Protocol Title: A Phase 1 Study of IDH1 inhibition using ivosidenib as maintenance therapy for IDH1-mutant myeloid neoplasms following allogeneic stem cell transplantation

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Robert J. Soiffer, MD / Dana Farber Cancer Institute

Main Consent Form

A. INTRODUCTION

You are invited to take part in a clinical trial, a type of research study, because you have IDH1-mutant myeloid neoplasms and will have an allogeneic stem cell transplantation (HSCT). This research study is studying a drug as a possible treatment for this diagnosis.

The name of the study drug involved in this study is ivosidenib (AG-120).

For purposes of this research, you will be referred to as a "participant".

It is expected that about 22 people will take part in this research study.

Servier, a pharmaceutical company, is supporting this research study by providing funding as well as the study drug.

This research consent form explains why this research study is being done, what is involved in participating in the research study, the possible risks and benefits of participation, alternatives to participation, and your rights as a research participant. The decision to participate is yours. If you decide to participate, please sign and date at the end of this form. We will give you a copy so that you can refer to it while you are involved in this research study. If you choose not to participate in this research study, the research doctors will discuss other treatment options with you and/or refer you back to your primary doctor.

We encourage you to take some time to think this over, to discuss it with other people and your primary doctor, and to ask questions now and at any time in the future.

B. WHY IS THIS RESEARCH STUDY BEING DONE?

This research study is a Phase I clinical trial, which tests the safety of an investigational drug and also tries to define the appropriate dose of the investigational drug to use for further studies. "Investigational" means that the drug is being studied.

The FDA (the U.S. Food and Drug Administration) has not approved ivosidenib as a treatment for any disease.

Ivosidenib is an inhibitor of the protein IDH1. Ivosidenib is currently being studied as a treatment for myeloid cancers like acute myeloid leukemia or myelodysplastic syndromes with an IDH1 mutation. This study is examining whether or not ivosidenib is beneficial and well-tolerated as an agent to prevent the relapse of IDH1-mutated acute myeloid leukemia or other myeloid neoplasms after hematopoietic stem cell transplantation. IDH1 is an enzyme that, when mutated, can overproduce metabolites (substances that help with metabolism) and compounds that contribute to the growth of tumors and cancerous cells. Ivosidenib may help block the over production of these substances and possibly reduce the chances of relapse.

C. WHAT OTHER OPTIONS ARE THERE?

Taking part in this research study is voluntary. Instead of being in this research study, you have other options which may include the following:

- Receive standard treatment including HSCT with standard of care drugs.
- Take part in another research study.
- Receive no therapy specific to your cancer.
- Comfort care, also called palliative care. This type of care may help to reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to treat the symptoms.

Please talk to the research doctor about your options before you decide whether you will take part in this research study.

D. WHAT IS INVOLVED IN THE RESEARCH STUDY?

Since we are looking for the highest dose of the study drug that can be administered safely without severe or unmanageable side effects in participants that have IDH1-mutant myeloid neoplasms and have had an allogeneic stem cell transplantation, not everyone who participates in this research study will receive the same dose of the study drug. The dose you get will depend on the number of participants who have been enrolled in the study before you and how well they have tolerated their doses.

Sometimes it is hard to keep track of all of the details and procedures that are part of a research study. We will describe them in this consent form and you can refer to this at any time during the research study.

Before the research starts (screening):
After signing this consent form, you will be asked to undergo some screening tests or procedures to find out if you can be in the research study. Many of these tests and procedures are likely to be part of regular cancer care and may be done even if it turns out that you do not take part in the research study. If you have had some of these tests or procedures recently, they may or may not have to be repeated.

- **A medical history,** which includes questions about your health, current medications, and any allergies.
- **A physical exam will be performed,** including exams of the head, neck, heart, lungs, abdomen, extremities, nervous system, and lymph nodes. **Electrocardiogram (ECG),** which measures your heart's electrical activity.
- **Echocardiogram (ECHO) or Multiple Gated Acquisition Scan (MUGA),** which are used to takes pictures of your heart using an ultrasound to see how strong your heartbeat/heart muscles are. Only one of these tests will be performed.
- **Blood Tests,** approximately 7 tablespoons of blood will be collected throughout this study for research purposes. Some of the blood samples may undergo genetic testing, which is when we look at the individual genes that make up your DNA (genetic material in cells).
- **Graft-vs-Host Disease (GVHD) Assessment,** symptoms of both acute and chronic GVHD will be assessed. This is a disease in which immune cells from the donor's tissue attack your organs. There are acute and chronic forms of GVHD. Acute GVHD usually affects the skin, intestines, and liver and may start one week to three months after transplant. Chronic

GVHD begins later and can affect these organs as well as the lung, mucous membranes and/or other organs. Both of these can require treatment and be serious or life threatening.

