DF/HCC Protocol #: 18-123

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

Coordinating Center: Program for Coordination and Oversight of Research Protocols (PCORP)
Massachusetts General Hospital

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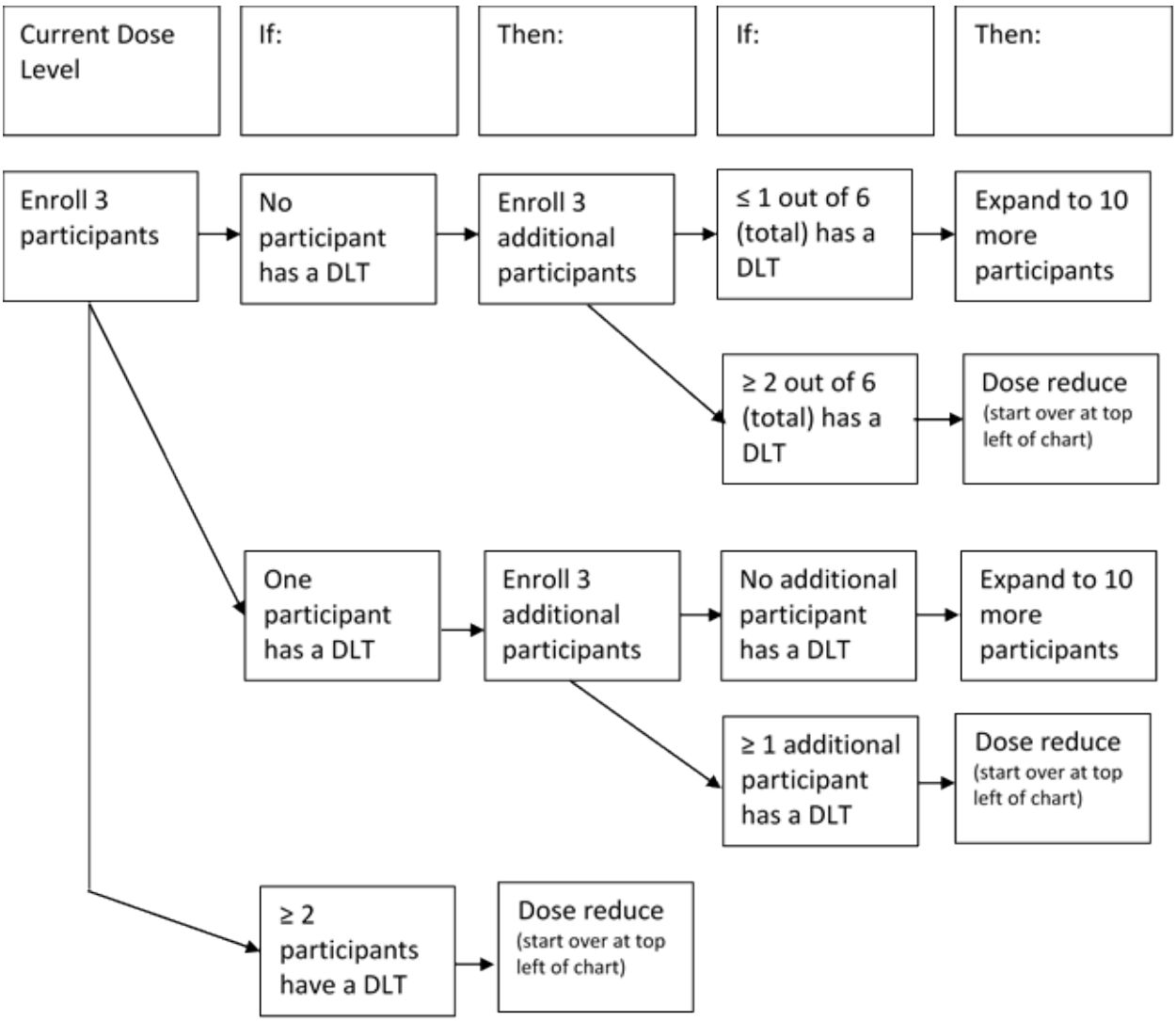
SCHEMA



If only three participants were enrolled at the RP2D level, then an additional 3 participants will be enrolled to confirm that ≤ 1 out of 6 participants experiences a DLT at this dose.

If two out of three (or two out of six) participants at 250 mg daily have a DLT, then this dose will be considered to be too toxic in this population.

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1. OBJECTIVES

1.1 Study Design

This is a prospective, non-randomized, open-label, multi-center, phase I study of the mutant *IDH1* inhibitor, ivosidenib, given to patients with *IDH1*-mutant myeloid neoplasms after hematopoietic stem cell transplantation (HSCT).

1.2 Primary Objectives

To identify the recommended phase 2 dose (RP2D) of ivosidenib in patients with *IDH1*-mutant myeloid neoplasms after hematopoietic stem cell transplantation.

To explore the safety and tolerability of ivosidenib in patients with *IDH1*-mutant myeloid neoplasms in the post-stem cell transplant setting.

1.3 Secondary Objectives

To detect and categorize, according to severity, ivosidenib-related toxicities in patients with *IDH1*-mutant myeloid neoplasms receiving ivosidenib after hematopoietic stem cell transplantation.

To examine the cumulative incidence of acute GVHD from start of ivosidenib in patients with *IDH1*-mutant myeloid neoplasms who receive ivosidenib after hematopoietic stem cell transplantation.

To examine the cumulative incidence of chronic GVHD from start of ivosidenib in patients with *IDH1*-mutant myeloid neoplasms who receive ivosidenib after hematopoietic stem cell transplantation.

To monitor plasma and marrow 2-hydroxyglutarate levels in patients with *IDH1*-mutant myeloid neoplasms who receive ivosidenib after hematopoietic stem cell transplantation.

To assess *IDH* clonal evolution and mutational burden in patients with *IDH1*-mutant myeloid neoplasms who receive ivosidenib after hematopoietic stem cell transplantation.

To measure minimal residual disease (MRD) in patients with *IDH1*-mutant myeloid neoplasms who receive ivosidenib after hematopoietic stem cell transplantation, through measurement of mutant IDH1 (mIDH1) allelic burden.

1.4 Exploratory Objectives

To examine the rate of relapse of *IDH1*-mutant myeloid neoplasms in patients receiving ivosidenib after hematopoietic stem cell transplantation.

To examine relapse-free survival in patients with *IDH1*-mutant myeloid neoplasms who receive ivosidenib after hematopoietic stem cell transplantation.

To examine overall survival in patients with *IDH1*-mutant myeloid neoplasms who receive ivosidenib after hematopoietic stem cell transplantation.

2. BACKGROUND

2.1 Study Disease

Acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS) are lethal hematologic malignancies associated with a poor prognosis. The estimated number of deaths from AML is nearly as many as the incidence of new diagnoses. While the majority of patients with AML achieve a complete remission with conventional cytotoxic induction therapy, approximately half subsequently relapse and most die from their disease (Dohner 2015, Tefferi 2009, Gangat 2016). Outcomes are far worse for those with relapsed or high-risk AML, such as those with adverse cytogenetics or with a history of preceding myelodysplastic or myeloproliferative conditions. Allogeneic hematopoietic stem cell transplantation (HSCT) is recommended as an appropriate consolidative approach for suitable patients with higher risk disease. The ongoing characterization of prognostically important chromosomal and molecular alterations in AML has engendered hope that novel and effective targeted therapies can be developed for this patient population.

2.2 IDH Inhibitors

Genomic sequencing of myeloid malignancies, including MDS and AML, has recently led to the discovery of a series of mutations, including those impacting the genes encoding isocitrate dehydrogenase (*IDH1/2*) (Mardis 2009). Sequence analysis has shown that *IDH* mutations occur in ~ 5% of patients with MDS and 10% of patients with secondary AML. (Kosmider 2010). *IDH1* is an important metabolic enzyme that catalyzes the conversion of isocitrate to α-ketoglutarate (α-KG) in the cytosol, leading to the production of reduced nicotinamide adenine dinucleotide phosphate (NADPH), while *IDH2* is a homologous protein catalyzing this reaction in mitochondria. *IDH1/2* mutations are frequently-found alterations in AML (approximately 5% with *IDH1* and 15% with *IDH*2 mutations), gliomas and secondary glioblastomas (Ducray 2009), and have also been detected less commonly in other malignancies. These recurrent mutations are missense alterations affecting arginine 132 (R132) of *IDH1*, and either the analogous arginine residue (R172) or arginine 140 (R140) of the *IDH2* protein (Mardis 2009, Gross 2010, Marcucci 2010, Paschka 2010, Ward 2010).

The identification of neomorphic *IDH*1/2 enzyme activity associated with underlying mutations provided a promising therapeutic direction in the treatment of AML and MDS (Abbas 2010, DiNardo 2016, Medeiros 2017). In place of catalyzing the normal process of isocitrate decarboxylation, the altered *IDH* proteins instead facilitate a reduction of α-KG to 2-hydroxyglutarate (2-HG) (Dang 2009), a metabolite normally present at very low levels. 2-HG has since been shown to directly confer oncogenic activity, likely through interfering with regulation of gene transcription controlled by epigenetic modification of DNA and histones (Xu 2011, Figueroa 2010). These findings have helped encourage the development of IDH1 and *IDH*2 inhibitors, which demonstrated great promise in preclinical evaluation. They are now

being actively studied in clinical trials, with very encouraging results, suggestive of effective clinical activity. Rates of remission, partial remission, and stable disease for enasidenib and ivosidenib are remarkable for such patients, including many with relapsed and refractory *IDH*-mutant disease. Enasidenib is now approved for use by the Food and Drug Administration in patients with relapsed/refractory *IDH2*-mutated AML.

The initial promise of *IDH* inhibitors has garnered interest to better understand the most optimal manner by which to incorporate such therapies into conventional paradigms for treatment of *IDH1/2*-mutant myeloid malignancies. Given the increasing employment and success of HSCT in patients with intermediate or high-risk AML (Davies 2008), as well as in those with myelodysplastic syndromes or myeloproliferative neoplasms, the role of novel targeted therapies as maintenance therapy following HSCT is being actively studied to determine their promise in enhancing relapse-free and overall survival. Maintenance following HSCT is routinely used with available inhibitors of the BCR-ABL tyrosine kinase in patients with chronic myeloid leukemia (CML) (Klyuchnikov 2010), or Philadelphia chromosome positive- acute lymphoid leukemia (Kebriaei 2012), even without any prospective trials showing a clear benefit. There is evidence, however, that introducing BCR-ABL inhibitors at the time of detectable minimal residual disease following HSCT can induce long-term remissions in CML (Hess 2005). In addition, anecdotal reports, followed by our own clinical research, suggest substantial promise in using FLT3 inhibitors, such as sorafenib, as maintenance therapy in *FLT3-ITD* mutated AML patients following HSCT (Chen 2014). As an increasing number of targeted and well-tolerated therapies are developed, the paradigm of maintenance therapy after HSCT will likely garner more attention, suggesting a need to conduct well-informed clinical trials to assess efficacy, tolerability, and cost-effectiveness of these therapies.

2.3 Ivosidenib

The investigational drug ivosidenib (AG-120) is a selective, potent inhibitor of the isocitrate dehydrogenase-1 (*IDH1*) mutant protein. Isocitrate dehydrogenase is a critical enzyme in the citric acid cycle catalyzing the oxidative decarboxylation of isocitrate to produce carbon dioxide (CO_2) and alpha-ketoglutarate (α-KG). The mutant *IDH* enzymes are not catalytically inactive, but rather possess a novel enzyme activity, catalyzing the reduction of α-KG to the "oncometabolite" 2-hydroxyglutarate (2-HG) (Dang 2009) which has been found to be elevated in patients with several tumor types, including both solid and liquid tumors (Fathi 2012, DiNardo 2013, Janin 2014).

Initial studies sought to identify *IDH1* mutant-selective inhibitors that can suppress 2-HG production in cancer cells. AG-120 is a selective inhibitor of *IDH1* (R132) mutant enzymes with concentrations of drug that achieved half maximal inhibition (IC_{50}) in the range of 2 to 17 nM. Ivosidenib is also a slow binding inhibitor of *IDH1* wild-type (WT) enzymes with an IC_{50} of 71 to 24 nM following incubation with nicotinamide adenine dinucleotide phosphate (NADP) for either 1 or 16 hours, respectively. Ivosidenib showed no inhibition of isocitrate dehydrogenase-2 (*IDH2*) isoforms at micromolar concentrations.

The results of a series of nonclinical PK studies, including both single dose and multiple dose evaluations, in Sprague-Dawley rats, beagle dogs, and cynomolgus monkeys showed that

ivosidenib has an acceptable ADME profile for continued evaluation and development in humans. The toxicity profile of ivosidenib was evaluated *in vitro* in a bacterial reverse mutation, a micronucleus, and a phototoxicity assay and *in vivo* in Sprague-Dawley rats, cynomolgus monkeys, and New Zealand white rabbits, including two 28-day and two 3-month repeat-dose pivotal GLP studies conducted in rats and monkeys, definitive embryo/fetal development studies in rats and rabbits and a micronucleus study in rats. Preliminary clinical data have shown ivosidenib to be generally well-tolerated at the doses evaluated. Substantial reductions in mean plasma 2-HG concentrations have been observed in patients treated with ivosidenib, as well as evidence of clinical activity.

An *in vitro* study of human liver microsomes using chemical inhibitors and recombinant human cytochrome P450 (CYP) enzymes suggested that ivosidenib is mainly metabolized by CYP3A4, with minor contributions from CYP2B6 and CYP2C8. Therefore, coadministration with CYP3A4 inhibitors could have an effect on the pharmacokinetics of ivosidenib.

The AG-120 clinical development program was initiated in March 2014 with 2 Phase 1 first-in-human studies, Study AG120-C-001 in subjects with advanced hematologic malignancies that harbor an *IDH1* mutation and Study AG120-C-002 in subjects with advanced solid tumors, including glioma, that harbor an *IDH1* mutation. Two combination studies in subjects with newly diagnosed AML are also ongoing. Study AG120-221-C-001 is evaluating treatment with AG-120 or AG-221 (an IDH2 mutant inhibitor) in combination with standard AML induction and consolidation therapy in subjects with AML who are eligible for intensive chemotherapy and Study AG-221-AML-005 is assessing the treatment with AG-120 or AG-221 in combination with azacitidine in subjects with AML not eligible for intensive induction chemotherapy.

Dose escalation has stopped in Studies AG120-C-001 and AG120-C-002. A dose of 500 mg QD has been identified to be used in the expansion arms of both studies to further evaluate the safety and efficacy of AG-120 in subjects with advanced malignancies; 500 mg QD is also the dose being used in the 2 Phase 1/2 combination studies of AG-120 and in the initiated/planned Phase 3 studies.

