# Addition of Sorafenib to G-CSF, Cladribine, Cytarabine and Mitoxantrone (G-CLAM) in Adults with Newly-Diagnosed Acute Myeloid Leukemia (AML) Independent of FLT3-ITD status: A Phase 1/2 Study

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**FRED HUTCHINSON CANCER CENTER**
**UNIVERSITY OF WASHINGTON SCHOOL OF MEDICINE**

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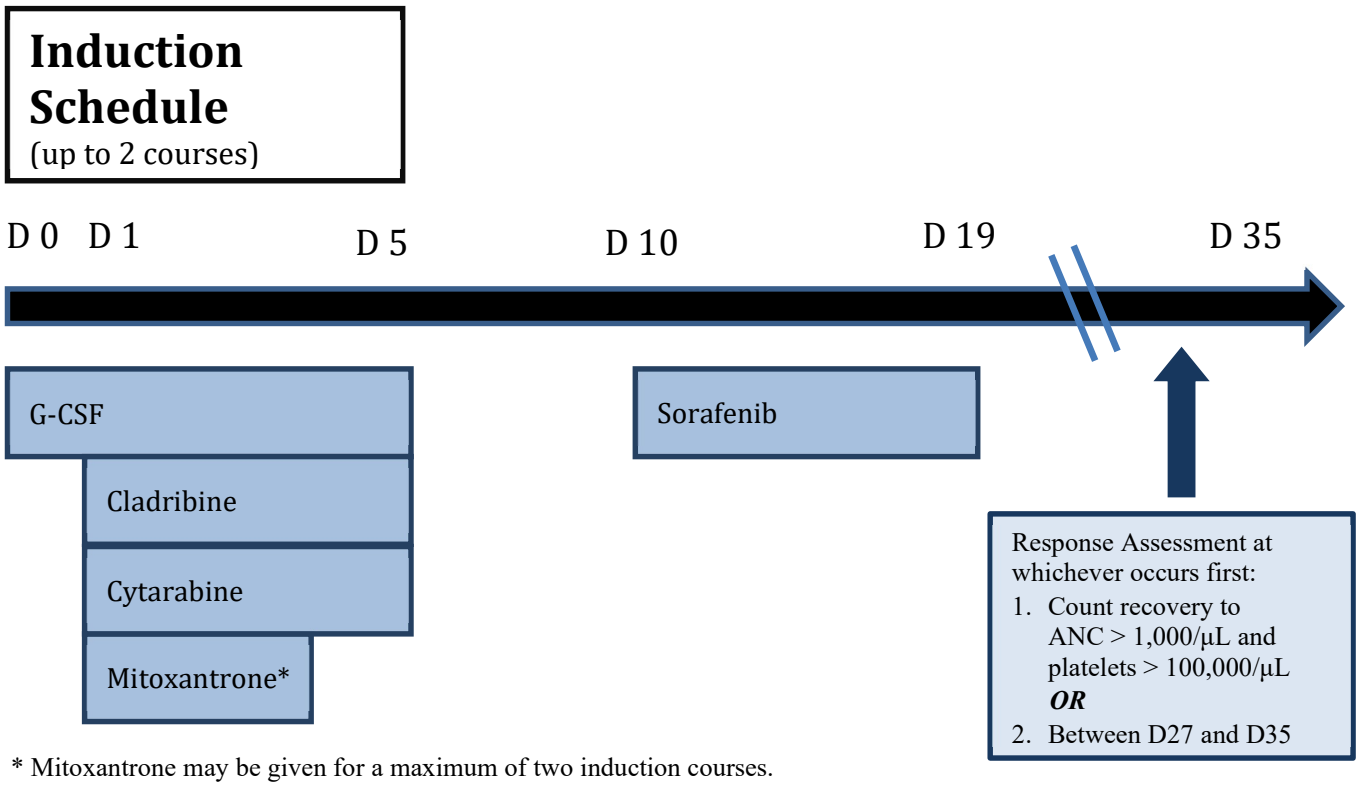
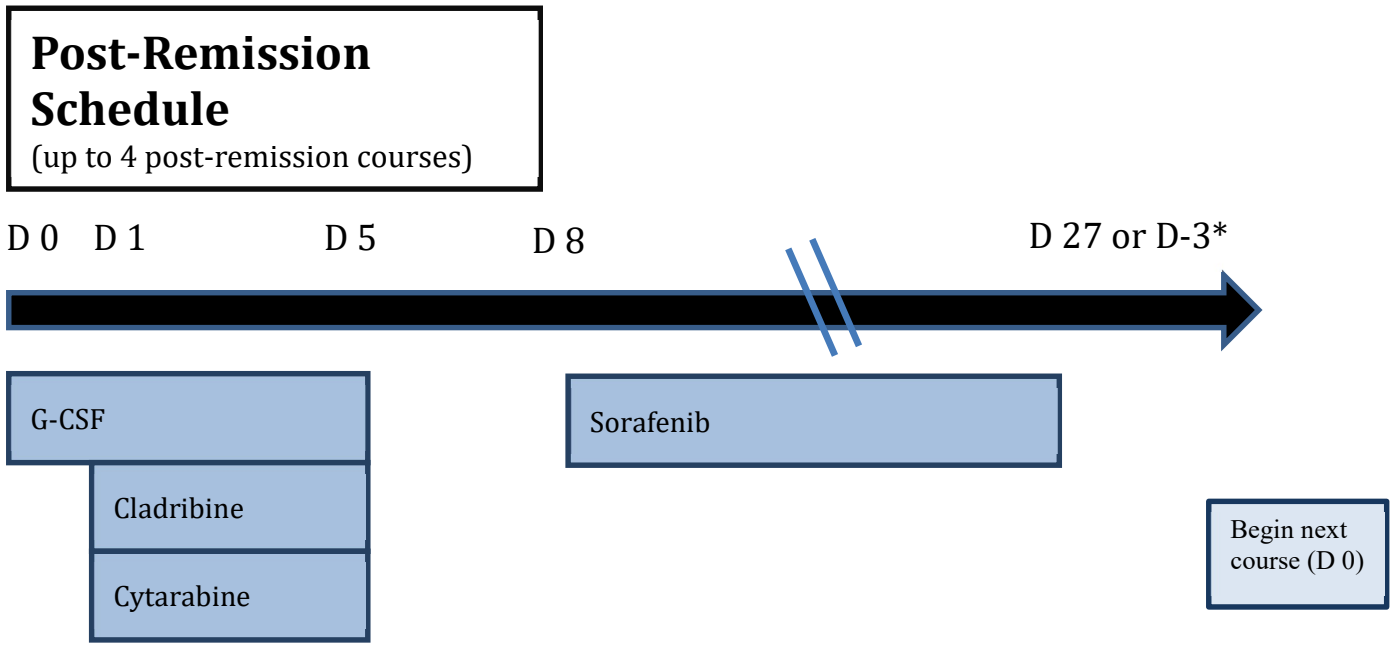
**OVERVIEW OF TREATMENT PLAN**




* Mitoxantrone may be given for a maximum of two induction courses.



## DOSE ESCALATION SCHEME

*Whichever occurs first

### Induction

| Level | G-CSF (SQ, D0-D5)[1] | Cladribine (IV, D1-D5)[2] | Cytarabine (IV, D1-D5)[2,3] | Mitoxantrone (IV, D1-D3)[2] | Sorafenib (PO, D10-D19) |
|---|---|---|---|---|---|
| **1** | 5 µcg/kg | 5 mg/m$^2$ | 2 g/m$^2$ | 10 mg/m$^2$ | 200 mg BID |
| **2** | 5 µcg/kg | 5 mg/m$^2$ | 2 g/m$^2$ | 12 mg/m$^2$ | 200 mg BID |
| **3** | 5 µcg/kg | 5 mg/m$^2$ | 2 g/m$^2$ | 15 mg/m$^2$ | 200 mg BID |
| **4** | 5 µcg/kg | 5 mg/m$^2$ | 2 g/m$^2$ | 18 mg/m$^2$ | 200 mg BID |
| **5** | 5 µcg/kg | 5 mg/m$^2$ | 2 g/m$^2$ | 18 mg/m$^2$ | 400 mg AM, 200 mg PM |
| **6** | 5 µcg/kg | 5 mg/m$^2$ | 2 g/m$^2$ | 18 mg/m$^2$ | 400 mg BID |
| **-1** | 5 µcg/kg | 5 mg/m$^2$ | 2 g/m$^2$ | 10 mg/m$^2$ | 200 mg QD |

[1]Dosing based on actual patient weight, rounded to either 300 or 480 µcg, whichever is closer; D0 and D1 dose may be omitted if WBC >20,000/µL. [2]Dosing based on body surface area (BSA) using actual patient weight. [3]Starting approximately 2h after completion of cladribine.

