University of Pittsburgh
Schools of Pharmacy and Medicine
Division of Pharmacy and Therapeutics and
Division of Pulmonary, Allergy, and Critical Care Medicine

CONSENT TO ACT AS A PARTICIPANT IN A RESEARCH STUDY

TITLE: Combination Therapy with the Proteasome Inhibitor Carfilzomib for the Antibody-Mediated Rejection Diagnosis in Lung Transplantation Trial (PICARD-Lung)

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Source of Support: Amgen

Why is this research being done?

This research is being done to help us understand how the immune system [composed of white blood cells and antibodies] responds to transplantation of the lung(s). These antibodies have attacked your new lungs and produced something called Antibody-Mediated Rejection (AMR), which leads to chronic rejection of the lungs. As a result of AMR, you are scheduled to receive a plasma exchange (PLEX) with IV (intravenous) immunoglobulin to remove these antibodies as part of your standard treatment. This research is to see whether a drug called Carfilzomib can help reduce the antibodies further when used with PLEX. Carfilzomib is FDA (Food and Drug Administration) approved for the treatment of a type of cancer called multiple myeloma, a cancer that starts in the bone marrow. It is not FDA approved for use in this study. This study is also being done to assess what factor(s) contribute to AMR. In particular, we are interested in the role that the B-cells and plasma cells and antibodies in your body play in AMR. In order to best study this condition, it is necessary to conduct studies in the laboratory using blood cells from individuals like yourself who have undergone lung transplantation. In this way, we can follow the way your immune system behaves over time. This will help us better understand why certain individuals may or may not develop chronic rejection.

A description of this clinical trial will be available on www.clinicaltrials.gov, as required by US 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 website at any time.

Who is being asked to take part in this research study?

You are being invited to take part in this research study because you have already undergone lung transplantation and have AMR. We will be enrolling up to 30 patients like yourself who are at least 18 years old. If you agree to participate, we will plan on studying you for 90 days.

What procedures will be performed for research purposes?

If you decide to take part in this research study, you will undergo the following:
Pregnancy Testing:
For women of childbearing potential, a serum pregnancy test will be performed within 7 days prior to study drug administration, as it is important to confirm that you are not pregnant. Pregnant or breastfeeding women are excluded from this study.

Carfilzomib Treatment:

1. You will be given pre-medications approximately 30 minutes prior to the Carfilzomib infusion to minimize infusion reactions: Tylenol 650 mg by mouth, Benadryl 25 mg by mouth, ondansetron (for nausea) 4 mg by mouth, prednisone (a steroid) 40 mg by mouth or by IV.
2. You will be given salt water (normal saline) through your IV approximately 30 minutes prior to the Carfilzomib infusion to make sure that you are hydrated and to minimize any side effects with the kidneys.
3. While you are admitted in the hospital in the Lung Transplant Unit, Carfilzomib will be administered at 20 mg/m^2 on days 1, 2, 8, 9, 15, and 16 which constitutes one therapeutic cycle. Carfilzomib will be administered via central access IV over 30 minutes; slowed to 60 minutes if infusion reactions occur. Possible reactions may include fever, chills, arthralgia, myalgia, facial flushing, facial edema, vomiting, weakness, hypotension, syncope, or chest tightness.
4. You may be given normal saline through your IV immediately after the Carfilzomib infusion to make sure that you are hydrated and to minimize any side effects with the kidneys.

A second cycle of Carfilzomib may be given to you for lack of resolution of AMR or for continued detection of Donor-specific antibodies in the absence of allograft improvement if you still meet the original enrollment criteria.

On days 28, 42 and 90, if you are discharged from hospital and do not return to your routine clinical visit as part of your standard of care treatment, a member of study team will call you to ask some questions about side effects.

Blood Draw: We will draw up to 4 tablespoons of blood at each visit on Days 1, 9, 16, 28, 42 and 90 in the least invasive manner possible- at the time of another blood draw, from an existing line or by putting a needle into a vein in your arm.

