INSTITUTE: National Cancer Institute

STUDY NUMBER: 14-C-0015 PRINCIPAL INVESTIGATOR: A. P. Chen, MD

STUDY TITLE: Pilot Trial of Talazoparib (BMN 673), an Oral PARP Inhibitor, in Patients with Advanced Solid Tumors and Deleterious BRCA Mutations

Continuing Review Approved by the IRB on 05/06/19
Amendment Approved by the IRB on 08/26/19 (J) Date Posted to Web: 09/06/19

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?

We are doing this study to develop better treatments for cancer. In this study, an experimental drug, **talazoparib (BMN 673)**, will be given to you. The purpose of this study is to determine what effects, good and/or bad, this drug may have on you and your cancer. This study will also look at how talazoparib (BMN 673) may affect the levels of certain proteins in your tumor and how well the drugs work against cancer cells by examining cells from a small piece of your tumor taken before the drug is given and again after talazoparib (BMN 673) is given.

Talazoparib (BMN 673) is thought to work by preventing DNA repair in tumor cells. It is an experimental drug that has shown some anti-cancer effects against tumor cells in experimental animals and in patients with defects in their DNA-repair pathways. This drug is in the beginning stages of being tested in humans. About 600 patients have received talazoparib (BMN 673) to date. Although we hope this experimental therapy will decrease the size of your tumor, we cannot promise or predict the benefits of the treatment at this time.

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

You are being asked to take part in this research study because you have ovarian or primary peritoneal carcinoma, breast carcinoma, or another type of cancer that has progressed after receiving standard treatment, or for which no effective therapy exists, and your tumor has a particular gene variation (a BRCA mutation) that changes how your tumor repairs DNA.

How many people will take part in this study?

Up to 24 patients will participate 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 examinations, tests, or procedures to find out if you can be in the study. Most of these examinations, tests, or procedures are part of your regular cancer care and may be done by your health care team, even if you do not join the study. If you have had them recently, they may not need to be repeated. This will be up to your study doctor. You will have the examinations, tests, and procedures listed below to see if you can take part in the study (this is called the screening or baseline evaluation).

- **Complete medical history.**
- **Physical examination:** including height, weight, blood pressure, pulse, and temperature.
- **Standard blood tests:** (requiring about 1 tablespoon of blood in total), which include measurement of your white blood cells, red blood cells, platelets, blood sugar and electrolytes, how your liver and kidneys work, and how well your blood clots.
- **Pregnancy test:** A blood test will be done to check for pregnancy in women who are able to become pregnant.
- **CT scans:** of your chest, abdomen, and pelvis to measure your tumor(s). Other imaging tests may be done as needed.

During the study

If you are accepted and you choose to take part, you will begin receiving talazoparib (BMN 673). You will take talazoparib (BMN 673) by mouth once per day for 28 days. The drug is given in cycles; each cycle is 28 days (4 weeks) long. You can take the drug with or without food.

You will be asked to maintain a diary to document the exact time you took the study drug, and to report any side effects that you may have. If you miss or vomit the dose, please make a note of this in your diary and contact your team immediately to receive further instructions. Please bring the study diary with you to each clinic visit.

You will also have tests and procedures done because you are in the study to see how talazoparib (BMN 673) is affecting your body. This will include repeating some of the imaging studies (e.g., CT scans, a computerized x-ray examination) every 8 weeks to find out if your cancer has responded. Descriptions of the tests and procedures that will be performed during the study are listed below. Please see the Study Chart below for more details.

Clinical Center Visits: We will ask that you come to the Clinical Center at the beginning of cycle 1, and weeks 1, 2, and 3 during cycle 1; and at the beginning of week 1 for all other cycles. While you are at the Clinical Center we will perform study tests and procedures to see how the study drug is affecting your body. If you develop any side effects, you may be asked to visit more often.

Standard procedures being done because you are in this study; these may be done more often because you are in the study:

- **Clinic visit:** to ask how you are feeling and to evaluate you with a physical examination during weeks 1 and 2 of cycle 1 and week 1 for all subsequent cycles.
- **Vital signs and physical examinations:** will be performed during the clinic visits.
- **Blood tests:** Measurement of your white blood cells, red blood cells, platelets, blood sugar, electrolytes, and of how your liver and kidneys work will be done during weeks 1, 2, and 3 of cycle 1; and then at the beginning of all subsequent cycles. Approximately 1 tablespoon (15 mL) of blood will be drawn per visit.
- **CT scans** (or other imaging tests): such as ultrasound (an examination using sound waves) or MRI (an examination using magnetic field and radio waves) that detect your tumor will be done before the study and every 8 weeks while you are receiving study drugs. This is done so that any benefit of the treatment can be determined, and if your cancer is not responding to the treatment, the study team can tell you and discuss other treatment options (discussed further below).