Preliminary data have shown AG-120 to be well tolerated at total daily doses up to 1200 mg; the maximum tolerated dose (MTD) was not reached in either of the dose escalation studies (DiNardo 2015; DiNardo 2016).

The most commonly reported adverse events (AEs) observed in subjects with cancer demonstrated an acceptable safety profile of ivosidenib. The most common AEs in Study AG120- C-001 were diarrhea (30%), nausea (26%), fatigue (26%), febrile neutropenia (22%), and leukocytosis (22%); in Study AG120-C-002, nausea (28%), fatigue (28%), and diarrhea (23%) were the most common AEs.

2.4 Rationale

Given that a substantial proportion of patients with *IDH1*/*2*-mutant myeloid malignancies are likely candidates for, and will undergo HSCT as a therapeutic modality for their disease, as well as the promise suggested by studies of other novel agents in the post-HSCT setting, it is important to establish the safety and tolerability of these agents in the post-transplant setting as

well as to gain an appreciation of their efficacy in maintaining relapse-free survival in this patient population. The primary goal of this phase I study is to define the recommended phase 2 dose (R2PD) of the mIDH1 inhibitor, ivosidenib (AG-120), as maintenance therapy following HSCT.

2.5 Correlative Studies Background

2.5.1 2-hydroxyglutarate levels

An intriguing finding in *IDH*-mutant AML is elevated levels of the oncometabolite 2-HG. Initial studies of patient samples revealed greater than 50-fold higher levels of 2-HG, when compared to those from *IDH*-WT patients (Ward 2010). 2-HG levels were then measured in sera and leukemic blasts from a limited number of patients with *IDH*-mutant AML. The *IDH*-mutant samples exhibited elevations of 2-HG above 1,000ng/ml in serum, in contrast to *IDH* wild-type samples (Gross 2010).

We have ongoing efforts to monitor 2-HG levels in *IDH*-mutant patients undergoing traditional chemotherapy for AML. To date, we have noted markedly elevated levels of circulating 2-HG in multiple fluid compartments, including blood, urine, and marrow (Fathi 2012). We found that blood and urine 2-HG levels, serially measured during therapy, directly parallel therapeutic response, and may serve as biomarkers of clinical activity. Assessing levels of a surrogate non-invasive biomarker, such as 2-HG, may allow clinicians to better prognosticate, risk-stratify, and manage patients with AML.

2.5.2 Next-generation sequencing (NGS)

IDH1/2 mutant allelic burden may play an important role in the clinical evolution, diagnostic features, and therapeutic response of *IDH*-mutant AML. The prognostic impact of *IDH* mutations has been evaluated in multiple retrospective studies to date, with largely inconclusive results (Patel 2012, Mardis 2009, Marcucci 2010, Paschka 2010). *IDH* allelic burden has not been extensively studied. Based on data from three *IDH*-mutant patients receiving induction chemotherapy, we found that 2-HG levels correlated with *IDH*-mutational burden during the course of treatment. Through next-generation sequencing (NGS) of serial samples, we found that *IDH1/2* mutational burden (mutant allele as fraction of total *IDH* reads) decreased over time concordantly with serum 2-HG. Based on these preliminary data, it appears that 2-HG levels, along with assessment of *IDH* mutational burden, may parallel the clinical course of *IDH* mutant disease and its response to treatment. We will use next-generation sequencing to assess *IDH1* mutational burden in our participants.

2.5.3 Whole Genome Sequencing (WGS)

Whole genome sequencing (WGS) has revealed extensive clonal heterogeneity in AML. The initial ("Founding") clone contains 500-1000 somatic mutations on average. Subclones frequently emerge, either during the natural history of the disease, or at relapse following therapy. Subclones acquire additional mutations, but retain all mutations present in ancestral clones (Welch 2012, Ding 2012, Jan 2012, Walter 2012).

The sequence of mutations acquired by preleukemic clones, as they transform, is informative since it can distinguish initiating mutations from those which are cooperating alterations. *IDH1/2* mutations are often present in the founding clone (and, therefore, are retained in subclones) (Ding 2012, Walter 2012). Little is known about the relative sensitivity of *IDH*-mutant vs. wildtype clones to conventional cytotoxic chemotherapy or the impact of targeted therapy on the clonal architecture of *IDH* mutant AML.

Indeed, the landscape of leukemic subpopulations is dynamic and evolves over time, either due to progression of disease, or in response to selective pressure from treatment (Jan 2012). The clonal architecture, comprised of subclones with distinct mutational profiles, can vary during the course of treatment, and a small subclone present at diagnosis may develop into the dominant clone at relapse. Through whole genome sequencing, we will more fully characterize the clonal architecture and evolution of relapse of *IDH*-mutant AML.

2.5.4 Minimal Residual Disease (MRD)

In the phase 1 study of ivosidenib in myeloid malignancies, a proportion of relapsed and refractory patients were found to have cleared the mutant (mIDH1) allelic burden (Stone 2017). Indeed, MRD-negativity was observed in 7 of 25 (28%) R/R AML patients who achieved CR, and those with MRD-negative CR had improved CR duration and overall survival, albeit the dataset was small. MRD-negativity by mIDH1 status was also observed in 5 of 9 patients with untreated AML who achieved CR or CRh. We therefore seek to assess MRD clearance by measuring mIDH1 allelic burden at time points throughout the study.

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

Participants must meet the following criteria to be eligible for enrollment on this study.

3.1.1 Pathologically confirmed diagnosis of *IDH1(R132)*-mutant acute myeloid leukemia (AML), myelodysplastic syndrome (MDS) or chronic myelomonocytic leukemia (CMML). IDH1 mutations could have been detected by any mutational technique at any prior point including at diagnosis or remission.

3.1.2 Age ≥ 18

3.1.3 Will undergo allogeneic hematopoietic stem cell transplantation (HSCT) for their malignancy. Conditioning may be either conventional myeloablative (MAC) or reduced intensity conditioning (RIC).

3.1.4 HSCT Donor will be one of the following:

- 5/6 or 6/6 (HLA-A, B, DR) matched related donor
- 7/8 or 8/8 (HLA-A, B, DR, C) matched unrelated donor. Matching in the unrelated setting must be at the allele level.
- Haploidentical related donor, defined as ≥ 3/6 (HLA-A, B, DR) matched
- ≥ 4/6 (HLA-A, B, DR) umbilical cord blood (UCB). Matching in the UCB setting is at the antigen level. Recipients may receive either one or two UCB units. In the case of 2 UCB units, both units must have been at least 4/6 matched with the recipient.

3.1.5 ECOG performance status ≤ 2

3.1.6 Participants must have normal organ and marrow function as defined below:

- Absolute neutrophil count ≥ 1000/μL without growth factor support (e.g. GCSF) in the previous 7 days. This criterion does not apply to patients with myelodysplastic syndromes, myeloproliferative neoplasms in leukemic phase, or CMML, who will not necessarily be expected to achieve marrow recovery prior to HSCT.
- Platelet count ≥ 50,000/μL without transfusional support in the previous 7 days. This criterion does not apply to patients with myelodysplastic syndromes, myeloproliferative neoplasms in leukemic phase, or CMML, who will not necessarily be expected to achieve marrow recovery prior to HSCT.
- AST (SGOT), ALT (SGPT) and Alkaline phosphatase < 3x institutional upper limit of normal (ULN)
- Direct bilirubin < 2.0 mg/dL
- Calculated creatinine clearance ≥ 40 mL/min (Cockcroft-Gault formula)

3.1.7 LVEF must be equal to or greater than 40%, as measured by MUGA scan or echocardiogram

3.1.8 Female patients of childbearing potential must have a negative pregnancy test

3.1.9 The effects of ivosidenib on the developing human fetus are unknown. For this reason female participants of child-bearing potential and male participants must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) during the entire study treatment period and through 90 days after the last dose of treatment

3.1.10 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

Participants meeting any of the following criteria are not eligible for study enrollment:

3.2.1 Prior allogeneic hematopoietic stem cell transplants.

3.2.2 For patients with acute myeloid leukemia, morphologically relapsed or refractory disease, as assessed by bone marrow aspirate and biopsy performed within 42 days prior to study entry, is exclusionary. For patients with myelodysplastic syndromes or chronic myelomonocytic leukemia, the presence of less than 5% myeloblasts is allowed on a bone marrow biopsy within 42 days prior to study entry.

3.2.3 History of other malignancy(ies) unless

- the participant has been disease-free for at least 5 years and is deemed by the investigator to be at low risk of recurrence of that malignancy, or
- the only prior malignancy was cervical cancer in situ and/or basal cell or squamous cell carcinoma of the skin

3.2.4 Known diagnosis of active hepatitis B or hepatitis C

3.2.5 Current or history of congestive heart failure New York Heart Association (NHYA) class 3 or 4, or any history of documented diastolic or systolic dysfunction (LVEF < 40%, as measured by MUGA scan or echocardiogram)

3.2.6 Current or history of ventricular or life-threatening arrhythmias or diagnosis of long-QT syndrome

3.2.7 QTc interval (i.e., Friderica's correction [QTcF]) ≥ 450 ms or other factors that increase the risk of QT prolongation or arrhythmic events (e.g., heart failure, hypokalemia, family history of long QT interval syndrome) at screening

3.2.8 Systemic uncontrolled infection

3.2.9 Uncontrolled intercurrent illness that would limit compliance with study requirements.

3.2.10 HIV-positive participants on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with study drug. In addition, these participants are at increased risk of lethal infections when treated with marrow-suppressive therapy.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of protocol-specific therapy. Any participant not registered to the protocol before protocol-specific therapy begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol-specific therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol-specific therapy following registration, the participant's registration on the study must be canceled. Registration cancellations must be made in OnCore as soon as possible.

4.2 Registration Process for DF/HCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

4.3 General Guidelines for Other Investigative Sites

Eligible participants will be entered on study centrally at Massachusetts General Hospital by the Coordinating Center. All sites should contact the Coordinating Center to verify treatment availability.

Following registration, participants may begin protocol treatment. Issues that would cause treatment delays should be discussed with the Principal Investigator/Sponsor. If the subject does not receive protocol-specific therapy following registration, then the subject must be taken off-study in the CTMS (OnCore) with an appropriate date and reason entered.

4.4 Registration Process for Other Investigative Sites

To register a subject, the following documents should be completed by the participating institution and forwarded to the Coordinating Center:

- Copy of source documentation for inclusion/exclusion criteria and screening procedures, including but not limited to
  - Pathology report
  - Medical history and physical exam
  - Laboratory reports
  - Radiology results/reports
  - Echo or MUGA report
  - ECG report
  - Concomitant medication list
- Demographics information
- Signed study consent form and HIPAA authorization form (if separate from consent)
- Study Entry Note and documentation of consent process
- Eligibility checklist

The Coordinating Center will review the above documentation to verify eligibility and consent. To complete the registration process, the Coordinating Center will follow DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) and register the participant on the protocol. Once registered, a confirmation email with the participant study number, and if applicable the dose treatment level, will be sent to the participating site.

NOTE: Registrations can only be conducted by the Coordinating Center during the business hours of 8:30 AM and 5:00 PM Eastern Standard Time (or Eastern Daylight Time when applicable), Monday through Friday. A complete registration packet, including all documents listed above, must be received at least 1 business day *prior to* the anticipated registration to ensure adequate review. Same day treatment registrations will only be accepted with prior notice and discussion with the Coordinating Center.

Treatment may not begin without confirmation from the Coordinating Center that the participant has been registered.

5. TREATMENT PLAN

5.1 Treatment Regimen

Ivosidenib will be administered orally every day for 28 consecutive days, defined as a treatment cycle. Appropriate dose modifications are described in Section 6. Reported adverse events and potential risks are described in Section 7. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's myeloid malignancy.

The starting dose of ivosidenib (AG-120) will be 500mg orally daily. After 3 (or 6) participants are treated at 500mg daily, if this dose is tolerated, then an additional 10 participants will be treated at 500mg daily. If the 500mg daily dose is NOT tolerated in the initial cohort of participants, then the dose will be decreased to 250mg daily. If 250mg daily is tolerated, then an additional 10 participants will be treated at 250mg daily. The only doses studied will be 500mg daily and 250mg daily (the latter, if necessary).

The first cohort will consist of three participants. After the third participant is enrolled to the cohort, enrollment will be put on hold until all three participants have completed the first 28-day cycle. The period for dose-limiting toxicity (DLT) evaluation is the first 28-day cycle. Individual participants must receive at least 50% of the dosing to be DLT evaluable for that cohort. If this criteria is not met, the patient in that dose-escalation cohort may be replaced.

If one of three participants in a cohort experiences a DLT, then an additional 3 participants will be observed at that dose. The recommended phase 2 dose (RP2D) is defined as the highest dose level at which 0 or 1 of six participants experiences a dose-limiting toxicity.

Dose Escalation Schedule	
Dose Level	**Dose of Ivosidenib**
Level 1	250mg daily
Level 2 – Starting Dose	500mg daily

Once the RP2D is defined, an additional 10 participants will be enrolled at that dose.

If 250mg daily dosing is not tolerated, then the study will end without expansion.

If the overall study is dose decreased to 250mg daily and there are still any participants receiving 500mg daily ivosidenib, those participants may continue to receive 500mg ivosidenib unless/until they develop a toxicity that requires a dose-reduction.

The participant will be required to maintain a medication diary of each dose of medication. He/she should record relevant information regarding study drug dosing in the diary (e.g. confirmation that each dose was taken, reasons for missed doses). The medication diary will be returned to clinic staff at the end of each cycle.

5.2 Pre-Treatment Criteria

5.2.1 Cycle 1, Day 1

Treatment may begin at any time between day 30 and day 90 following stem cell transplantation. However, at time of treatment start, it must be ensured that:

- The patient has continued willingness and interest in participating in the study.
- Chimerism studies reveal that ≥ 70% of blood or bone marrow cells, or of the CD33 expressing fraction, are of donor origin,
- There is no acute graft versus host disease (GVHD), requiring an equivalent dose of ≥ 0.5mg/kg/day of prednisone within one week of starting ivosidenib, or have escalation of systemic immunosuppression in terms of increase of corticosteroids or addition of new agent/modality within two weeks of starting ivosidenib.
- There is no evidence of relapsed/recurrent/residual disease.
- There is no systemic infection requiring IV antibiotic therapy within 7 days of starting ivosidenib

Prior to the start of ivosidenib administration, the participant must have adequate hematological function, defined as:

- ANC ≥ 1000/μL
- Platelets ≥ 50,000/μL

and adequate organ function defined as

- Direct bilirubin level < 2.0 mg/dL
- AST (SGOT), ALT (SGPT) and Alkaline phosphatase < 3x institutional upper limit of normal (ULN)
- Presence of congestive heart failure, defined by New York Heart Association (NHYA) criteria as class 3 or 4
- Calculated creatinine clearance ≥ 40 mL/min (Cockcroft-Gault formula)

5.2.2 Subsequent Cycles

Subsequent cycles will require study visits within the first week of ivosidenib therapy, but will not require specific evaluations to begin the cycle given the continuous dosing nature of this study. A total of 12 cycles will be administered.

