INSTITUTE: National Cancer Institute

STUDY NUMBER: 07-C-0189 PRINCIPAL INVESTIGATOR: Brigitte Widemann, M.D.

STUDY TITLE: Phase I/II Trial of Vandetanib (ZD6474, ZACTIMA) in Children and Adolescents with Hereditary Medullary Thyroid Carcinoma

Continuing Review Approved by the IRB on 04/22/20

Amendment Approved by the IRB on 04/14/20 (M) Date Posted to Web: 04/24/20

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.

If you are signing for a minor child, “you” refers to “your child” throughout the consent document.

Why is this study being done?

Vandetanib is a new drug that is being tested as a new medication for a variety of cancers, including medullary thyroid carcinoma. It has been recently approved by the US Food and Drug Administration (FDA) for treatment of adults with medullary thyroid cancer, but has not been previously given to children with your type of cancer, and is therefore considered experimental. Vandetanib is given once daily by mouth as a pill or liquid. Vandetanib works by blocking proteins called receptors on the surface of cancer cells or on the lining of blood vessels within cancers. New blood vessels provide oxygen and nutrients to growing cancers. Blocking these receptors can cause cancer cells or the blood vessels to stop growing. In people with MEN, the receptor called RET is defective and is felt to be a primary cause of the medullary thyroid carcinomas that frequently develop. Vandetanib can block this defective RET receptor.

In a small number of adults with MEN and medullary thyroid carcinoma, Vandetanib decreases the level of calcitonin (a protein made by the cancer cells) in the blood in most and decreases the size of cancers in a minority. We do not know whether Vandetanib will slow or stop the growth of medullary thyroid cancer in children and adolescents or whether this drug will be effective in your cancer. The safety and effectiveness of Vandetanib in children and adolescents with cancer has not been tested.

The purposes of this research study are:

- to determine the activity of Vandetanib in children and adolescents with MEN-related medullary thyroid cancer by measuring the change in tumor size on MRI or CT scans, change in blood levels of proteins produced by this type of cancer (calcitonin and CEA), and change in tumor-related diarrhea.
- to determine the safety and tolerability of Vandetanib in children and adolescents at a dose equivalent to the recommended adult dose (300 mg),
- to study how the body handles Vandetanib in children and adolescents by measuring the amount of drug in the bloodstream over time after a dose is given, and
- to determine the survival of children and adolescents with medullary thyroid carcinoma taking Vandetanib

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

You have a form of cancer that arose in your thyroid gland called medullary thyroid carcinoma. This type of cancer is very common in people with a genetic disorder called multiple endocrine neoplasia (MEN). Your medullary thyroid carcinoma cannot be surgically removed, has grown back after treatment, or has spread beyond the thyroid gland to other parts of your body (metastasized). Because your doctors have no other standard forms of treatment to offer you for

the medullary thyroid carcinoma, you are being offered the opportunity to participate in a research study of an experimental drug called Vandetanib (also called ZD6474 or ZACTIMA).

How many people will take part in this study?

The plan is to enter 21 children and adolescents (5 to 18 years old) onto this study. This study is not enrolling new patients. Your parent(s)/guardian(s) gave permission for you to participate in this study previously. We are asking you to sign this consent verifying that you would like to continue on this study now that you have reached 18 years of age and are legally considered an adult.

Description of Research Study

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

Vandetanib will be given by mouth once daily continuously (a cycle of Vandetanib is 28 days). You will be provided with an instruction sheet about how to take Vandetanib.

DO NOT take other medications without first discussing them with your doctor or research nurse.

After every 3 cycles, you will be examined by a doctor at the NIH or at home, and you will have routine blood tests performed. At this time you will also have an electrocardiogram (ECG or EKG), which is a test used to evaluate your heart rate and rhythm by measuring electrical impulses from the heart through electrodes that are placed on the skin. You must lie down and be still without talking during the 5 minutes the ECG is being recorded. These tests are done to look for side effects of Vandetanib, and they will be performed periodically for as long as you are on the study. Procedures or tests that need to be done by your own physician at home will incur costs that may or may not be covered by your health insurance.

The effect of Vandetanib on your cancer will also be closely monitored while you are on the study using:

- scans to assess the size of your cancer (may include CT scan, MRI, or bone scan),
- blood levels of calcitonin and CEA (markers produced by the cancer cells), and
- if you have diarrhea from elevated calcitonin levels, you will need to tell us the number and consistency of your bowel movements.