### Post-Remission Therapy

| Level | G-CSF (SQ, D0-D5)[1] | Cladribine (IV, D1-D5)[2] | Cytarabine (IV, D1-D5)[2,3] | Sorafenib (PO, D8 to D-3)[4] |
|---|---|---|---|---|
| **1** | 5 µcg/kg | 5 mg/m$^2$ | 2 g/m$^2$ | 200 mg BID |
| **2** | 5 µcg/kg | 5 mg/m$^2$ | 2 g/m$^2$ | 200 mg BID |
| **3** | 5 µcg/kg | 5 mg/m$^2$ | 2 g/m$^2$ | 200 mg BID |
| **4** | 5 µcg/kg | 5 mg/m$^2$ | 2 g/m$^2$ | 200 mg BID |
| **5** | 5 µcg/kg | 5 mg/m$^2$ | 2 g/m$^2$ | 400 mg AM, 200 mg PM |
| **6** | 5 µcg/kg | 5 mg/m$^2$ | 2 g/m$^2$ | 400 mg BID |
| **-1** | 5 µcg/kg | 5 mg/m$^2$ | 2 g/m$^2$ | 200 mg QD |

[1]Dosing based on actual patient weight, rounded to either 300 or 480 µcg, whichever is closer; D0 and D1 dose may be omitted if WBC >20,000/µL. [2]Dosing based on BSA using actual patient weight. [3]Starting approximately 2h after completion of cladribine. [4]D27 or D-3 (3 days before start of next treatment cycle), whichever occurs first

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# 1.0 BACKGROUND AND RATIONALE

Acute myeloid leukemia (AML) in adults remains difficult to treat, with only gradual improvements made over the last 3-4 decades [1, 2]. Although many patients will achieve a complete remission (CR) with 1 or 2 courses of intensive induction chemotherapy, the majority will ultimately relapse, and few patients will be alive 3-5 years after diagnosis [1, 2]. Therefore, the need for improved first-line therapies for AML is unquestioned. A major area of current interest is the use of small molecule inhibitors as a means to improve outcomes in AML. The major impetus for this current study are early results from a randomized trial reported by Röllig et al. at the 2014 annual meeting of the American Society of Hematology (ASH) [3] showing that the addition of the multikinase inhibitor sorafenib to standard induction therapy with 7+3 improves event-free survival (EFS) in adults <60 years of age with newly-diagnosed AML compared to placebo independent of the FLT3/ITD mutation status. The latter is relevant since 75-80% of patients with newly diagnosed AML do not harbor FLT3/ITD abnormalities. Two noteworthy aspects of this proposal are the use of G-CLAM (G-CSF, Cladribine, CytArabine, and Mitoxantrone) as the chemotherapy backbone and its choice of endpoints: CR without minimal residual disease (MRD) as primary efficacy endpoint and exploratory endpoints including quality of life (QOL) and healthcare resource utilization.

**G-CLAM**

The MRC/NCRI AML 15 trial involved approximately 3,200 newly diagnosed patients with AML and strongly suggested that FLAG-Ida (Fludarabine, CytArabine, G-CSF, and Idarubicin) is a more effective anti-AML regimen than daunorubicin with standard dose cytarabine (DA) or DA with addition of etoposide ([ADE]; 1,268 of these patients participated in the direct comparison of FLAG-Ida to ADE with a median age 48 [12-13% age 60+]) [4]. This study found that patients randomized to FLAG-Ida had a lower cumulative incidence of relapse than the other regimens ($p<0.001$; at 3 years: 38% vs. 55%), perhaps reflective of more patients achieving CR after 1 course of therapy. Death in CR was more common with FLAG-Ida (17% vs 11%), thus narrowing the difference in survival. However, given improvements in supportive care [5], it is likely only a matter of time before FLAG-Ida replaces 7+3 as the standard induction regimen for newly-diagnosed AML.

At our institution, we have used G-CLAM rather than FLAG-Ida based on previously published data and our phase 1/2 trial experience using this regimen ( [6, 7]; additionally, an abstract based on the Phase I data for the relapsed/refractory arm has been accepted for presentation at ASH in December 2015). G-CLAM differs from FLAG-Ida in the use of mitoxantrone rather than idarubicin and, primarily, in the substitution of cladribine for fludarabine. Cladribine is a more active single agent in AML than fludarabine; a Polish 3-way randomized trial in 652 adults aged < 60 years found that while addition of fludarabine to 7+3 did not improve survival, addition of cladribine to 7+3 did, with results principally due to superior outcome in patients with adverse cytogenetics [8]. Single arm studies from the Moffitt Cancer Center suggest that cladribine plus high-dose cytarabine is more effective than mitoxantrone, etoposide and cytarabine (MEC) for relapsed/refractory disease [9], and the combination of cladribine, cytarabine, and mitoxantrone has produced encouraging results in similar patients at Moffitt [10] and in Poland [11].

Since 2014, we have treated 61 patients with newly-diagnosed AML/high-risk MDS on our clinical trial with G-CLAM with dose-escalated doses of mitoxantrone. This cohort had a median

age of 57 years with the following cytogenetic profiles by MRC criteria [12]: cytogenetically favorable (n=4), intermediate (n=43), adverse (n=13), and unknown (n=1). The study investigated mitoxantrone at 12 mg/m$^2$, 14 mg/m$^2$, 16 mg/m$^2$, and 18 mg/m$^2$ (rather than 10 mg/m$^2$ as used in the original G-CLAM regimen), and the highest dose level was found to have acceptable toxicity and tolerability. Among the 57 treated patients that are thus far evaluable for response, the overall response rate (ORR) was 87.7% with 75.4% achieving a CR, 5.3% a CR with incomplete platelet recovery (CRp), and 7.0% a CR with incomplete blood count recovery (CRi). Of the responders (including CRp/i), 90.0% had no evidence of MRD by flow cytometry at best response (MRDneg). Overall, the MRDneg CR rate for all patients was 68.4%. Generally, the regimen has been well tolerated, with neutropenic fever, rash, nausea, and hypoxia (fluid overload/infection-related) seen as the most common grade ≥3 adverse events. Our phase 2 study is now ongoing with mitoxantrone at the 18 mg/m$^2$ dose level, and G-CLAM continues to serve as our principal treatment for newly-diagnosed AML. The MRDneg CR rate from this study will serve as the null rate for comparison with G-CLAM plus sorafenib.

**Sorafenib**

Sorafenib is an oral, small molecular, multikinase inhibitor which affects specific targets that are critical for tumor cell proliferation including the serine/threonine kinases c-Raf and B-Raf and the receptor tyrosine kinases RET, Flt-3 and c-Kit [13]. Sorafenib has potent *in vitro* activity against receptor tyrosine kinases important in tumor angiogenesis including the vascular endothelial growth factor receptor family (VEGFR1-3) and platelet derived growth factor-beta (PDGFR) [13]. In vivo, the anti-tumor activity of sorafenib is driven by its direct effects on tumor growth through its inhibition of the Raf/MEK/ERK pathway and the anti-angiogenic activity of the compound. Sorafenib demonstrates broad anti-tumor activity in human tumor xenograft models of liver, kidney, lung, prostate, breast and leukemia.