Most commonly, these blood draws will occur during your initial hospital stay for the study drug and during normal visits to the hospital or clinic. As much as possible we will attempt to obtain this blood at the same time you are undergoing routine laboratory tests to monitor your body after the transplant. It is possible that you may require more frequent visits if you are having trouble with your lung transplant, but we will only draw the amount of blood as described and will not draw blood if your blood counts are low for other reasons.

Any samples collected during this research will only be used for the purposes described in the protocol and destroyed at the end of this research study. The results of these research studies are not going to be shared with you, nor will it impact on your medical care, since as of now, we are not sure of the meaning of the results.

Medical Records Review: As part of this study and your routine clinical care, we will look at your medical records. We may use some of the information about your health and medical care for this study. We will only use information that is related to your lung transplant and routine clinical care during your participation in this study (90 days) and up to 360 days if you have any additional clinic visit as part of your standard of care.

What are the possible risks, side effects, and discomforts of this research study?

As with any experimental procedure, there may be adverse events or side effects that are currently unknown and certain of these unknown risks could be permanent, severe or life-threatening.

Everyone taking part in the study will be watched carefully for any side effects. You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks of Carfilzomib

You should seek medical care immediately if you develop any of the following symptoms: severe shortness of breath, chest pain, fevers, chills, shaking with fever, vomiting, muscle weakness or cramping, seizures, fainting and/or significantly decreased urine output.

Carfilzomib may impair ability to operate a car, other motorized vehicle, or machinery because of tiredness, dizziness, changes in blood pressure, or fainting.

If side effects occur, your health care team may give you medicines to help lessen side effects. Your doctor may have you stop taking carfilzomib or take a lower dose of carfilzomib because of the side effects, or the side effects may go away on their own even if you continue to take carfilzomib.

The information provided below is based on data from approximately 800 patients who took carfilzomib while taking part in clinical studies over the past 6 years. During this time period the following side effects have been observed and may be due to carfilzomib.

Likely Side Effects: those occurring in more than 20% of patients (or more than 20 out of 100 persons) who received carfilzomib:

- Fatigue (tiredness), Fever, Headache, Cough, Shortness of breath (at rest or with exertion) which in rare cases may be life-threatening or resulting in death, Nausea, Vomiting, Diarrhea, Constipation, Decreased red blood cell count which may lead to feeling tired, Decreased platelet counts which may lead to increase bleeding or bruising, Decreased white blood cell count which may decrease your ability to fight infection, Upper respiratory tract infection, Mild decreases in kidney function which are generally reversible, Swelling of the arms or legs, Back pain

Less Likely Side Effects: those occurring in 5-20% of patients (or 5 to 20 out of 100 persons) who received carfilzomib:

- Flu-like symptoms such as fever, chills, or shaking that may occur at any time but are more likely to occur on the day of or the day after carfilzomib infusion, Loss of or decreased appetite which may lead to weight loss, Insomnia (difficulty sleeping), Anxiety, Dizziness, Confusion or changes in mental state, Blurred or double vision, Numbness, tingling, or decreased sensation in hands and/or feet , Blood chemistry and electrolyte alterations, Rash and/or itching, or dry skin, Pain, burning, or irritation at the infusion site, Generalized pain, Pain in the bones or joint pain, Muscle spasm, pain, or weakness, General weakness, or lack of energy or strength, Abdominal pain, discomfort, or swelling, Indigestion (upset stomach), Inflammation of the liver (mild, reversible changes in liver function tests), Increase or decrease in blood pressure, Pneumonia or other lower respiratory tract infections, Urinary tract infection, Nosebleeds, Dehydration, Sore throat, inflammation of the nose and throat, runny nose or nasal congestion

Rare and/or Potentially Serious Side Effects: those occurring in less than 5% of patients (or in less than 5 out of 100 persons) who received carfilzomib; side effects can be serious enough to be life-threatening or even fatal in rare cases:

