as "foreign" invaders. If your immune system responds to this invasion, your tumor may become susceptible

to your body's immune system. By using this vaccine, we are attempting to stimulate your body's immune system to recognize and destroy the tumor cells that produce two specific proteins.

The purpose of this study is to compare the good and bad effects of using this poxvirus vaccine, PANVAC™ and the usual BCG therapy to using the standard BCG therapy alone. For example, treatment with the PANVAC™ vaccine could shrink your cancer but it could also cause side effects. This study will allow the researchers to know whether this different approach is better, the same, or worse than the usual approach.

Why am I being asked to take part in this study?

You are being asked to take part in this study because you have high grade non-muscle invasive bladder cancer and have had at least one unsuccessful induction course (which means you still have cancer present after at least one 6-week course) of bacillus Calmette-Guerin (BCG) immunotherapy.

How many people will take part in this study?

There will be about **54** people taking part in this study.

Description of Research Study

What are the study groups?

This study has two study groups.

- Group 1 will get the usual BCG therapy used for this type of cancer.
- Group 2 will get the usual BCG therapy used for this type of cancer plus a study drug called the PANVAC™ vaccine. The PANVAC™ vaccine consists of two steps, the initial priming followed by the boost. The vaccinia priming vaccine is administered on week 0, and the fowlpox boosting vaccine is administered on weeks 3, 7, 11 and 15.

A computer will randomly put you in a study group. This is done because no one knows if one study group is better, the same, or worse than the other. Once you are put in one group, you cannot switch to another group. Neither you nor your doctor can choose which group you will be in.

How long will I be in this study?
You will receive the study drugs for up to 15 weeks, depending on which group you are in. After you finish the study drugs, your doctor will continue to watch you for side effects until you undergo another bladder scope/biopsy. Afterwards, your condition will be followed using standard-of-care surveillance for this type of bladder cancer for one year.

What extra tests and procedures will I have if I take part in this study?

Most of the exams, tests, and procedures you will have are part of the usual approach for your cancer. However, there are some extra tests, and/or procedures that you will need to have if you take part in this study.

Before you begin the study:

You will need to have the following extra tests, and/or procedures to find out if you can be in the study:

- Blood and urine tests for studies that assess your immune system
- Echocardiogram to see how your heart is working
- Chest X-ray and CT imaging of the abdomen

During the study:

- Blood test for research at
  - Group 1: weeks 0 (or at randomization), 3, 8, and at the end of the study.
  - Group 2: weeks 0, 3, 8, 11, 15 and at the end of the study.
- Urine test for research at
  - Group 1: weeks 3, 5, and at the end of the study.
  - Group 2: weeks 0, 3, 5, and at the end of the study.
- Between weeks 17-20, you will undergo an end-of-study cystoscopy, exam under anesthesia, and bladder biopsy. Such a procedure is part of standard-of-care management for patients being treated with BCG therapy. Part of the biopsy specimens that are taken at the time of this procedure will be used to assess the immunologic response in the bladder as part of the research study.

Other medical assessments and laboratory exams will be performed as part of the standard management of your cancer, but will not be used for research purposes.

A study calendar that shows how often these tests, and/or procedures will be done is below. Start reading at the left side and read across to the right, following the lines.

Procedure	Baseline	Week									Follow-up
		3	4	5	6	7	8	11	15	17-20	
Medical examination	X	X	X	X	X	X	X	X	X	X	X
Routine blood work	X										
Blood tests for research	X	X					X	X*	X*	X	
Routine urine testing	X	X	X	X	X	X	X			X	X
Urine tests for research	X*	X		X						X	
CT scan	X									X	
Chest x-ray	X									X	
EKG	X										
BCG		X	X	X	X	X	X				
PANVAC™ vaccine	X	X				X		X	X		

*Group 2 only

Risks or Discomforts of Participation

What possible risks can I expect from taking part in this study?

If you choose to take part in this study, there is a risk that you may:

- Lose time at work or home and spend more time in the hospital or doctor's office than usual
- Be asked sensitive or private questions which you normally do not discuss

The vaccines used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects. Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.

- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drugs to try to reduce side effects.

The tables below show the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Study Group 1 and Study Group 2 - Possible side effects of BCG vaccine:

Possible Side Effects of BCG

COMMON, SOME MAY BE SERIOUS In 100 people receiving BCG, more than 10 may have:
• Fever • Chills • Malaise • Flu-like symptoms • Increased fatigue. • Visible blood in urine • Irritative voiding symptoms • Urinary tract infection

Study Group 2 - In addition to side effects outlined above, people who are in Group 2 may also experience the possible side effects of PANVAC™ listed below:

Possible Side Effects of PANVAC™

Vaccinia (Priming Vaccination)
Many of the potential side effects from the vaccination are related to allergic responses to vaccinia or to an abnormal immune system. If you previously have had a smallpox (vaccinia) vaccination, you must have never had an allergic or severe reaction to such a vaccination.

Because you may "shed" live virus through your lesion for several days after vaccination, you must be able to avoid close contact with certain individuals for at least two weeks after each vaccination. These individuals include children under 3 years of age; women who are pregnant or breast-feeding; individuals with active or a history of eczema or other eczematoid skin disorders such as active cases of extensive psoriasis, exfoliative skin diseases, severe rashes, generalized itching, infections, burns, chicken pox, or skin trauma; and/or immune suppressed individuals such as individuals with leukemia or lymphoma, with AIDS or HIV positive blood test, or those receiving immunosuppressive treatment. "Close contact" means that these people share your house, you have repeated bodily contact with them, and/or you take care of them and touch them with your hands. You must not start treatment if you have any healing scars or skin rashes (for example, a burn or poison ivy), until the skin condition has healed. If you have any questions about this list of precautions or any of these medical terms and diagnoses, you should ask about them before starting treatment. It is very important that you tell us if you have any concerns about these precautions for your own safety and the safety of those you may come in contact with.