5.3 Agent Administration

Ivosidenib will be given orally (PO) once daily (QD) in 28-day continuous cycles. Dosing should occur at approximately the same time each day.

Ivosidenib may be taken with or without food. If it is taken with food, participants should be advised to avoid consuming with a high-fat meal. All participants will be advised to avoid grapefruit and grapefruit products.

Ivosidenib tablets should be taken whole; they should not be crushed or chewed. If the participant forgets to take the daily dose, he/she should make up the dose within 12 hours after the missed dose. If more than 12 hours have elapsed or if the dose was vomited, that dose should be omitted and the subject should resume treatment with the next scheduled dose.

Dosing will be escalated as described above in section 5.1.

5.4 Definition of Dose-Limiting Toxicity (DLT)

Dose-limiting toxicities will be evaluated during cycle 1 (first 28 days) of treatment. Toxicities will be graded and documented according to NCI CTCAE version 4.03.

Non-hematologic DLTs will be defined as any drug-related grade 3 or greater event.

The following exceptions will NOT be considered DLTs in this population:

- grade 3 nausea, vomiting, or diarrhea that lasts ≤ 72 hours and responds to medical intervention

Hematologic DLTs will be defined as any drug-related grade 4 neutropenia (ANC < 500/μL) or thrombocytopenia (platelets < 25,000/μL) that

- has not resolved to grade 1 or less within 14 days of holding ivosidenib, or
- resolves within 14 days, but then recurs after resuming study drug

Note that anemia is not included as a DLT.

Additionally, febrile neutropenia of any duration, and not due or attributable to the underlying disease or other extraneous causes such as infection, will be considered a DLT.

In addition, any ≥ grade 2 non-hematologic toxicity that the participant finds intolerable or renders the participant unable to take 75% of the assigned doses (e.g. multiple dose interruptions) during the first cycle will be considered a DLT.

Management and dose modifications associated with the above events are outlined in Section 6.

Dosing will proceed within each cohort according to the following scheme.

Number of observed DLTs at a Given Dose Level	Decision Rule
0/3	3 additional evaluable patients will be treated at the dose level. If <=1 of the 6 treated patients experience a DLT, this is the RP2D. If >=2 of the 6 treated patients experience a DLT and current dose is dose level 2, de-escalate to dose level 1.
≥2	De-escalate to dose level 1 if current dose is dose level 2.

1/3	Add 3 more patients at current dose level a) If 0 of these 3 additional patients experience DLT, current dose is RP2D. b) If ≥1 of these 3 additional patients experience DLT, then de-escalate to dose level 1 if current dose is dose level 2.
≤1/6	Current dose is the RP2D

Subsequent (after cycle 1) cycles of ivosidenib will continue, with participants monitored for toxicity and adverse event reporting, but will not be used for DLT evaluation.

5.5 General Concomitant Medication and Supportive Care Guidelines

Ivosidenib (AG-120) is a substrate and a potential inducer of CYP2B6 and CYP3A4. Co-administration of AG120 with drugs primarily metabolized by CYP2B6 or 3A4 may result in decreased plasma concentrations of the co-administered drug. Therefore, concurrent use of CYP3A4 substrates should be avoided when possible, but when medically necessary, appropriate dose adjustments of the co-administered drug may be necessary. Examples of CYP3A4 substrates with narrow therapeutic index include cyclosporine, everolimus, sirolimus, and tacrolimus. Careful monitoring of drug levels of immunosuppressant agents is required. Careful consideration should be given to whether participants require the use of azoles and quinolones. An appendix E outlines list of strong CYP3A4 inhibitors, CYP3A4 substrates, and inducers.

Concomitant administration with strong CYP3A4 inhibitors is predicted to increase ivosidenib steady-state C max by up to 52% and AUC by up to 90% which may increase the risk of QTc interval prolongation. Treatment with strong CYP3A4 inhibitors is allowed on this study when they are medically necessary and cannot be avoided or substituted with another medication. However dose adjustment will be necessary with strong CYP3A4 inhibitors (listed in Appendix E) are used concurrently. This will be outlined in section 6.4. Additionally, the investigators must monitor for any changes in toxicity or QT interval, as outlined in section 6.5. Monitoring of subjects receiving study treatment with the combination of these drugs is essential. Providers and investigators should evaluate ECG and electrolytes (including potassium, magnesium, and calcium) at least weekly for the first cycle of therapy. Vigilance is particularly important in subjects presenting with nausea, vomiting, or diarrhea.

Intrathecal chemotherapy for the purposes of prophylaxis is allowed. Intrathecal chemotherapy for the purpose of treating active leukemic disease is not allowed.

If treatment pauses are necessary, per guidance below, due to adverse events on study, if and when ivosidenib is held in the midst of a cycle, the cycle day will not change, and once the drug is resumed it will be either on the day that that cycle has progressed to, or if the pause is beyond 28 days of that cycle, the resumption will be called the day 1 of the subsequent cycle.

5.5.1 Prolonged QT Interval

Participants may be at increased risk for the development of QT prolongation when treated with ivosidenib (AG-120) in combination with fluoroquinolones, azole antifungal agents or serotonin (5-HT3) antagonists. Therefore, treating clinicians need to be vigilant and closely monitor participants receiving any of these drugs; this includes regular evaluation of ECG and electrolytes (including potassium, magnesium, and calcium), particularly in subjects presenting with nausea, vomiting, or diarrhea. Participants will need careful monitoring of the QTcF interval. (See section 6.4 for further information.)

5.5.2 IDH Differentiation Syndrome

Subjects treated with ivosidenib (AG-120) have developed signs and symptoms of IDH differentiation syndrome. However, this trial will be in the setting of disease remission, and therefore profound differentiation and differentiation syndrome are highly unlikely in this setting. Nevertheless, the clinical features of differentiation syndrome may include some or all of the following: unexplained fever, skin rash, hypoxia, respiratory compromise, interstitial pulmonary infiltrates, pleural and/or pericardial effusion, weight gain, and clinical deterioration. Laboratory features may include an increase in ANC and/or platelets. An increase in mature leukocytes may be observed in the bone marrow aspirate differential if a bone marrow biopsy is conducted during this time. However, no single sign or symptom may be considered *per se* as diagnostic of the syndrome. If IDH differentiation syndrome is suspected, Investigators need to report the suspected diagnosis as an SAE. It is recommended that the prophylactic and therapeutic measures indicated below are undertaken at the earliest manifestations of suspected IDH differentiation syndrome:

- Temporary hold of AG-120 treatment only if symptoms cannot be medically managed with the following:
    - Prompt initiation of hydroxyurea at a suggested dose of 2 to 3 g PO two or three times daily
    - Prompt administration of corticosteroids at a suggested dose 10 mg of dexamethasone IV every 12 hours until disappearance of symptoms and signs, and for a minimum of 3 days
    - Initiation of furosemide, if clinically required
    - Prompt initiation of leukapheresis, if required
    - Immediate communication with the Prinicipal Investigator, Dr. Fathi, is encouraged for guidance regarding treatment. Once the signs and symptoms resolve and the subject's clinical condition improves, AG-120 may be reinitiated if study treatment was withheld. The dose of AG-120 at re-initiation is to be discussed with the Principal Investigator.

5.5.3 Leukocytosis

Ivosidenib/AG-120 may be associated with leukocytosis that can occur without progression of AML. It is recommended that the prophylactic and therapeutic measures indicated below be

undertaken at the earliest manifestations of leukocytosis:

- Temporary hold of study treatment only if symptoms cannot be medically managed with the following:
    - Prompt initiation of hydroxyurea at up to a dose of 2000 or 3000 mg PO BID
    - Prompt initiation of leukapheresis, if required

Treatment with hydroxyurea is allowed after the start of AG-120 for initial control of peripheral leukemic blasts in subjects with leukocytosis (for example, WBC >30,000/μL) during the course of AG-120 therapy with approval of the Principal Investigator.

Immediate communication with the Principal Investigator is encouraged for guidance regarding treatment. Once the signs and symptoms resolve and the subject's clinical condition improves, AG-120 may be reinitiated if study treatment was held. If it was held, then the dose of AG-120 at reinitiation is to be discussed with the Principal Investigator.

5.6 Criteria for Taking a Participant Off Therapy

Participants with persistent remission can continue receiving ivosidenib for 12 cycles.

Duration of therapy will depend on tolerance and evidence of disease progression. In the absence of treatment delays due to adverse event(s), treatment may continue for 12 cycles or until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

Participants will be removed from protocol therapy when any of these criteria apply. Alternative care options will be discussed with the participant. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). The DF/HCC research team will update the relevant Off Treatment/Off Study information in the CTMS, OnCore. The Coordinating Center will update this information for external site participants.

5.7 Duration of Follow Up

Participants will be followed for 24 months from the start of protocol therapy or until death, whichever occurs first. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event. Participants who

conclude or are removed from protocol treatment and begin a new therapy will be followed for survival only. Adverse event and toxicity data will not be collected for patients who initiate new therapy. Follow-up assessments for study purposes will occur every 3 months per the study calendar in Section 10.

5.8 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria applies:

- Lost to follow-up
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF). The DF/HCC research team will update the relevant Off Treatment/Off Study information in the CTMS, OnCore in accordance with DF/HCC policy REGIST-101. The Coordinating Center will update this information for external site participants.

6. DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made as indicated below. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 4.03 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

If a participant experiences several adverse events and there are conflicting dose reduction recommendations, the dose should be adjusted to the lowest recommended level.

Regarding pauses in dosing due to adverse events on study, if and when ivosidenib is held in the midst of a cycle, the cycle day will not change, and once the drug is resumed it will be either on the day that that cycle has progressed to, or if the pause is beyond 28 days of a cycle, the resumption will be called the day 1 of the subsequent cycle.

6.1 Acute GVHD

As mentioned previously, acute GVHD prior to study entry must be clinically stable and requiring ≤ 0.5 mg/kg/day of prednisone. For patients who initiate therapy and develop new onset acute GVHD:

- Therapy with topical / local agents such as corticosteroid / tacrolimus cream, oral non-absorbable steroids, ursodiol, etc. are allowed to be used and ivosidenib will continue. Discussion with the Principal Investigator is encouraged.

- Systemic therapy ≤ 0.5 mg/kg/day of prednisone is allowed to be used with continuation of ivosidenib – i.e. starting 20 mg / day for presumed upper GI GVHD. In no way is this study advocating for the use of a specific dose of steroids for initial therapy of acute GVHD, and treatment of such should not be compromised to continue ivosidenib.

- If requiring systemic steroids > 0.5 mg/kg/day of prednisone, ivosidenib will be held and initial therapy for acute GVHD initiated. If within the next 28 days, the participant is able to improve and be on a stable dose of steroids which is ≤ 0.5 mg/kg/day of prednisone (or equivalent), ivosidenib may be restarted at the original dose.

- Participants are forbidden from receiving any "investigational" agents for the treatment of acute GVHD. Discussion with the overall PI is encouraged to define "investigational." Patients are allowed to participate on clinical trials investigating initial therapy for acute GVHD – i.e. using agents with steroids or agents alone which are not "investigational."

- If acute GVHD occurs in the dose-escalation cohorts, and this occurs during the first cycle of treatment and patient has taken < 14 days of drug, the participant may be replaced, as DLT evaluation would be impacted.

- Any initiation of systemic therapy beyond steroids for steroid-refractory acute GVHD will result in the participant stopping ivosidenib. Systemic therapy beyond steroids for participants with *steroid-dependent* acute GVHD is allowed and will not result in participant stopping ivosidenib. Discussion with the PI is encouraged.

- For flares of acute GVHD, participants are allowed to increase systemic steroid dose, however, if exceeding 0.5 mg/kg/day of prednisone or equivalent, ivosidenib will be held and the patient will have 28 days to restart if symptoms and steroid requirement guidelines can be met.

6.2 Chronic Graft versus Host Disease (GVHD)

For patients who initiate therapy and develop new onset chronic GVHD:

- Therapy with topical / local agents such as corticosteroid / tacrolimus cream, oral non-absorbable steroids, ursodiol, etc. are allowed to be used and ivosidenib will continue. Discussion with the Principal Investigator is encouraged.

- Systemic therapy ≤ 1 mg/kg/day of prednisone is allowed to be used with continuation of ivosidenib. In no way is this study advocating for the use of a specific dose of steroids for initial therapy of chronic GVHD, and treatment of such should not be compromised to continue ivosidenib.

- If requiring systemic steroids > 1 mg/kg/day of prednisone, ivosidenib will be held and initial therapy for chronic GVHD initiated. If within the next 28 days, the participant is able to improve and be on a stable dose of steroids which is ≤ 1 mg/kg/day of prednisone (or equivalent), ivosidenib may be restarted at the original dose.

- Participants are forbidden from receiving any "investigational" agents for the treatment of chronic GVHD. Discussion with the overall PI is encouraged to defined "investigational." Participants are allowed to participate on clinical trials investigating initial therapy for chronic GVHD – i.e. using agents with steroids or agents alone which are not "investigational."

- Any initiation of systemic therapy beyond steroids for steroid-refractory chronic GVHD will result in the patient stopping ivosidenib Systemic therapy beyond steroids for participants with *steroid-dependent* chronic GVHD is allowed and will not result in participant stopping ivosidenib. Discussion with the PI is encouraged.

- For flares of chronic GVHD, participants are allowed to increase systemic steroid dose, however, if exceeding 1 mg/kg/day of prednisone or equivalent, ivosidenib will be held and the patient will have 28 days to restart if symptoms and steroid requirement guidelines can be met.

6.3 Non-Hematologic Toxicity (except QT prolongation)

If at any time during ivosidenib dosing, a participant experiences a grade 3 or higher toxicity that is possibly, probably or definitely related to ivosidenib, drug must be held until the toxicity resolves to a grade 1 or lower. If it is during the first cycle (28 days) of dosing, the toxicity will be considered to be a DLT (see section 5.4). In participants with known Gilbert's disease, grade 3 elevated bilirubin that is possibly, probably or definitely related to ivosidenib would not require study drug hold if the elevation is not due to liver GVHD or veno-occlusive disease. For these participants, study drug must be held for grade 4 elevated bilirubin and resolution/recurrence of toxicity to follow the instructions below in 6.3.1 and 6.3.2.

If and when ivosidenib is held in the midst of a cycle, the cycle day will not change, and once the drug is resumed it will be either on the day that that cycle has progressed to, or if the pause is beyond 28 days of a cycle, the resumption will be called the day 1 of the subsequent cycle.

