PRINCIPAL INVESTIGATOR: **Christina M. Annunziata, MD, PhD**

STUDY TITLE: **Phase 1 Study of Intraperitoneal Infusion of Autologous Monocytes with Sylatron® (Peginterferon Alfa-2b) and Actimmune® (Interferon Gamma-1b) in Women with Recurrent or Refractory Ovarian Cancer, Fallopian Tube Cancer or Primary Peritoneal Cancer**

STUDY SITE: **NIH Clinical Center**

Cohort: Standard

Consent Version: February 11, 2020

WHO DO YOU CONTACT ABOUT THIS STUDY?

Principal Investigator: Christina Annunziata, MD

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This consent form describes a research study and is designed to help you decide if you would like to be a part of the research study.

You are being asked to take part in a research study at the National Institutes of Health (NIH). Members of the study team will talk with you about the information described in this document. 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). Take the time needed to ask any questions and discuss this study with NIH staff, and with your family, friends, and personal health care providers. Taking part in research at the NIH is your choice.

If the individual being asked to participate in this research study is not able to give consent for themselves, you, as the Legally Authorized Representative, will be their decision-maker and you are being asked to give permission for this person to be in this study. For the remainder of this document, the term "you" refers to you as the decision-maker and/or the individual being asked to participate in this research.

IT IS YOUR CHOICE TO TAKE PART IN THE STUDY

You may choose not to take part in this study for any reason. If you join this study, you may change your mind and stop participating in the study at any time and for any reason. In either case, you will not lose any benefits to which you are otherwise entitled. However, to be seen at the NIH, you must be taking part in a study or are being considered for a study. If you do choose to leave the study, please inform your study team to ensure a safe withdrawal from the research.

WHY IS THIS STUDY BEING DONE?

We are investigating the ability of an immune cell found in blood, called monocytes, in combination with inflammatory signals, cytokines Interferon Alfa-2b and Interferon Gamma-1 to kill tumor cells.

Monocytes are a type of white blood cell found in human blood which play a role in the body's immune system.

Interferons (IFNs) belong to the large class of proteins known as cytokines, molecules used for communication between cells to trigger the protective defenses of the immune system that help destroy the microorganisms that can cause disease. IFNs activate immune cells, such as natural killer cells and macrophages, and boost the immune system by increasing the cancer targets available for the white blood cells. By combining monocytes with interferons, we have found in our trials with mice that the monocytes turn into cells that can kill the cancer cells.

The purpose of this study is to find a safe dose of interferons in combination with your monocytes obtained the previous day and to measure whether the study therapy can shrink your tumor and lengthen the time it takes for your disease to get worse. The combination of the medications used in this study, Sylatron® (Peginterferon Alfa-2b) and Actimmune® (Interferon Gamma-1b), with your monocytes, plus the preparation of the monocytes and route of administration, infusion into the abdomen, is investigational, which means it has not yet been approved by the FDA.

WHY ARE YOU BEING ASKED TO TAKE PART IN THIS STUDY?

You are being asked to take part in this study because you have been diagnosed with metastatic or unresectable epithelial ovarian cancer, primary peritoneal cancer or fallopian tube cancer that is relapsed and resistant to prior standard care systemic treatment.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

Up to 40 women will take part in this study.

DESCRIPTION OF RESEARCH STUDY

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

Before you begin the study

This study includes a screening period to determine if you meet all of the criteria for study participation, called study eligibility. If you choose to participate, Dr. Annunziata and her research study staff will explain all procedures to be followed.

Screening Period

Once you have signed this consent, you will undergo several tests and evaluations to determine if you are a suitable candidate for this study, including your medical and cancer history.

You will need to have the following exams, tests or procedures when you first enroll 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 study doctor.

- Medical history, including your age, current activity level, and dates of prior treatments.
- A physical examination.
- Routine blood tests.
- A pregnancy test if you are a woman who can have children.
- Scans: A CT of the chest, abdomen and pelvis to assess the disease process.
- A report confirming your diagnosis based on your biopsy results or sample from a previous biopsy to confirm the type of tumor you have.

The various procedures described above provide a baseline assessment of your health and the status of your cancer so that you can be monitored effectively throughout your participation in the trial. The results of this testing will be reviewed and discussed with you. If the results of this testing indicate that you are not eligible for this study, you will be removed from this study and alternative therapies for your cancer may be discussed. Only after you are confirmed to be eligible thus far will the next steps occur.

