INSTITUTE: National Cancer Institute

STUDY NUMBER: 11-C-0060 PRINCIPAL INVESTIGATOR: A. P. Chen, MD

STUDY TITLE: Phase I Pharmacokinetic Study of Belinostat for Solid Tumors and Lymphomas in Patients with Varying Degrees of Hepatic Dysfunction

Continuing Review Approved by the IRB on 01/09/17
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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.

Description of Research Study

The purpose of this study is to test the safety of belinostat at different dose levels in patients with cancer who have different degrees of liver function. Belinostat is an experimental drug that works by helping to turn on genes that control cell growth and survival that are switched off in cancer cells. This is the first study in which belinostat will be given to patients with different degrees of liver function. We already know the safe dose for patients with normal liver function. Other purposes of this study are to find out what side effects occur when belinostat is given to patients with different degrees of liver function, how much belinostat is in your blood at specific times, and whether or not belinostat is effective in treating your cancer. We will compare how the patients

with abnormal liver function do in comparison with patients with normal liver function. That is the reason that a group of patients with normal liver function will also be included on this trial.

How many people will take part in this study?

Up to 80 patients will take part in this study at multiple centers across the United States.

Has this drug been given to other people?

Belinostat has been given to about 500 patients with different types of cancer to measure its safety and how the body handles the drug. Belinostat has not been given in a formal trial to patients with cancer who have abnormal liver function to learn how these patients tolerate and respond to the drug.

What will happen if I take part in this 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. These examinations, tests, or procedures are part of your regular cancer care and should 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.

If you decide that you would like to participate in this study, you will be asked to sign this consent form. You will then have the examinations, tests, and procedures listed below done to see if you can take part in the study (this is called the screening/baseline evaluation).

- **Complete medical history.**
- **Physical examination,** including height, weight, blood pressure, pulse, and temperature.
- **Standard blood tests** (requiring about 1 tablespoon of blood 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.
- **Urine tests:** Depending on the results of blood tests, you may be asked to give a collect your urine for 24 hours for further testing.
- **Pregnancy test:** A blood test will be done to check for pregnancy in women who are able to become pregnant.
- **EKG** to check your heart.
- **CT scans** of your chest, abdomen, and pelvis to measure your tumor(s). Other imaging tests may be done as needed.

During the study
After you are accepted for this study and you choose to take part, you will begin taking the study drug, belinostat. Belinostat is given through a vein for 30 minutes. Belinostat will be given in cycles. Except for cycle 1, all cycles are 3 weeks long. Cycle 1 is 4 weeks long. Now, we will

describe what will happen during each cycle.

For cycle 1 only, you will receive one extra dose of belinostat 1 week before the regular treatment starts (Day -7). **In each cycle,** belinostat will be given once a day for 5 days (Day 1-5).

For some study procedures we will need you to come to the Clinical Center. You will also have tests performed because you are in the study to see how the study drugs are affecting your body. This will include imaging studies (for example, CT scans) every 2 cycles (about every 6 weeks) to find out if your cancer has responded.

Clinical Center Visits: We will ask that you come to the Clinical Center each day you receive belinostat (6 days in cycle 1 and 5 days in all other cycles) (see Study Chart). While you are at the Clinical Center, we will also perform study tests and procedures to see how the study drugs are affecting your body.

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 at the beginning of each cycle.
- **Vital signs:** You will need to have your vital signs, including your temperature, heart rate, blood pressure, and respiratory rate, measured each time you are seen in the outpatient clinic.
- **Blood tests:** Measurement of your white blood cells, red blood cells and platelets, and measurements of your blood sugar and electrolytes and of how your liver and kidneys work will be done each time you are seen in the outpatient clinic. All of these blood tests combined will require 1-2 tablespoons (20-30 mL) of blood each time.
- **Urine test:** Depending on the results of blood tests, you may be asked to give a urine sample for testing or to collect your urine for 24 hours for further testing.
- **EKG** to check your heart on Day 5 of cycle 1, at the beginning of cycle 2, and more often if needed.
- **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 every 2 cycles (about every 6 weeks) while you are receiving treatment. This is done so that any benefit of the treatment can be determined, and so that if your cancer is not responding to the treatment, the study team can tell you and help you move to a different treatment program (discussed further below).