6.3.1 250 mg dosing

If the participant was at the 250mg daily dosing level when the toxicity occurred, and it takes longer than 14 days for the event to resolve to ≤ grade 1, then the participant will be taken off treatment and will remain on study only for survival and other outcomes.

If the toxicity takes less than 14 days to resolve to ≤ grade 1, then ivosidenib can be restarted at 250mg daily dosing upon resolution. If the attributable toxicity recurs at ≥ grade 3 (or grade 4 bilirubinemia in those with known Gilbert's disease – see above section 6.3) during the course of the study, then the participant will come off treatment and will remain on study only for survival and other outcomes. If the toxicity recurrence (to ≥ grade 3) happens during the first cycle of dosing, then the event will be a DLT.

6.3.2 500 mg dosing

If the participant was at the 500mg daily dosing level when the toxicity occurred, and the toxicity resolves to ≤ grade 1 *after* 14 days, but *before* 28 days (total) have elapsed, then dosing with ivosidenib can resume at the reduced dose of 250 mg daily. If the attributable toxicity recurs at ≥ grade 3 (or grade 4 bilirubinemia in those with known Gilbert's disease – see above section 6.3) during the course of the study, then the participant will come off treatment and will remain on study only for survival and other outcomes.

If the participant was at the 500mg daily dosing level when the toxicity occurred, and it takes *less than* 14 days for the event to resolve to ≤ grade 1, then dosing with ivosidenib can resume at 500mg daily. If the toxicity recurs at ≥ grade 3 (or grade 4 bilirubinemia in those with known Gilbert's disease – see above section 6.3), then dosing will again be held. (This will be a DLT if it occurs during cycle 1). If the toxicity again resolves to ≤ grade 1 within 28 days, then dosing with ivosidenib can resume at the reduced dose of 250mg daily. If the toxicity recurs yet again at ≥ grade 3 (or grade 4 bilirubinemia in those with known Gilbert's disease – see above section 6.3), then the participant will come off treatment and will remain on study only for survival and other outcomes.

A participant who starts at 500mg daily dosing and is subsequently reduced to 250mg daily dosing due to toxicity can potentially increase back up to 500mg daily dosing if subsequent evaluation of the observed toxicity indicates no relation to study drug. Any such re-escalation must have the approval of the principal investigator, Dr. Fathi.

6.4 Concurrent Use of CYP3A4 Inhibitors, CYP3A Inducers, and CYP3A Substrates

Dose adjustment of ivosidenib will be necessary when strong CYP3A4 inhibitors (listed in Appendix E) are initiated or used concurrently, given that concomitant administration with strong CYP3A4 inhibitors is predicted to increase ivosidenib steady-state C max by up to 52% and AUC by up to 90%. For patients at an ivosidenib dose of 500mg daily, concomitant use of strong CYP3A4 inhibitors, the ivosidenib dose will be reduced to 250mg daily, with close monitoring for any toxicity or QT interval prolongation.

The concomitant use of CYP3A inducers (listed in Appendix E) should be avoided. As for concomitant use of CYP3A substrates, this should be avoided when possible, but when this is medically necessary, very close monitoring for toxicity is needed. As an example, tacrolimus and sirolimus are both common immunosuppressive medications, and CYP3A substrates, that post-transplant participants may be taking. Both of these agents will be monitored closely in terms of trough levels, with levels will be doses closely followed and adjusted.

6.5 QT Prolongation

Subjects may be at increased risk for the development of QT prolongation when treated with ivosidenib in combination with fluoroquinolones, azole antifungal agents, or serotonin ($5\text{-}HT_3$) antagonists. Investigators must be vigilant and attempt to avoid administering concomitant medications associated with QT prolongation whenever possible, and if no other therapeutic options are available, monitor subjects receiving study treatment with the combination of these drugs. They should evaluate ECG and electrolytes (including potassium, magnesium, and calcium) at least weekly for the first cycle of therapy. Vigilance is particularly important in

subjects presenting with nausea, vomiting, or diarrhea. Systemic administration of a moderate or strong CYP3A4 inhibitor requires careful monitoring of QTcF.

Participants who experience QTcF prolongation to > 480 msec (Grade ≥ 2) while treated with ivosidenib should be promptly evaluated for causality of the QTc prolongation and managed according to the following guidelines:

- Levels of electrolytes (potassium, calcium, and magnesium) should be checked and supplementation given to correct any values outside the normal range.
- Concomitant therapies should be reviewed and adjusted as appropriate for medication with known QT prolonging effects.
- ECGs should be conducted at least weekly for 2 weeks following QTcF reduction ≤480 msec.

If no other cause is identified and the investigator believes it is appropriate, particularly if QTc remains elevated (after above measures have been implemented, or as determined by the investigator), ivosidenib dosing may be interrupted. An ECG should be rechecked in approximately 1 week after the QTcF prolongation was first observed or more frequently as clinically indicated.

If QTc has recovered or improved and the investigator believes it is safe to do so, re-challenge with ivosidenib should be considered if held.

If Grade 2 (QTcF > 480 and ≤ 500 msec), the dose of ivosidenib may be reduced without interruption of dosing. The ivosidenib dose may be re-escalated to the prior dose in ≥ 14 days after QT prolongation has decreased to ≤ Grade 1.

If Grade 3 (QTcF > 500 msec), when QTc prolongation is first observed, hospitalization for continuous cardiac monitoring and evaluation by a cardiologist should both be considered. Dosing with ivosidenib will be interrupted. If QTc returns to within 30 ms of baseline or < 450 msec within 14 days, treatment may be resumed at a reduced dose. The ivosidenib dose cannot be re-escalated following dose reduction for Grade 3 QTcF prolongation unless the prolongation was associated with an electrolyte abnormality or concomitant medication.

If Grade 4 (QTcF > 500 msec or > 60 msec change from baseline with torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia), subjects should be admitted to hospital when QTc prolongation is first observed for continuous cardiac monitoring and be discharged only after review by a cardiologist. Dosing with ivosidenib should be permanently discontinued. If, in the dose-escalation cohorts, this discontinuation occurs during the first cycle of treatment, the participant can be replaced, as this would impact DLT assessment

6.6 Neurologic Toxicities

According to the Investigator's Brochure (IB v7 dated March 31 2018), in the single-agent studies of ivosidenib, events of Guillain-Barre syndrome (GBS) and leukoencephalopathy have been observed; these events have been identified as potential risks associated with ivosidenib administration, and leukoencephalopathy is a potential risk associated with ivosidenib treatment

based on clinical safety findings. Subjects should be monitored for onset of signs or symptoms suggestive of leukoencephalopathy or GBS. Diagnostic evaluations may include consultation with a neurologist, MRI of the brain, lumbar puncture, and/or biopsy as clinically warranted. . Ivosidenib should be permanently discontinued in subjects if these diagnoses are confirmed.

Leukoencephalopathy AEs identified using the search strategy reported during Study AG120-C-001 included preferred terms of encephalopathy, PML, and PRES. The events of PML and PRES were serious; all events were Grade ≥3. No events of leukoencephalopathy were reported in any other study of ivosidenib as of 16 January 2018.

A patient with R/R AML receiving 500 mg QD of ivosidenib experienced progressive multifocal leukoencephalopathy (PML). The subject withdrew consent from study participation and ivosidenib was permanently discontinued. The Investigator and Sponsor assessed the 2 SAEs of PML as not related to ivosidenib based on his history of cladribine exposure and his underlying disease. PML is a rare opportunistic infection of the central nervous system caused by the JC polyomavirus, which has been observed in patients with AML and in patients with hematologic malignancies who were previously treated with purine nucleoside analogs, such as cladribine. PML is a very serious condition that may result in severe disability or death. The signs and/or symptoms of PML may begin gradually, usually worsen rapidly, and vary depending on which part of the brain is infected. Signs and symptoms may include difficulty with walking and other movements, progressive weakness, decline in mental function, visual field deficits, headaches, seizures, and speech and language disturbances.

On this study, subjects should be monitored for onset of signs or symptoms suggestive of PML. Diagnostic evaluations may include consultation with a neurologist, MRI of the brain, lumbar puncture, and/or brain biopsy as clinically warranted. Ivosidenib should be permanently discontinued in subjects with confirmed PML.

An 81-year-old female subject with untreated AML receiving 500 mg QD of ivosidenib experienced the SAE of PRES (Posterior Reversible Encephalopathy Syndrome) on Study Day 94. The subject's symptoms included bilateral upper extremity weakness, hypertension, mild frontal to right-sided headache, and seizure activity with bilateral hand twitching and abdominal contractions. MRI results of the brain were suspicious for atypical PRES. Ivosidenib was permanently discontinued due to the SAE of PRES. The Investigator and Sponsor assessed the SAE of PRES as possibly related to ivosidenib. PRES is a rare clinico-radiological neurological syndrome. Clinical characteristics may include sub-acute onset of headache, hypertension, seizures, altered mental status, visual disturbances, and occasionally other focal neurological signs. Radiologically, signs of vasogenic edema are usually seen bilaterally in the white matter of the parieto-occipital lobes, but changes can also be seen in frontal and temporal lobes, brainstem, cerebellum, and in cortical as well as deep gray matter.

On this study, subjects should be monitored for onset of neurological signs and/or symptoms that are clinically associated with PRES. Diagnostic evaluations may include consultation with a neurologist, MRI of the brain, and other recognized standard of care measures as clinically warranted to address and treat any diagnosis of PRES.

6.7 Hematologic Toxicity

If at any time during ivosidenib dosing, a participant experience a grade 4 thrombocytopenia or grade 4 neutropenia that is possibly, probably or definitely related to ivosidenib, drug must be held until the toxicity resolves to a grade 1 or lower. If it takes more than 14 days for the event to resolve, and it is during the first cycle (28 days) of dosing, the toxicity will be considered to be a DLT (see section 5.4)

6.7.1 250 mg dosing

If the participant was at the 250mg daily dosing level when the toxicity occurred, and it takes longer than 14 days for the event to resolve to ≤ grade 1, then the participant will be taken off treatment and will remain on study only for survival and other outcomes.

If the toxicity takes less than 14 days to resolve to ≤ grade 1, then ivosidenib can be restarted at 250mg daily dosing upon resolution. If the toxicity recurs at grade 4 during the course of the study, then the participant will come off treatment and will remain on study only for survival and other outcomes. If the toxicity recurrence (to grade 4) happens during the first cycle of dosing, then the event will be a DLT.

6.7.2 500 mg dosing

If the participant was at the 500mg daily dosing level when the toxicity occurred, and the toxicity resolves to ≤ grade 1 *after* 14 days, but *before* 28 days (total) have elapsed, then dosing with ivosidenib can resume at the reduced dose of 250 mg daily. If the toxicity recurs at grade 4 during the course of the study, then the participant will come off treatment and will remain on study only for survival and other outcomes.

If the participant was at the 500mg daily dosing level when the toxicity occurred, and it takes *less than* 14 days for the event to resolve to ≤ grade 1, then dosing with ivosidenib can resume at 500mg daily. If the toxicity recurs at grade 4, then dosing will again be held. (This will be a DLT if it occurs during cycle 1). If the toxicity again resolves to ≤ grade 1 within 28 days, then dosing with ivosidenib can resume at the reduced dose of 250mg daily. If the toxicity recurs yet again at grade 4, then the participant will come off treatment and will remain on study only for survival and other outcomes.

A participant who starts at 500mg daily dosing and is subsequently reduced to 250mg daily dosing due to toxicity can potentially increase back up to 500mg daily dosing if subsequent evaluation of the observed toxicity indicates no relation to study drug. Any such re-escalation must have the approval of the principal investigator, Dr. Fathi.

6.8 General

Any subject who is unable to tolerate 250mg daily dosing of ivosidenib should be discontinued from study treatment.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting in addition to routine reporting.

7.1 Potential Risks and Adverse Drug Reactions (ADRs) for Ivosidenib

Please refer to the current Investigator's Brochure (IB) for ivosidenib which includes any additional updated safety data and drug-drug interaction information.

7.1.1 Expected events/ADR's (Common, 1-10%)

- Prolonged QT Interval
- IDH Differentiation Syndrome
  Clinical features may include some or all of the following:
  - Unexplained fever
  - Skin rash
  - Hypoxia
  - Respiratory compromise
  - Interstitial pulmonary infiltrates
  - Pleural and/or pericardial effusion
  - Weight gain
  - Clinical deterioration

  Laboratory features may include
  - An increase in ANC
  - An increase in platelets

  An increase in mature leukocytes may be observed in the bone marrow aspirate differential if a bone marrow biopsy is conducted during this time.
- Leukocytosis (without progression of AML)

7.1.2 Potential Risks

- Rash
- Tumor Lysis Syndrome
- Liver dysfunction
  - Increased transaminases
  - Increased blood bilirubin
  - Hepatocellular injury
  - Increased gamma glutamyl transferase
  - Jaundice
- Renal dysfunction
  - Acute renal failure
  - Chronic renal failure
  - Increased blood creatinine

- Hematologic Abnormalities
    - Anemia
    - Neutropenia (including febrile neutropenia)
    - Thrombocytopenia
    - Lymphopenia
    - Decreased white blood cell count
- Gastrointestinal Symptoms
    - Nausea
    - Diarrhea
    - Vomiting
    - Constipation
- Sensorimotor Neuropathy (may result in weakness, loss of muscle function, numbness, tingling or burning)

7.2 Definitions

7.2.1 Adverse Event (AE)

An adverse event (AE) is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study.

Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests. Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a serious adverse event.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page/screen of the CRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE. If possible, the laboratory abnormality should be recorded as a medical term and not simply as an abnormal laboratory result (e.g., record thrombocytopenia rather than decreased platelets).

7.2.2 Serious Adverse Event (SAE)

A qualified Investigator will evaluate all adverse events as to seriousness. A serious adverse event (SAE) is any adverse event, occurring at any dose and regardless of causality that:

- Results in death.
- Is life-threatening. Life-threatening means that the person was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- Requires or prolongs inpatient hospitalization (i.e., the event required at least a 24-hour hospitalization or prolonged a hospitalization beyond the expected length of stay). Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered SAEs if the illness or disease

existed before the person was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly or birth defect; or
- Is an important medical event when, based upon appropriate medical judgment, it may jeopardize the participant and require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Events **not** considered to be serious adverse events are hospitalizations for:
- A standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- The administration of blood or platelet transfusion as routine treatment of studied Indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- A procedure for protocol/disease-related investigations (e.g., surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- Elective or pre-planned treatment for a pre-existing condition that did not worsen
- Emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- Respite care

For each SAE, the Investigator will provide information on severity, start and stop dates, relationship to IP, action taken regarding IP, and outcome.

7.2.3 Expectedness

Adverse events can be expected or unexpected.

