

Official Title: APN401 in Treating Patients With Recurrent or Metastatic Pancreatic Cancer, Colorectal Cancer, or Other Solid Tumors That Cannot Be Removed by Surgery

IRB-Approved Date: 5-13-2019

NCT03087591

Section on *Hematology and Oncology*

Safety and Immunologic Activity of Multiple Infusions of APN401

Informed Consent Form to Participate in Research

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INTRODUCTION

You are invited to be in a research study. Research studies are designed to gain scientific knowledge that may help other people in the future. You are being asked to take part in this study because you have been diagnosed with a cancer that has spread and cannot be surgically removed. Your participation is voluntary. Please take your time in making your decision as to whether or not you wish to participate. Ask your study doctor or the study staff to explain any words or information contained in this informed consent document that you do not understand. You may also discuss the study with your friends and family.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to test the effects of a treatment to boost your immune system to treat your cancer, called APN401. There are factors in immune cells in the blood that impede their ability to kill cancers. Cbl-b is one of these factors. APN401 treats your own white blood cells in the laboratory with a genetic inhibitor of Cbl-b. This treatment will require you to undergo leukapheresis, a laboratory procedure in which white blood cells are separated from a sample of blood. Your white blood cells are then treated in the laboratory and then infused back into you the next day. We would like to find out what effects, good and bad, APN401 may have on you and your cancer.

APN401 is an investigational drug. This means it has not been approved by the U.S. Food and Drug Administration (FDA). Drugs and devices that do not have approval by the FDA cannot be sold or prescribed by your physician.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

We plan to have 12 people take part in this study.

WHAT IS INVOLVED IN THE STUDY?

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests, or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your doctor. These include:

- Medical history: You will be asked questions about your health, current medications, and any allergies.
- Physical exam: The research doctor or another research healthcare professional will complete a physical assessment, including blood pressure, pulse, rate of breathing, temperature, and height and weight.
- Assessment of your cancer: This will include CT scans (computerized tomography, also

known as a CAT scan). A CT scan uses computers and x-rays to take detailed pictures of areas inside your body. A CT of your chest and abdomen must be performed within 4 weeks of starting study treatment. Your doctor may also recommend other CT scans or other types of scans, such as a magnetic resonance imaging (MRI) scan, a positron emission tomography (PET) scan, or a bone scan to assess the extent of your tumor. MRI and PET scans use computers and magnets to see detailed pictures of areas inside your body. These scans are part of regular medical care.

- Blood tests: Blood (about 4-6 tablespoons) will be taken from a vein in your arm to check blood cell counts and how well your organs are functioning. The presence of infection with HIV and hepatitis viruses will also be checked. Tests of your immune system will be performed as part of the research.
- Blood test for pregnancy: if you are a woman of child-bearing potential. This test must be collected within 3 days of study enrollment. Approximately one teaspoon of blood or less will be drawn for this test.

If these tests show that you are eligible to participate in the research study, you will begin the study treatment. If you do not meet the eligibility criteria, you will not be able to participate in this research study.

During treatment

If you meet the screening entry criteria, your white blood cells will be collected by leukapheresis. Your white blood cells will be taken to a laboratory and treated to make your specific APN401. The day after leukapheresis you will receive an infusion of your specific APN401. All visits and procedures related to treatment will be performed on an outpatient basis. You will receive up to three infusions of APN401.

- Leukapheresis: Leukapheresis is a laboratory procedure in which white blood cells are separated from a sample of blood. If you meet the screening entry criteria, your white blood cells will be collected by leukapheresis. You must sign a separate clinical consent forms before you have the procedure. A needle is inserted into one arm and blood is withdrawn and passed through a machine that removes only white blood cells. The rest of the blood is returned to you through a needle in your other arm. You will undergo this procedure the day, before the APN401 infusion. Before the leukapheresis procedure, you will be seen by one of the nurses in the leukapheresis unit to determine if your arm veins are large enough for this procedure. If the nurses do not think your veins are large enough, a small flexible tube called a “catheter” must be placed in the large vein. This procedure will be performed by an experienced physician as an outpatient procedure. You must sign a separate clinical consent form for this procedure. During the leukapheresis procedure, you will receive two solutions, saline and a low dose of a medication that helps your blood from clotting, through your vein. The equipment used is sterile and never re-used. Leukapheresis will take up to three hours. A doctor will be available on call in the hospital and a nurse will be in attendance and in charge of your immediate medical care. In addition, white blood cells and plasma from the procedure will be saved. After your white blood cells are collected, they will be taken to a laboratory and treated to make your specific APN401. This process takes one day.
- APN401 infusion: You will return the day after the leukapheresis to have your treated

white blood cells infused back into you by injection into a vein or catheter.