Sorafenib as a single agent has been evaluated globally in multiple phase 1 and 2 trials in various malignancies. Two pivotal international, multi-institutional, single agent, randomized, placebo-controlled trials led to sorafenib's approval for renal cell carcinoma and hepatocellular carcinoma worldwide [14, 15]. Since then, sorafenib has also been approved for locally recurrent or metastatic differentiated thyroid cancer refractory to radioactive iodine (2013). In patients with AML, there is thus far some limited experience with sorafenib in combination with standard chemotherapy in early phase clinical trials in both younger and older age populations. In a phase 1/2 study of sorafenib in combination with cytarabine (1.5g/m$^2$ daily via continuous infusion x 4 days) and idarubicin (IA) in patients <65 years with newly-diagnosed AML, Ravandi et al. demonstrated that sorafenib in doses up to 400 mg PO BID was safe and well tolerated. Among 61 patients, a CR rate of 79% was observed. Overall, there was a 95% CR/CRp rate for FLT3-mutated patients and an 84% CR/CRp rate for FLT3 wild-type patients. The median overall survival (OS) and disease-free survival were 29 and 13.8 months for mutated and wild-type patients, respectively [16, 17]. The most common grade 3 and 4 adverse events that were considered possibly associated with the addition of sorafenib to the induction regimen occurred in 15 patients and included nausea/vomiting, cardiac/hypertension, diarrhea, infections, hand and foot syndrome, liver toxicity, and pancreatitis.

Likewise, in the abstract noted above by Röllig et al. [3], 276 younger adults with AML were randomized to either daunorubicin with cytarabine (or cytarabine and mitoxantrone [HAM] if no response to initial induction) with placebo or sorafenib at 800 mg PO daily on days 10-19 during

induction, starting on day 8 up to 3 days prior to the next cycle during consolidation, and then daily for 12 months after the end of consolidation. CR rates were 59% vs. 60% in the placebo vs. sorafenib arm (p=0.76) but median event-free survival (EFS) was 9.2 months in placebo compared with 20.5 months in sorafenib arm, translating to a 3-year EFS of 22% vs. 40% respectively (p=0.013). Median OS has not yet been reached and is similar in both arms. There was a higher rate of fever, bleeding, and hand-foot syndrome in the sorafenib arm. Of note, the beneficial effect of sorafenib was due mostly to results in patients who were FLT3/ITD wild-type and who comprised the majority of patients in the study, as is true in the general AML population. In contrast, Serve et al. conducted a randomized trial with sorafenib, involving 211 patients >60 years of age to either cytarabine, daunorubicin (7+3) and placebo or 7+3 in combination with sorafenib, and found higher treatment-related mortality (early death) for sorafenib vs. placebo (17% vs. 7%, p=0.052), and non-significantly lower CR rates in the sorafenib arm (48% vs 60%, p=0.12) [18]. Therefore, sorafenib given in combination with chemotherapy is not currently recommended for elderly patients with AML.

The above considerations lead to this current trial in which the primary objective is to assess whether G-CLAM + sorafenib might improve MRDneg CR rates compared to G-CLAM alone in patients age ≤60. Because there is no experience with addition of sorafenib to G-CLAM, the first phase of the trial will involve both escalating the dose of mitoxantrone and establishing a maximally tolerated dose (MTD) of sorafenib when added to G-CLAM. The initial dose of mitoxantrone, 10 mg/m$^2$ daily for 3 days, is below FDA-labeling for AML at 12mg/m$^2$, and the initial dose of sorafenib is 50% that used by Röllig et al. We chose this mitoxantrone dose as the starting dose as it is the dose used in conjunction with G-CLAM as initially developed by the Polish AML group and published in the literature [11]. We are increasing the dose of mitoxantrone, as we did in G-CLAM alone, due to past studies suggesting a benefit of escalated doses of anthracyclines in adults AML [19, 20] , as well as our own prior experience with tolerance and efficacy of escalated doses of mitoxantrone in G-CLAM. In the phase 1 portion of this study, we plan to determine if sorafenib can be added to G-CLAM and if the higher doses of mitoxantrone remain well tolerated when given in conjunction with sorafenib. After establishing tolerability and determining the MTD of both mitoxantrone and sorafenib, we will move to the phase 2 portion to assess the efficacy of this combination. Of note, as prior studies incorporating sorafenib in combination with chemotherapy had varying schedules of administration of sorafenib – either concurrent or starting after chemotherapy commencement – and while the optimal delivery of drug is unknown, our study will generally mimic the administration schedule used by Röllig et al. due to their success with this schedule.

**MRDneg CR**

Similar to other malignancies, overall survival is the most relevant drug efficacy endpoint in AML. However, events can occur in a relatively delayed fashion compared to the treatment under investigation, and surrogate endpoints are typically considered to render early phase drug testing more efficient [21]. For many years, CR was regarded as such an endpoint. Although achieving a CR appears necessary for long-term survival in AML after intensive chemotherapy, CR in itself is not sufficient to prolong survival [22, 23]. One plausible explanation is that conventionally defined CRs vary widely in their quality, with only high quality CRs translating into a survival advantage. In particular, presence of MRD at the time of CR (as contrasted with lesser degrees of response such as CR with incomplete platelet or neutrophil recovery [CRp/CRi], either of which is more prone to relapse than CR) is independently associated with

relapse and thus indicates a poor quality CR [24]. Indeed, once account is made for response (CR vs CRp/CRi) and presence/absence of MRD at CR, pre-treatment covariates conventionally predictive of relapse (adverse cytogenetics, secondary AML, newly-diagnosed vs. relapsed disease) lose much of their significance. Consequently, the goal of induction therapy in AML might be attainment of a CR without MRD, with MRD defined by multi-parameter flow cytometry and/or persistent cytogenetic abnormalities. An attractive feature of CR without MRD is that this rate is only about 75% as high as CR rates, which in younger patients have averaged 75-80%. Hence, the ability to detect improved rates of MRDneg CR is greater than the ability to do the same with CR. Therefore, the primary focus of this study is the MRDneg CR rate.

**QOL/Resource Utilization Endpoints**

In addition to using MRDneg CR as our primary endpoint, we will also plan to evaluate QOL and healthcare resource utilization as exploratory endpoints since, as we note above, some argue that an emphasis on endpoints other than survival - which can take years to demonstrate in AML - might facilitate faster drug development for this disease [25]. Given that improvements in survival have been difficult to demonstrate in AML, studies that measure QOL over time and in different phases of disease (remission vs. relapse), are critical to define criteria for non-survival benefits provided by AML therapies. For example, while response to a certain therapy may not prolong survival for a patient, being in a CR in itself might provide some QOL benefit. Thus far, the relationship between treatment response and better QOL has been poorly-studied [25, 26], although intuitively there would be a positive relationship given the high morbidity of this disease.

Despite the acceptance of QOL as a valid endpoint for drug development, it is underutilized in AML as methodological limitations have historically impeded the use of QOL metrics in this disease. Due to the morbidity and mortality of AML, the dropout rate for use of these types of measures is high [25], requiring large sample sizes that often are not available in AML trials, especially if they are not tied to new therapeutic options. Additionally, while there are a number of clinical events associated with AML and its treatment that are objective, easily measured, and likely have a large impact on QOL - such as hospitalizations, infection rates, transfusion needs, or “healthcare resource utilization” - there is no currently available composite score that incorporates these measures and thus they can be difficult to compare across treatment regimens. We hope to address these historical limitations by incorporating the evaluations of QOL and resource assessments into an induction and remission therapy protocol with regular clinic visits tied to the patient’s therapy.

It is conceivable that a reduction of the high burden of morbidity of AML and its treatment on both the patient and the healthcare system could lead to improvements in QOL and healthcare costs and therefore would be valuable. In our prior trial of G-CLAM alone, we have been tracking some healthcare resource utilization measures, such as time to blood count recovery, and its effect on infection rates, hospitalization duration and transfusion needs. We would like to expand this evaluation to the proposed trial on a larger scale and include QOL and cost analysis as well.

# 2.0 OBJECTIVES

## 2.1 Primary Objective

**2.1.1** For phase 1, to assess the maximum tolerated dose (MTD) of sorafenib used in combination with dose-intensified mitoxantrone as part of the G-CLAM regimen in adults with newly-diagnosed AML/high-risk myelodysplastic syndromes (MDS).