7.2.3.1 Expected Adverse Event

Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as an associated risk. Refer to Section 6.1 for a listing of expected adverse events associated with the study agent(s).

7.2.3.2 Unexpected Adverse Event

For the purposes of this study, an adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list, the Investigator's Brochure, the package insert or when it is not included in the informed consent document as an associated risk.

7.2.4 Attribution

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study treatment.
- Probable – The AE is likely related to the study treatment
- Possible – The AE may be related to the study treatment.
- Unlikely - The AE is doubtfully related to the study treatment.
- Unrelated - The AE is clearly NOT related to the study treatment

7.3 Adverse Event Characteristics

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

AEs that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.

7.4 Expedited Adverse Event Reporting

All serious adverse event (SAE) that occur after the initial dose of study treatment, during treatment, or within 30 days of the last dose of ivosidenib must be reported to the Coordinating Center and the Principal Investigator, Amir Fathi, M.D., on the local institutional SAE form.

This includes events meeting the criteria outlined in Section 7.2.2, as well as the following:

- Grade 2 (moderate) and Grade 3 (severe) events that are unexpected and at least possibly related/associated with the intervention.
- All Grade 4 (life-threatening or disabling) events that are unexpected or not specifically listed in the protocol as not requiring reporting.
- All Grade 5 (fatal) events while the participant is enrolled and actively participating in the trial OR when the event occurs within 30 days of the last study intervention. Note: If the participant is in long term follow up, report the death at the time of continuing review.

For multi-center studies where a DF/HCC investigator is serving as the Overall Principal Investigator, each participating institution **must** abide by the reporting requirements set by the

DF/HCC.

In the event of an unanticipated problem or life-threatening complications, treating investigators must immediately notify the overall PI.

7.4.1 DF/HCC Expedited Reporting Guidelines

Investigative sites within DF/HCC will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

Other investigative sites will report AEs to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. A copy of the submitted institutional AE form should be forwarded to the Coordinating Center within the timeframes detailed in the table below. The Coordinating Center will submit AE reports from outside institutions to the DFCI OHRS according to DFCI IRB policies and procedures in reporting adverse events.

	DF/HCC Reportable AEs				
Attribution	**Gr. 2 & 3 AE Expected**	**Gr. 2 & 3 AE Unexpected**	**Gr. 4 AE Expected**	**Gr. 4 AE Unexpected**	**Gr. 5 AE Expected or Unexpected**
Unrelated Unlikely	Not required	Not required	5 calendar days#	5 calendar days	24 hours*
Possible Probable Definite	Not required	5 calendar days	5 calendar days#	5 calendar days	24 hours*
# If listed in protocol as expected and not requiring expedited reporting, event does not need to be reported.					
* For participants enrolled and actively participating in the study ***or*** for AEs occurring within 30 days of the last intervention, the AE should be reported within 1 business day of learning of the event.					

Participating investigators must report each adverse event to the Coordinating Center in accordance with these timeframes. In the event that the participating investigator does not become aware of the adverse event immediately (e.g., participant sought treatment elsewhere) or within the reporting timeframes listed in the table above, the participating investigator is to report the event within 1 business day after learning of it and document the time of his or her first awareness of the adverse event.

7.5 Expedited Reporting to the Food and Drug Administration (FDA)

The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Overall PI will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

7.6 Expedited Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant

safety reports or sentinel events that require reporting according to institutional policy.

7.7 Safety Reporting to Servier

A listing of all SAEs should be reported to Servier on a quarterly basis. Any adverse event requiring expedited reporting (serious, unexpected event suspected of being related to AG-120) will be reported by the Coordinating Center to Servier immediately but no later than 24 hours after regulatory submission .

Should the site become aware of a pregnancy or drug mis-dose/overdose, this should be reported to the Coordinating Center and Overall PI within 24 hours of becoming aware.

The Coordinating Center will submit reports to Servier to: pharmacovigilance-US@servier.com

7.8 Routine Adverse Event Reporting

All Adverse Events must be reported in routine study data submissions to the Overall PI on the toxicity case report forms. AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must also be reported in routine study data submissions. All adverse events that occur through 30 days after the last dose of study drug will be recorded in the protocol-specific case report forms.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with ivosidenib can be found in Section 7.1.

8.1 Ivosidenib

8.1.1 Description

Ivosidenib is also known as AG-120 or AGI-16678.

AG-120 demonstrated good oral bioavailability, rapid absorption, and a long $t_{1/2}$ in subjects with IDH1m AML and solid tumors, supporting a QD dosing regimen. Following multiple doses of AG-120, steady state was reached within 15 days, with approximately 2-fold accumulation in plasma exposure. Plasma exposure of AG-120 increased less than dose proportionally from 100 to 1200 mg. Results from Studies AG120-C-001 and AG120-C-002 indicate that plasma 2-HG levels were substantially reduced in subjects with an IDH1 mutation (achieving levels similar to those in healthy volunteers) at dose ranging from 200 to 1200 mg QD. Multiple doses of AG-120 also decreased 2-HG levels in bone marrow (AML) and tumor biopsies (cholangiocarcinoma, chondrosarcoma) at dose ranging from 200 mg to 1200 mg QD. Maximal inhibition of 2-HG in plasma did not appear to change upon multiple daily dosing with AG-120.

8.1.2 Form

Ivosidenib/ AG-120 tablets are available in 250 mg strength for clinical studies.

AG-120 250 mg film-coated tablets are blue oval shape tablets containing 250 mg of AG-120.

AG-120 250 mg tablets contain the inactive ingredients hypromellose acetate succinate, microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulfate, colloidal silicon dioxide, and magnesium stearate. AG-120 250 mg film-coated tablets also include the inactive ingredient Opadry® II Blue.

8.1.3 Packaging

Ivosidenib/AG-120 tablets are supplied in appropriate containers and are labeled appropriately as investigational product for clinical studies. Tablets will be supplied in high density polyethylene (HDPE) bottles with a desiccant silica gel and child-resistant closures with heat induction seal.

8.1.4 Availability

Ivosidenib/AG-120 will be provided by Servier Pharmaceuticals, Inc.

8.1.5 Administration

Drug will be administered orally, once per day, at doses as specified above in the Treatment Plan (section 5).

Subjects may take ivosidenib/AG-120 tablets with or without food. To minimize the effects of a high-fat meal on AG-120 exposure, subjects should avoid consuming a high-fat meal when AG-120 is administered with food. All subjects will also be advised to avoid grapefruit and grapefruit products.

8.1.6 Accountability

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

Correlative studies for 2-Hydroxyglutarate and minimal residual disease will be performed on all participants' samples. Next generation and whole genome sequencing will be performed only on samples from DF/HCC participants.

9.1 2-Hydroxyglutarate analysis

We will measure plasma and marrow levels of 2-hydroxyglutarate.
• Pretreatment: Blood 2 mL , Bone marrow aspirate 2 mL
• Day 8 (Range Days 6-10): Blood 2 mL
• Day 15 (Range Days 13-16): Blood 2 mL
• Day 30: Blood 2 mL
• Day 60: Blood 2 mL
• At any point of relapse: Blood 2 mL, Bone marrow aspirate 2 mL (if available)

Blood will be collected in 2mL lavender top K2EDTA tubes. Collected samples will be stored on ice until centrifuged. Plasma will be stored frozen at -80^{o}C (+/- 10^{o}C) until shipped.

Bone marrow will be collected in 4mL Na Heparin tubes and then aliquoted into cryovials that will be stored frozen at -80^{o}C (+/- 10^{o}C) until shipped.

Frozen samples will be shipped on dry ice (shipping out on Monday, Tuesday, or Wednesday) to

PPD
Attn: Jay Schaefgen, Sr. Group Leader Specimen Management
3230 Deming Way
Middleton WI, 53562
T: 608.662.7706
F: 608.662.9025
Email: jay.schaefgen@ppdi.com

Collection and processing details are available in a separate document.

9.2 Next-generation and whole genome sequencing (DF/HCC participating sites ONLY)

The following volumes of blood and aspirated bone marrow will be required:
• Pretreatment: Blood 15 mL x 2, Bone marrow aspirate 15 mL
• Day 8 (Range Days 6-10): Blood 15 mL
• Day 15 (Range days 13-16): Blood 15 mL
• Day 30: Blood 15 mL
• Day 60: Blood 15 mL,
• At any point of relapse: Blood 15 mL, Bone marrow aspirate 15 mL (if available)

Bone marrow aspirate and peripheral blood shall be collected in purple-top (EDTA) tubes.

All specimens should be maintained at room temperature and delivered within one day to the processing laboratory. Specimens may be shipped via FedEx priority overnight Monday through Thursday (excluding holidays). For after-hours / evening collections, specimens may be maintained at room temperature and shipped within 4 days of collection.

Samples will be sent to:

MGH Tissue Repository
c/o Jennifer Lombardi Story
326 Cambridge Street, 3rd Floor
Boston MA 02114-3002
(617) 724-7355

All samples will be processed in a CLIA certified lab. DNA obtained from blood and bone marrow may be subjected to broader sequence analysis (whole exome or genome).

Whole genome sequencing (WGS) will allow us to look at the clonal architecture of *IDH1*-mutant disease at various time points during maintenance after hematopoietic stem cell transplant. This will help us look at which clones or subclones respond to therapy and whether the disease course is influenced by the outgrowth of *IDH*-wildtype clones.

We will also perform next-generation sequencing (NGS) to assess for mutational burden (i.e. the fraction of AML cells harboring *IDH* mutations, corrected for copy number) at various time points. We will utilize the SNaPshot genotyping analysis platform to perform these analyses. This assay uses multiplex polymerase chain reaction technology for single nucleotide variant and insertion/deletion detection in genomic DNA. The sequencing targets hotspots and exons including *IDH1/2*. We will monitor the dynamics of *IDH1* mutational burden and assess for the presence / absence of the *IDH* mutant allele at these timepoints.

9.3 Minimal Residual Disease (MRD)

We will measure MRD from bone marrow aspirate whenever possible. If bone marrow aspirate is not available, peripheral blood should be collected.

- Pretreatment: Bone marrow aspirate 8 mL (or peripheral blood)
- Pre-Cycle 12: Bone marrow aspirate 8 mL (or peripheral blood)
- At any point of relapse or discontinuation from study: Bone marrow aspirate 8 mL (or peripheral blood)

Sample will be collected in 8 mL CPT Sodium Heparin tubes. Collected samples can be stored at room temperature until processed. **Samples must be processed within 4 hours of collection**. Processed cells will be aliquoted into cryovials that will be stored frozen at -80^{o}C (+/- 10^{o}C) until they are shipped.

Detailed collection, processing and shipping instructions are provided in a separate laboratory manual.

Frozen samples will be batch shipped to:

Sysmex Inostics GmbH
ATTN: Denise Heim
Falkenried 88
Building A, 1st floor

20251 Hamburg
Germany

All specimens should be labeled with study ID (#18-123), participant study ID number, visit cycle/day, date and time of collection, specimen type, and must be accompanied by the appropriate requisition form and inventory manifest.

On the day of shipping, the Coordinating Center should be emailed a copy of the inventory manifest, date of shipment and the tracking number.

10. STUDY CALENDAR

Pre-study screening evaluations are to be conducted within 42 days prior to registration.
All cycles are 28 days in duration. There are no rest periods between cycles.
Whenever possible, the study visit should occur on the scheduled visit day. A ± 5-day window is allowed in order to accommodate participants' schedules.

	Screening	**Pre-Treatment[1]**	**Cycle 1**			**Pre-Cycles 2, 3**	**Pre-Cycles 4, 5, 7, 8, 10, 11**	**Pre-Cycles 6, 9, 12**	**Relapse**	**End of Treatment[7]**	**Follow-Up[9]**
	Pre-HSCT	**D-14**	**D1[2,3]**	**D8**	**D15**						
Informed Consent	X										
Medical History	X	X									
Physical Exam	X	X	X	X	X	X	X	X	X	X	
Vitals (BP, HR, RR)	X	X	X	X	X	X	X	X	X	X	
Performance Status	X	X	X							X	
12-lead ECG	X		X	X	X	X	X	X	X	X	
Echocardiogram or MUGA scan	X										
CBC w/ diff	X	X	X	X	X	X	X	X	X	X	
Chemistries[4]	X	X	X	X	X	X	X	X	X	X	
GVHD assessment[5]		X	X	X	X	X	X	X		X	X
Peripheral blood chimerism		X						X	X	X	
Coagulation parameters (PT, PTT, INR, D-dimer, fibrinogen)	X	X	X	X	X	X	X	X	X	X	
Pregnancy Test[6]	X		X			X	X	X		X	
Bone Marrow Biopsy and Aspirate[11]	X	X						C6 and C12 only	X		
Adverse Event Evaluation	X		X	X	X	X	X	X	X	X	X
Blood for correlative studies (2-HG, NGS,		X		X	X	X			X		

WGS)											
Survival											X
Disease Assessment[8]								C6 and C12 only	X		
New Antineoplastic Therapy[10]											X

[1] Pre-treatment evaluations are to be conducted within 14 days prior to start of protocol therapy. Pre-treatment bone marrow biopsy is to be conducted after neutrophil engraftment (defined as ANC ≥1000/μL). In the event that the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.
[2] Any evaluations that are required at both pre-treatment and Cycle 1 Day 1 do not need to be repeated on Cycle 1 Day 1 if they were done in the previous 7 days.
[3] Cycle 1 Day 1 assessments must be performed prior to administration of ivosidenib. Patients must fulfill Day 1 laboratory criteria as outlined in Section 5.2.1.
[4] Chemistries include sodium, potassium, calcium, magnesium, phosphorus, chloride, blood urea nitrogen (BUN), total bilirubin, direct bilirubin, creatinine, albumin, total protein, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH).
[5] Symptoms of both acute and chronic GVHD should be assessed. Criteria are listed in section 11.2 and 11.3.
[6] Pregnancy test is only required for women of childbearing potential. This must be done within 7 days prior to study drug administration at each cycle.
[7] An End of Treatment visit should occur within 5 days of the last dose of study drug. If the required evaluations have been performed as part of another study visit, they do not need to be repeated.
[8] Disease assessment will be based on modified IWG criteria or other appropriate response criteria for the malignancy being studied.
[9] Follow-up data will be collected every 3 months for 24 months from the start of treatment until participant withdrawal, change of therapy following conclusion of study treatment, removal from study, or death. These evaluations may occur at an outside hospital or clinic, as long as documentation is received by the study site for reporting purposes.
[10] All new therapies administered after the last dose of ivosidenib are to be captured during follow-up.
[11] Post-transplant bone marrow biopsies and aspirates are allowed a ± 1 month window

11. MEASUREMENT OF EFFECT

Although response is not the primary endpoint of this trial, participants will be assessed by standard criteria for disease assessment. Response will be assessed through the evaluation of bone marrow biopsies and/or aspirates along with complete blood counts and differentials. Treatment decisions will be based on the treating physician's assessment.