These scans and blood tests will be performed before you start the Vandetanib, then every 6 cycles (about 6 months) as long as you are receiving the experimental drug. The visits every 6

months may be done by your physician at home, and the results can be sent to NIH. Once a year you will be asked to return to NIH for your evaluation.

If you are female and able to have children, a urine or blood pregnancy test will be done each time you have scans (every 6 cycles).

While you are on this research study, we will perform a blood test once a year to screen you for pheochromocytoma, which is another type of tumor that occurs more frequently in people with MEN. This test is called metanephines and nor-metanephrines are elevated in patients with a pheochromocytoma.

You may continue to receive Vandetanib indefinitely unless you decide to stop for any reason, you have unacceptable side effects that are not controlled by lowering the dose, your tumor grows, you are unable to keep scheduled medical appointments or take the study medication as instructed, the doctors taking care of you feel it is not in your best interest to continue, or a better therapy becomes available. If you become pregnant you will need to stop taking Vandetanib. While you are being treated with Vandetanib, doctors at the NIH will provide you with any new information that develops which may affect your health, welfare, or willingness to stay on the study. If you come off of the treatment for any of the reasons listed above, we would like to continue to check up on you periodically through phone calls to you, your family or your home doctor's office.

Tumor Biopsy

You may have been asked to have a biopsy of your tumor that would be used for research to help us better understand your cancer. If you agreed to having the biopsy and you enrolled on an additional Pediatrics Oncology Branch protocol, 12-C-0178, *Longitudinal Assessment and Natural History Study of Children and Young Adults with MEN2A or MEN2B with or without Medullary Thyroid Carcinoma,* the biopsy sample will be shared with the researchers in charge of that study. On that study, the sample will be used to find changes in your gene make up and to grow pediatric MTC cell lines. Whole blood may have been obtained to assess your gene make up. These tests would also be done on 12-C-0178. The risks of genetic testing will be explained in the consent for that study (12-C-0178).

Risks or Discomforts of Participation

You should talk to your study doctor about any symptoms that you experience while taking part in the study

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

The side effects of Vandetanib have been studied in animals and in over 500 adults. Vandetanib may involve other risks, including possible life-threatening reactions that are not known at present. You may experience some, none, or all the possible side effects of vandetanib. The side effects most likely to occur (Very common – experienced by more than 10% of patients taking vandetanib) are:

- skin rashes
- diarrhea
- fatigue
- nausea and/or vomiting
- cramping pain in the abdomen associated with diarrhea
- loss of appetite
- weight loss
- indigestion
- headache
- high blood pressure
- a change in the heart's electrical conduction system (QTc prolongation) that could lead to an irregular heart beat or sudden death (the heart rhythm change has been observed in one adult)
- trouble sleeping

Patients taking vandetanib may develop a skin rash which may become severe but is manageable with proper treatment. Vandetanib may also make your skin more sensitive to the sun. It is recommended that you take preventative action to prevent the rash from occurring whilst receiving study medication and for 3 to 4 weeks after stopping treatment by using the following guidelines:

- Avoiding direct sunlight
- Covering sun exposed skin with clothing (long pants, long sleeve shirts and hats)
- Using a SPF 45 or higher sunblock or sun protection cream
- Notifying study doctor when the first sign of a rash occurs so he or she may take the appropriate steps in preventing the rash from becoming severe

Your blood pressure will be monitored carefully on the study and, if found to be elevated, a medication (enalapril) to lower your blood pressure can be used. If you have uncontrolled high blood pressure, this elevated pressure can cause damage to other organs including the heart,

kidneys, or brain. Having uncontrolled blood pressure increases the risk of heart attack and stroke in adults. Usually there are no symptoms of high blood pressure, however, dizziness, headache or nose bleed can occur.

AstraZeneca has observed changes in ECGs in some patients being treated with vandetanib. These changes in the ECG may be drug-related and usually occur without symptoms; accordingly, frequent safety follow-up visits have been built into all studies. Similar changes in the ECGs of patients receiving other medications have led to heart rhythm changes, some of which have been life threatening. **However, it is estimated that between 0.1 to 1% of patients receiving vandetanib 300 mg have developed heart rhythm changes linked to life-threatening arrhythmia called Torsades de Pointes. Torsades de Pointes has been associated with sudden death.** If any such changes are noted on your ECGs, you may need to attend additional visits for further safety assessments.

The risk of developing changes in the ECG and serious heart rhythm changes will be greater if you have diarrhea, blood electrolyte imbalance (imbalance of minerals in your blood), vomiting, high fever, faintness or dizzy spells, or are unable to maintain a normal diet. You should report any of these symptoms to your study doctor immediately. You should review your medications and diet with your study doctor at each visit while you are continuing to receive study drug.