Research Procedures

Once you have completed the eligibility assessments described above, you will have the following research procedures.

- Blood samples: Blood will be collected to study immune cells.
- Ascites samples: If you have a collection of fluid in your abdominal cavity known as ascites, a sample will be taken to study the immune cells in a manner similar to the blood samples.
- Intraperitoneal (IP) catheter placement: An IP catheter will be placed inside the abdominal cavity unless you already have one, or unless you have a port. This catheter will be used to administer the monocytes mixed with Sylatron® and Actimmune®.
- Port placement: If you don't already have a port, and the IP catheter isn't a viable option for you, a port may be placed. This port will be used to administer the monocytes mixed with Sylatron® and Actimmune®.
- Leukapheresis: An IV will be placed and a portion of your blood will be removed and passed through an apparatus that separates out the monocytes, returning the rest of your cells and blood to your body. This process can take up to 3-4 hours and will be done at the Department of Transfusion Medicine. On days of apheresis, stay well hydrated and avoid caffeine. Eat a calcium rich breakfast preferably including yogurt, milk, calcium-fortified orange juice, bananas, blueberries, cereal or almonds.

  Extra monocyte cells collected during leukapheresis will be stored and used for treatment for up to 3 subsequent treatments. Therefore, depending on the cells collected, the leukapheresis process can occur every 1-3 cycles.

- Biopsy: If you are a member of the expansion group, you will have an optional biopsy of your tumor at the time of catheter or port placement. The tissue obtained from this

biopsy will be used to study the different types of immune cells present in your tumor. You will be given the chance to decide whether you want to have the biopsy at the scheduled collection time.

If you are determined to be ineligible for this study on the basis of any of the screening tests or procedures, you will be referred back to your home doctor for care.

During the study

Day	What to do and what will happen to you
Cycle 1	
Day -1or Day -2	Blood samples may be collected if the samples provided during the screening period were longer than 7 days prior to the treatment start date.
Day 1	The first three participants in this study received interferon only. All others will receive the monocytes mixed with Sylatron® (Interferon Alfa-2b) and Actimmune® (Interferon Gamma-1b). You will be observed overnight in the hospital.
Day 2	You will be discharged from the hospital with the IP catheter or port in place.
Day 27	Blood samples will be collected. Ascites samples will be collected, if present.
Cycle 2 and beyond	
Day 1	The first three participants in this study received interferon only. All others will receive the monocytes mixed with Sylatron® and Actimmune®. You will be observed overnight at the clinic. If you are a member of the expansion group, an optional biopsy of your tumor will be done. You will be given the chance to decide whether you want to have the biopsy at the scheduled collection time.
Day 2	You will be discharged from the hospital with the IP catheter in place.
Day 27-28	Imaging will be performed every 2 cycles. IV placement and leukapheresis will be performed every 1-3 cycles, depending on how many cells are collected during the leukapheresis.
Off Treatment	

	If you are a member of the expansion group, an optional biopsy may be performed at the time your disease worsens, to allow the investigators to study the effects the treatment may or may not have had on your tumor. You will be given the chance to decide whether you want to have the biopsy at the scheduled collection time. The research team's health care provider will go over your medical history and will perform a physical exam. Blood samples will be collected. You will receive follow-up phone calls every month.

When you are finished taking the treatment

Once you stop receiving treatment, you will have a clinic visit approximately 1 month after you discontinue taking the study drugs, in which the health care provider will perform a physical exam, blood will be drawn, and you will have a CT scan. You will then receive follow-up phone calls from the study team every month.

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, you will need to practice an effective form of birth control before starting, and during study treatment. If you think that you are pregnant, you should tell your study doctor or nurse at once.

Effective forms of birth control include**:**

- abstinence
- intrauterine device (IUD)
- hormonal [birth control pills, injections, or implants]
- tubal ligation
- vasectomy

RISKS OR DISCOMFORTS OF PARTICIPATION

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

Sylatron® (Peginterferon Alfa-2b)

Likely

- Flu- like symptoms in more than 30% of patients, including fever, chills, generalized aches and pains, headache, poor appetite. Occurs within 1-2 hours of treatment, may last up to 24 hours (over time the intensity of these symptoms decreases depending on the dose, how it is given, and the schedule of administration.