Disease will be assessed while on study drug treatment prior to cycles 6 and 12, and/or at any time that progression of disease is suspected. An assessment will also be done at the End of Treatment study visit for participants who discontinue ivosidenib for a reason other than disease progression.

11.1 Assessment / Response Criteria

11.1.1 AML

Recurrence/Morphologic Relapse:

- Reappearance of leukemic blasts in the peripheral blood or

- ≥ 5% blasts in the bone marrow not attributable to any other cause Development of extramedullary disease
- The appearance of new dysplastic changes should be considered relapse.
- The reappearance or development of cytologically proven extramedullary disease indicates relapse.
- Molecular and/or genetic relapse is characterized by reappearance of a cytogenetic or molecular abnormality.

Complete remission (CR):

- Bone marrow showing less than 5% myeloblasts with normal maturation of all cell lines,
- ANC of at least 1000/μL
- Platelet count of 100,000/μL
- Absence of blasts in peripheral blood
- Absence of identifiable leukemic cells in the bone marrow
- Absence of extramedullary disease.

If possible, at least one bone marrow biopsy should be performed to confirm CR.

Complete Remission with Incomplete Blood Count Recovery (CRi):

- Same as for CR but without achievement of ANC at least 1000/uL (CRi) and/or platelet count of 100,000/uL (CRp).

Partial Remission:

- All hematologic criteria of CR are fulfilled, and
- A decrease of bone marrow blast percentage to 5% to 25%, and
- Decrease of pretreatment bone marrow blast percentage by at least 50%.

Morphologic Leukemia Free State:

- Bone marrow blasts <5%;
- Absence of blasts with Auer rods;
- Absence of extramedullary disease;
- No hematologic recovery required

Resistant Disease:

- Failure to achieve CR or CRi.

11.1.2 MDS and CMML (Savona 2015)

Disease Progression
Combination of 2 major criteria, 1 major and 2 minor criteria, or 3 minor criteria from list

Major Criteria

- Increase in blast count
    - Less than 5% blasts: ≥ 50% increase and to > 5% blasts
    - 5% - 10% blasts: ≥ 50% increase and to > 10% blasts

  - 10% - 20% blasts: ≥ 50% increase and to > 20% blasts
  - 20% - 30% blasts: ≥ 50% increase and to > 30% blasts
- Evidence of cytogenetic evolution
  - Appearance of a previously present or new cytogenetic abnormality in complete cytogenetic remission via FISH or classic karyotyping
  - Increase in cytogenetic burden of disease by ≥ 50% in partial cytogenetic remission via FISH or classic karyotyping
- New extramedullary disease
  - Worsening splenomegaly
  - Progressive splenomegaly that is defined by IWG-MRT: the appearance of a previously absent splenomegaly that is palpable at > 5 cm below the left costal margin or a minimum 100% increase in palpable distance for baseline splenomegaly of 5-10 cm or a minimum 50% increase in palpable distance for baseline splenomegaly of > 10 cm
  - Extramedullary disease outside of the spleen
    - To include new/worsening hepatomegaly, granulocytic sarcoma, skin lesions, etc.

Minor Criteria

- Transfusion dependence
- Significant loss of maximal response on cytopenias ≥ 50% decrement from maximum remission/response in granulocytes or platelets
- Reduction in hemoglobin by ≥ 1.5 g/dL from best response or from baseline as noted on complete blood count
- Increasing symptoms as noted by increase in ≥ 50% as per the MPN-SAF TSS
- Evidence of clonal evolution (molecular)

Complete Remission:

Presence of all of the following improvements:

- Bone marrow ≤ 5% myeloblasts (including monocytic blast equivalents in case of CMML) with normal maturation of all cell lines and return to normal cellularity
- Osteomyelofibrosis absent or equal to "mild reticulin fibrosis" (≤ grade 1 fibrosis)
- Peripheral blood:
  - Hemglobin ≥ 11 g/dL
  - Platelets ≥ 100,000/μL; ≤ 450,000/μL
  - Neutrophils ≥ 1000/μL
  - WBC ≤ 10,000 cells/ μL
  - Blasts 0%
  - Neutrophil precursors reduced to ≤ 2%
  - Monocytes ≤ 1000/μL
- Complete resolution of extramedullary disease present before therapy (e.g. cutaneous disease, disease-related serous effusions), including palpable hepatosplenomegaly
- Persistent low-level dysplasia is permitted given subjectivity of assignment of dysplasia

Partial Remission:

- Normalization of peripheral counts and hepatosplenomegaly with bone marrow blasts

(and blast equivalents) reduced by 50%, but remaining > 5% of cellularity *except* in cases of MDS/MPN with ≤ 5 % bone marrow blasts at baseline

Marrow Response

- Optimal marrow response: Presence of all marrow criteria necessary for CR without normalization of peripheral blood indices as presented above.
- Partial marrow response: Bone marrow blasts (and blast equivalents) reduced by 50%, but remaining > 5% of cellularity, *or* reduction in grading of reticulin fibrosis from baseline on at least 2 bone marrow evaluations spaced at least 2 months apart

Complete Cytogenetic Response

- Resolution of previously present chromosomal abnormality (known to be associated with myelodysplastic syndrome, myeloproliferative neoplasms, or MDS/MPN), as seen on classic karyotyping with minimal of 20 metaphases or FISH

Clinical Benefit

Requires 1 of the following in the absence of progression or CR/partial response and independent of marrow response to be considered a clinical benefit:

- Erythroid response
    - Hgb increase by ≥2.0 g/dL
    - Transfusion Independence (TI) for ≥ 8 weeks for patients requiring at least 4 packed red blood cell transfusions in the previous 8 weeks
    - Only red blood cell transfusions given based on physician's judgment for a pretreatment Hgb of ≤ 8.5 g/dL will count in the red blood cell TI response evaluation.
- Platelet response
    - Transfusion independence when previously requiring platelet transfusions of at least a rate of 4 platelet transfusions in the previous 8 weeks
    - Pretreatment ≤20 × 10^9/L: increase from <20 × 10^9/L to >20 × 10^9/L and by at least 100%
    - Pretreatment >20 × 10^9/L but ≤ 100 × 10^9/L: absolute increase of ≥30 × 10^9/L
- Neutrophil response
    - Pretreatment ≤0.5 × 10^9/L: at least 100% increase and an absolute increase ≥0.5 × 10^9/L
    - Pretreatment, >0.5 × 10^9/L and ≤1.0 × 10^9/L: at least 50% increase and an absolute increase ≥0.5 × 10^9/L
- Spleen response
    - Either a minimum 50% reduction in palpable splenomegaly of a spleen that is at least 10 cm at baseline or a spleen that is palpable at more than 5 cm at baseline becomes not palpable
- Symptom response
    - Improvement in symptoms as noted by decrease of ≥50% as per the MPN-SAF TSS scoring <20 were not considered eligible for measuring clinical benefit.

11.2 Acute GVHD

Participants will be evaluated for the presence or absence of acute GVHD at various timepoints as defined in Section 10. Clinical stage and grade of acute graft-versus-host-disease (GVHD) is based on Przepiorka et al, 1995.

Clinical Stage

Stage	Skin	Liver	Intestinal Tract
		Bilirubin: SI units	Diarrhea/ day
1	Maculopapular rash < 25% of body surface area	34-50 µmol/L (2-3 mg/dL)	> 500 mL diarrhea / day
2	Maculopapular rash 25% - 50% of body surface area	51-102 µmol/L (3.1 – 6 mg/dL)	> 1000 mL diarrhea / day
3	Rash > 50% of body surface	103 – 225 µmol/L (6.1 – 15 mg/dL)	> 1500 mL diarrhea / day
4	Generalized erythroderma with bullous formation	> 225 µmol/L (> 15 mg/dL)	Severe abdominal pain, with or without ileus

(a) Use the "Rule of Nines" or burn chart to determine the extent of the rash.

Grade

Grade	Skin	Liver	Intestinal Tract
I	Stage 1-2	None	None
II	Stage 3 or	Stage 1 or	Stage 1
III	--	Stage 2-3 or	Stage 2-4
IV	Stage 4 or	Stage 4	--

11.3 Chronic GVHD

Participants will be evaluated for the presence or absence of chronic GVHD at various timepoints as defined in Section 10. Chronic GVHD will be assessed as per the National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease – see Appendix D.

The diagnosis of chronic GVHD requires the following:

- Distinction from acute GVHD
- Presence of at least 1 diagnostic clinical sign of chronic GVHD or presence of at least 1 distinctive manifestation confirmed by pertinent biopsy or other relevant tests.
- Exclusion of other possible diagnoses.
- Scoring of organ manifestations requires careful assessment of signs, symptoms, laboratory values, and other study results. A clinical scoring system (0-3) is provided for evaluation of the involvement of individual organs and sites. The proposed global assessment of severity (mild, moderate, or severe) is derived by combining organ- and site-specific scores.

Overall Scoring (compiled from individual organ scores shown in the Appendix):

- Mild – involves only 1 or 2 organs or sites (except the lung), with no clinically significant

functional impairment (maximum score of 1 in all affected organs or sites).

- Moderate – involves (1) at least 1 organ or site with clinically significant but no major disability (maximum score of 2 in any affected organ or site) or (2) 3 or more organs or sites with no clinically significant functional impairment (maximum score of 1 in all affected organs or sites). A lung score of 1 will also be considered moderate cGVHD.
- Severe – indicates major disability caused by cGVHD (score of 3 in any affected organ or site). A lung score of 2 will also be considered severe cGVHD.

11.4 Endpoints

Overall Survival (OS): Overall Survival is defined as the time from first dose of study drug to the date of death due to any cause. Participants who are alive at the analysis / cutoff date will be censored at the last contact date.

Relapse-Free Survival (RFS): Relapse-Free Survival is defined as the time from first dose of study drug to the earlier of relapse or death due to any cause. Participants alive without disease progression are censored at the date of last disease evaluation.

IDH clonal evolution and mutational burden will be explored with descriptive and graphical methods. Identification of factors that influence the relationship of mutations with safety and efficacy endpoints will be explored, as appropriate. Summary statistics, including the mean, standard deviation, median, minimum, maximum, and 25th and 75th percentiles for 2-HG and allele burdens will be recorded at each time point. Although exploratory and insufficiently powered to detect survival differences, we will attempt to assess the relationships of relapse-free survival and overall survival with 2-HG levels and/or *IDH* mutational burden.

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

12.1.1 Method

The Office of Data Quality (ODQ) will collect, manage, and perform quality checks on the data for this study.

12.1.2 Responsibility for Data Submission

Investigative sites are responsible for submitting data and/or data forms to the Office of Data Quality in accordance with DF/HCC SOPs.

12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of medical oncologists, research nurses, pharmacists and biostatisticians with direct experience in cancer clinical research. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review each protocol up to four times a year or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring with 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3 Multicenter Guidelines

This protocol will adhere to the policies and requirements of the DF/HCC Multi-Center Data and Safety Monitoring Plan. The specific responsibilities of the Overall PI, Coordinating Center, and Participating Institutions and the procedures for auditing are presented in Appendix B.

- The Overall PI/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports to all participating institutions for submission to their individual IRBs for action as required.

- Mechanisms will be in place to ensure quality assurance, protocol compliance, and adverse event reporting at each site.

- Except in very unusual circumstances, each participating institution will order the study agent(s) directly from supplier. A participating site may order the agent(s) only after the initial IRB approval for the site has been forwarded to the Coordinating Center.

13. STATISTICAL CONSIDERATIONS

The primary endpoint of this phase I study is to determine the recommended phase 2 dose (RP2D) of ivosidenib in patients with *IDH1*-mutant myeloid neoplasms after allogeneic HSCT. Each cohort of patients will be treated starting somewhere between days 30 and 90 after HSCT. Dose-limiting toxicities (DLTs), as defined in section 5, will be assessed within the first cycle of treatment (1 cycle = 28 days).

Two doses of ivosidenib will be considered: 250mg daily (dose level 1), and 500mg daily (dose level 2). Dose level 2 is the starting dose level.

A 3+3 design will be used. A cohort of 3 evaluable patients will be treated at each dose level. Patients will be considered unevaluable for the determination of RP2D if they never start

ivosidenib maintenance therapy, drop out or die within 28 days of starting treatment without developing DLT for reasons unrelated to therapy. Only patients who start ivosidenib but are unevaluable for DLT can be replaced, to ensure 3 or 6 patients are evaluable for DLT per dose level. Proportion of patients who consent but never start ivosidenib, and proportion of patients who are replaced, will be monitored and reported. All patients who receive any amount of ivosidenib will be evaluated for toxicity.

RP2D will be determined according to the rules described in the Table below.

Number of observed DLTs at a Given Dose Level	**Decision Rule**
0/3	3 additional evaluable patients will be treated at the dose level. If <=1 of the 6 treated patients experience a DLT, this is the RP2D. If >=2 of the 6 treated patients experience a DLT and current dose is dose level 2, de-escalate to dose level 1.
≥2	De-escalate to dose level 1 if current dose is dose level 2.
1/3	Add 3 more patients at current dose level c) If 0 of these 3 additional patients experience DLT, current dose is RP2D. d) If ≥1 of these 3 additional patients experience DLT, then de-escalate to dose level 1 if current dose is dose level 2.
≤1/6	Current dose is the RP2D

*Note:If ≥2/3 or ≥2/6 DLTs are observed at dose level 1 (250mg daily), the trial will be discontinued.

Once the RP2D is established, an additional 10 patients will be treated at the RP2D to provide a better estimate of the toxicity of ivosidenib. With 16 evaluable patients treated on the RP2D, the 90% confidence interval of the toxicity rate will be within +/- 22%. The RP2D defined in this study will then be used to plan a larger phase II study.

Sample Size

The sample size will range from 6-22 evaluable patients. The expected accrual rate will be approximately 1-2 patients / month for this patient population, thus requiring up to 22 months to complete the accrual.

Secondary endpoints

All secondary endpoints will be reported descriptively. This includes median number of days of ivosidenib tolerated, cumulative incidence of acute GVHD, cumulative incidence of significant chronic GVHD, and Kaplan-Meier estimates of overall and relapse-free survival. All laboratory correlative measurements will also be reported descriptively.

14. PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

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APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B

Dana-Farber/Harvard Cancer Center
Multi-Center Data and Safety Monitoring Plan

TABLE OF CONTENTS

1. INTRODUCTION

The Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (DF/HCC DSMP) outlines the procedures for conducting a DF/HCC Multi-Center research protocol. The DF/HCC DSMP serves as a reference for any sites external to DF/HCC that are participating in a DF/HCC clinical trial.