- **Bone marrow biopsy and/or aspirate,** to evaluate the extent of your disease. For this test, a sample of bone marrow cells is taken by a needle inserted into a bone in your body. If a bone marrow biopsy is needed, a small piece of bone and the attached bone marrow is removed. These tests may be done under local anesthesia. Any time a bone marrow exam is done in the study, a sample will also be sent to a laboratory for research studies.

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

Study Treatment Overview:

- **Oral Study Drug:** Each study treatment cycle lasts 28 days during which time you will be taking the study drug once a day. This will continue for up to 12 cycles.

If you take part in this research study you will be given a drug diary. You will be asked to document information in the drug diary about the study treatment you are being asked to take.

Research Study Plan:

	Screening	Pre-Treatment	Cycle 1			Pre-Cycles 2, 3	Pre-Cycles 4, 5, 7, 8, 10, 11	Pre-cycles 6, 9, 12	Relapse[A]	End of Treatment[B]	Follow-Up
	Pre-HSCT	Day -14	Day 1	Day 8	Day 15	Days 28, 56	Days 84, 112, 168, 196, 252, 280	Days 140, 224, 308			
Medical History	X	X									
Vital Signs	X	X	X	X	X	X	X	X	X	X	
Performance Status	X	X	X							X	
Physical Exam	X	X	X	X	X	X	X	X	X	X	
ECG	X		X	X	X	X	X	X	X	X	
ECHO or MUGA	X										
Blood Tests	X	X		X	X	X			X		
GVHD Assessment		X	X	X	X	X	X	X		X	X
Bone Marrow Biopsy or Aspirate	X	X						Cycles 6 and 12 only	X		

A: If your cancer comes back at any point during this study then we will ask you to come into the clinic for a study visit.
B: The End of Treatment visit will occur 5 days after your last dose of ivosidenib.

Planned Follow-up:

We would like to keep track of your medical condition. We would like to do this by having you come into the clinic every 3 months for 24 months after beginning treatment. Keeping in touch with you and checking your condition helps us look at the long-term effects of the research study.

E. HOW LONG WILL I BE IN THIS RESEARCH STUDY?

You will be in this research study for up to 12 cycles and followed for 24 months after beginning treatment.

F. WHAT ARE THE RISKS OR DISCOMFORTS OF THE RESEARCH STUDY?

There are risks to taking part in any research study. One risk is that you may get a study drug or study dose of a drug that does not help treat your disease or that makes your condition or disease worse. Another risk is that there may be side effects.

All cancer treatments can have side effects, which can range from mild and reversible to severe, long lasting and possibly life-threatening. There is a great deal of variability among side effects of different cancer treatments and between individuals. In a research study, all of the risks or side effects may not be known before you start the study. **You need to tell your doctor or a member of the study team immediately if you experience any side effects.**

Everyone in the research study will be watched carefully for side effects. You will be monitored during the administration of study drugs to keep track of your blood counts and organ function, particularly your kidney and liver function. If you experience side effects, they may go away after you stop taking the study drug. Some side effects can be mild; but others can be long lasting and may never go away. Some may be life-threatening or fatal.

Since the effect of the study drug taken with other medications may not be known, it is important that you tell the research doctor about all prescription and non-prescription drugs, herbal preparations and nutritional supplements that you are taking or planning to take. There may also be some foods that you should avoid while on this research study and your research doctor will review this information with you.

During the research study, you will be notified of newly discovered side effects or significant findings, which may affect your health or willingness to participate. You may be asked to sign a new consent form that shows that you have been informed of new information relating to this research study.

Risks Associated with Ivosidenib:

Frequent (Between a 10-50% chance that this will happen)*:*

- Fatigue (very tired)
- Diarrhea
- Nausea
- Increase in the number of white blood cells (blood cells that help fight infection) and may require hospitalization
- Fever sometimes with very low white blood cell counts (blood cells that help fight infection), which may increase your chance of getting an infection. This may require hospitalization
- Swelling of arms and legs
- Anemia (a decrease in the number of red blood cells in blood), which may make you feel weak or tired
- Shortness of breath

- Constipation
- Pain in joints
- Vomiting
- Cough
- Decreased appetite
- Rash
- Weakness
- Pneumonia, which may cause a cough, shortness of breath, and may require treatment with antibiotics and/or hospitalization.
- Hypotension (low blood pressure), which may cause dizziness, lightheadedness or fainting
- Mouth sores
- A decrease in number of platelets (blood cells that help with clotting), which may cause bleeding and bruising. Bleeding may be serious or life threatening and may require a blood transfusion.
- QT prolongation, which can cause irregular heartbeats that can be life-threatening. Tell your doctor right away if you feel new chest pain or discomfort, dizziness or lightheadedness or if you faint.
- Elevations of liver function tests; abnormal liver function tests may mean that your liver is not functioning properly and may be associated with fatigue and yellowing of the skin and eyes (jaundice).