Changes in the heart rhythm may cause rapid or irregular heartbeat, dizziness, light-headedness, chest discomfort, shortness of breath, or losing consciousness. These or other new symptoms or possible side effects should be reported immediately to your study doctor.

In addition, anxiety, depressed mood, and trouble sleeping have been seen in some patients. These events may not be directly related to vandetanib, but rather to symptoms associated with cancer or other effects related to vandetanib such as skin rash.

Common (Experienced by 1 – 10% of patients taking vandetanib)

- Weakness,
- dehydration,
- abnormalities in tests of blood or urine (generally mild),
- stroke,
- cough,
- mild nose bleeding,
- feeling depressed,
- abnormal taste in mouth,

- dry mouth,
- blurry vision, dry or irritated eyes, and
- kidney stones have been reported.

Uncommon (Experienced by fewer than 1% of patients taking vandetanib)

- Small bluish/purple spots on the skin are uncommon.
- Heart failure, which is the weakening of the heart's ability to pump blood, has also been reported and may be related to vandetanib. We will be monitoring your heart function with an echocardiogram. If significant changes occur, we may need to stop therapy.
- Some patients have had seizures while taking vandetanib, and in one case a patient with seizures also had swelling in the brain that was found on an MRI scan, which got better after vandetanib was stopped. If you develop seizures, dizziness, headache, changes in your vision, or confusion, you should let your study doctor know as soon as possible. These may be symptoms of reversible posterior leukoencephalopathy syndrome (RPLS).
- **A very small number of patients with lung cancer receiving vandetanib have developed shortness of breath and cough because of an inflammation of scar tissue formation in the lungs, although this symptom could also be due to the underlying lung cancer.**
- A few patients have developed an inflammation of the pancreas.

The long-term side effects of Vandetanib for the treatment of MEN-related medullary thyroid cancer in children and adolescents are not known. It is possible that there may be temporary or permanent side effects of Vandetanib that have not yet been identified. Studies in mice have suggested that Vandetanib can slow wound healing. In growing animals, Vandetanib can cause a reversible widening of the growth plate in the bones, and this could affect the growth of all bones in the body. We will perform an MRI of your knee before starting treatment, and if the growth plate of the thigh bone is still open (the bone is still growing), we will monitor the effects of Vandetanib on this growth plate periodically by MRI.

There are minor risks associated with drawing blood for the pharmacokinetic studies and other research tests. If blood needs to be drawn from a vein in your arm, this will cause some pain and may result in bruising at the site of the needle stick. If a bruise does form at the end of the needle puncture site, it will generally go away on its own without any treatment. If you have a central venous catheter, drawing blood from this line is associated with a small chance of infection, which could require treatment with antibiotics or, rarely, removal of the line. The total amount of blood to be drawn for this study for research studies is approximately 3 tablespoons.

If you are a woman of child-bearing potential, there might be unknown risks to the unborn child if you are or if you become pregnant during the study. Due to these risks, you must not participate in this study if you are pregnant, or plan to become pregnant during the research study period, or are breast-feeding a child.

If you are a woman of child-bearing potential:

- By signing this consent form, you confirm to the best of your knowledge that you are not pregnant now and you do not intend to become pregnant during this study
- A pregnancy test will be done to confirm that you are not pregnant before you take part in this study
- You must avoid becoming pregnant and use an acceptable method of birth control during this study.

If at any time during this study you think you might be pregnant, or later learn that you were pregnant during the study, you must contact the study doctor immediately for further instructions about your participation in this study and follow-up.

If you are a male subject, the study drug used in this study could affect your sperm and could potentially harm a child that you may father while in this study. You must avoid unprotected sex with a pregnant partner (or woman of child-bearing potential not using birth control) or donating sperm during the study and for three months following the last dose, since the potential for problems with the fetus has not yet been thoroughly investigated. You should use a condom during the trial and for three months following the last dose.

If your partner becomes pregnant, you must notify the study doctor of any outcomes of the pregnancy from the date of the first dose until 14 days after last dose of vandetanib.