- Infusion reactions (which can occur during or shortly after carfilzomib infusion) including flushing or feeling hot, fever, shakes, nausea, vomiting, weakness, shortness of breath, swelling of the face, pain in the muscles or joints, tightness or pain in the chest, laryngeal edema, and low blood pressure, Allergic reaction including total body rash, hives, and difficulty breathing, Inflammation of the pancreas (pancreatitis), Kidney failure which can lead to dialysis, Worsening liver function up to and including liver failure, hepatitis B virus reactivation, Decreased or worsening of heart function including chest pain, abnormal heart rhythm, heart attack, and heart failure,

Increase in the blood pressure in the arteries of the lungs, Blood clots in the leg or lungs, and Infections in the blood.

- Sepsis (the body's overwhelming and life-threatening response to infection) and death could be a rare complication on the therapy.

Posterior reversible encephalopathy syndrome (PRES): There have been cases reported of PRES with carfilzomib. PRES is a syndrome characterized by headache, confusion, seizures, high blood pressure, altered mental status (encephalopathy), associated with carfilzomib. Other standard immunosuppressive medications (tacrolimus, cyclosporine) prescribed as part of your standard treatment for your condition may also cause PRES. PRES resolves on its own over a period of time after stopping the drugs that can cause PRES.

Hydration Risks: There may be risks associated with over hydrating (having too much fluid in your body) so it is important to follow your doctor's instructions regarding how much water or other fluids you should drink. Over hydration may negatively affect the heart, lungs, and kidneys.

Pregnancy Risks**:**

Female: Women of childbearing potential must either agree to abstain from sexual intercourse or use an effective birth control method during treatment with carfilzomib. As a precaution, women of childbearing potential and/or their male partners should use effective contraception methods or abstain from sexual activity during and for 30 days after treatment with carfilzomib. If pregnancy occurs during this time, patients should be apprised of the potential hazard to the fetus.

Based in research performed in animals, carfilzomib can cause fetal harm when administered to a pregnant woman. Carfilzomib caused embryo-fetal toxicity in pregnant rabbits at doses that were lower than in subjects receiving the recommended dose. If carfilzomib is used during pregnancy, or if the subject becomes pregnant while taking this drug, she should inform the investigator or study staff immediately. The investigator should notify Amgen of the pregnancy and discuss follow-up with the subject. It is not known if carfilzomib will reduce the efficacy of oral contraceptives. Due to an increased risk of venous thrombosis associated with carfilzomib, subjects currently using oral contraceptives or a hormonal method of contraception associated with a risk of thrombosis should consider an alternative method of effective contraception.

Male: Men who are sexually active with woman of childbearing potential should avoid fathering a child while being treated with carfilzomib. The potential for carfilzomib to be transferred via semen and its effect on sperm are unknown. Male subjects treated with carfilzomib and/or their female partners (if of childbearing potential) should use effective contraceptive methods or abstain from sexual activity while treated with carfilzomib and refrain from donating sperm while on carfilzomib and for 90 days after treatment. If pregnancy occurs during this time, patients should be apprised of the potential hazard to the fetus, study drug should be interrupted, and a serum pregnancy test performed.

Study drug administration may resume if result is negative and study drug be discontinued, if positive.

Male subjects should be advised to inform the investigator or study staff immediately in the event that their female partner becomes pregnant during the study. Upon receipt of this information, the investigator should notify Amgen of the pregnancy and discuss follow-up regarding the pregnancy outcome with the subject.

Breastfeeding:
If a woman breastfeeds during the study, she must inform the investigator or study staff immediately.

It is not known whether Kyprolis is present in human breast milk. No studies of carfilzomib have been conducted in breastfeeding women. Due to the potential for adverse effects in nursing infants from carfilzomib, a decision should be made whether to discontinue nursing or to discontinue the study drug. The decision will be made taking into account the potential benefit of carfilzomib to the mother.

Carfilzomib should not be used during breastfeeding. Breastfeeding women and women planning on breastfeeding may not participate in clinical trials with carfilzomib.