**2.1.2** For phase 2, to determine if the addition of sorafenib to G-CLAM improves the rate of MRDneg CR compared with our center's historical control of G-CLAM alone in adults with newly-diagnosed AML/high-risk MDS.

## 2.2 Secondary Objectives

**2.2.1** To estimate rates of CR, ORR, OS, EFS, and relapse-free survival (RFS) after the addition of sorafenib to G-CLAM in patients with newly-diagnosed AML/high-risk MDS.

**2.2.2** To describe the toxicity profile and safety (rate of adverse events) of sorafenib in combination with G-CLAM.

## 2.3 Exploratory Objectives

**2.3.1** To assess the feasibility of incorporating QOL, cost and healthcare resource utilization endpoints in to a phase 1/2 clinical trial for newly diagnosed AML.

**2.3.2** To investigate, within the limits of a phase 1/2 trial, the impact of study treatment and response on quality of life, cost, and healthcare resource utilization for patients with AML undergoing intensive chemotherapy.

# 3.0 PATIENT ELIGIBILITY

## 3.1 Inclusion Criteria

**3.1.1** Age 18-60 years, inclusive

**3.1.2** Newly diagnosed disease with either a diagnosis of "high-risk" MDS (≥10% blasts in marrow or blood), high-risk myeloproliferative neoplasm (MPN; ≥10% blasts in blood or bone marrow), or AML other than acute promyelocytic leukemia (APL) with t(15;17)(q22;q12) or variants according to the 2008 WHO classification [27, 28]. Patients with biphenotypic AML are eligible. Such "high-risk" MDS or MPN have natural history much closer to AML than to lower risk MDS or MPN and have responded similarly to "AML-type" therapy [29].

**3.1.3** Outside diagnostic material is acceptable as long as peripheral blood and/or bone marrow slides are reviewed at the study institution by appropriate clinical staff. Flow cytometric analysis of peripheral blood and/or bone marrow should be performed according to institutional practice guidelines.

**3.1.4** Treatment-related mortality (TRM) score ≤13.1as calculated with simplified model: https://cstaging.fhcrc-research.org/**TRM**/Default.aspx or APPENDIX A [30].

**3.1.5** The use of hydroxyurea prior to study registration is allowed. Patients with symptoms/signs of hyperleukocytosis, WBC >100,000/μL, or acute symptoms can be treated with leukapheresis or may receive up to 2 doses of cytarabine (up to 500 mg/m$^2$/dose) prior to study day 0 enrollment.

**3.1.6** Adequate organ function:
**3.1.6.1** Bilirubin ≤2 times Institutional Upper Limit of Normal unless elevation is thought to be due to hepatic infiltration by AML, Gilbert's syndrome, or hemolysis (assessed within 10 days prior to study day 0).
**3.1.6.2** Serum creatinine ≤2.0 mg/dL (assessed within 10 days prior to study day 0).
**3.1.6.3** Left ventricular ejection fraction ≥45%, assessed within 3 months prior to study day 0, e.g. by MUGA scan or echocardiography, or other appropriate diagnostic modality and no clinical evidence of congestive heart failure.

**3.1.7** Women of childbearing potential and men must agree to use adequate contraception beginning at the signing of the consent until at least 3 months after the last dose of study drug.

**3.1.8** Provide written informed consent (or legal representative).

## 3.2 Exclusion Criteria

**3.2.1** Myeloid blast crisis of chronic myeloid leukemia (CML), unless patient is not considered candidate for CML-directed tyrosine kinase inhibitor treatment (excluding sorafenib).

**3.2.2** Concomitant illness associated with a likely survival of <1 year.

**3.2.3** Active systemic fungal, bacterial, viral, or other infection, unless disease is under treatment with anti-microbials and/or controlled or stable (e.g. if specific, effective therapy is not available/feasible or desired [e.g. chronic viral hepatitis, HIV]). Patient needs to be clinically stable as defined as being afebrile and hemodynamically stable for 24-48 hours prior to study day 0, unless fever is thought to be secondary to the underlying hematologic disease.

**3.2.4** Active or clinically significant (or symptomatic) cardiac disease, including active coronary artery disease, cardiac arrhythmias requiring anti-arrhythmic therapy other than beta blockers or digoxin within the last 3 months, unstable angina (anginal symptoms at rest), new-onset angina within 3 months before randomization, or myocardial infarction within 6 months before study day 0.

**3.2.5** Previous receipt of azacitidine, decitabine, anthracyclines, cytarabine, or other nucleoside analogues for treatment of AML or MPN/MDS other than as noted for cytarabine in 3.1.5.

**3.2.6** Pregnancy or lactation.

**3.2.7** Concurrent treatment with any other investigational agent that has anti-leukemia activity or another drug with anti-AML-activity.

# 4.0 EVALUATION AND COUNSELING OF PATIENT

The patient will be completely evaluated with a history, physical examination, diagnostic testing if necessary, and review of outside slides and records if available. The protocol will be discussed thoroughly with the patient and family (if present), with description of all known risks to the patient. Alternative forms of treatment will be presented as objectively as possible, and the risks and hazards of the study explained to the patient. Consent will be obtained using forms approved by the local Institutional Review Board (IRB).

# 5.0 PROTOCOL REGISTRATION

Subjects will be registered by the UW Study Coordinator and entered into the institutional clinical trials management system. A complete, signed, study consent and HIPAA consent are required for registration.

All eligibility requirements according to section 3.0 must be met. To complete the registration process, the Principal Investigator or her designee will assign a patient study number, and register the patient on the study.

# 6.0 TREATMENT PLAN

This study is a single-center, open-label phase 1/2 study of sorafenib in combination with G-CLAM for adults with newly diagnosed AML or high-risk MDS/MPN at the Fred Hutchinson Cancer Research Center/University of Washington. It will employ a 6+6 dose escalation rule in phase 1 and a Simon 2-stage design in phase 2 as described in Section 15.

**Study Overview**

After study enrollment, patients will receive a first cycle of G-CLAM + sorafenib at one designated dose level. Post-induction bone marrows will be reassessed upon blood count recovery or between day Days +28 to +35 after start of chemotherapy, whichever occurs first, unless otherwise dictated by the patient's course of clinical treatment. If the patient remains without count recovery (defined as ANC <500/μL and platelet count <50,000/μL) in the setting of an aplastic marrow (with <5% blasts), the next course of therapy will be held until (a) until bone marrow blasts are ≥5% OR (b) the patient has count recovery to ANC >500/μL and platelet count >50,000/μL. Patients with MRDneg CR can go on to receive up to 4 courses of post-remission therapy with G-CLA + sorafenib (i.e. with same regimen as used during induction but omission of mitoxantrone). Patients with partial remission (including MRDpos CR, CR with incomplete platelet recovery [CRp], CR with incomplete count recovery[CRi]) or persistent AML are eligible to receive a 2$^{nd}$ course identical to induction provided any extra-medullary toxicities have resolved to ≤grade 2 with appropriate dose reductions if extra- medullary toxicities ≥grade 3 occurred during cycle 1. Patients in MRDpos CR, CRp or CRi after a 2$^{nd}$ course may receive a 3$^{rd}$ course with G-CLA + sorafenib (mitoxantrone omitted) at their current dose level. Patients still not in MRDneg CR after this 3$^{rd}$ course are removed from study. Patients with MRDneg CR after completion of post-remission therapy are eligible to receive maintenance therapy for up to 1 year with daily sorafenib at the final dose they received during induction,

with subsequent dose adjustments if necessary based on cytopenias and extra-medullary toxicities.

## 6.1 Baseline/Pre-Treatment Assessment

The following studies should be obtained at baseline before initiation of study therapy to establish trial eligibility and allow patient characterization and disease prognostication. Results of tests and/or procedures conducted as per standard of care may be used to determine study eligibility if conducted within an appropriate window prior to screening. Outside testing and previously collected clinical data may be used if within the appropriate time frame.

