Informed Consent Form

A Single-Dose Study of Orally Administrated Defactinib or AVUTOMETINIB in Patients with Glioblastoma

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EMORY | WINSHIP CANCER INSTITUTE

National Cancer Institute-Designated Comprehensive Cancer Center

You Are Being Asked to Be in a Research Study
Concise presentation of key concepts

You are being asked to be in a research study. A research study is designed to answer a scientific question. If you agree to be in the study, you will be one of 17 people who are being studied, at Emory.

Why is this study being done?

Recently, two new drugs that seem to work together have been shown to have promising treatment effects in tissue culture and animal models of glioblastoma. These are defactinib (sometimes called PF-04554878), and avutometinib. Each inhibits a different glioblastoma growth pathway and when used together seem to create a larger effect on tumor growth than either alone. These drugs have not been used in brain tumor patients before. This study is being done to determine if useful amounts of defactinib and avutometinibreach human glioblastomas You are being asked to be in this research study to evaluate if defactinib or avutometinib can reach glioblastomas. The study will also see how much of the drugs may reach brain around the tumor and how much accumulates in the blood.

Do you have to be in the study?

It is your decision to be part of this research study. You do not have to be in it. Your choice will not affect your access to medical care for your condition. Before you make your decision, you should take time to learn about the study.

What do I have to do if I choose to participate in this study?

If you are eligible and want to be part of the study, you will participate for the period of 1-2 hours before your planned tumor resection surgery. The researchers will ask you to do the following: to take orally a single dose of either defactinib or avutometinib (which of these drugs will be offered to you is to be determined by your study doctor) 1-2 hours before the planned tumor resection surgery and to donate resected tumor tissue for the study analysis. The study requires 1.5 cm^3 sample of tumor tissue, 0.25 cm^3 sample of tumor adjusting tissue, and 10mL of blood during your planned surgery. You must use prophylactic medications for a minimum of two weeks after receiving defactinib to mitigate against dermatologic toxicities. Hydrocortisone 1% cream, moisturizer, and

sunscreen (sun protection factor [SPF] ≥ 50) should be applied topically two times a day, along with a systemic antibiotic (minocycline 100 mg daily or doxycycline 100 mg two times a day). Application of topical agents should include the most commonly affected skin areas such as face, scalp, neck, upper chest, and upper back. In addition, avoid unnecessary exposure to sunlight. If you are unable to tolerate a component of the prophylaxis, that component may be eliminated, or another agent could be used.
None of these procedures will be paid for by the study, except for the cost of the administered drug.

How is this study going to help you?
If you are in the study, you will be helping the researchers answer the study question. You will not get any cost or medical benefits of the participation.

What are the risks or discomforts I should know about before making a decision?
The study will take time. The drug that is being tested may not work any better than regular care and may even cause harm. All studies have some risks. Some risks are relatively small, like being bored or losing time. Some are more serious. Risks for this study include:

- transient fatigue, visual disturbances, decreased appetite, rash and diarrhea
- loss of privacy
- breach of confidentiality

You can find a full list of expected risks, their frequency and severity in the section titled "What are the possible risks and discomforts?"

Alternatives to Joining This Study
If you decide not to enter this study, you will receive a standard clinical care, offered to you by your primary doctor. Your treatment will not be affected if you decide not to take part. The study doctor will discuss these with you. You do not have to be in this study to be treated for brain tumor.

Costs
There will be no costs to you for participating in this study, other than basic expenses like transportation. You will not be charged for any research activities. for any costs of research associated with this study.

There is more information in the "Costs" section further below.

What Should I Do Next?

Read this form, or have it read to you. Make sure the study doctor or study staff explains the study to you. Ask questions (e.g., about exact time commitment, about unfamiliar words, more details on specific procedures, etc.) Make sure you understand which parts of the treatment are research and which are standard care that you would have even if you did not join the study. Take time to consider this and talk about it with your family and friends.

Emory University
Consent to be a Research Subject / HIPAA Authorization

Title: A single-dose study of orally administrated defactinib or avutometinib **in patients with glioblastoma**

IRB #: STUDY00004876

Principal Investigator: Jeffrey Olson, MD

Investigator-Sponsor: Jeffrey Olson, MD

Study-Supporter: Verastem Inc. and University of Puerto Rico

Introduction

You are being asked to be in a medical research study. This form tells you what you need to think about before you choose if you want to join the study. **It is your choice. If you choose to join, you can change your mind later and leave the study.** Your choice will not cause you to lose any medical benefits. If you choose not to join this study, your doctor will still treat you.