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

- **Measurements of the drug in your blood:** We will collect blood samples to measure amounts of belinostat in your blood several times during cycle 1. Because we will collect several blood draws, a thin, flexible plastic tube (called a "catheter") will be placed in your arm, and all blood samples would be taken from this tube. Using a catheter will reduce the

number of times a needle would be placed in your vein. The total amount of blood that we collect will be about 4 tablespoons (52 mL).

Patients in this study will be divided into 4 groups. You will be placed in one of these groups based on how your liver is functioning (determined from the results of the blood tests done to check your liver). Up to 12 patients with normal liver function will be included in the study. All of the patients with normal liver function will receive the same dose of belinostat. For each group of patients with abnormal liver function, 3 patients will be enrolled and will begin with a low dose of belinostat. If no serious side effects are reported, the next set of 3 patients enrolled in that group will receive a higher dose of belinostat. This will continue as long as belinostat is well tolerated, or the dose reaches the level that caused side effects in patients with normal liver function. The dose level of the study drug you receive will depend on when you enter the study, and whether patients enrolled before you had any serious side effects at their dose levels. If serious side effects are seen, the dose of the study drug may be lowered or stopped depending on the severity of the side effects.

Study Chart

The chart below shows what will happen to you while you take part in this study. The left-hand column shows the day in the cycle, and the right-hand column tells you what will happen on that day.

Day	What to do and what will happen to you
Before starting study drug	• Check in at Outpatient Clinic • Get routine blood tests • EKG will be done to check your heart • Pregnancy test • Have a history taken of how you feel and undergo a physical examination by a Health Care Provider • CT scan will be done
Cycle 1, Day -7	• Check in at Outpatient Clinic • Have a history taken of how you feel and undergo a physical examination • Get routine blood tests • Receive belinostat through a vein for 30 minutes • Have blood samples taken for research
Cycle 1, Day -6	• Have blood samples taken for research
Cycle 1, Days 1-5	• Check in at Outpatient Clinic • Have a history taken of how you feel and undergo a physical examination • Receive belinostat through a vein once a day for 30 minutes • EKG will be done on Day 5 to check your heart

Day	What to do and what will happen to you
	• Get routine blood tests
Cycle 1, Days 6-21	• Get routine blood tests once a week
Cycle 2 and onwards, Days 1-5	• Check in at Outpatient Clinic • Have a history taken of how you feel and undergo a physical examination • Get routine blood tests • Receive belinostat through a vein once a day for 30 minutes • EKG will be done on Day 1 of cycle 2 only to check your heart
Cycle 3 onwards	• CT scans to determine how your tumor is responding to the treatment will be done every 2 cycles (about every 6 weeks).

Risks or Discomforts of Taking Part
What side effects or risks can I expect from being 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 agents 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 from the study drug(s)/study approach. 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.

It is important to remember that this is a dose-ranging study, meaning that the dose of belinostat will increase between groups of patients until notable side effects are seen. Because of this, some patients may have severe side effects as the study investigators find the highest dose of belinostat can be given safely to patients with different degrees of liver function. We already know the "safe dose" for patients with normal liver function and will not give you a dose bigger than this. If a dose has too many or certain unacceptable side effects, a lower dose may be recommended as the "safe dose" for future testing in patients with abnormal liver function.

Risks and side effects observed with **belinostat** include:

COMMON, SOME MAY BE SERIOUS

In 100 people receiving belinostat, more than 20 and up to 100 may have:

- Diarrhea, nausea, vomiting
- Tiredness

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving belinostat, from 4 to 20 may have:

- Anemia which may require blood transfusion
- Belly pain
- Constipation
- Dry mouth
- Swelling of arms, legs
- Fever
- Swelling and redness at the site of the medication injection
- Infection
- Change in the heart rhythm
- Bruising, bleeding
- Weight loss, loss of appetite
- Dehydration
- Dizziness, headache
- Changes in taste
- Shortness of breath
- Rash
- Flushing

Side Effects of Blood Draw:

Infrequent (occurs in 1 to 10 out of 100 people): persistent pain and discomfort at the injection or needle insertion site as well as possible infection, bleeding, bruising, and soreness.