**6.1.1** History and physical examination (assessed within 10 days prior to study day 0).

**6.1.2** Peripheral blood or bone marrow examination with morphologic and flow cytometric assessment, routine cytogenetic analysis, and molecular testing (FLT3/ITD, NPM1, CEBPA, or mutation profiling assay when available); a bone marrow biopsy should be obtained if spicules are absent from the aspirate sample (aspirate and biopsy to be assessed within 2 months prior to study day 0).

**6.1.2** Complete blood counts with differential blood count and platelet count (assessed within 10 days prior to study day 0).

**6.1.3** Metabolic panel, including bilirubin, albumin, and creatinine (assessed within 10 days prior to study day 0).

**6.1.4** MUGA scan or echocardiography, or other appropriate diagnostic modality, to assess left ventricular ejection fraction (LVEF; assessed within 3 months prior to study day 0).

**6.1.5** For patients with a history of cardiac disease, a baseline ECG is recommended. Further ECG monitoring while taking sorafenib should be done at the discretion of the treating physician and PI, taking into account any concomitant QTc prolongation medications and electrolyte abnormalities.

## 6.2 Pre-Treatment

At the discretion of the treating physician, allopurinol 300 mg PO daily (or equivalent dose adjusted for renal function) may be considered in all patients without known allergies to allopurinol to reduce the risk of tumor lysis. Higher doses of allopurinol are permitted if patients develop tumor lysis syndrome. Patients may receive rasburicase, a recombinant uric acid oxidase, for the prevention and/or treatment of tumor lysis syndrome at the discretion of the treating physician. All patients should be adequately hydrated and receive anti-emetics as necessary.

## 6.3 Administration of Sorafenib and Mitoxantrone

**6.3.1** For induction: patients will receive sorafenib and mitoxantrone at 1 of 6 total dose levels as allocated (see section Dose Escalation Scheme page 2 or 15.1.2). Mitoxantrone will be given IV daily over 60 minutes Days 1-3 and sorafenib orally Days 10-19 for all levels. Allowances of +/- 2 days for this window will be allowed for logistical purposes. Levels are as follows: Level 1, mitoxantrone 10 $mg/m^2$ with sorafenib 200 mg PO twice daily; Level 2, mitoxantrone 12 $mg/m^2$ with sorafenib 200 mg PO twice daily; Level 3, mitoxantrone 15 $mg/m^2$ with

sorafenib 200 mg PO twice daily; Level 4, mitoxantrone 18 mg/m$^2$ with sorafenib 200 mg PO twice daily; Level 5, mitoxantrone 18 mg/m$^2$ with sorafenib 400 mg PO in the morning and 200 mg in the evening; Level 6, mitoxantrone 18 mg/m$^2$ with sorafenib 400 mg PO twice daily. Level -1, dosed at mitoxantrone 10 mg/m$^2$ and sorafenib 200 mg PO once daily will also be available for dose de-escalation due to toxicities, as described in Section 6.8. For baseline organ dysfunction within the allowable limits of the eligibility criteria, dose reduction of individual medications specific to the organ impairment (e.g. liver, kidney) are allowed but not required, as described in section 6.10, and should be done in conjunction with the Oncology Pharmacist and PI.

**6.**3.2 The dose of mitoxantrone is calculated using the patient's actual weight.

**6.3.3** For post-remission therapy: sorafenib will be given per dose level as above, starting on day 8 until day 27 or 3 days prior to next cycle of treatment, whichever occurs first. Allowances of +/- 3 days for this window will be allowed for logistical purposes (i.e. timing of clinic visit for count evaluation).

**6.3.4** For maintenance: sorafenib will be given daily for up to 12 months following post-remission at the final dose the patient received during induction, with subsequent dose adjustment based on blood counts and extra-medullary toxicities.

**6.3.5** All treatment is given as intent-to-treat; missed doses will not be made up.

## 6.4 Administration of G-CSF, Cladribine, and Cytarabine

**6.4.1** The doses of the elements of G-CLAM chemotherapy will be as follows: G-CSF 5 µcg/kg rounded to 300 or 480 µcg daily subcutaneously daily on Days 0-5, Cladribine 5 mg/m$^2$ IV daily over 2 hours on Days 1-5, and Cytarabine 2 g/m$^2$ IV daily over 2 hours on Days 1-5.

**6.4.2** The doses of G-CSF, cladribine, and cytarabine are calculated using the patient's actual weight.

**6.4.3** Days 0 and 1 G-CSF may be omitted at physician discretion for WBC >20,000/µL or signs/symptoms of leukostasis.

**6.4.4** Administration in the outpatient clinic can be considered but should be discussed with the study investigators.

**6.4.5** All treatment is given as intent-to-treat; missed doses will not be made up.

**6.4.6** No investigational or commercial agents or therapies other than those described herein may be administered with the intent to treat the patient's malignancy.

## 6.5 Monitoring during/after Induction and Post-Remission Therapy

For patient monitoring, the following studies and study intervals are suggested:

**6.5.1** Complete blood counts with differential blood count, including immature cells/blasts, and platelet count at least 2 times weekly until ANC >1,000/µL and then at least weekly until platelet count >100,000/µL.

**6.5.2** Metabolic panel, including bilirubin, ALT/AST, and creatinine at least weekly until ANC >1,000/µL and platelet count >100,000/µL.

**6.5.3** Blood pressure monitoring on a weekly basis through the first 6 weeks of therapy is recommended. Thereafter, it is recommended that blood pressure should be monitored monthly as long as the patient remains on sorafenib.

**6.5.4** If patients develop signs or symptoms suggestive of cardiac dysfunction, LVEF should be assessed using the same method to evaluate baseline LVEF status (MUGA scan or echocardiography, or other appropriate diagnostic modality).

## 6.6 Assessment for Response after First Induction Course

A bone marrow aspirate should be obtained upon blood count recovery (i.e. ANC >1,000/μL and platelet count >100,000/μL) or between Days +28 to +35 after start of G-CLAM chemotherapy, whichever occurs first; unless otherwise dictated by the patient's course of clinical treatment (e.g. can be delayed per treating physician discretion if clinically indicated). A bone marrow biopsy need only be obtained during this procedure if spicules are absent from the aspirate sample.. MRD will be defined in all response assessments by evidence of disease on flow cytometry at any level greater than zero.

**6.6.1** Patients achieving MRDneg CR: Patients are eligible to receive up to 4 courses of post-remission therapy with G-CLA + sorafenib (mitoxantrone omitted).

**6.6.2** Patients achieving an MRDpos CR: Patients are eligible for a second course of therapy using the same dosing guidelines as course 1 (e.g. G-CLAM and Sorafenib given days 10-19) on their assigned dose level. If they again achieve an MRDpos CR, they can go on to receive a 3rd course, per discretion of the treating physician, with mitoxantrone omitted for course 3. If an MRDneg CR is not achieved after course 3, they will be removed from the study.

**6.6.3** Patients with CRi/CRp: Patients with incomplete blood count or platelet recovery, regardless of MRD status, are eligible for a second course of therapy using the same dosing guidelines as course 1 (e.g. G-CLAM and Sorafenib given days 10-19) on their assigned dose level. If they again achieve a CRi/p (regardless of MRD), they can go on to receive a 3rd course, per discretion of the treating physician, with mitoxantrone omitted for course 3. If an MRDneg CR is not achieved after course 3, they will be removed from the study.

**6.6.4** Patients with persistent disease: Patients with persistent AML (≥5% blasts) are eligible for a second course of induction chemotherapy at the same dosing used in course 1 (e.g. G-CLAM and Sorafenib given days 10-19) on their assigned dose level, provided all non-hematologic toxicities have resolved to Grade <2. If they are not in CR after the 2nd induction course, they can go on to receive a 3rd course, per discretion of the treating physician, with mitoxantrone omitted for course 3. If an MRDneg CR is not achieved after course 3, they will be removed from the study.

**6.6.5** Patients with persistent aplasia without evidence of disease after Day +49: patients will be removed from protocol.

**6.**6.6 For patients who experienced ≥Grade 3 non-hematologic toxicities excluding neutropenic fever and infections during the first induction, dose reductions are allowed but not required for this cycle as discussed in section 6.10.