Before you decide:

- Read this form or have it read to you
- Listen to the study doctor or study staff explain the study to you
- Ask questions about anything that is not clear

You will get a copy of this form. Take your time to think about joining the study. You may wish to discuss it with family or friends. Do not sign this form if you still have questions or something does not make sense to you. By signing this form, you will not give up any legal rights.

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.

This trial will be registered and may report results on www.ClinicalTrials.gov, a publicly available registry of clinical trials.

What is the purpose of this study?

The purpose of this study is to identify how much of the research drugs defactinib and avutometinibcan reach brain tumors and to learn about their safety when given to brain tumor patients.

It is known that glioblastoma tumor cells can grow because of lack of regulation. Both Pyk2 and the closely related kinase (FAK) proteins help regulate tumor cell invasion, unless they are over expressed. Specifically, Raf and FAK/Pyk2 regulation of cell division is activated quite a bit more in gliomas compared to normal tissues. Recently developed inhibitors of Raf (avutometinib) and FAK (defactinib) are aimed to bring their activity to proper levels and to stop tumor growth. Preclinical studies in animals demonstrated that each of these drugs significantly reduce tumor growth, and when these drugs are given together, their combination effect on tumor growth prevention is better than when each drug is used by itself. In order to identify the best treatment protocol for defactinib and avutometinib used together, the working concentrations for each of defactinib and avutometinibneed to be determined.

Defactinib and avutometinibhave been studied in previous human clinical trials for number of non-brain tumors, and demonstrated promising results. The working concentrations of defactinib and avutometinib were identified previously. However, brain is a unique organ that has increased protection from entering substances, which is controlled through blood-brain barrier. Blood-brain barrier serves to protect brain from toxic, antigen and immune attacks, but at the same time it significantly reduces the access of medications to brain tissue, making the treatment of brain-related diseases more difficult. For this reason, this is highly important to identify the minimal working concentrations of defactinib and avutometinib, that enter the brain tumor tissue and results in proper FAK/Pyk2 and Faf signaling inhibition, leading to therapeutic effect.

A total 17 participants will be enrolled to the study. Either defactinib or avutometinib will be given to participants orally in a single dose 1-2 hours prior the planned glioblastoma tumor resection surgery. In the described investigation, we will use blood sample of 10ml, tissue samples taken from the glioblastoma tumors removed during surgical resection, and a sample from tumor adjacent tissue. The concentration of defactinib and avutometinib in these tissues and blood samples will be analyzed. Additionally, the level of FAK/Pyk2 and Raf activation in tumor cells will be investigated. The research will not include dual defactinib and avutometinib treatment at this step of the study.

We invite for the study all patients diagnosed with brain neoplasia (abnormal growth of tissue) with suspected glioblastoma, by neuroimaging techniques or previously resected/biopsied tumors.

What will I be asked to do?

If you take part in the described research investigation, defactinib or avutometinib will be given to participants orally in a single dose 1-2- hours prior the planned glioblastoma tumor removal surgery. Then participants will undergo their planned brain surgery in the same way as if they do not participate in the study. No additional treatments or procedures will be performed during the surgery or after.

You must use prophylactic medications for a minimum of two weeks after receiving defactinib to mitigate against dermatologic toxicities. Hydrocortisone 1% cream, moisturizer, and sunscreen (sun protection factor [SPF] ≥ 50) should be applied topically two times a day, along with a systemic antibiotic (minocycline 100 mg daily or doxycycline 100 mg two times a day). Application of topical agents should include the most commonly affected skin areas such as face, scalp, neck, upper chest, and upper back. In addition, avoid unnecessary exposure to sunlight. If you are unable to tolerate a component of the prophylaxis, that component may be eliminated, or another agent could be used.

During the surgery, the 1.5 cm^3 tissue sample (about the size of a large marble) will be separated from the total removed tumor and together with a 5 ml blood sample and 0.25 cm^3 (about the size of a pea)of brain tissue next to the tumor will be sent to the laboratory at Emory University and the Universidad Central del Caribe in Puerto Rico for the proposed investigation. Sample tissue and blood will be used for the investigation described in this Participation Sheet.

The duration of participation in the study is within a standard timeline of pre- and post-surgical observation.

Participant can be withdrawn from the study if the brain tumor removal surgery is cancelled or if surgery is postponed for longer than 6 to 7 hours after defactinib or avutometinib administration. In these cases, the blood sample and sample of resected tumor will not be taken for analysis.

If you are a woman, you will be required to take a pregnancy test prior to joining the study.

How will my medicine be provided?