- Physical Exams: Before and after the APN401 infusion, you will have a physical exam, including measuring your weight. You will be asked questions about your general health and specific questions about any problems that you might be having and any medications you may be taking.
- Please tell your doctor about any medical treatments that you will have to get during the study (such as elective surgery).
- Blood Tests: Every 2 weeks, you will undergo blood tests to closely follow you after you receive the infusions. These tests will check blood cell counts and how well your organs are functioning. These tests will be done more often than if you were not on this study. Approximately 4-6 tablespoons of blood will be needed at each visit.

After treatment

You will be asked to return to the clinic 2 weeks following the final infusion of APN401 and then every 8 weeks. The following tests/exams will be performed:

- Physical Exam: This includes weight and vital signs and questions about your current health, including any changes in your symptoms and any medications you are taking.
- Blood tests: About 4-6 tablespoons of blood will be drawn to check your blood cell counts, how your organs are functioning, and any effects the infusions may have on your blood. Blood tests to see how the drug affects your immune system will also be performed. These blood tests are for research purposes. This will be done up to 10 times and possibly more over a year.
- Assessment of your cancer: a CT scan of your chest, abdomen, and pelvis, and/or an MRI and/or a PET scan will be performed. If your disease is found to be improving, you may be asked to repeat the CT and/or MRI and/or PET scans in about 4 weeks. These scans are part of regular medical care.
- After you are finished taking all study-related treatment, the study doctor will ask you to visit the office for follow-up every 2 months for at least one year. These will include physical exams, blood tests and assessment of your cancer. We will also call you on the phone to keep track of your medical condition every 2 months (if within 2 years of study registration) and every 6 months (if within 2-5 years of study registration). We would like to keep track of your medical condition for 5 years from study entry.

HOW LONG WILL I BE IN THE STUDY?

You will be in the study possibly for up to a year or more. If you experience serious side effects, however, you may be taken off of the study at any point this occurs or for if the Principal Investigators feels it is necessary regarding your care.

You can stop participating at any time. If you decide to stop participating in the study we encourage you to talk to the investigators or study staff first to learn about any potential health or safety consequences.

WHAT ARE THE RISKS OF THE STUDY?

Being in this study involves some risk to you. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen.

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 soon after you stop taking the infusions. In some cases, side effects can be serious, long lasting, or may never go away. There is also the risk of death. You should talk to your doctor about any side effects that you have while taking part in the study.

- **Blood Draws:** Occasionally, bruising, swelling, redness or tenderness at the blood drawing site and lightheadedness (fainting) or infection could occur.
- **Catheter:** If you do not have adequate veins in the arms for leukapheresis, a catheter may need to be placed in your neck or under your collar bone for the leukapheresis, instead of using IV lines in your arms. This procedure may be painful. An expected side effect is a reaction at the insertion site, including redness or skin ulceration. Shortly after the insertion of the catheter, the site may be slightly red and swollen. There is a small chance of bleeding or infection as a result of the catheter insertion. Sterile techniques will be used for this procedure. One of the rare but serious effects of leukapheresis and catheter placement is development of a blood clot in the vein where the catheter is placed.
- **Leukapheresis:** Leukapheresis is commonly used to treat patients with certain blood diseases, as well as to collect cells and plasma in healthy donors at clinics or at the Red Cross. Leukapheresis is considered safe, but some discomforts may occur during the procedure. These include discomfort and bleeding at the site where the needles are inserted, headache, muscle cramping, feeling of anxiety, rarely hypotension (decrease in blood pressure), chills, nausea, vomiting, dizziness, and fainting. There may also be a slight increased bleeding tendency for up to twenty minutes after the procedure. There is also a risk of infection at the site. If a severe discomfort should occur during leukapheresis, the procedure will be stopped immediately and you will be monitored until you are ready to go home. Serious adverse reactions to leukapheresis are extremely rare because your blood never leaves the sterile tubing circuit and every precaution is taken to ensure safety. You may experience mild side effects such as chills, a tingling sensation on your face or body, or lightheadedness. You will be instructed to limit your activities for several hours afterwards. One common side effect from the leukapheresis procedure is caused by the medication used to prevent clotting, which may cause a drop in the concentration of calcium in your blood. The first symptoms of this occurring are tingling, vibrating, or a numb feeling of the face, lips, teeth, hands, or feet. You will be instructed to tell the nurse immediately if you have any of these symptoms. You will be given calcium replacement to prevent or treat these symptoms. There are rarely serious complications resulting from leukapheresis. These include but are not limited to air entry into the blood stream, infection, shock, irregular heartbeat or heart failure. Also, as in any donation of blood, there are a variety of minor reactions that may occur such as fainting, dizziness, nausea, and bruising/swelling around the needle site. In rare instances, the small amount of blood remaining in the tubing cannot be returned to the patient. Any feeling of discomfort experienced during or after should be brought to the attention of the Leukapheresis Unit staff. If any complications arise, the Leukapheresis nurse and medical staff will provide immediate treatment.