Blood Draw: The risks of having blood drawn from a vein include some pain when the needle goes in and a small risk of bruising and/or infection at that site (just like with the regular blood draws you have). It is possible that you might get light-headed, nauseous, or faint.

Medical Record Review: There is some risk of loss of confidentiality. To protect the privacy of research records, all of the data used for this study will be assigned a code and the linking information will be stored in a secure, password-protected computer file only accessible by the principal investigator and his research team.

What are possible benefits from taking part in this study?

There may be no benefit for your participating in this study. However, the information learned from this study may benefit individuals who undergo lung transplants in the future.

What treatments or procedures are available if I decide not to take part in this research study?

If you decide not to take part in this research study, you will continue to have your routine medical care for lung transplantation.

If I agree to take part in this research study, will I be told of any new risks that may be found during the course of the study?

You will be promptly notified if, during the conduct of this research study, any new information develops which may cause you to change your mind about continuing to participate.

Will my insurance provider or I be charged for the costs of any procedures performed as part of this research study?

Neither you, nor your insurance provider, will be charged for the costs of any of the procedures performed for the purpose of this research study. You and/or your insurance provider will be charged, in the standard manner, for any procedures performed for your routine medical care.

Will I be paid if I take part in this research study?

You will not be paid for being in this study. Your blood samples used in this research study may contribute to a new invention or discovery. In some instances, these inventions or discoveries may be of commercial value and may be sold, patented, or licensed by the investigators and the University of Pittsburgh for use in other research or the development of new products related to lung rejection. If you agree to participate in this research study, you voluntarily and freely donate your samples to the investigators and the University of Pittsburgh. You will not retain any property rights to the samples, nor will you share in any money or other benefits that the investigators, the University of Pittsburgh, or their agents may realize from the samples or their use in this research study. You retain the right to have your samples destroyed should you decide to withdraw from this research study.

Who will pay if I am injured as a result of taking part in this study?

If you believe that the research procedures have resulted in an injury to you, immediately contact the Principal Investigator who is listed on the first page of this form. Emergency medical treatment for injuries solely and directly related to your participation in this research study will be provided to you by the hospitals of UPMC. Your insurance provider may be billed for the costs of this emergency treatment, but none of those costs will be charged directly to you.

If your research-related injury requires medical care beyond this emergency treatment, you will be responsible for the costs of this follow-up care. At this time, there is no plan for any additional financial compensation. You do not, however, waive any legal rights by signing this form. The sponsor of this study will not provide any compensation for a research-related injury.

Who will know about my participation in this research study?

Any information about you obtained from this research will be kept as confidential as possible. All records related to your involvement in this research study will be stored in password protected computer files or a locked file cabinet. Your identity on these records will be indicated by only a case number rather than by your name, and the

information linking these case numbers with your identity will be kept separate from the research records. You will not be identified by name in any publication of the research results.

Will this research study involve the use or disclosure of my identifiable medical information?

This research study will involve the recording of past, current and/or future identifiable medical information from your hospital and/or other (e.g., physician office) records as part of your routine care with your transplant physicians. The information that will be recorded will be limited to information related to your lung transplant. As noted above, all of this information will be de-identified with regards to the actual studies on your blood cells so that no one besides the investigators will know it is your information.

May I have access to my medical record information resulting from participation in this research study?

In accordance with the UPMC Notices of Privacy Practices document that you have been provided, you are permitted access to information (including information resulting from your participation in this research study) contained within your medical records filed with your health care provider.

Who will have access to identifiable information related to my participation in this research study?

In addition to the investigators listed on the first page of this authorization (consent) form and their research staff, the following individuals may have access to identifiable information (which may include your identifiable medical information) related to your participation in this research study:

Authorized representatives of the University of Pittsburgh Research Conduct and Compliance Office may review your identifiable research information (which may include your identifiable medical information) for the purpose of monitoring the appropriate conduct of this research study.