The study drug that you will take will be dispensed by the pharmacy and delivered to the principal investigator or study team member. The principal investigator or health care providers on his/her research team will provide the study drug to you. If you have questions about the study drug, you should ask the principal investigator or study nurse. You may also call the pharmacy if you have questions about the study drug. The number for the pharmacy is included on your study drug package, if given one.

Note: The research team for this study includes non-licensed team members who may obtain your consent, or help guide you through the study. There are some kinds of questions only licensed clinicians can answer. For example, detailed questions about drug interactions. If you have questions like these, the non-licensed coordinator will ask a licensed study team member to answer your questions.

Who owns my study information and samples?

If you join this study, you will be donating your samples and study information. You will not receive any compensation if your samples or information are used to make a new product. If you withdraw from the study, data and samples that were already collected may be still be used for this study.

What are the possible risks and discomforts?

There may be side effects from the study drug defactinib and avutometinib that are not known at this time.

Most frequent defactinib and avutometinib treatment-related adverse effects detected in previous clinical trials were transient fatigue, visual disturbances, decreased appetite, rash and diarrhea when given for 21 days continuously. These reactions were mostly not observed at lower concentrations. Our study proposes a single dose of defactinib or avutometinib, but not a continuous use. For this reason, despite some extent of adverse reactions, observed in previous studies, are possible, these reactions expected to be transient. However, defactinib and avutometinib administration may involve risks that are currently unforeseeable.

If brain tissue removal is necessary to reach the tumor, this will be collected for research and studied for amounts of the study drug that might be in it. Collection of brain around the tumor could be associated with new or increased neurologic symptoms. This will vary depending on the part of the brain in which the tumor is growing and your surgeons can tell you about your unique circumstances. Your surgeons will take steps to avoid removing any brain tissue not involved in reaching your tumor or that would be likely to cause you new neurological symptoms.

It is possible that your surgery will be delayed or cancelled due to emergencies in the operating room or circumstances related to your health. Therefore, you might end up taking defactinib and avutometinib and no research can be done. If this occurs, it is possible that you may have side effects from the dose of defactinib and avutometinib despite there being no benefit to you or the research study. The surgery itself would be rescheduled as soon as is feasible, but you would not be asked to take a repeat dose of the research drug.

If you are a woman: to protect against possible side effects of the study drug, women who are pregnant or nursing a child may not take part in this study. If you become pregnant, there may be risks to you, the embryo, or fetus. These risks are not yet known. If you are a woman of childbearing ability, you and the study doctor must agree on a method of birth control to use throughout the study and for 30 days after the dose of the investigational drug. If you think that you have gotten pregnant during the study, you must tell the study doctor immediately. Pregnant women will be taken out of the study.

If you are a man: the effect of the study drug on sperm is not known. To protect against possible side effects, if you are a man you should not get a sexual partner pregnant or donate sperm for 3 months after taking the dose of the study drug. You and the study doctor should agree on a method of birth control to use throughout the study.

If you will take the study drug home, keep it out of the reach of children or anyone else who may not be able to read or understand the label. Do not let anyone else take the study drug besides you.

Researchers may learn something new during the study that may affect your choice to be in the study. If this happens, they will tell you about it. Then you can choose if you want to stay in this study. You may be asked to sign a new form if you choose to stay in the study.

Will I benefit directly from the study?

This study is not designed to benefit you directly. Your condition may improve while you are in this study but it may not, and it may even get worse. This study is designed to learn more about the treatment capacity of defactinib and avutometinib in glioblastoma patients. The study results may be used to help others in the future.

Will I be compensated for my time and effort?

You will not be offered compensation for being in this study.

What are my other options?

If you decide not to enter this study, you will receive surgery alone, offered to you by your primary doctor. Your treatment will not be affected if you decide not to take part. The study doctor will discuss these with you. You do not have to be in this study to be treated for brain tumor.

If you choose to join this study, you may not be able to join other research studies. Discuss this with the researchers if you have concerns. You may wish to look on websites such as clinicaltrials.gov and ResearchMatch.org for other research studies you may want to join.

How will your private information be protected?

Whenever possible, a study number, rather than your name, will be used on study records. Your name and other identifying information will not appear when we present or publish the study results.

Study records can be opened by court order. They also may be provided in response to a subpoena or a request for the production of documents.

Storing and Sharing your Information

Your data and specimens from this study will not be shared with anyone outside this study, even if we take out all the information that can identify you.

Your data and specimens from this study may be useful for other research being done by investigators at Emory or elsewhere. To help further science, we may provide your de-identified data and/or specimens to other researchers. If we do, we will not include any information that could identify you. If your data or specimens are labeled with your study ID, we will not allow the other investigators to link that ID to your identifiable information.