- APN401: The side effects of APN401 are not known. Similar types of cells from patients have been infused and have been well tolerated. Side effects have included fever, chills, nausea, vomiting, shortness of breath, itching, fatigue, low blood pressure, fast/irregular heartbeat, and joint pain. If you have a reaction to the infusion, you will be treated with medications to treat your symptoms. The study infusions may be associated with the risk of infection due to potential contamination of the cells in the laboratory, which may lead to injection of a product infected with bacteria/fungus. This may result in localized redness, swelling, or an area of hardening at the infusion site. In the most extreme situation, this may lead to generalized bacterial/fungal infection and possibly death. The probability of this risk is relatively low, given the fact that APN401 will be strictly tested for sterility prior to each injection.

The treatment or procedure may involve risks that are currently unforeseeable. You should tell your doctor immediately if you think you are developing any unusual side effects even if they weren't listed here or any of the side effects or symptoms listed.

As part of this study, you will be tested for HIV (human immunodeficiency virus, which is the virus that causes the acquired immunodeficiency syndrome [AIDS]); Hepatitis B and C. You will be told of the results of the testing, and counseled as to the meaning of the results, whether they are positive or negative. If the test indicates that you are infected with HIV, Hepatitis B or C, you will receive additional counseling about the significance of your care and possible risks to other people. We are required by law to report all positive results to the North Carolina State Board of Health. The test results will be released only as permitted by applicable law. If you do not want to be tested for HIV, Hepatitis B or C, you should not agree to participate in this study.

Over-the-counter (OTC) drugs may cause major side effects. Acetaminophen (Tylenol) and NSAIDS (such as Advil, Motrin, Motrin IB, Nuprin) found in most common OTC products for cold, headaches, muscle aches, and fever are safe and effective when used correctly, but too much can damage the liver. Be cautious when using OTC products. If you choose to take an OTC product, inform the nursing staff or your doctor about the drug.

In addition, there is a slight risk of a breach of confidentiality. We will do our best to protect your confidential information. There also may be other side effects that we cannot predict. You should tell the research staff about all the medications, vitamins and supplements you take and any medical conditions you have. This may help avoid side effects, interactions and other risks.

Taking part in this research study may involve providing information that you consider confidential or private. Efforts, such as coding research records, keeping research records secure and allowing only authorized people to have access to research records, will be made to keep your information safe.

REPRODUCTIVE RISKS AND OTHER ISSUES PARTICIPATING IN RESEARCH

You should not become pregnant or father a baby while on this study because the drugs in this study can affect a fetus. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your doctor about what kind of birth control methods to use and how long to use them. Some methods might

not be approved for use in this study.

The drugs used in this research study may affect a fetus/embryo. While participating in this research study, you should not become pregnant, father a baby, or nurse a baby. Let your doctor know immediately if you become pregnant or find out that you are going to be the father of a child. We can provide counseling about preventing pregnancy for either male or female study participants.

Laboratory studies have been done to test for any possible reproductive risks. Studies that help us see if APN401 may affect your ability to have children have not been done. It is not known whether APN401 can cause fetal harm when administered to a pregnant woman or whether APN401 can affect reproductive health. It is possible that if the study drugs are given to a pregnant woman it will harm the fetus (unborn baby). Therefore, pregnant women must not take part in this study. Women who could become pregnant will be asked to have a pregnancy test prior to and throughout participation on this study and must use an approved form of birth control during the course of this study and for up to 26 weeks after your last infusion with APN401. Tell your doctor immediately if you suspect you have become pregnant.