1.1 Purpose

To establish standards that will ensure that a Dana-Farber/Harvard Cancer Center Multi-Center protocol will comply with Federal Regulations, Health Insurance Portability and Accountability Act (HIPAA) requirements and applicable DF/HCC Standard Operating Procedures.

1.2 Multi-Center Data and Safety Monitoring Plan Definitions

DF/HCC Multi-Center Protocol: A research protocol in which one or more outside institutions are collaborating with Dana-Farber/Harvard Cancer Center where a DF/HCC investigator is the sponsor. DF/HCC includes Dana-Farber/Partners Cancer Care (DF/PCC) Network Clinical Trial Affiliates.

Lead Institution: One of the Dana-Farber/Harvard Cancer Center consortium members (Dana-Farber Cancer Institute (DFCI), Massachusetts General Hospital (MGH), Beth Israel Deaconess Medical Center (BIDMC), Boston Children's Hospital (BCH), Brigham and Women's Hospital (BWH)) responsible for the coordination, development, submission, and approval of a protocol as well as its subsequent amendments per the DFCI IRB and applicable regulatory guidelines (CTEP, Food and Drug Administration (FDA), Office of Biotechnology Activities (OBA) etc.). The Lead Institution is typically the home of the DF/HCC Sponsor. The Lead Institution also typically serves as the Coordinating Center for the DF/HCC Multi-Center Protocol.

DF/HCC Sponsor: The person sponsoring the submitted Multi-Center protocol who takes responsibility for initiation, management and conduct of the protocol at all research locations. In applicable protocols, the DF/HCC Sponsor will serve as the single liaison with any regulatory agencies. The DF/HCC Sponsor has ultimate authority over the protocol and is responsible for the conduct of the study at DF/HCC and all Participating Institutions. In most cases the DF/HCC Sponsor is the same person as the DF/HCC Overall Principal Investigator; however, both roles can be filled by two different people.

Participating Institution: An institution that is outside the DF/HCC and DF/PCC consortium that is collaborating with DF/HCC on a protocol where the sponsor is a DF/HCC Investigator. The Participating Institution acknowledges the DF/HCC Sponsor as having the ultimate authority and responsibility for the overall conduct of the study.

Coordinating Center: The entity that provides administrative support to the DF/HCC Sponsor in order that he/she may fulfill the responsibilities outlined in the protocol document and DSMP, and as specified in applicable regulatory guidelines. In general, the Lead Institution is the Coordinating Center for the DF/HCC Multi-Center Protocol.

DF/HCC Office of Data Quality (ODQ): A group within DF/HCC responsible ensuring high-quality standards are used for data collection and the ongoing management of clinical trials, auditing, and data and safety monitoring. ODQ also coordinates quality assurance efforts related to multi-center clinical research.

DF/HCC Clinical Trials Research Informatics Office (CTRIO): A group within DF/HCC responsible for providing a comprehensive data management platform for managing clinical trial data.

2. GENERAL ROLES AND RESPONSIBILITIES

For DF/HCC Multi-Center Protocols, the DF/HCC Sponsor, the Coordinating Center, and the Participating Institutions are expected to adhere to the following general responsibilities:

2.1 DF/HCC Sponsor

The DF/HCC Sponsor, Amir Fathi, M.D. will accept responsibility for all aspects of conducting a DF/HCC Multi-Center protocol which includes but is not limited to:

- Oversee the coordination, development, submission, and approval of the protocol as well as subsequent amendments.
- Ensure that the investigators, study team members, and Participating Institutions are qualified and appropriately resourced to conduct the protocol.
- Include the Multi-Center Data and Safety Monitoring Plan as an appendix to the protocol.
- Ensure all Participating Institutions are using the correct version of the protocol.
- Ensure that each participating investigator and study team member receives adequate protocol training and/or a Site Initiation Visit prior to enrolling participants and throughout trial's conduct as needed.
- Ensure the protocol will be provided to each participating site in a language understandable to all applicable site personnel when English is not the primary language.
- Monitor progress and overall conduct of the study at all Participating Institutions.
- Ensure all DFCI Institutional Review Board (IRB), DF/HCC and other applicable (i.e. CTEP, FDA, OBA) reporting requirements are met.
- Review data and maintain timely submission of data for study analysis.
- Act as the single liaison with the FDA (investigator-held IND trials) as applicable.
- Ensure compliance with all requirements as set forth in the Code of Federal Regulations, applicable DF/HCC requirements, HIPAA requirements, and the approved protocol.
- Commit to the provision that the protocol will not be rewritten or modified by anyone other than the DF/HCC Sponsor.
- Identify and qualify Participating Institutions and obtain accrual commitments prior to extending the protocol to that site.
- Monitor accrual and address Participating Institutions that are not meeting their accrual requirements.

2.2 Coordinating Center

The general responsibilities of the Coordinating Center may include but are not limited to:

- Assist in protocol development.
- Maintain FDA correspondence, as applicable.

- Review registration materials for eligibility and register participants from Participating Institutions in the DF/HCC clinical trial management system (CTMS).
- Distribute protocol and informed consent document updates to Participating Institutions as needed.
- Review and approve Participating Site informed consent forms
- Conduct and document initial and ongoing protocol training
- Oversee the data collection process from Participating Institutions.
- Maintain documentation and cumulative reports of Serious Adverse Event (SAE) reports and Deviations/Violations across all sites and provide to the DF/HCC Sponsor for timely review and submission to the DFCI IRB, as necessary.
- Distribute serious adverse events reported to the DF/HCC Sponsor that fall under the DFCI IRB Adverse Event Reporting Policy to all Participating Institutions.
- Provide Participating Institutions with information regarding DF/HCC requirements that they will be expected to comply with.
- Carry out approved protocol monitoring plan either by on-site or remote monitoring.
- Maintain essential regulatory documents of all Participating Institutions which includes but is not limited to the following: local IRB approvals/notifications from all Participating Institutions, confirmation of Federalwide Assurances (FWAs) for all sites, all SAE submissions, Screening Logs for all sites, IRB approved consents for all sites, and protocol training documentation
- Conduct regular communications with all Participating Institutions (conference calls, emails, etc) and maintain documentation all relevant communications.

2.3 Participating Institution

Each Participating Institution is expected to comply with all applicable federal regulations and DF/HCC requirements, the protocol and HIPAA requirements.

The general responsibilities for each Participating Institution may include but are not limited to:

- Document the delegation of research specific activities to study personnel.
- Commit to the accrual of participants to the protocol.
- Submit protocol and/or amendments to their local IRB.
- Maintain regulatory files as per sponsor requirements.
- Provide the Coordinating Center with regulatory documents, including enrollment log, biospecimen log, violation/deviation log,or source documents as requested.
- Participate in protocol training prior to enrolling participants and throughout the trial as required (i.e. teleconferences).
- Update Coordinating Center with research staff changes on a timely basis.
- Register participants through the Coordinating Center prior to beginning research related activities.
- Submit Adverse Event (SAE) reports to local IRB per institutional requirements and to the Coordinating Center, in accordance with DF/HCC or other sponsor requirements.

- Submit protocol deviations and violations to local IRB per institutional requirements and to the DF/HCC Sponsor in accordance with DF/HCC requirements.
- Order, store and dispense investigational agents and/or other protocol mandated drugs per federal guidelines and protocol requirements.
- Have office space, office equipment, and internet access that meet HIPAA standards.
- Participate in any quality assurance activities and meet with monitors or auditors at the conclusion of a visit to review findings.
- Promptly provide follow-up and/or corrective action plans for any monitoring queries or audit findings.

3. DF/HCC REQUIREMENTS FOR MULTI-CENTER PROTOCOLS

The following section will clarify DF/HCC Requirements and further detail the expectations for participating in a DF/HCC Multi-Center protocol.

3.1 Protocol Distribution

The Coordinating Center will distribute the final DFCI IRB approved protocol and any subsequent amended protocols to all Participating Institutions.

3.2 Protocol Revisions and Closures

The Participating Institutions will receive notification of protocol revisions and closures from the Coordinating Center. It is the individual Participating Institution's responsibility to notify its IRB of these revisions.

- **Non life-threatening revisions:** Participating Institutions will receive written notification of protocol revisions regarding non life-threatening events from the Coordinating Center. Non-life-threatening protocol revisions must be IRB approved and implemented within 90 days from receipt of the notification.

- **Revisions for life-threatening causes:** Participating Institutions will receive immediate notification from the Coordinating Center concerning protocol revisions required to protect lives with follow-up by fax, mail, e-mail, etc. Life-threatening protocol revisions will be implemented immediately followed by IRB request for approval.

- **Protocol closures and temporary holds:** Participating Institutions will receive notification of protocol closures and temporary holds from the Coordinating Center. Closures and holds will be effective immediately. In addition, the Coordinating Center, will update the Participating Institutions on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

3.3 Informed Consent Requirements

The DF/HCC approved informed consent document will serve as a template for the informed consent for Participating Institutions. The Participating Institution consent form must follow the consent template as closely as possible and should adhere to specifications outlined in the DF/HCC Guidance Document on Model Consent Language for PI-Initiated Multi-Center Protocols. This document will be provided separately to each Participating Institution upon request.

Participating Institutions are to send their version of the informed consent document and HIPAA authorization, if a separate document, to the Coordinating Center for review and approval **prior to** submission to their local IRB. The approved consent form must also be submitted to the Coordinating Center after approval by the local IRB for all consent versions.

The Principal Investigator (PI) at each Participating Institution will identify the physician members of the study team who will be obtaining consent and signing the consent form for therapeutic protocols. Participating institutions must follow the DF/HCC requirement that for all interventional drug, biologic, or device research, only attending physicians may obtain initial informed consent and any re-consent that requires a full revised informed consent form.

3.4 IRB Documentation

The following must be on file with the Coordinating Center:

- Initial approval letter of the Participating Institution's IRB.
- Copy of the Informed Consent Form(s) approved by the Participating Institution's IRB.
- Participating Institution's IRB approval for all amendments.
- Annual approval letters by the Participating Institution's IRB.

3.5 IRB Re-Approval

Verification of IRB re-approval from the Participating Institutions is required in order to continue research activities. There is no grace period for continuing approvals.

The Coordinating Center will not register participants if a re-approval letter is not received from the Participating Institution on or before the anniversary of the previous approval date.

3.6 Participant Confidentiality and Authorization Statement

In 1996, congress passed the first federal law covering the privacy of health information known as the Health Insurance Portability and Accountability Act (HIPPA). Any information, related to the physical or mental health of an individual is called Protected Health Information (PHI). HIPAA outlines how and under what circumstances PHI can be used or disclosed.

In order for covered entities to use or disclose protected health information during the course of a study, the study participant must sign an authorization statement. This authorization statement may or may not be separate from the informed consent document. The Coordinating Center, with the approval from the DFCI IRB and if applicable NCI/CTEP, will provide a consent template, with information regarding authorization for the disclosure of protected health information.

The DF/HCC Sponsor will use all efforts to limit its use of protected health information in its trials. However, because of the nature of these trials, certain protected health information must be collected. DF/HCC has chosen to use authorizations, signed by the participant in the trial, rather than limited data sets with data use agreements.

3.6.1 DF/HCC Multi-Center Protocol Confidentiality

All documents, investigative reports, or information relating to the participant are strictly confidential. Whenever reasonably feasible, any participant specific reports (i.e. Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the Coordinating Center should be de-identified. It is recommended that the assigned DF/HCC QACT case number (as described below) be used for all participant specific documents. Participant initials may be included or retained for cross verification of identification.

3.7 DF/HCC Multi-Center Protocol Registration Policy

All participants must be centrally registered with DF/HCC prior to conducting any research-related procedures and start of protocol treatment.

3.7.1 Participant Registration and Randomization

Please refer to protocol **Section 4.0: Registration Procedures**

3.7.2 Initiation of Therapy

Participants must be registered with the DF/HCC CTMS before the initiation of treatment or other protocol-specific interventions. Treatment and other protocol-specific interventions may not be initiated until the Participating Institution receives confirmation of the participant's registration from the Coordinating Center. The DF/HCC Sponsor and DFCI IRB must be notified of any violations to this policy.

3.7.3 Eligibility Exceptions

CTEP specifically prohibits registration of a participant on any NCI Sponsored protocol that does not fully and completely meet all eligibility requirements. No exceptions to the eligibility requirements for a protocol without DFCI IRB approval will be permitted. All Participating Institutions are required to fully comply with this requirement. The process for requesting an eligibility exception is defined below.

3.8 DF/HCC Protocol Case Number

At the time of registration, the following identifiers are required for all subjects: initials, date of birth, gender, race and ethnicity. Once eligibility has been established and the participant successfully registered, the participant is assigned a unique protocol case number. Participating Institutions should submit all de-identified subsequent communication and documents to the Coordinating Center, using this case number to identify the subject.

3.8.1 Protocol Deviations, Exceptions and Violations

Federal Regulations require an IRB to review proposed changes in a research activity to ensure that researchers do not initiate changes in approved research without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the participant. DF/HCC requires all departures from the defined procedures set forth in the IRB approved protocol to be reported to the DF/HCC Sponsor, who in turn is responsible for reporting to the DFCI IRB.

For reporting purposes, DF/HCC uses the terms "violation", "deviation" and "exception" to describe departures from a protocol. All Participating Institutions must adhere to these requirements for reporting to the DF/HCC Sponsor and will follow their institutional policy for reporting to their local IRB.

3.8.2 Definitions

Protocol Deviation: Any departure from the defined procedures set forth in the IRB-approved protocol which is prospectively approved prior to its implementation.

Protocol Exception: Any protocol deviation that relates to the eligibility criteria, e.g. enrollment of a participant who does not meet all inclusion/exclusion criteria.

Protocol Violation: Any protocol departure that was not prospectively approved by the IRB prior to its initiation or implementation.

3.8.3 Reporting Procedures

DF/HCC Sponsor: is responsible for ensuring that clear documentation is available in the medical record and/or regulatory documents to describe all protocol exceptions, deviations and violations. The DF/HCC Sponsor will also be responsible for ensuring that all protocol violations/deviations are promptly reported per DFCI IRB guidelines.

Participating Institutions: Protocol deviations require prospective approval from the DFCI IRB. The Participating Institution must submit the deviation request to the Coordinating Center who will then submit the deviation request to the DFCI IRB. Upon DFCI IRB approval the deviation is submitted to the Participating Institution IRB, per institutional policy. A copy of the Participating Institution's IRB report and determination will be forwarded to the Coordinating Center within 10 business days after

the original submission. The deviation may not be implemented without all required approvals

All protocol violations must be sent to the Coordinating Center in a timely manner. The Coordinating Center will provide training for the requirements for the reporting of violations.

Coordinating Center: Upon receipt of the violation/deviation report from the Participating Institution, the Coordinating Center will submit the report to the DF/HCC Sponsor for review. Subsequently, the Participating Institution's IRB violation/deviation report will be submitted to the DFCI IRB for review per DFCI IRB reporting guidelines. DF/HCC will forward all violation reports to CTEP via an internal DF/HCC process, as applicable.