## 6.7 Assessment for Response after a Second Induction Course

If a patient receives a second induction course (s per section 6.6.2-6.6.4), a bone marrow aspirate should again be obtained upon blood count recovery (i.e. ANC >1,000/μL and platelet count >100,000/μL) or between Days +28 to +35 after start of G-CLAM chemotherapy, whichever occurs first, unless otherwise dictated by the patient's course of clinical treatment. A bone marrow biopsy need only be obtained during this procedure if spicules are absent from the aspirate sample.

**6.7.1** Patients achieving MRDneg CR: Patients are eligible to receive up to 4 courses of post-remission therapy with G-CLA + sorafenib (mitoxantrone omitted).

**6.7.2** **All other patients (**MRDpos CR, CRi/CRp, persistent disease): Patients are eligible for a third course of therapy, per discretion of the treating physician, with mitoxantrone omitted for course 3 (G-CLA) and Sorafenib given on days 8-27 or 3 days prior to next cycle of treatment, whichever occurs first. **If an MRDneg CR is not achieved after course 3, they will be removed from the study.**

**6.7.3** Patients with persistent aplasia without evidence of disease after Day +49: patients will be removed from protocol.

## 6.8 Post-Remission Therapy

After achievement of an MRDneg CR with G-CLAM+sorafenib, patients are eligible for post-remission therapy with G-CLA+sorafenib.

**6.8.1** The treatment is identical to the induction course but without mitoxantrone (i.e. G-CSF, cladribine, and cytarabine, or "G-CLA" + sorafenib, at same dose level as induction). If that patient had excessive toxicities (grade ≥3 non-hematologic toxicity excluding neutropenic fever and infections) during induction, doses should be reduced as described in section 6.10.

**6.8.2** Post-remission courses should start within 6 weeks of achieving CR once patients have recovered to ≤Grade 2 toxicities from the previous course of therapy.

**6.8.3** Patients can receive up to 4 courses of post-remission therapy.

**6.8.4** Patients can proceed to transplantation barring contraindications and if a suitable donor is available.

## 6.9 Maintenance Therapy

**6.9.1** Patients in MRDneg CR at the end of post-remission therapy with G-CLA+sorafenib can continue to receive sorafenib for up to 12 months, as long as it is tolerated and as long as an MRDneg CR is maintained. Sorafenib will be given daily at the assigned dose level, unless dose reductions are needed for toxicity, in which case that dose would be continued. The MRDneg CR state should be confirmed every 3 months with bone marrow evaluations.

## 6.10 Dose Modifications of Chemotherapeutic Drugs for Baseline Organ Dysfunction or Subsequent Treatment Cycles

For patients with baseline organ dysfunction within the allowed limits of the eligibility criteria, or for those who experienced ≥Grade 3 non-hematologic toxicities excluding neutropenic fever and infections during the first induction, a dose reduction is

recommended. The following dose modifications are suggested for all subsequent treatment cycles:

**6.10.1** If a patient develops Grade ≥3 non-hematologic toxicity other than Grade 3 infections within 28 days from the last dose of G-CLAM, the next course of G-CLAM will be given once toxicity is < grade 2. The following dose reductions can be considered: cladribine 4 mg/m$^2$ days 1-5, cytarabine 1.5 g/m$^2$ days 1-4, mitoxantrone at one dose level below initial regimen days 1-3, G-CSF dose unchanged, and sorafenib at one dose level below their initial regimen. Additionally, the mitoxantrone may be omitted entirely if a 2$^{nd}$ induction course is indicated (any response less than CR without MRD) per treating physician discretion in discussion with the PI. Assuming these doses are well-tolerated the first course of G-CLA will be administered at these doses, omitting mitoxantrone. If Grade ≥3 non-hematologic toxicity occurs again, there will be a further reduction in doses of cladribine to 3 mg/m2 daily days 1-5 and cytarabine to 1 g/m2 daily days 1-5 for the first cycle of G-CLA. Doses for subsequent courses of G-CLA will be discussed with the Principal Investigator. Patients who were receiving dose level -1 sorafenib or mitoxantrone when grade ≥ 3 toxicity occurred will be taken off study.

**6.10.2** Mitoxantrone: Reduce mitoxantrone dose by 50% if the bilirubin concentration is 1.5-4.5 x IULN and to 25% if the bilirubin concentration is >4.5 x IULN. As per 6.10.1 can omit mitoxantrone entirely if clinically indicated.

**6.10.3** Cladribine: If the serum creatinine exceeds 2.0 mg/dL and/or estimated creatinine clearance (calculated by Cockcroft-Gault) decreases to less than 50 mL/min during therapy, we will consider dose reduction in discussion with the Oncology Pharmacist.

**6.10.4** Cytarabine: If the serum creatinine exceeds 2.0 mg/dL and/or estimated creatinine clearance (calculated by Cockcroft-Gault) decreases significantly during therapy, we will consider dose reduction in discussion with the Oncology Pharmacist.

**6.10.5** Sorafenib: If transaminitis occurs with liver function tests exceeding 6 x IULN with concurrent hyperbilirubinemia (bilirubin concentration > 4.5 x IULN), and any evidence of hepatic injury such as elevated INR and ascites, sorafenib should be held/discontinued. Further therapy should be resumed based on physician discretion after discussion with Principal Investigator and the Oncology Pharmacist.

## 6.11 Supportive Therapy

**6.11.1** All patients will be adequately hydrated and receive appropriate anti-emetics based upon institutional guidelines.

**6.11.2** Additional growth factors may be used according to institutional practice guidelines or the preference of the attending physician.

**6.11.3** Antimicrobial prophylaxis should be used according to institutional practice guidelines. In case of neutropenic fever, standard diagnostic testing will be performed, and empiric antibiotic coverage will be utilized as per usual care and standard institutional practices.

**6.11.4** Transfusional support should be carried out according to institutional practice guidelines.

### 6.12 Treatment of CNS Disease

Treatment of CNS disease is done according to institutional practice guidelines or the preference of the attending physician.

### 6.13 Recommended Follow-up Care

**6.13.1** For patients who continue to receive sorafenib for up to 12 months after the completion of G-CLA+sorafenib, they should have complete blood counts and a metabolic panel (to include kidney and liver function) done at least monthly and a bone marrow exam every 3 months, including after the completion of sorafenib**.**

**6.13.2** While still on sorafenib, blood pressure should be monitored at least monthly.

**6.13.3** After completion of protocol treatment, patients should be evaluated by treating physicians according to institutional and/or national guidelines or the discretion of the attending physician. These evaluations may include peripheral blood studies and/or bone marrow examinations, as clinically indicated.

### 6.14 Criteria for Removal from Treatment

All reasons for discontinuation of treatment must be documented:

**6.14.1** Completion of protocol treatment.

**6.14.2** HCT after achievement of CR.

**6.14.3** Initiation of any other leukemia-directed therapy other than protocol therapy

**6.14.4** Failure to achieve MRDneg CR after 3 courses of therapy.

**6.14.5** Persistent aplasia (ANC <500/μL or platelets <50,000/ μL) without evidence of leukemia after Day +49.

**6.14.6** Relapse (including recurrence of MRD) after achievement of CR during treatment.

**6.14.7** Adverse toxicities that prevent continuation with study treatment.

**6.14.8** Withdrawal of consent; the patient may withdraw from the study at any time for any reason.

## 7.0 INFORMATION ON STUDY DRUGS

G-CSF, cladribine, cytarabine and mitoxantrone will be obtained commercially. Sorafenib will be provided free of charge by Bayer HealthCare Pharmaceuticals.

### 7.1 Drug Information on G-CSF (Granulocyte colony-stimulating factor)

**7.1.1** Mechanism of Action: G-CSF is a growth factor that stimulates the production, maturation, and activation of neutrophils. Further, it promotes premature release of neutrophils from the bone marrow and enhances their phagocytic capacity.