For women: You must use birth control while participating in this study. If you are able to have children, you must always use a type of birth control that your study doctor thinks is reliable while you are participating in this study and for 26 weeks after your infusion with APN401. For example: (1) surgical sterilization (such as hysterectomy, surgical removal or tying/ligation of fallopian tubes), (2) approved hormonal contraceptives such as birth control pills, (3) barrier methods (such as condom or diaphragm) used with a spermicide, or (4) an intrauterine device (IUD). If you do become pregnant during this study, you must inform your study physician immediately. Your study doctor should be informed of any hormonal contraception (oral contraceptives, implantable or injectable agents) not prescribed by him/her. The purpose of this is to identify any potential interactions between the product on study and the contraceptive, which might reduce the effectiveness of the contraceptive method. You must have a negative pregnancy test before study medication can be given at each visit.

For men: Sexually active males in this study must use appropriate precautions. If sexually active, you must agree to use adequate contraception, for the duration of the study and for 26 weeks after your infusion of APN401. Practicing abstinence is an acceptable method of contraception. Medically acceptable contraceptives include: (1) surgical sterilization (such as a vasectomy), or (2) a condom used with a spermicide. Contraceptive measures such as Plan B (TM), sold for emergency use after unprotected sex, are not acceptable methods for routine use. You should inform your partner of the potential for harm to an unborn child. She should know that if pregnancy occurs, you will need to report it to the study doctor, and she should promptly notify her doctor.

There is no information available to know if the treatment under investigation will damage sperm, which could potentially lead to fetal damage. Sexually active males in this study must use appropriate precautions. You are asked to inform your study doctor if your partner becomes pregnant while you are enrolled in this clinical trial, and you and your partner will be asked to provide information about the pregnancy outcome. The Sponsor has not set aside any funds to

pay for any aspects of obstetric, child, or related care and does not plan to pay for them. If you become pregnant, suspect pregnancy, if you have a change in your menstrual cycle, or change in your contraception method, you should immediately contact your doctor. Should you become pregnant during the study, you will be withdrawn from the study immediately and should seek care from a doctor who specializes in pregnant women (an OB/GYN, or obstetrics and gynecologist physician). If you become pregnant during the study, the sponsor has no plan or policy to reimburse you for medical costs associated with the pregnancy, or for the cost of your child's care.

In the case of a pregnancy your doctor will ask you to agree to allow access to your medical records and to the medical records of your infant for a minimum of 8 weeks after delivery.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

Taking part in this study may or may not make your health better. While doctors hope that APN401 will reduce your cancer, there is no proof of this. We do know that the information from this study will help doctors learn more about this approach as a treatment for cancer. This information could help future cancer patients.

WHAT OTHER CHOICES ARE THERE?

You do not have to be in this study to receive treatment. You should talk to your doctor about all the choices you have. Instead of being in the study, you have these options:

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting no treatment
- 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, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

WHAT ABOUT MY HEALTH INFORMATION?

In this research study, any new information we collect from you and information we get from your medical records about your health or behaviors is considered Protected Health Information. The information we will collect for this research study includes: demographic information, medical history, current medications, treatment information, results of blood tests and imaging scans.

If this research study involves the diagnosis or treatment of a medical condition, then Protected Health Information collected from you during this study will be placed in your medical record, and may be used to help treat you, arrange payment for your care, or assist with Medical Center operations.

We will make every effort to keep your Protected Health Information private. We will store records of your Protected Health Information in a cabinet in a locked office or on a password protected computer. Only the following people or organizations will be granted access to your Protected Health Information:

- 1) The study investigator and his/her staff, or others at Wake Forest University Health Sciences who oversee research
- 2) Other people or laboratories providing services for this research project on behalf of Wake Forest University Health Sciences and Wake Forest University Baptist Medical Center
- 3) Apeiron Biologics

If required by law or court order, we might also have to share your Protected Health Information with a judge, law enforcement officer, government agencies, or others. If your Protected Health Information is shared with any of these groups it may no longer be protected by federal or state law.

Any Protected Health Information collected from you in this study that is maintained in the research records will be kept for an indeterminate period of time. This authorization does not expire. Any research information entered into your medical record will be kept for as long as your medical record is kept by the Medical Center. You will not be able to obtain a copy of your Protected Health Information in the research records until all activities in the study are completely finished.

You can tell **Dr. Pierre L. Triozzi** that you want to take away your permission to use and share your Protected Health Information at any time by sending a letter to this address:

Pierre L. Triozzi, MD



However, if you take away permission to use your Protected Health Information you will not be able to be in the study any longer. We will stop collecting any more information about you, but any information we have already collected can still be used for the purposes of the research study.

By signing this form you give us permission to use your Protected Health Information for this study.