- Fatigue
- Increased liver enzymes (ALT, AST)
- Decreased appetite
- Injection site reaction in 10-30% of patients
- Nausea

Less Likely

- Rash
- Difficulty breathing, cough
- Dizziness
- Numbness, tingling
- Changes in hearing and taste
- Depression or anxiety

Rare but Serious

- Suicidal or homicidal thoughts, relapse of drug addiction/overdose and aggressive behavior. If you experience any of these neuropsychiatric events, you should tell your study doctor or nurse at once.
- Heart attack or irregular heart rhythm
- Visual changes, retinopathy
- Liver failure
- Hormonal gland abnormalities such has hypothyroidism, hyperthyroidism or diabetes mellitus

Actimmune® (Interferon Gamma-1b)

Likely

- Flu- like symptoms in more than 30% of patients, including fever, chills, generalized aches and pains, headache, poor appetite. Occurs within 1-2 hours of treatment, may last up to 24 hours (over time the intensity of these symptoms decreases depending on the dose, how it is given, and the schedule of administration).
- Rash
- Fatigue

Less Likely

- Diarrhea
- Vomiting
- Nausea
- Muscle aches
- Back pain
- Abdominal pain

- Depression

Rare but Serious

- Hypotension
- Heart attack or irregular heart beat
- Seizure
- Hallucination
- Pancreatitis
- Liver damage
- Deep venous thrombosis or pulmonary embolism
- Pneumonitis

Autologous Monocytes

Likely

- Fever
- Chills
- Abdominal Pain

Less Likely

- Nausea
- Shortness of breath

Rare but Serious

- **None reported**

Other Risks

Blood draws: The risks of taking blood are minor. Bruising may occur at the puncture site. You may feel some pain when the blood is drawn. Rarely, an infection may occur at the site where the needle was inserted. You may experience a feeling of lightheadedness that can be quickly relieved by lying down. To reduce your risk of falling, we will monitor you closely and ask you about these symptoms before we allow you to stand up. We will also collect additional blood specimens for research purposes, which may be obtained during routine blood drawing.

CT Scans: A CT scan is an X-ray procedure where a high-speed computer is used to make multiple images or pictures of your body. Sometimes, a contrast dye that contains iodine is administered into one of your veins to improve these images. In some cases, people might have an allergic reaction to this dye. You will be asked to lie still on a table and at times may have to

hold your breath for a few seconds in order to avoid blurring the pictures. You may hear a slight buzzing, clicking and/or whirring sounds as the CT scanner moves around your body.

IP Catheter/Port Placement: Possible side effects of IP catheter or port placement include allergic reaction to the local anesthetic, perforation of intestines, causing accumulation of intestinal bacteria in the peritoneal cavity, causing abdominal pain; and/or fluid collection in the abdomen, causing fever, low blood pressure, lightheadedness, or even death. With port placement, there is an added risk from general anesthesia if it is placed by a surgeon. This could include an allergic reaction to the drugs used, postoperative confusion, pneumonia, or even stroke and heart attack.

Leukapheresis: Side effects of leukapheresis include pain and bruising, dizziness, fatigue, feeling cold and nausea, and rarely, fainting. You can have tingling around the fingers and the mouth. On the days of leukapheresis, make sure that you stay well hydrated and avoid caffeine to prevent these symptoms and eat a calcium rich breakfast ideally including yogurt, milk, calcium fortified orange juice, bananas, blueberries, cereal or almonds.

Ascites collection: The risks associated with colleting ascites are pain and bleeding at the catheter site. In order to minimize pain, local anesthesia will be used. Rarely, there is a risk of infection at the sampling site. Ultrasound guidance may be used in obtaining ascites.

Biopsies: The risks of radiation associated with the biopsy procedure are described in the section below. Local anesthesia of the skin will be given prior to any tumor biopsy, in order to prevent painful sensations. However, you may still experience pain or discomfort at the biopsy site. Irritation, redness, swelling and/or bleeding may also occur. There is a risk of abnormal healing, fever, infection or of an allergic reaction to the anesthetic agent used to anesthetize the skin at the biopsy site. Once the sample has been obtained, a stitch may be used to close the wound and facilitate healing.