**7.1.2** Pharmacokinetics: Peak G-CSF concentrations after sub-cutaneous dosing occur in 2 to 8 hours, though the onset of action is approximately 24 hours, with plateau concentrations in 3-5 days, and elimination over an 11-20 day period. G-CSF is cleared by systemic degradation. Notably, as G-CSF binds neutrophils, plasma levels are controlled in large part by the absolute neutrophil count.[31]

**7.1.3** Adverse Effects (AEs): *Common drug-related AEs (occurring in >10% of patients)* include fever, petechiae, elevated uric acid, splenomegaly, bone pain, and epistaxis. *Less common drug-related AEs (occurring in 1% -10% of patients)* include hyper- or hypotension, arrhythmias, headache, nausea, vomiting, leukocytosis, and transfusion reaction. *Infrequent drug-related AEs (occurring in <1% of patients)* include acute respiratory distress syndrome, allergic reactions, alopecia, alveolar hemorrhage, arthralgia, bone density decrease, capillary leak syndrome, cerebral hemorrhage, vasculitis, dyspnea, edema, erythema nodosum, hematuria, hemoptysis, hepatomegaly, hypersensitivity, injection site reaction, pericarditis, proteinuria, psoriasis exacerbation, pulmonary infiltrates, renal insufficiency, sickle cell crisis, splenic rupture, Sweet's syndrome, tachycardia, and thrombophlebitis.

**7.1.4** Recommended dose adjustments for organ dysfunction: There is limited or no data examining the toxicity of G-CSF in patients with renal or liver dysfunction. Therefore, administration of G-CSF to patients with liver or kidney disease must be done with caution.

## 7.2 Drug Information on Cladribine (2-chloro-2'-deoxyadenosnie, 2-CdA)

**7.2.1** Mechanism of Action: Cladribine is a prodrug that is converted to an adenosine deaminase-resistant triphosphate derivative (2-CdATP). This molecule is then activated by deoxycytidine kinase to a 5'-triphosphate derivative (2-CdAMP), which is incorporated into DNA where it acts as a transcription regulator. In addition to its cytotoxic properties in dividing cells, cladribine induces death in quiescent cells of lymphoid origin through an unknown mechanism.[32]

**7.2.2** Pharmacokinetics: Cladribine is renally excreted, with 18-35% as unchanged drug. It is able to penetrate the CSF, where it achieves 25% of plasma concentrations. It is 20% protein-bound. The half-life for elimination after a 2-hour infusion is 6.7±2.5 hours in patients with normal renal function.

**7.2.3** Adverse Effects: *Common adverse effects (occurring in >10% of patients)* include fever, fatigue, headache, rash, nausea, anorexia, vomiting, myelosuppression (including grade 3/4 neutropenia/thrombocytopenia), injection site reaction, and infection. *Less common adverse effects (occurring in 1 to 10% of patients)* include edema, tachycardia, thrombosis, chills, dizziness, insomnia, malaise, diarrhea or constipation, weakness, myalgias and arthralgias, cough, dyspnea, epistaxis, and diaphoresis. *Rare adverse effects (occurring in <1% of patients)* include aplastic anemia, bacteremia, opportunistic infections, lymphocytopenia, altered mental status, hemolytic anemia, hypersensitivity, myelodysplastic syndrome, quadriparesis, and renal dysfunction/failure.

**7.2.4** Reconstitution: Cladribine is supplied as a sterile, preservative-free, isotonic solution containing 10 mg of cladribine (1 mg/mL) in 10 mL single-use vials.

Cladribine should be passed through a sterile 0.22µm filter prior to introduction into the infusion bag containing 0.9% Sodium Chloride Injection, USP.

**7.2.5** Administration and Compatibility: The use of 5% dextrose is not recommended as a diluent because of increased degradation of cladribine. The infusion solution is stable for 24 hours at room temperature.

**7.2.6** Storage and Stability: Store refrigerated 2° to 8°C (36° to 46°F). Protect from light during storage.

**7.2.7** Recommended Dose Adjustments for Organ Dysfunction: Specific guidelines for cladribine dosing in patients with hepatic/renal dysfunction or hypoalbuminemia are not clearly defined. Because of the potential for compensatory elimination of cladribine in patients with hepatic and/or renal dysfunction, specific guidelines for dosing are difficult to define. Thus, when deciding whether to adjust cladribine doses for renal dysfunction, the risks for potential toxicities (e.g., myelosuppression, neurotoxicity) against the benefits and goals of treatment must be considered.

## 7.3 Drug Information on Cytarabine (Cytosine arabinoside)

**7.3.1** Mechanism of Action: Cytarabine is a synthetic pyrimidine analog, in which the sugar moiety (normally a ribose or deoxyribose) has been replaced with arabinose. Although its mechanism of action is not completely understood, the active form of cytarabine is probably incorporated into the DNA and interferes with DNA synthesis. As such, cytarabine has been found to primarily effect dividing cells, blocking their progression from $G_1$ to S phase.

**7.3.2** Pharmacokinetics: Cytarabine is metabolized by deoxycytidine kinase and other kinases into its most active form (aracytidine triphosphate). Aracytidine triphosphate is converted to nontoxic uracil derivatives by pyrimidine nucleoside deaminases. This balance between the levels of kinases and deaminases is critical for regulating the sensitivity/resistance of cells to the drug. The plasma clearance of cytarabine is biphasic, with an initial rapid phase and more prolonged second clearance phase. The rapid clearance phase has a relatively short half-life ($t_{1/2\alpha}$ = 10 minutes), while the half- life of the second clearance phase is slightly longer ($t_{1/2\beta}$ = 1 – 3 hours). The nontoxic metabolites from the drug are excreted in the urine, and within 24 hours after the infusion, approximately 80% of these nontoxic metabolites can be recovered from the urine.

**7.3.3** Adverse Effects: The dose-limiting toxicity for cytarabine is myelosuppression. *Adverse Events Associated with Standard Dose Cytarabine: Frequent AEs (not definitely quantified)* include the following: myelosuppression (leucopenia, anemia, neutropenia, thrombocytopenia), pyrexia, rash, anorexia, diarrhea, nausea, vomiting, mucositis, anal inflammation or ulceration, hepatic dysfunction or increased liver enzymes, and local thrombophlebitis. *Less frequent AEs (not definitely quantified)* include chest pain, pericarditis, dyspnea dizziness, headache, neural toxicity, neuritis, alopecia, pruritis, skin freckling, skin ulceration, urticaria, abdominal pain, bowel necrosis, esophageal ulceration, esophagitis, pancreatitis, sore throat, urinary retention, jaundice/hyperbilirubinemia, local site cellulites, renal dysfunction, allergic edema or anaphylaxis, sepsis, and sudden

respiratory distress syndrome. *Infrequent AEs (not definitely quantified)* include aseptic meningitis, cardiopulmonary arrest, cerebral dysfunction, cytarabine syndrome (bone pain, chest pain, conjunctivitis, fever, maculopapular rash, malaise, myalgia), exanthematous pustulosis, hyperuricemia, intestinal pneumonitis, increased lipase, paralysis with intrathecal and IV combination therapy, rhabdomyolysis, veno-occlusive disorder, and death. *Adverse Events Associated with High Dose Cytarabine* include cardiomegaly and cardiomyopathy, coma, severe neurotoxicity, personality change, somnolence, total body alopecia, severe rash or skin desquamation, gastrointestinal ulceration, peritonitis, intestinal pneumatosis, necrotizing colitis, liver abscess or damage, peripheral neuropathy, corneal toxicity, hemorrhagic conjunctivitis, pulmonary edema, sudden respiratory distress syndrome, and sepsis.

**7.3.4** Reconstitution: Cytarabine should be reconstituted in sterile water and can be further diluted using either 5% dextrose or sodium chloride solutions into appropriate concentrations for infusion.

**7.3.5** Administration and Compatibility: The diluted cytarabine solution should be inspected for particulate matter, discoloration, and haze prior to infusion. If there is evidence of particulate matter, discoloration, or haze the solution should not be infused. Patients should be medicated with standard anti-emetic therapy. Cytarabine is not compatible (1) during Y-site administration with allopurinol, amphotericin B, ganciclovir; (2) in syringe with metoclopropamide; or (3) admixed with fluorouracil, heparin, insulin (regular), nafcillin, oxacillin, penicillin G. Cytarabine may have variable compatibility when admixed with gentamycin, hydrocortisone, and methylpredinsone.