We will use your sample and data only for research. We will not sell them. However, the results of this research might someday lead to the development of products (such as a commercial cell line, a medical or genetic test, a drug, or other commercial product) that could be sold by a company. You will not receive money from the sale of any such product.

No results returned to participants

In general, we will not give you any individual results from the study of the samples you give us. If we find something of urgent medical importance to you, we will inform you, although we expect that this will be a very rare occurrence.

Medical Record

If you have been an Emory Healthcare patient before, then you already have an Emory Healthcare medical record. If you have never been an Emory Healthcare patient, you do not have one. An Emory Healthcare medical record will be made for you if an Emory provider or facility gives you any services or procedures for this study.

Copies of the consent form/HIPAA authorization that you sign will be put in any Emory Healthcare medical record you have now or any time during the study.

The results of some study tests and procedures will be used only for research purposes and will *not* be placed in your medical record.

For this study, those items include: Defactinib and avutometinib concentrations, and Pyk2/FAK and MEK/ERK phosphorylation levels in the brain tumor, brain and blood.

Tests and procedures done at non-Emory places may not become part of your Emory medical record. Also, if you decide to be in this study, it is up to you to let your other health providers know.

In Case of Injury

If you believe you have become ill or injured from this research, you should contact Dr. Jeffrey Olson at telephone number [redacted] You should also let any health care provider who treats you know that you are in a research study.

If you get ill or injured from being in the study, Emory will help you to get medical treatment. Neither Emory nor the sponsor have set aside money to pay for this medical treatment. Your insurer will be billed for your treatment costs. If you do not have insurance, or if your insurance does not pay, then you will have to pay these costs.

For Emory, the only exception is if it is proven that your injury or illness is directly caused by the negligence of an Emory employee. "Negligence" is the failure to follow a standard duty of care. You do not give up any legal rights you may have by being in this study, including any right to bring a claim for negligence.

Costs

There will be no costs to you for participating in this study, other than basic expenses like transportation. You will not be charged for any of the research activities. If the study procedures result in any medical complications that would not fall under "injury" as discussed above, the cost of treatment for those complications may be charged to you or your insurance.

Withdrawal from the Study

You have the right to leave a study at any time without penalty.

For your safety, however, you should consider the study doctor's advice about how to go off the study treatment. If you leave the study before the last planned study visit, the researchers may ask you to complete some of the final steps such as lab work or imaging as applicable.

The researchers also have the right to stop your participation in this study without your consent for any reason, especially if they believe it is in your best interest or if you were to object to any future changes that may be made in the study plan.

Researchers may stop your participation if the brain tumor resection surgery is cancelled, or if surgery is postponed for longer than 12 hours after defactinib or avutometinib administration. In these cases, the blood sample and sample of resected tumor will not be taken for analysis.

Authorization to Use and Disclose Protected Health Information

The privacy of your health information is important to us. We call your health information that identifies you, your "protected health information" or "PHI." To protect your PHI, we will follow federal and state privacy laws, including the Health Insurance Portability and Accountability Act and regulations (HIPAA). We refer to all of these laws as the "Privacy Rules." Here we let you know how we will use and disclose your PHI for the study.

PHI that Will be Used/Disclosed:

The PHI that we will use or share for the research study includes:

- Medical information about you including your medical history and present/past medications.
- Results of exams, procedures and tests you have before and during the study.
- Laboratory test results

Purposes for Which Your PHI Will be Used/Disclosed:
We will use and share your PHI for the conduct and oversight of the research study. We will use and share your PHI to provide you with study related treatment and for payment for such treatment. We will also use and share your PHI to conduct normal business operations. We may share your PHI with other people and places that help us conduct or carry out the study, such as laboratories, data management centers, data monitors, contract research organizations, Institutional Review Boards (IRBs) and other study sites. If you leave the study, we may use your PHI to determine your health, vital status or contact information.

Use and Disclosure of Your Information That is Required by Law:
We will use and disclose your PHI when we are required to do so by law. This includes laws that require us to report child abuse or abuse of elderly or disabled adults. We will also comply with legal requests or orders that require us to disclose your PHI. These include subpoenas or court orders.

Authorization to Use PHI is Required to Participate:
By signing this form, you give us permission to use and share your PHI as described in this document. You do not have to sign this form. If you do not sign this form, you may still receive non-research related treatment.