Radiation Exposure:

During your participation in this research study, you will be exposed to radiation from CT scans. The amount of radiation exposure you will receive from these procedures is equal to approximately 10.1 rem. A rem is a unit of absorbed radiation.

Every day, people are exposed to low levels of radiation that come from the sun and the environment around them. The average person in the United States receives a radiation exposure of 0.3 rem per year from these sources. This type of radiation is called “background radiation”. This study will expose you to more radiation than you get from everyday background radiation. No one knows for sure whether exposure to these low amounts of radiation is harmful to your body.

The CT scans that you get in this study will expose you to roughly the same amount of radiation as 33.7 years’ worth of background radiation. Being exposed to too much radiation can cause harmful side effects such as an increase in the risk of cancer. The risk depends on how much radiation you are exposed to. Please be aware that about 40 out of 100 people (40%) will get cancer during their lifetime, and 20 out of 100 (20%) will die from cancer. The risk of getting cancer from the radiation exposure in this study is 1 out of 100 (1%) and of getting a fatal cancer is 0.5 out of

100 (0.5%).

You may not participate in this study if you are pregnant. If you are able to become pregnant, we will perform a pregnancy test before exposing you to radiation. You must tell us if you may have become pregnant within the previous 14 days because the pregnancy test is unreliable during that time.

POTENTIAL BENEFITS OF PARTICIPATION

Are there benefits to taking part in this study?

The aim of this study is to see if this experimental treatment is safe and will cause your tumors to shrink. 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.
- Getting treatment with a drug called Olaparib (AZD-2281, Lynparza), which has been approved by the FDA for women with the BRCA mutation who have relapsed after three prior treatment regimens

Please talk to your doctor about these and other 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 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 Horizon Pharma, Inc. 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.

Horizon Pharma, Inc. is providing the drug, Actimmune® (Interferon gamma-1b), for this study to NIH without charge. No NIH employee involved in this study receives any payment or other benefits from Horizon Pharma, Inc.

Merck Sharp & Dohme Corp. is providing the drug, Sylatron® (Peginterferon alfa-2b), for this study to NIH without charge. No NIH employee involved in this study receives any payment or other benefits from Merck Sharp & Dohme Corp.

USE OF SPECIMENS AND DATA FOR FUTURE RESEARCH

To advance science, it is helpful for researchers to share information they get from studying human samples. They do this by putting it into one or more scientific databases, where it is stored along with information from other studies. A researcher who wants to study the information must apply to the database and be approved. Researchers use specimens and data stored in scientific databases to advance science and learn about health and disease.

We plan to keep some of your specimens and data that we collect and use them for future research and share them with other researchers. We will not contact you to ask about each of these future uses. These specimens and data will be stripped of identifiers such as name, address or account number, so that they may be used for future research on any topic and shared broadly for research purposes. Your specimens and data will be used for research purposes only and will not benefit you. It is also possible that the stored specimens and data may never be used. Results of research done on your specimens and data will not be available to you or your doctor. It might help people who have cancer and other diseases in the future.

If you do not want your stored specimens and data used for future research, please contact us in writing and let us know that you do not want us to use your specimens and/or data. Then any specimens that have not already been used or shared will be destroyed and your data will not be

used for future research. However, it may not be possible to withdraw or delete materials or data once they have been shared with other researchers.

COMPENSATION, REIMBURSEMENT, AND PAYMENT

Will you receive compensation for participation in the study?

Some NIH Clinical Center studies offer compensation for participation in research. The amount of compensation, if any, is guided by NIH policies and guidelines.

You will not receive compensation for participation in this study.

Will you receive reimbursement or direct payment by NIH as part of your participation?

Some NIH Clinical Center studies offer reimbursement or payment for travel, lodging or meals while participating in the research. The amount, if any, is guided by NIH policies and guidelines.

On this study, the NCI will cover the cost for some of your expenses. Some of these costs may be paid directly by the NIH and some may be reimbursed after you have paid. The amount and form of these payments are determined by the NCI Travel and Lodging Reimbursement Policy. You will be given a summary of the policy which provides more information.

Will taking part in this research study cost you anything?

NIH does not bill health insurance companies or participants for any research or related clinical care that you receive at the NIH Clinical Center.

- If some tests and procedures are performed outside the NIH Clinical Center, 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 NIH Clinical Center.
- Once you have completed taking part in the study, medical care will no longer be provided by the NIH Clinical Center.