Occasional (Between a 5-10% chance that this will happen):

- IDH differentiation syndrome, which may cause unexplained fever, shortness of breath, high white blood cell counts (blood cells that fight infection), high platelet counts (blood cells that help with clotting), and/or fluid in or around the lungs or heart. Some of these complications may require further medical intervention and could be fatal.
- For those with advanced blood cancers only: Tumor Lysis Syndrome (TLS) has occurred in patients receiving ivosidenib. TLS results from the rapid breakdown of cancer cells in response to treatment. This can result in problems with many of the body's normal functions and may cause weakness, low blood pressure, muscle cramps, kidney damage, irregular heartbeat and/or other organ damage. TLS can be life threatening. Fever with dangerously low white blood cell counts which may require hospitalization.
- A severe infection throughout the body (sepsis) which may require hospitalization.

Rare (Less than a 5% chance that this will happen):

- Damage to nerves and the nervous system which may cause weakness, loss of muscle function, numbness, tingling or burning.
- Respiratory failure, difficulty breathing with low levels of oxygen in the blood, which could be serious and life threatening and require you to have a tube inserted into your windpipe that is hooked up to a machine to help you breathe.
- Headache
- Abdominal pain
- Build-up of fluid in the abdomen, which causes bloating and discomfort.
- Low sodium counts, a type of body salt or chemical that helps control blood pressure and the function of muscles and nerves.
- A rare and severe viral infection of the brain, called Progressive Multifocal Leukoencephalopathy (PML), which can cause brain damage, memory loss, trouble thinking, muscle weakness, blindness and death. Notify your study doctor immediately if you develop trouble thinking or walking, a decrease in strength in your arms or legs, or changes in your vision or hearing. This is a serious and life-threatening infection.

Cancer research often includes biopsies, scans, x-rays that are also provided as routine care. The following describes the side effects of procedures done only for the purposes of research.

Risks Associated with Bone Marrow Biopsies and Bone Marrow Aspiration:
For these procedures, a numbing drug is injected into the skin over one of your hipbones. A needle is then inserted into the hipbones and a small piece of bone is removed (biopsy) or a sample of bone marrow fluid is removed (aspiration). The risks may include:

- Pain from the needle sticks
- Moderate pain and discomfort
- Pain from aspirating the bone marrow with a syringe
- Bleeding at the biopsy site
- Scarring at the biopsy site
- Rarely, an infection at the biopsy site
- Rarely, nerve injury at the biopsy site

Reproductive Risks:
The drugs used in this research study may affect a fetus. While participating in this research study and for 90 days after, you should not become pregnant or father a baby, and should not nurse a baby. We can provide counseling about preventing pregnancy for either male or female study participants. Let your

doctor know immediately if you become pregnant or find out that you are going to be the father of a child.

Non-Physical Risks:
Because of side effects or the time required for tests and clinic visits while you are on this research study, you may be unable to keep up with your normal daily activities.

G. WHAT ARE THE BENEFITS OF THE RESEARCH STUDY?

We do not know if taking part in this study will help you. This study may help researchers learn information that could help people in the future.

H. CAN I STOP BEING IN THE RESEARCH STUDY AND WHAT ARE MY RIGHTS?

You have the right to choose not to sign this form. If you decide not to sign this form, you cannot participate in this research study.
You may be taken off the research study drug for many reasons including if:

- It is considered to be in your best interest
- The study treatment or procedures are found to be unsafe or ineffective
- There is any problem with following study treatments and procedures
- You are a female and become pregnant or plan to become pregnant
- Your condition worsens
- A decision is made to close the study
- Or for other unforeseen reasons that make it necessary to stop your participation in the research study

If you are removed from the research study, the research doctor will explain to you why you were removed.

You can also stop being in the research study at any time. Tell the research doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop. Leaving the research study will not affect your medical care outside of the research study.

Although you may withdraw from study participation, the FDA requires that any information collected up to the point of your withdrawal cannot be removed from the study.

If you choose not to participate, are not eligible to participate, or withdraw from this research study, this will not affect your present or future care and will not cause any penalty or loss of benefits to which you are otherwise entitled.