Tests and procedures that are either being tested in this study or being done to see how the drug is affecting your body:

- **Research blood samples:** We will collect blood samples to find out the effects of the drug on any tumor cells in the blood. Blood samples will be collected at the beginning of the study and then several times during cycle 1 and cycle 2, and at the start of all other cycles. Please see the study chart for more details. The total blood for all these tests will be about 7 tablespoons (100 mL).

- **Tumor biopsy:** After you are accepted to take part in the study, you will be asked to undergo imaging-directed biopsy of your tumor (removal of a small bit of tissue for microscopic examination) once before you receive the study drug and after you have taken the drug on day 8. We are collecting biopsy samples to study the effects of talazoparib (BMN 673) on your tumor. Biopsies are an important part of this trial and are done for research purposes. Willingness to undergo tumor biopsies is required for taking part in this study. We may also ask you for an optional third biopsy if your disease comes back during treatment.

  After the first biopsy, if you decide not to have further biopsies, you will still receive study drugs and have other tests that are part of the study. You will be asked to sign a separate consent form for each biopsy procedure.

  Tumor biopsies are only collected by trained personnel. Biopsies are collected using a small needle under imaging guidance (CT, MRI, or ultrasound as deemed appropriate by the interventional radiologist performing the biopsy). Imaging helps the specialized radiologist know that the needle has been placed into the tumor mass.

  The biopsy to be performed is exclusively for research purposes and will not benefit you. It might help other people in the future. Even if you sign "yes" to have the biopsy you can change your mind at any time. Please read the sentence below and think about your choice. After reading the sentence, circle and initial the answer that is right for you.

  I agree to allow biopsies for research purposes:

  Yes ____ No _____ Initials_____

When you are finished taking the drugs

When you have finished taking talazoparib (BMN 673), your study doctor will watch you carefully for up to 30 days after the last treatment or until another treatment is started. You will need these tests and procedures at that time:

- Vital signs and a physical examination
- Blood tests
- CT scans or other imaging tests such as ultrasound or MRI

You will be followed for 30 days after taking the last dose of study drugs. We will call you between days 27-30 to ask about any side effects that were ongoing when you stopped therapy, or any new side effects that might be related to the study therapy. If you have side effects that might be related to the study drugs that have not gotten better after 30 days, we will call you every 2 weeks until the side effects have become stable or gotten better. The follow-up period will end if you enroll in another study or start receiving standard therapy.

Study Chart

The study drug is given over 28-day periods of time called cycles. The chart below and on the next page shows what will happen to you during cycle 1 and future cycles after you sign the consent form and start the study. Each cycle is numbered in consecutive order. The left-hand column shows the day in the cycle and the right-hand column shows what will happen on that day.

Day	What to do and what will happen to you
Before starting study drug	• Check in at the Outpatient Clinic • Get routine blood tests • Pregnancy test for women who are able to become pregnant • Have a history taken of how you feel and undergo a physical examination by a Health Care Provider • CT or MRI scan will be done • Tumor biopsy will be taken • Blood sample for research will be taken
Cycle 1, Day 1	• Admitted to the Clinical Center • Have a history taken of how you feel and undergo a physical examination by a Health Care Provider (does not need to be repeated if done within 3 days before starting treatment) • Get routine blood tests (does not need to be repeated if done within 3 days before starting treatment) • Begin taking talazoparib (BMN 673) by mouth

Day	What to do and what will happen to you
	• Blood samples for research will be taken 30 minutes and then 1, 2, 3, 4, 6, 8, and 24 hours after you take talazoparib (BMN 673)
Cycle 1, Day 8	• Get routine blood tests • Blood sample for research will be taken 3-6 hours after you take talazoparib (BMN 673) • Continue taking talazoparib (BMN 673) • Tumor biopsy will be taken
Cycle 1, Week 3	• Get routine blood tests • Continue taking talazoparib (BMN 673)
Cycle 2 and onwards, Day 1	• Check in at the Outpatient Clinic • Have a history taken of how you feel and undergo a physical examination by a Health Care Provider • Get routine blood tests • CT scan or MRI to determine how your tumor is responding to the treatment will be done every 2 cycles (8 weeks) • Blood sample for research will be taken before taking talazoparib (BMN 673) (every 3 cycles if you have been on study for more than a year) • Continue taking talazoparib (BMN 673) • Blood sample for research will be taken 3-6 hours after you take talazoparib (BMN 673) (cycle 2 only)