Authorized representatives of the sponsor of this research, Onyx Pharmaceuticals, inc., the FDA, may review and/or obtain identifiable information (which may include your identifiable medical information) related to your participation in this research study for the purpose of monitoring the accuracy and completeness of the research data and for performing required scientific analysis of the research data. While the study sponsor understands the importance of maintaining the confidentiality of your identifiable research and medical information, UPMC and the University of Pittsburgh cannot guarantee the confidentiality of this information after it has been obtained by the study sponsor.

In unusual cases, the investigators may be required to release identifiable information (which may include your identifiable medical information) related to your participation in this research study in response to an order from a court of law. If the investigators learn that you or someone with whom you are involved is in serious danger or potential harm, they will need to inform, as required by Pennsylvania law, the appropriate agencies.

Authorized representatives of the UPMC hospitals or other affiliated health care providers may have access to identifiable information (which may include your identifiable medical information) related to your participation in this research study for the purpose of (1) fulfilling orders, made by the investigators, for hospital and health care services (e.g., laboratory tests, diagnostic procedures) associated with research study participation; (2) addressing correct payment for tests and procedures ordered by the investigators; and/or (3) assessing internal hospital operations (i.e. quality assurance).

Is my participation in this research study voluntary?

Your participation in this research study, to include the use and disclosure of your identifiable information for the purposes described above, is completely voluntary. (Note, however, that if you do not provide your consent for the use and disclosure of your identifiable information for the purposes described above, you will not be allowed to participate in the research study.) Whether or not you provide your consent for participation in this research study will have no effect on your current or future relationship with the University of Pittsburgh. Whether or not you provide your consent for participation in this research study will have no effect on your current or future medical care at a UPMC hospital or affiliated health care provider or your current or future relationship with a health care insurance provider.

Your doctor is involved as an investigator in this research study. As both your doctor and a research investigator, s/he is interested both in your medical care and the conduct of this research study. Before agreeing to participate in this research study, or at any time during your study participation, you may discuss your care with another doctor who is not associated with this research study. You are not under any obligation to participate in any research study offered by your doctor.

May I withdraw, at a future date, my consent for participation in this research study?

You may withdraw, at any time, your consent for participation in this research study. Any identifiable research or medical information recorded for your participation in this research study and blood samples obtained prior to the date that you formally withdrew your consent may continue to be used and disclosed by the investigators for the purposes described above.

You have the rights to request destruction of samples obtained for purpose of this

research study. To formally withdraw your consent for participation in this research study you should provide a written and dated notice of this decision to the principal investigator of this research study at the address listed on the first page of this form.

If I agree to take part in this research study, can I be removed from the study without my consent?

It is possible that you may be removed from the research study if the research doctors think that being in the study may harm you. Research samples previously obtained, and the data obtained from them, will remain with the investigators unless you request in writing to have these items destroyed.

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VOLUNTARY CONSENT

The above information has been explained to me and all of my current questions have been answered. I understand that I am encouraged to ask questions about any aspect of this research study during the course of this study, and that such future questions will be answered by a qualified individual or by the investigator(s) listed on the first page of this consent document at the telephone number(s) given. I understand that I may always request that my questions, concerns or complaints be addressed by a listed investigator.

I understand that I may contact the Human Subjects Protection Advocate of the IRB Office, University of Pittsburgh (1-866-212-2668) to discuss problems, concerns, and questions; obtain information; offer input; or discuss situations that have occurred during my participation.

By signing this form, I agree to participate in this research study and provide my authorization to share my medical records with the research team. A copy of this consent form will be given to me.

_____	_____	_____
Subject's Signature	Subject Printed Name	Date and Time

CERTIFICATION of INFORMED CONSENT

I certify that I have explained the nature and purpose of this research study to the above-named individual(s), and I have discussed the potential benefits and possible risks of study participation. Any questions the individual(s) have about this study have been answered, and we will always be available to address future questions as they arise. I further certify that no research component of this protocol was begun until this consent form was signed.

_____	_____
Investigator's Printed Name	Role in Research Study
_____	_____
Investigator's Signature	Date and Time