It is important to tell the research doctor if you are thinking about stopping so your research doctor can evaluate the risks from stopping the drug. Another reason to tell your research doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

I. WILL I BE PAID TO TAKE PART IN THIS RESEARCH STUDY?

You will not be paid for participating in this study.

We may use your samples and information to develop a new product or medical test to be sold. The sponsor and hospital may benefit if this happens. There are no plans to pay you if your samples are used for this purpose.

J. WHAT ARE THE COSTS?

Taking part in this research study might lead to added costs to you or your insurance company.

You will not be charged for ivosidenib.

You or your insurance company will be charged for portions of your care during this research study that are considered standard care. You may be responsible for co-payments and deductibles that are typical for your insurance coverage.

If you have questions about your insurance coverage, or the items you might be required to pay for, please call financial services for information. The contact information for financial services is:

- Massachusetts General Hospital: (617) 726-2191
- Dana Farber Cancer Institute: (617) 632-3455

The National Cancer Institute provides an online resource to help people participating in cancer clinical trials understand which services their insurance company is required by law to pay. This can be found at the website below or can be provided by the study team:

www.cancer.gov or 1-800-4-CANCER (1-800-422-6237)

K. WHAT HAPPENS IF I AM INJURED OR BECOME SICK BECAUSE I TOOK PART IN THIS RESEARCH STUDY?

If you think you have been injured as a result of taking part in this research study, tell the person in charge of this research study as soon as possible. The research doctor's name and phone number are listed in this consent form.

The treating hospital will offer you the care needed to treat injuries directly resulting from taking part in this research. These treatments will be billed to your insurance company. You will be responsible for deductibles and co-payments. There are no plans to pay you or give you other compensation for the injury. You do not give up your legal rights by signing this form.

We will need to collect certain personal information about you for insurance or payment reporting purposes, such as your name, date of birth, gender, social security number or Medicare identification number and information related to this research study. We may be required to report this information to the Centers for Medicare & Medicaid Services. We will not use this information for any other purpose.

L. WHAT ABOUT CONFIDENTIALITY?

We will take measures to protect the privacy and security of all your personal information, but we cannot guarantee complete confidentiality of study data.

Medical information created by this research study may become part of your hospital medical record and may be forwarded to your primary doctor. Information that does not become part of your medical record will be stored in your study file. It may also become part of a DF/HCC research database.

The study team plans to publish the results of this research study and when we do, we may be asked to make the data we collect available to other researchers. We will not include information that identifies you in any publications or to the researchers who request the data to do additional research.

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.

M. WHOM DO I CONTACT IF I HAVE QUESTIONS ABOUT THE RESEARCH STUDY?

If you have questions about the study, please contact the research doctor or study staff as listed below:

Massachusetts General Hospital

- Amir Fathi, MD: (617) 724-1124

24-hour contact: Please contact Massachusetts General Hospital at 617-724-4000 and ask that your doctor be paged.

Dana Farber Cancer Institute

- Robert Soiffer, MD: (617)-632-4731

For questions about your rights as a research participant, please contact a representative of the Office for Human Research Studies at Dana-Farber Cancer Institute (617) 632-3029. This can include questions about your participation in the study, concerns about the study, a research related injury, or if you feel/felt under pressure to enroll in this research study or to continue to participate in this research study.

N. RETURN OF RESEARCH RESULTS

Tests done on samples in this research study are only for research and have no clear meaning for your health care. For this reason, your study doctor will not share the results with you.

O. FUTURE USE OF DATA AND SPECIMENS

Your personal information and/or biospecimens collected during this study will not be used or distributed for future research studies even if the information is de-identified and cannot be linked back to you.

P. GENETIC RESEARCH

This research will involve genomic testing.

The Genetic Information Nondiscrimination Act of 2008 (GINA) is a federal law that protects Americans from being treated unfairly because of differences in

their DNA that may affect their health, and may prevent discrimination by health insurers and employers based on genetic information. GINA is intended to ease concerns about discrimination that might keep some people from getting genetic tests that could benefit their health, and enable people to take part in research studies such as this without fear that their DNA information might be used against them by health insurers or their workplace. This protection does not extend to disability or life insurance. Additional information can be found at http://www.genome.gov/10002328.

Q. PRIVACY OF PROTECTED HEALTH INFORMATION

Federal law requires Dana-Farber/Harvard Cancer Center (DF/HCC) and its affiliated research doctors, health care providers, and physician network to protect the privacy of information that identifies you and relates to your past, present, and future physical and mental health conditions ("protected health information"). If you enroll in this research study, your "protected health information" will be used and shared with others as explained below.