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 30 days after you finish study treatment. Men participating in this study must also agree to use adequate contraception prior to the study, for the duration of study participation, and for 3 months after finishing 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
- vasectomy
- hormonal (birth control pills, injections, or implants)
- intrauterine device (IUD)
- tubal ligation

Risks or Discomforts of Participation

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

You may have side effects while on this study. Everyone taking part in the study will be watched carefully for any side effects. But, doctors do not know all the side effects that may happen when taking talazoparib (BMN 673). There may be other side effects that we cannot predict. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away with those medicines, and others can go away soon after you stop taking the study drug. In some cases, side effects can be serious, long lasting, may never go away, or may result in death. You should talk to your study team about all side effects that you have while taking part in the study.

Risks and side effects related to talazoparib (BMN 673) may include:

COMMON, SOME MAY BE SERIOUS In 100 people receiving talazoparib (BMN 673), more than 20 and up to 100 may have:
• Anemia which may require blood transfusion • Diarrhea, nausea, vomiting • Tiredness • Bruising, bleeding • Headache • Hair loss

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving talazoparib (BMN 673), from 4 to 20 may have:
• Pain • Constipation, heartburn • Sores in the mouth which may cause difficulty swallowing • Fever • Infection, especially when white blood cell count is low • Loss of appetite • Dizziness

RARE, AND SERIOUS In 100 people receiving talazoparib (BMN 673), 3 or fewer may have:

- Swelling of the bowels which may require surgery
- Cancer of bone marrow caused by chemotherapy
- Damage to the bone marrow (irreversible) which may cause infection, bleeding, may require transfusions
- A new cancer resulting from treatment of earlier cancer

Because many of the adverse events seen in patients taking talazoparib (BMN 673) were decreased numbers of the cells you need to fight infection, please tell your study team immediately if you have any of the symptoms of a fever, sore throat, or other signs of an infection.

Potential Risks Related to Research-Related Imaging Studies:

This research study involves exposure to radiation from up to 3 CT scans (used in biopsy collections). 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 2.4 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.

Potential Benefits of Participation

Are there benefits to taking part in this study?

Taking part in this study may or may not make your health better. 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.

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.
- The NCI will supply the talazoparib (BMN 673) at no charge while you take part in this study. The NCI does not cover the cost of getting the talazoparib (BMN 673) ready and giving it to you, so you or your insurance company may have to pay for this.

- Even though it probably won't happen, it is possible that the manufacturer may not continue to provide the talazoparib (BMN 673) to the NCI for some reason. If this would occur, other possible options are:
  - You might be able to get the talazoparib (BMN 673) from the manufacturer or your pharmacy but you or your insurance company may have to pay for it.
  - If there is no talazoparib (BMN 673) available at all, no one will be able to get more and the study would close.
- If a problem with getting talazoparib (BMN 673) occurs, your study doctor will talk to you about these options.

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 Institutional Review Board.
- Pharmaceutical Collaborator.

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 too many patients in the study experience severe side effects
- if you become pregnant

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 agent manufacturer, Pfizer, 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 **cannot** be recalled and destroyed.

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 talazoparib (BMN 673) developed by Pfizer through a joint study with your researchers and the company. 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 talazoparib (BMN 673).

Use of Specimens and Data for Future Research

We would like 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 identified by a number and not your name. Your specimens and data will be used for research purposes only and will not benefit you.

Researchers use specimens and data stored in scientific databases to advance science and learn about health and disease. 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 decide now that your specimens and data can be kept for research and shared, you can change your mind at any time. Just contact us 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.

Please read the sentence below and think about your choice. After reading the sentence, circle and initial the answer that is right for you. No matter what you decide to do, it will not affect your care.

My specimens and data may be kept and shared for use in research to learn about, prevent, or treat cancer or other health problems.

Yes No Initials_____

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, Dr. Alice Chen, 31 Center Drive, Building 31, room 3A44, Bethesda, Maryland, Telephone: 240-781-3320. 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. You may also call the Clinical Center Patient Representative at 301-496-2626.

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 06, 2019 THROUGH MAY 06, 2020.

_____ _____

Signature of Investigator Date Signature of Witness Date

_____ _____

Print Name Print Name