You will have a CT scan, MRI, and bone scan to measure the size of your cancer(s) before starting the treatment and some or all of these scans will be used to periodically monitor the change in the size of your cancer(s) on Vandetanib. These scans are common standard imaging tests used in the diagnosis and monitoring of many diseases. Although these tests have been in use for many years, their potential long term effects on the body are still being learned. The most common discomfort is the length of time you must lay still or flat while a scan is being performed. Occasionally, a patient may become uncomfortable within the enclosed space of the scanners (claustrophobia), particularly during a MRI. If this occurs, cool air can be blown over you by a fan if desired or your doctor can order a medicine to help you relax during this scan. Keeping the room well lit can also reduce this claustrophobic feeling. If a contrast agent (the special dye) is given with the scan there is a small risk of having a reaction to the contrast. These reactions can include nausea, pain in the vein where the contrast was given, headache, a metallic or bitter taste in the mouth, and a warm or flushing feeling that lasts from 1-3 minutes. Rarely, these symptoms may require treatment. In very rare cases, people have had more severe allergic reactions that result in shortness of breath, wheezing, or lowering of the blood pressure.

If you have had a reaction in the past, be sure to tell your doctor or nurse about it. The radiation dose you receive, if your scans include the use of X-rays or radioactive chemicals, is within the safe limits defined by the NIH Radiation Safety Guidelines, and is considered essential for your medical care.

In some cases, you may require medicines to make you sleep so you can be still during the procedure. The risks from this sedation or anesthesia are dependent on the types of medication used. These risks will be fully explained to you prior to the procedure and a separate informed consent will be obtained for anesthesia.

We may need to insert an IV line for administration of the contrast or anesthesia. This can cause pain at the site where the IV is placed and carries a small risk of bruising or infection.

Patients with a cardiac pacemaker, neural pacemaker, some types of surgical clips, cochlear implants, foreign metal objects, permanent retainers, or any iron-containing material within the body should not undergo a MRI, because of the effect of the strong magnet on these objects.

Potential Benefits of Participation

Are there benefits to taking part in this study?

Vandetanib may cause your cancer to stop growing or shrink in size for a period of time or it may lessen the symptoms, such as diarrhea, that are caused by the cancer. Because there is little information about the drug's effect on cancer in children and adolescents, we do not know if you will benefit from taking part in this study, although the knowledge gained from this study may benefit others.

Alternative Approaches or Treatments

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

Alternatives to Vandetanib include:

- the use of conventional drugs that were previously used in the treatment of your cancer,
- other conventional anticancer drugs that are not routinely used to treat your type of cancer,
- other experimental therapies, or
- getting no anticancer treatment but receiving comfort care, also called palliative care. This type of care tries to 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

Joining this research study is voluntary. You may ask the doctors and nurses any questions about this treatment. If you decide at any time that you do not want to receive this treatment any more, then tell us and we will discontinue it. You may be eligible to receive experimental therapy other than the Vandetanib or you can receive therapy consisting of symptomatic treatment only. Participation in this research trial may make you ineligible to participate in other experimental drug trials.

AstraZeneca is the pharmaceutical manufacturer of Vandetanib.

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 other authorized people including representatives of the NCI or drug manufacturer (AstraZeneca Pharmaceuticals, LP).

What are the costs of taking part in this study?

If you choose to take part in the study, the following will apply, in keeping with the NIH policy:

- You will receive study treatment at no charge to you. This may include surgery, medicines, laboratory testing, x-rays or scans done at the Clinical Center, National Institutes of Health (NIH), or arranged for you by the research team to be done outside the Clinical Center, NIH if the study related treatment is not available at the NIH.

- There are limited funds available to cover the cost of some tests and procedures performed outside the Clinical Center, NIH. You may have to pay for these costs if they are not covered by your insurance company.

- Medicines that are not part of the study treatment will not be provided or paid for by the Clinical Center, NIH.

- Once you have completed taking part in the study, medical care will no longer be provided by the Clinical Center, NIH.

Will your medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- National Cancer Institute Institutional Review Board
- The study Sponsor CTEP or their agent(s)
- Qualified representatives from AstraZeneca, the pharmaceutical company who initially produced Vandetanib.
- Qualified representatives from Genzyme Corporation, the pharmaceutical company who is now responsible for Vandetanib.

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

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 AstraZeneca 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.

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.

AstraZeneca was providing vandetanib for this study to NIH without charge. Genzyme is currently providing vandetanib for the study. No NIH investigator involved in this study receives payments or other benefits from any company whose drug, product or device is being tested. However, there are some non-NIH collaborators on this study who may receive payments or benefits, limited by the rules of their workplace.

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, 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, Brigitte Widemann; 10/1-5750; Telephone: 240-760-6203. Another researcher you may call is: Trish Whitcomb, Telephone: 240-760-6104. 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 APRIL 22, 2020 THROUGH APRIL 21, 2021.

Signature of Investigator _____ Date _____ Signature of Witness _____ Date _____

Print Name _____ Print Name _____