1. What protected health information about me will be used or shared with others during this research?

- Existing medical records, including mental health records.
- New health information created from study-related tests, procedures, visits, and/or questionnaires

2. Why will protected information about me be used or shared with others?

The main reasons include the following:

- To conduct and oversee the research described earlier in this form;
- To ensure the research meets legal, institutional, and accreditation requirements;
- To conduct public health activities (including reporting of adverse events or situations where you or others may be at risk of harm); and
- To provide the study sponsor with information arising from an adverse event or other event that relates to the safety or toxicity of the drug used in the study and for the purpose of this or other research relating the study drug and their use in cancer;
- To better understand the diseases being studied and to improve the design of future studies; and,
- Other reasons may include for treatment, payment, or health care operations. For example, some medical information produced by this

research study may become part of your hospital medical record because the information may be necessary for your medical care. (You will also be given a notice for use and sharing of protected health information.)

3. Who will use or share protected health information about me?

- DF/HCC and its affiliated research doctors and entities participating in the research will use and share your protected health information. In addition, other DF/HCC offices that deal with research oversight, billing or quality assurance will be able to use and share your protected health information.

4. With whom outside of DF/HCC may my protected health information be shared?

While all reasonable efforts will be made to protect the confidentiality of your protected health information, it may also be shared with the following entities:

- Outside individuals or entities that have a need to access this information to perform functions relating to the conduct of this research such as analysis by outside laboratories on behalf of DF/HCC and its affiliates (for example, data storage companies, insurers, or legal advisors).
- The sponsor of the study, its subcontractors, representatives, business partners, and its agents: DF/HCC
- The funder of the study, its subcontractors, representatives, business partners, and its agents: Servier
- Other research doctors and medical centers participating in this research, if applicable
- Federal and state agencies (for example, the Department of Health and Human Services, the Food and Drug Administration, the National Institutes of Health, and/or the Office for Human Research Protections), or other domestic or foreign government bodies if required by law and/or necessary for oversight purposes. A qualified representative of the FDA and the National Cancer Institute may review your medical records.
- Hospital accrediting agencies
- A data safety monitoring board organized to oversee this research, if applicable

Some who may receive your protected health information may not have to satisfy the privacy rules and requirements. They, in fact, may share your information with others without your permission.

5. For how long will protected health information about me be used or shared with others?

- There is no scheduled date at which your protected health information that is being used or shared for this research will be destroyed, because research is an ongoing process.

6. Statement of privacy rights:

- You have the right to withdraw your permission for the research doctors and participating DF/HCC entities to use or share your protected health information. We will not be able to withdraw all the information that already has been used or shared with others to carry out related activities such as oversight, or that is needed to ensure quality of the study. To withdraw your permission, you must do so in writing by contacting the researcher listed above in the section: "Whom do I contact if I have questions about the research study?"
- You have the right to request access to your protected health information that is used or shared during this research and that is related to your treatment or payment for your treatment, but you may access this information only after the study is completed. To request this information, please contact the researcher listed above in the section: "Whom do I contact if I have questions about the research study?"

R. DOCUMENTATION OF CONSENT

My signature below indicates:

- I have had enough time to read the consent and think about participating in this study;
- I have had all of my questions answered to my satisfaction;
- I am willing to participate in this study;
- I have been told that my participation is voluntary and I can withdraw at any time

_____ _____

Signature of Participant or Legally Authorized Representative

Date

Relationship of Legally Authorized Representative to Participant

To be completed by person obtaining consent:

Adult Participant

The consent discussion was initiated on _____ (date).

Signature of individual obtaining consent: _____

Printed name of above: _____

Date: _____

☐ A copy of this signed consent form will be given to the participant or legally authorized representative.

☐ 1) The participant is an adult and provided consent to participate.

☐ 1a) Participant (or legally authorized representative) is a non-English speaker and signed the translated Short Form in lieu of English consent document:

As someone who understands both English and the language spoken by the participant, I interpreted and/or witnessed, in the participant's language, the researcher's presentation of the English consent form. The participant was given the opportunity to ask questions.

Signature of Interpreter/Witness: _____

Printed Name of Interpreter/Witness: _____

Date: _____

☐ 1b) Participant is physically unable to sign the consent form because:

☐ The participant is illiterate.

☐ The participant has a physical disability.

☐ Other (please describe): _____

The consent form was presented to the participant who was given the opportunity to ask questions and who communicated agreement to participate in the research.

Signature of Witness: _____

Printed Name of Witness: _____

Date: _____

☐ 2) The participant is an adult who lacks capacity to provide consent and his/her legally authorized representative:

☐ 2a) gave permission for the adult participant to participate

☐ 2b) did not give permission for the adult participant to participate