Reproductive Risks: Because the effect of Belinostat on unborn babies is not known, you should not become pregnant or father a baby while on this study.

Women of childbearing potential will be required to have a pregnancy test. If you are a woman who is breast feeding or pregnant, you may not participate 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 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. Avoiding sexual activity is the only certain method to prevent pregnancy. But, if you choose to be sexually active, you should use an appropriate "double barrier" method of birth control (such as female use of a diaphragm, intrauterine device (IUD), or contraceptive sponge, in addition to male use of a condom) or the female should be using prescribed "birth control" pills, injections, or implants. Male participants must also use adequate contraception.

If you choose to be sexually active during this study, you understand that even with use of these birth control measures, pregnancy could still result. Some methods might not be approved for use in this study. Ask about counseling and more information about preventing pregnancy. Belinostat may reduce a man's ability to father a child or a woman's ability to become pregnant, and in some cases this may be permanent. Women should not breast feed during the study and for 30 days after finishing study treatment. For more information about risks and side effects, ask your study team.

Potential Benefits of Taking Part

Are there benefits to taking part in this study?

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?

Talk to your doctor about your choices before you decide if you will take part in this study. Your other choices may include:

- Getting treatment or care for your cancer without being in a study.
- Taking part in another study. However, if you have moderate or severe abnormal liver function, you may not be eligible for most other studies.
- Getting comfort care, also called palliative care. This kind of care helps reduce pain, tiredness, appetite problems, and other problems caused by cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Research Subject's Rights

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in this study. If you decide to participate, you may leave the study at any time. No matter what decision you make, there will be no penalty to you, and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution if you are eligible and choose to participate in another trial. We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study. In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

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:

The National Cancer Institute will supply the Belinostat at no charge while you take part in this study. The NCI does not cover the cost for getting the Belinostat 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 Belinostat to the NCI for some reason. If this would occur, other possible options are:

- You may be able to get the Belinostat from the manufacturer or your pharmacy but you or your insurance company may have to pay for it.

- If there is no Belinostat available at all, no one will be able to get more and the study would close.

If there is a problem with getting Belinostat, your study doctor will talk to you about these options.

Stopping Therapy

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

- if he/she believes that it is in your best interest
- if your disease gets worse 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

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 Cancer Therapy Evaluation Program (CTEP) at the National Cancer Institute (NCI) 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.

Will my 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. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records, including research 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), involved in keeping research safe for people
- Qualified representatives from the maker of belinostat.
- Member institutions of the NCI Organ Dysfunction Working Group and their associated scientific review and Institutional Review Boards

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.

Research Subject's Rights

Taking part in this research study is voluntary, and you can withdraw at any time. We encourage you to ask questions so you can make the most informed decisions while you take part in this study. Refusal to take part will not result in penalty or loss of benefits to which you are otherwise entitled.

It is important to stress that being in this study does not promise long-term medical care here at the NIH Clinical Center. If there is no further research study that is suitable for you and your state of disease, or if you are not now on another research study, you will be returned to the care of your referring doctor or institution or other source of care closer to your home. If you have any questions about your treatment at NIH, you can contact the Principal Investigator, Dr. Alice Chen (301-496-4291) or the patient care representative (301-496-2626).

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at: 1-800-4-CANCER (1-800-422-6237). You may also visit the NCI Web site at http://cancer.gov/

- For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
- For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

You will get a copy of this form. If you want more information about this study, ask your study doctor.

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

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, (301) 496-4291. If you have any questions about the use of your specimens 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 JANUARY 9, 2017 THROUGH JANUARY 8, 2018.

Signature of Investigator _____ Date _____

Print Name _____

Signature of Witness _____ Date _____

Print Name _____