3.9 Safety Assessments and Toxicity Monitoring

The study teams at all participating institutions are responsible for protecting the safety, rights and well-being of study participants. Recording and reporting of adverse events that occur during the course of a study help ensure the continuing safety of study participants.

All participants receiving investigational agents and/or other protocol mandated therapy will be evaluated for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical examination findings, and spontaneous reports of adverse events reported by participants. All toxicities encountered during the study will be evaluated according to the NCI criteria specified in the protocol. Life-threatening toxicities must be reported immediately to the DF/HCC Sponsor via the Coordinating Center. Protocols using CTEP supplied agents must report these toxicities via the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS). The DF/HCC Sponsor will be notified of these events via CTEP-AERS.

Additional safety assessments and toxicity monitoring will be outlined in the protocol.

3.9.1 Guidelines for Reporting Serious Adverse Events

Guidelines for reporting Adverse Events (AEs) and Serious Adverse Events (SAEs) are detailed in protocol **Section 7: Adverse Events**.

Participating Institutions must report the SAEs to the DF/HCC Sponsor and the Coordinating Center following the DFCI IRB Adverse Event Reporting Policy.

The Coordinating Center will maintain documentation of all Participating Institution Adverse Event reports and be responsible for communicating to all participating investigators, any observations reportable under the DFCI IRB Reporting Requirements. Participating Institutions will review and submit to their IRB according to their institutional policies and procedures

3.9.2 Guidelines for Processing IND Safety Reports

The DF/HCC Sponsor will review all IND Safety Reports and ensure that all IND Safety Reports are distributed to the Participating Institutions. Participating Institutions will review /submit to their IRB according to their institutional policies and procedures.

3.10 Data Management

DF/HCC CTRIO develops case report forms (CRF/eCRFs), for use with the protocol. These forms are designed to collect data for each study. DF/HCC CTRIO provides a web based training for all eCRF users.

3.10.1 Data Forms Review

Data submissions are monitored for timeliness and completeness of submission. If study forms are received with missing or questionable data, the submitting institution will receive a written or electronic query from the DF/HCC Office of Data Quality, Coordinating Center, or designee.

Responses to all queries should be completed and submitted within 14 calendar days.

Responses may be returned on the written query or on an amended paper case report form, or in the case of electronic queries, within the electronic data capture (eDC) system. In the case of a written query for data submitted on a paper case report form, the query must be attached to the specific data being re-submitted in response.

If study forms are not submitted on schedule, the Participating Institution will periodically receive a Missing Form Report from the Coordinating Center noting the missing forms.

4. REQUISITIONING INVESTIGATIONAL DRUG

The ordering of investigational agent is specified in the protocol **Section 8: Pharmaceutical Information**.

Participating Institutions should order their own agent regardless of the supplier. (i.e., NCI or a pharmaceutical company.)

If the agent is commercially available, check with the local Director of Pharmacy and/or the Research Pharmacy to ensure that the agent is in stock. If the agent is not stocked, ensure that the agent can be ordered once the protocol is approved by the local IRB.

If the agent is investigational, ensure that the pharmacy will be able to receive and store the agent according to state and federal requirements. The local IRB should be kept informed of who will supply the agent (i.e., NCI or a pharmaceutical company) so that any regulatory responsibilities can be met in a timely fashion.

5. MONITORING: QUALITY CONTROL

The quality control process for a clinical trial requires verification of protocol compliance and data accuracy. The Coordinating Center, with the aid of the DF/HCC Office of Data Quality, provides quality control oversight for the protocol.

5.1 Ongoing Monitoring of Protocol Compliance

The Coordinating Center will implement ongoing monitoring activities to ensure that Participating Institutions are complying with regulatory and protocol requirements, data quality, and participant safety. Monitoring practices may include but are not limited to source data verification, and review and analysis of eligibility requirements, informed consent procedures, adverse events and all associated documentation, review of study drug administration/treatment, regulatory files, protocol departures reporting, pharmacy records, response assessments, and data management.

Participating Institutions will be required to submit participant source documents to the Coordinating Center for eligibility confirmation as well as for ongoing, remote monitoring. Participating Institution are also subject to on-site monitoring conducted by the Coordinating Center.

Participating Institutions will undergo on-site monitoring by the Coordinating Center within 3 months of enrollment of the first patient; Combination on-site and remote monitoring will occur every 4-6 months thereafter while patients are on treatment or in active follow-up. Remote monitoring may be done in lieu of on-site monitoring if no active patients are on trial at that site. Once all site participants are off treatment and in long-term follow-up, remote monitoring will be conducted annually for confirmation of long term follow-up data and regulatory compliance.

For remote monitoring visits, Participating Institutions will be asked to provide remote electronic medical record access to the monitor or will be required to forward redacted copies of participants' medical record and source documents to the Coordinating Center to aid in source data verification. The participants and CRFs to be reviewed at the visit will be communicated at least 2 weeks in advance of the scheduled monitoring visit. Source documentation can be provided to the Coordinating Center via an encrypted memory stick or via a secure file transfer system. During remote monitoring visits, the Site Specific File will be reviewed in lieu of the site regulatory binder.

On-Site Monitoring will be scheduled several weeks in advance and will be conducted over a 2-3 day period. During an on-site monitoring visit, 2-4 participants will be monitored as well as the complete regulatory binder. Source documentation verification (SDV) will be conducted by having access to participants' complete medical record and source documents. Participating Institutions will be expected to coordinate the necessary resources for the monitor, including a desk, access to all participant medical and research records (electronic and hard copy), the regulatory binders and access to a photocopier. The Participating

Institution will also be asked to assist in scheduling a pharmacy visit and a brief exit interview on the final day of the visit with the Study Coordinator and the Site investigator.

All Participating Institutions will be required to participate in monthly Coordinating Center initiated teleconferences. Once all participants have completed treatment, teleconferences will be scheduled as needed.

5.2 Monitoring Reports

Following each monitoring visit, a monitoring follow-up report will be provided to the Participating Site (i.e. Site PI and Coordinator). The monitoring report will summarize any issued queries or data clarification requests, identify any reportable events or required follow-up on prior events and will specify details of any non-compliance. Participating Sites are requested to respond to all queries and data clarifications requests within 10 business days.

The DF/HCC Sponsor will review all monitoring reports to ensure protocol compliance. The DF/HCC Sponsor may increase the monitoring activities at Participating Institutions that are unable to comply with the protocol, DF/HCC Sponsor requirements or federal and local regulations.

5.3 Accrual Monitoring

Prior to extending a protocol to an external site, the DF/HCC Sponsor will establish accrual requirements for each participating institution. Accrual will be monitored for each participating institution by the DF/HCC Sponsor or designee. Sites that are not meeting their accrual expectations may be subject to termination.

The **minimum** accrual per participating site is 2 patients annually in consideration of the regulatory and monitoring cost and effort of overseeing each site.

6. AUDITING: QUALITY ASSURANCE

Auditing is a method of Quality Assurance and involves the systematic and independent examination of all trial related activities and documents. Audits determine if evaluated activities were appropriately conducted and whether data was generated, recorded and analyzed, and accurately reported per the protocol, applicable Standard Operating Procedures (SOPs), and the Code of Federal Regulations (CFR).

6.1 Audit Plan: NCI Sponsored Trials

N/A

6.2 DF/HCC Internal Audits

All Participating Institutions are subject to audit by the DF/HCC Office of Data Quality (ODQ). Typically, approximately 3-4 participants would be audited at the site over a 2 day period. If violations which impact participant safety or the integrity of the study are found, more participant records may be audited.

6.3 Audit Notifications

It is the Participating Institution's responsibility to notify the Coordinating Center of all scheduled audit dates (internal or NCI) and re-audit dates (if applicable), which involve this protocol. All institutions will forward a copy of final audit and/or re-audit reports and corrective action plans (if applicable) to the Coordinating Center, within 12 weeks after the audit date.

6.4 Audit Reports

The DF/HCC Sponsor will review all final audit reports and corrective action plans, if applicable. The Coordinating Center must forward any reports to the DF/HCC ODQ per DF/HCC policy for review by the DF/HCC Audit Committee. For unacceptable audits, the DF/HCC Audit Committee would forward the final audit report and corrective action plan to the DFCI IRB as applicable.

6.5 Participating Institution Performance

The DF/HCC Sponsor, DFCI IRB and the NCI for CTEP trials, is charged with considering the totality of an institution's performance in considering institutional participation in the protocol. Participating Institutions that fail to meet the performance goals of accrual, submission of timely and accurate data, adherence to protocol requirements, and compliance with state and federal regulations, may be recommended for a six-month probation period. Such institutions must respond with a corrective action plan and must demonstrate during the probation period that deficiencies have been corrected, as evidenced by the improved performance measures. Participating Institutions that fail to demonstrate significant improvement will be considered by the DF/HCC Sponsor for revocation of participation. A DF/HCC Sponsor and/or the DFCI IRB may terminate a site's participation if it is determined that a site is not fulfilling its responsibilities as described above

APPENDIX C DRUG DIARY

APPENDIX D CHRONIC GVHD SCORING

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
PERFORMANCE SCORE: ☐ **KPS ECOG LPS**	☐ Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	☐ Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)	☐ Symptomatic, ambulatory, capable of self-care, >50% of waking hours out of bed (ECOG 2, KPS or LPS 60-70%)	☐ Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%)
SKIN *Clinical features:* ☐ Maculopapular rash ☐ Lichen planus-like features ☐ Papulosquamous lesions or ichthyosis ☐ Hyperpigmentation ☐ Hypopigmentation ☐ Keratosis pilaris ☐ Erythema ☐ Erythroderma ☐ Poikiloderma ☐ Sclerotic features ☐ Pruritus ☐ Hair involvement ☐ Nail involvement **% BSA involved** ☐	☐ No Symptoms	☐ <18% BSA with disease signs but **NO** sclerotic features	☐ 19-50% BSA **OR** involvement with superficial sclerotic features "not hidebound" (able to pinch)	☐ >50% BSA **OR** deep sclerotic features "hidebound" (unable to pinch) **OR** impaired mobility, ulceration or severe pruritus
MOUTH	☐ No symptoms	☐ Mild symptoms with disease signs but not limiting oral intake significantly	☐ Moderate symptoms with disease signs **with** partial limitation of oral intake	☐ Severe symptoms with disease signs on examination **with** major limitation of oral intake
EYES Mean tear test (mm): ☐ >10 ☐ 6-10 ☐ ≤5 ☐ Not done	☐ No symptoms	☐ Mild dry eye symptoms not affecting ADL (requiring eyedrops ≤ 3 x per day) **OR** asymptomatic signs of keratoconjunctivitis sicca	☐ Moderate dry eye symptoms partially affecting ADL (requiring drops > 3 x per day or punctal plugs), **WITHOUT** vision impairment	☐ Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision caused by keratoconjunctivitis sicca
GI TRACT	☐ No symptoms	☐ Symptoms such as dysphagia, anorexia, nausea, vomiting, abdominal pain or diarrhea without significant weight loss (<5%)	☐ Symptoms associated with mild to moderate weight loss (5-15%)	☐ Symptoms associated with significant weight loss >15%, requires nutritional supplement for most calorie needs **OR** esophageal dilation
LIVER	☐ Normal LFT	☐ Elevated Bilirubin, AP*, AST or ALT <2 x ULN	☐ Bilirubin >3 mg/dl or Bilirubin, enzymes 2-5 x ULN	☐ Bilirubin or enzymes > 5 x ULN

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
LUNGS[†] **FEV1** ☐ **DLCO** ☐	☐ No symptoms ☐ FEV1 > 80% **OR** LFS=2	☐ Mild symptoms (shortness of breath after climbing one flight of steps) ☐ FEV1 60-79% **OR** LFS 3-5	☐ Moderate symptoms (shortness of breath after walking on flat ground) ☐ FEV1 40-59% **OR** LFS 6-9	☐ Severe symptoms (shortness of breath at rest; requiring 0_2) ☐ FEV1 ≤39% **OR** LFS 10-12
JOINTS AND FASCIA	☐ No symptoms	☐ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL	☐ Tightness of arms or legs **OR** joint contractures, erythema thought due to fasciitis, moderate decrease ROM **AND** mild to moderate limitation of ADL	☐ Contractures **WITH** significant decrease of ROM ***AND*** significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
GENITAL TRACT	☐ No symptoms	☐ Symptomatic with mild signs on exam **AND** no effect on coitus and minimal discomfort with gynecologic exam	☐ Symptomatic with moderate signs on exam **AND** with mild dyspareunia or discomfort with gynecologic exam	☐ Symptomatic **WITH** advanced signs (stricture, labial agglutination or severe ulceration) **AND** severe pain with coitus or inability to insert vaginal speculum

Other indicators, clinical manifestations or complications related to chronic GVHD (check all that apply and assign a score to its severity (0-3) based on its functional impact where applicable (none – 0,mild -1, moderate -2, severe – 3)

Esophageal stricture or web___	Pericardial Effusion___	Pleural Effusion(s)___
Ascites (serositis)___	Nephrotic syndrome___	Peripheral Neuropathy___
M yasthenia Gravis___	Cardiomyopathy___	Eosinophilia > 500µl___
Polymyositis___	Cardiac conduction defects___	Coronary artery involvement___
Platelets <100,000/µl___	Progressive onset___	

OTHERS: Specify:_____

Appendix E

Strong CYP3A4 inhibitors – this will trigger dose reduction to 250 mg daily

Drug Type	Generic
HIV Protease Inhibitors	Indinavir Nelfinavir Lopinavir Ritonavir Saquinavir
Food	Grapefruit juice
Others – note common antifungals	Boceprevir Telaprevir Clarithromycin Telithromycin Conivaptan Itraconazole Ketoconazole Posaconazole Voriconazole Nefazodone

CYP3A substrates (use caution and monitor) – examples include: alfentanil, avanafil, buspirone, conivaptan, darifenacin, darunavir, ebastine, everolimus, ibrutinib, lomitapide, lovastatin, midazolam, naloxegol, nisoldipine, saquinavir, simvastatin, sirolimus, tacrolimus, tipranavir, triazolam, vardenafil, budesonide, dasatanib, dronedarone, eletriptan, eplerenone, felodipine, indinavir, lurasidone, maraviroc, quetiapine, sildenafil, ticagrelor, tolvaptan.
Note: Tacrolimus and sirolimus are both listed here and are common immunosuppressive medications that participants will be taking. Both of these agents will be monitored closely in terms of trough levels with doses adjusted.

CYP3A inducers (avoid)

Drug Type	Generic
Anticonvulsant	Carbamazepine Phenytoin
Antibiotic	Rifampicin
Food / Supplement	St. John's Wort