On average, vaccinia stays active in your body for approximately 13-14 days. Therefore, prior to receiving your next vaccine, you will be evaluated for evidence of pyoderma, vesicles (lesions seen on your skin at or around your vaccine site), or evidence of persistent vaccinia infection. Physical evidence of persistent viral replication (which would be evidenced by the skin lesions, swelling of lymph nodes, and or fever) would require an evaluation prior to next vaccine administration that might include a skin or lymph node biopsy and may delay the next vaccine.

Side effects from the vaccinia vaccine are most common in young children, patients with disorders of the immune system, and individuals with skin disorders. That is why precautions are taken to exclude such individuals from exposure. It is important that you not touch the vaccination site and then touch other parts of your body. This is because the vaccinia virus may be transferred to other sites including the eye, the mucus membrane of the nose or mouth, or other area by rubbing the vaccination site and subsequently rubbing the eye or an open skin area. Spreading the virus in this way is known as autoinoculation. Healing usually occurs in 5-7 days. Blindness can result if vaccinia gets into the eye. A dressing will be placed over the vaccination site to reduce this risk.

Fowlpox (Boosting Vaccination)
The virus does not grow (replicate) in human cells, thus it does not have some of the safety concerns listed above with vaccinia. However, with any experimental compound, there is the risk of unexpected and serious or deadly complications even if they have not been seen previously. Patients receiving fowlpox vaccines should avoid direct contact with pet birds for at least 72 hours after vaccination or while there are any visible lesions at the injection site.

POSSIBLE, SOME MAY BE SERIOUS
• Anemia which may require blood transfusion • Diarrhea, nausea, vomiting • Pain • Chills, tiredness, fever • Flu-like symptoms including body aches • Swelling and redness at the site of the medication injection • Loss of appetite • Muscle weakness • Headache, fainting • Cough • Increased sweating • Itching, skin changes

Reported But Undetermined: Rash

Other possible side effects associated with the vaccinia virus used to make the PANVAC-V vaccine:

- Caution is advised as touching the vaccination site can cause accidental spread of the live virus to other parts of your body or to other people.
- Serious side effects can occur if the virus is spread to your eyes (including blindness).
- Swelling of the heart which may cause chest pain or shortness of breath.
- Severe skin rash with or without blisters that can involve the inside of your mouth and other parts of the body and may be wide-spread. Areas of the skin that have or previously had eczema can also be affected.
- Skin lesions and blisters on the skin can develop and not heal properly. When this happens, the virus can cause damage to large areas of your skin and tissue and cause damage to your bones and organs. This condition can become severe and cause death.

- Confusion and headache.
- Serious adverse events or death can occur if the virus is spread to young children, women who are pregnant, individuals with a weakened immune system, or individuals with certain types of skin disorders.
- Infection or death of fetus if you are or become pregnant or accidentally spread the live virus to another woman who is pregnant.

Let your study doctor know of any questions you have about possible side effects. You can ask the study doctor questions about side effects at any time.

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)
- hormonal [birth control pills, injections, or implants]
- tubal ligation
- vasectomy

Potential Benefits of Participation

What possible benefits can I expect from taking part in this study?

This study may or may not help you but researchers should learn if it can improve your survival by six months or more compared to the usual survival of about two years with the usual approach. This study may help researchers learn things that may help people in the future.

Alternative Approaches or Treatments

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

If you decide not to take part in this study, you have other choices. For example:

- you may choose to have the usual approach described above, i.e., multiple courses of BCG therapy
- if you fail a second induction course, you may have radical cystectomy with pelvic lymphadenectomy, although it is a major surgery and carries a small, but real, mortality rate
- you may choose to take part in a different study, if one is available
- or you could decide not to be treated

Can I stop taking part in this study?

Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study.

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

Even though it probably won't happen, it is possible that the manufacturer may not continue to provide the PANVAC™ to the NCI for some reason. If this would occur, other possible options are:

- You might be able to get the PANVAC™ from the manufacturer or your pharmacy but you or your insurance company may have to pay for it.
- If there is no PANVAC™ available at all, no one will be able to get more and the study would close.

If a problem with getting BCG and/or PANVAC™ occurs, your study doctor will talk to you about these options.

The study doctor may take you out of the study:

- If your health changes and the study is no longer in your best interest
- If new information becomes available
- If you do not follow the instructions given to you by the study doctor
- If the study is stopped by the sponsor
- 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

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

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 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.

Research Subject's Rights

What are my rights in this study?

Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal 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.

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

Who will see my medical information?

Your privacy is very important to us and the researchers will make every effort to protect it. Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, the researchers will do their best to make sure that any information that is released will not identify you. Some of your health information, and/or information about your specimen, from this study will be kept in a central database for research. Your name or contact information will not be put in the database.

There are organizations that may inspect your records. These organizations are required to make sure your information is kept private, unless required by law to provide information. Some of these organizations are:

- The study sponsor and any drug company supporting the study.
- The Institutional Review Board, IRB, is a group of people who review the research with the goal of protecting the people who take part in the study.
- The Food and Drug Administration and the National Cancer Institute in the U.S., and similar ones if other countries are involved in the study.

Where can I get more information?

You may visit the NCI Web site at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

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.

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 accepted 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.

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, Piyush Agarwal, M.D., Building 10, Room 2W-5940, Telephone: 240-760-6242. 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 07, 2018 THROUGH MAY 06, 2019.

Signature of Investigator _____ Date _____

Print Name _____

Signature of Witness _____ Date _____

Print Name _____