If you choose to participate in this study, your medical record at Wake Forest University Baptist Medical Center will indicate that you are enrolled in a clinical trial. Information about the research and any medications or devices you are being given as a participant may also be included in your medical record. This part of the medical record will only be available to people who have authorized access to your medical record. If you are not a patient at this Medical Center, a medical record will be created for you anyway to ensure that this important information is available to doctors in case of an emergency.

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This website will not include information that can identify you. At most, the

website will include a summary of the results. You can search this Web site at any time.

Laboratory test results and other medical reports created as a result of your participation in the research study may be entered into the computer systems of Wake Forest University Health Sciences and North Carolina Baptist Hospital. These will be kept secure, with access to this information limited to individuals with proper authority, but who may not be directly involved with this research study.

WHAT ARE THE COSTS?

Taking part in this study may lead to added costs to you or your insurance company. We will give you an estimate of what the added cost may be based on your particular situation and insurance coverage.

The study drug, APN401, will be provided to you at no cost. The following tests and procedures are for research purposes only and will be paid for by the study: screening blood tests (HIV, Hepatitis B, Hepatitis C, and tests to determine the time it takes for your blood to clot (PT/PTT), costs associated with leukapheresis, and placement of the central venous catheter (if required).

WILL YOU BE PAID FOR PARTICIPATING?

You will receive no payment or other compensation for taking part in this study. Parking validation will be provided for all study-related visits.

The findings from this research may result in the future development of products that are of commercial value. There are no plans to provide you with financial compensation or for you to share in any profits if this should occur.

WHO IS SPONSORING THIS STUDY?

This study is being sponsored by Wake Forest University Health Sciences. Apeiron Biologics is providing money or other support to Wake Forest University Health Sciences to help conduct this study. The researchers do not, however, hold a direct financial interest in the sponsor or the product being studied.

WHAT HAPPENS IF YOU EXPERIENCE AN INJURY OR ILLNESS AS A RESULT OF PARTICIPATING IN THIS STUDY?

Should you experience a physical injury or illness as a direct result of your participation in this study, Wake Forest University School of Medicine maintains limited research insurance coverage for the usual and customary medical fees for reasonable and necessary treatment of such injuries or illnesses. To the extent research insurance coverage is available under this policy the reasonable costs of these necessary medical services will be paid, up to a maximum of \$25,000. Wake Forest University Baptist Medical Center holds the insurance policy for this coverage. It provides a maximum of \$25,000 coverage for each claim and is limited to a total of \$250,000 for all claims in any one year. The Wake Forest University School of Medicine, and the North Carolina Baptist Hospitals, Incorporated do not assume responsibility to pay for these medical services or to provide any other compensation for such injury or illness. Additional information may be obtained from the Medical Center's Director of Risk and Insurance Management, at [REDACTED].

You do not give up any legal rights as a research participant by signing this consent form. For more information on medical treatment for research related injuries or to report a study related illness, adverse event, or injury you should call **Dr. Pierre L. Triozzi** at [REDACTED] (**24 hour number**).

WHAT ARE MY RIGHTS AS A RESEARCH STUDY PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or you may leave the study at any time. Refusing to participate or leaving the study will not result in any penalty or loss of benefits to which you are entitled. If you decide to stop participating in the study we encourage you to talk to the investigators or study staff first to learn about any potential health or safety consequences. The investigators also have the right to stop your participation in the study at any time. This could be because it is in your best medical interest, your condition worsened, new information becomes available, you had an unexpected reaction, you failed to follow instructions, or because the entire study has been stopped.

You will be given any new information we become aware of that would affect your willingness to continue to participate in the study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or in the event of a research-related injury, contact the study investigator, **Dr. Pierre L. Triozzi** at [REDACTED] (**24 hour number**).

The Institutional Review Board (IRB) is a group of people who review the research to protect your rights. If you have a question about your rights as a research participant, or you would like to discuss problems or concerns, have questions or want to offer input, or you want to obtain additional information, you should contact the Chairman of the IRB at [REDACTED]

You will be given a copy of this signed consent form.

SIGNATURES

I agree to take part in this study. I authorize the use and disclosure of my health information as described in this consent and authorization form. If I have not already received a copy of the Privacy Notice, I may request one or one will be made available to me. I have had a chance to ask questions about being in this study and have those questions answered. By signing this consent and authorization form, I am not releasing or agreeing to release the investigator, the sponsor, the institution or its agents from liability for negligence.

Subject Name (Printed): _____

Subject Signature: _____ Date: _____ Time: _____ am pm

Person Obtaining Consent (Printed): _____

Person Obtaining Consent: _____ Date: _____ Time: _____ am pm