CLINICAL TRIAL REGISTRATION AND RESULTS REPORTING

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.

CONFIDENTIALITY PROTECTIONS PROVIDED IN THIS STUDY

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 NIH and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- National Institutes of Health Intramural Institutional Review Board
- The study Sponsor, Center for Cancer Research or their agent(s)
- Qualified representatives from Horizon Pharma, Inc., the pharmaceutical company who produces Actimmune® (Interferon gamma-1b).
- Qualified representatives from Merck Sharp & Dohme Corp., the pharmaceutical company who produces Sylatron® (Peginterferon alfa-2b).

The researchers conducting this study and the NIH follow applicable laws and policies to keep your identifying information private to the extent possible. However, there is always a chance that, despite our best efforts, your identity and/or information about your participation in this research may be inadvertently released or improperly accessed by unauthorized persons.

In most cases, the NIH will not release any identifiable information collected about you without your written permission. However, your information may be shared as described in the section of this document on sharing of specimens and data, and as further outlined in the following sections.

Further, the information collected for this study is protected by NIH under a Certificate of Confidentiality and the Privacy Act.

Certificate of Confidentiality

To help us protect your privacy, the NIH Intramural Program has received a Certificate of Confidentiality (Certificate). With this certificate, researchers may not release or use data or information about you except in certain circumstances.

NIH researchers must not share information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if requested by a court.

The Certificate does not protect your information when it:

1. is disclosed to people connected with the research, for example, information may be used for auditing or program evaluation internally by the NIH; or
2. is required to be disclosed by Federal, State, or local laws, for example, when information must be disclosed to meet the legal requirements of the federal Food and Drug Administration (FDA);
3. is for other research;
4. is disclosed with your consent.

The Certificate does not prevent you from voluntarily releasing information about yourself or your involvement in this research.

The Certificate will not be used to prevent disclosure to state or local authorities of harm to self or others including, for example, child abuse and neglect, and by signing below you consent to those disclosures. Other permissions for release may be made by signing NIH forms, such as the Notice and Acknowledgement of Information Practices consent.

Privacy Act

The Federal Privacy Act generally protects the confidentiality of your NIH medical records we collect under the authority of the Public Health Service Act. In some cases, the Privacy Act protections differ from the Certificate of Confidentiality. For example, sometimes the Privacy Act allows release of information from your medical record without your permission, for example, if it is requested by Congress. Information may also be released for certain research purposes with due consideration and protection, to those engaged by the agency for research purposes, to certain federal and state agencies, for HIV partner notification, for infectious disease or abuse or neglect reporting, to tumor registries, for quality assessment and medical audits, or when the NIH is involved in a lawsuit. However, NIH will only release information from your medical record if it is permitted by both the Certificate of Confidentiality and the Privacy Act.

POLICY REGARDING RESEARCH-RELATED INJURIES

The NIH 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 NIH, the NIH Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

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. Christina Annunziata, annunzic@mail.nih.gov, 240 760-6125. You may also call the NIH Clinical Center Patient Representative at 301-496-2626, or the NIH Office of IRB Operations at 301-402-3713, if you have a research-related complaint or concern.

CONSENT DOCUMENT

Please keep a copy of this document in case you want to read it again.

Adult Research Participant: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I consent to participate in this study.

Signature of Research Participant	Print Name of Research Participant	Date

Legally Authorized Representative (LAR) for an Adult Unable to Consent: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I am legally authorized to make research decisions on behalf of the adult participant unable to consent and have the authority to provide consent to this study. As applicable, the information in the above consent was described to the adult participant unable to consent who agrees to participate in the study.

Signature of LAR	Print Name of LAR	Date

Investigator:

Signature of Investigator	Print Name of Investigator	Date

Witness to the oral short-form consent process only: This section is only required if you are doing the oral short-consent process and this English consent form has been approved by the IRB for use as the basis of translation.

Witness:

Signature of Witness*	Print Name of Witness	Date

***NIH ADMINISTRATIVE SECTION TO BE COMPLETED REGARDING THE USE OF AN INTERPRETER:**

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent and served as a witness. The investigator obtaining consent may not also serve as the witness.

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent but did not serve as a witness. The name or ID code of the person providing interpretive support is: _____.