People Who will Use/Disclose Your PHI:
The following people and groups will use and disclose your PHI in connection with the research study:

- The Principal Investigator and research staff will will use and disclose your PHI to conduct the study and give you study related treatment.
- Emory may use and disclose your PHI to get payment for study related treatment and to run normal business operations.
- The Investigator-Sponsor and research staff will disclose your PHI to other people and groups to help conduct the study or to provide oversight for the study.
- Verastem Inc. is a Supporter of the study. The Investigator-Sponsor and the study supporter may use and disclose your PHI to make sure the research is done correctly and to collect and analyze the results of the research. The Supporter may disclose your PHI to other people and groups like study monitors to help conduct the study or to provide oversight for the study.
- The research team may use and disclose your PHI including disclosure to insurance carriers to administer payment for subject injury.
- Universidad Central del Caribe in Puerto Rico will receive tumor, brain and blood samples and therefore data developed there as part of this study will be shared with Emory, Verastem, and the below governmental and monitoring agencies. All reasonable efforts

will be made to de-identify information as it is shared, keeping mind that this may be limited so as to maintain integrity of the data.

The following people and groups will use your PHI to make sure the research is done correctly and safely:

- Emory offices that are part of the Human Research Participant Protection Program and those that are involved in study administration and billing. These include the Emory IRB, the Emory Research and Healthcare Compliance Offices, and the Emory Office for Clinical Research.
- Other researchers and centers that are part of this study.
- Government agencies that regulate the research including: Office for Human Research Protections; Food and Drug Administration.
- Public health agencies.
- Research monitors and reviewer.
- Accreditation agencies.
- Study Supporter: Verastem Inc.

- Sometimes a Principal Investigator or other researcher moves to a different institution. If this happens, your PHI may be shared with that new institution and their oversight offices. PHI will be shared securely and under a legal agreement to ensure it continues to be used under the terms of this consent and HIPAA authorization.

Expiration of Your Authorization
Your HIPAA authorization will expire when this research study ends.

Revoking Your Authorization
If you sign this form, at any time later you may revoke (take back) your permission to use your information. If you want to do this, you must contact the study team at:

Jeffrey J. Olson, MD
[redacted]

At that point, we will not collect any more of your PHI. We may use or disclose the PHI already collected so we can follow the law, protect your safety, or make sure that the study was done properly and the data is correct. If you revoke your authorization, you will not be able to stay in the study.

Other Items You Should Know about Your Privacy
Not all people and entities are covered by the Privacy Rules. HIPAA only applies to health care providers, health care payers, and health care clearinghouses. If we disclose your PHI to people who are not covered by the Privacy Rules, then your PHI won't be protected by the Privacy Rules. People who do not have to follow the Privacy Rules can use or disclose your PHI to others without your permission if they are allowed to do so by the laws that cover them.

To maintain the integrity of this research study, you generally will not have access to your PHI related to this research until the study is complete. When the study ends, and at your request, you generally

will have access to your PHI that we maintain in a designated record set. A designated record set is data that includes medical information or billing records that your health care providers use to make decisions about you. If it is necessary for your health care, your health information will be provided to your doctor.

We will remove identifying information from your PHI. Once we do this, the remaining information will not be subject to the Privacy Rules. Information without identifiers may be used or disclosed with other people or organizations for purposes besides this study.

Contact Information: If you have questions about the study procedures, appointments, research-related injuries or bad reactions, or other questions or concerns about the research or your part in it, contact Jeffrey J. Olson, MD at [redacted]

Contact Dr. Jeffrey J. Olson at telephone number(s): [redacted]

- if you have any questions about this study or your part in it,
- if you feel you have had a research-related injury or a bad reaction to the study drug, or
- if you have questions, or concerns about the research

This study has been reviewed by an ethics committee to ensure the protection of research participants. If you have questions about your **rights as a research participant**, or if you have **complaints** about the research or an issue you would rather discuss with someone outside the research team, contact the Emory Institutional Review Board at [redacted]

To tell the IRB about your experience as a research participant, fill out the Research Participant Survey at [redacted]

Consent and Authorization

TO BE FILLED OUT BY SUBJECT ONLY

Please **print** your name, **sign**, and **date** below if you agree to be in this research study. By signing this consent and authorization form, you will not give up any of your legal rights. We will give you a copy of the signed form to keep.

Name of Subject

Signature of Subject (18 or older and able to consent) **Date** **Time**

Signature of Legally Authorized Representative **Date** **Time**

Authority of Legally Authorized Representative or Relationship to Subject

TO BE FILLED OUT BY STUDY TEAM ONLY

Name of Person Conducting Informed Consent Discussion

Signature of Person Conducting Informed Consent Discussion **Date** **Time**