**7.3.6** Storage and Stability: Vials of non-reconstituted cytarabine should be stored at room temperature 15°C - 30°C (59°F - 86°F). The diluted cytarabine solution may be stable for up to 48 hours if stored at room temperature.

**7.3.7** Drug-Drug Interaction: Reversible decreases in the plasma steady-state concentration for digoxin and cardiac glycosides may occur. Cytarabine may diminish the therapeutic effect of flucytosine. There is *ex vivo* data suggesting that cytarabine may reduce the effectiveness gentamycin for killing *K. pneumoniae*.

**7.3.8** Warnings and Precautions: *Ex vivo* and *in vivo* studies have found that cytarabine causes extensive chromosomal damage and potential malignant transformation. Although there have been some case reports describing cytarabine use in pregnant humans, these cases reports are few. Thus, cytarabine is considered Pregnancy Category D. Women should be advised not to become pregnant while receiving cytarabine, and men should be advised not to father a child while receiving cytarabine and for at least 3 months after completing the therapy. It is not known whether cytarabine or its metabolites are excreted in breast milk; thus, it is not recommended for lactating females who are breast-feeding. As with any highly immunosuppressive medication, cytarabine may diminish the effectiveness of dead and live vaccines and enhance the toxic/adverse effect of live vaccines. One should avoid use of live vaccines while receiving it. A small percentage of patients will have a hypersensitivity reaction to cytarabine, and these individuals should not receive the drug again.

**7.3.9** Recommended Dose Adjustments for Organ Dysfunction: Guidelines for adjusting cytarabine dose due to renal or liver dysfunction are not standardized, but many clinicians will adjust the dose based upon the function of these organs.

## 7.4 Drug Information on Mitoxantrone

**7.4.1** Mechanism of Action: Mitoxantrone (dihydroxyanthracenedione) is an anthracenedione derivative that intercalates with DNA, resulting in inhibition of nucleic acid synthesis.

**7.4.2** Pharmacokinetics: Mitoxantrone is 78% bound to plasma proteins. A three-compartment model was described after a single intravenous dose of mitoxantrone. The mean alpha half-life is 6 to 12 minutes, the mean beta half-life is 1.1 to 3.1 hours, and the mean terminal (gamma) or elimination half-life is 23 to 215 hours (median 75 hours). Mitoxantrone has extensive distribution into body tissues and is metabolized in the liver to two main inactive metabolites (monocarboxylic acid derivative and dicarboxylic acid derivative). The major route of excretion for mitoxantrone appears to be biliary into the feces; approximately 11% of the dose is recovered in the urine within 5 days of drug administration, with 65% of this being unchanged drug.

**7.4.3** Adverse Effects: *Common adverse effects (occurring in >10% of patients)* include edema, fever, fatigue, headache, alopecia, nausea/vomiting, diarrhea, mucositis/stomatitis, myelosuppression, weakness, dyspnea, cough, and infection. *Less common adverse effects (occurring in 1 to 10% of patients)* include congestive heart failure, decreased left ventricular ejection fraction (LVEF), hypertension, chills, anxiety, cutaneous mycosis, hypcalcemia, hypokalemia, hyponatremia, menorrhagia, jaundice, myalgia, arthralgia, renal failure, proteinuria, rhinitis, diaphoresis, and infection.

Mitoxantrone may cause cardiac toxicity with prolonged administration and doses exceeding 80 to 100 mg/m$^2$; Appendix B provides an overview of the cardiotoxicity index of individual anthracyclines as well as mitoxantrone. When used after doxorubicin, cardiotoxicity is more frequent; an analysis by the Southwest Oncology Group revealed a risk of 6% at 134 mg/m$^2$ prior doxorubicin and 60 mg/m$^2$ mitoxantrone, rising to a 15% risk at 120 mg/m$^2$ mitoxantrone. Cardiac events reported included arrhythmias, decreased left ventricular function, chronic heart failure, tachycardia, ECG changes, and, infrequently, myocardial infarction. Bradycardia has been rarely reported. Patients with prior treatment with anthracyclines, prior mediastinal radiotherapy, or with preexisting cardiovascular disease may have more frequent occurrences of cardiac toxicity.

**7.4.4** Reconstitution: Mitoxantrone must be diluted prior to use. The dose of mitoxantrone should be to at least 50 mL with either 0.9% Sodium Chloride Injection (USP) or 5% Dextrose Injection (USP). Mitoxantrone may be further diluted into Dextrose 5% in Water, Normal Saline or Dextrose 5% with Normal Saline and used immediately.

**7.4.5** Administration and Compatibility: Care in the administration of mitoxantrone will reduce the chance of extravasation. Mitoxantrone should be administered into the tubing of a freely running intravenous infusion of 0.9% Sodium Chloride

Injection, USP or 5% Dextrose Injection, USP. Care should be taken to avoid extravasation at the infusion site and to avoid contact of mitoxantrone with the skin, mucous membranes, or eyes. If any signs or symptoms of extravasation have occurred, including burning, pain, pruritis, erythema, swelling, blue discoloration, or ulceration, the injection or infusion should be immediately terminated and restarted in another vein.
Mitoxantrone should not be mixed in the same infusion as heparin since a precipitate may form.

**7.4.6** Storage and Stability: Mitoxantrone should be stored between 15°C - 25°C (59°F - 77°F).

## 7.4 Drug Information on Sorafenib

**7.4.1** Mechanism of Action: Sorafenib is a kinase inhibitor that decreases tumor proliferation *in vitro*. Although in AML conventionally viewed as a FLT3 ITD kinase inhibitor, sorafenib inhibits multiple kinases (c-CRAF, BRAF, mutant BRAF, KIT, FLT-3, RET, RET/PTC, VEGFR-1/2/3, PDGFR-β). Several of these kinases are thought to be in involved in tumor cell signaling, angiogenesis, and apoptosis.

**7.4.2** Pharmacokinetics: The mean elimination half-life of sorafenib is 25-48 hours. Steady-state plasma concentrations are achieved within 7 days. Following oral administration, sorafenib reaches peak concentrations in approximately 3 hours. With a high fat meal, bioavailability is reduced by 29% compared to that in the fasting state. Sorafenib undergoes oxidative metabolism via hepatic CYP3A4, as well as glucuronidation by UGT1A9. Inducers of CYP3A4 can decrease serum concentration of sorafenib.

**7.4.3** Adverse Effects: The most common adverse reactions (> 20%) for sorafenib are diarrhea, fatigue, infection, alopecia, hand-foot skin reaction, rash, weight loss, decreased appetite, nausea, gastrointestinal and abdominal pains, hypertension, and hemorrhage. When used in combination with chemotherapy for treatment of AML, the most common adverse reactions thought to be related to the addition of sorafenib include hyperbilirubinemia/transaminitis, nausea/vomiting, diarrhea, rash, hand-foot syndrome, pancreatitis/colitis, and cardiac/hypertension. Please see Appendix F for management of adverse events specific to sorafenib.

**7.4.4** Administration: Subjects will be instructed on the proper administration of sorafenib. Sorafenib tablets should be taken 12 hours apart, at approximately the same time each morning and evening. Sorafenib tablets should be taken without food, at least 1 hour before or at least 2 hours after a meal, and with up to 240 mL (approximately 1 cup or 8 oz.) of water. Consumption of grapefruit and grapefruit juice should be avoided while receiving study drug. If a dose of sorafenib is missed, the next dose should be taken at the regularly scheduled time.

**7.4.5** Drug-Drug Interactions: Strong CYP3A4 inducers (such as carbamazepine, dexamethasone, phenobarbital, phenytoin, rifampin, rifabutin, St. John's wort) can decrease systemic exposure to sorafenib, and concomitant use of these medications should be avoided whenever possible. Concomitant use of strong CYP3A4 inhibitors (such as azithromycin, ketoconazole, ritonavir) may be allowed, but patients should be closely monitored for signs/symptoms of toxicity from increased exposure to sorafenib.

Interactions with strong CYP3A4 inhibitors has not been well studied, although ketoconazole administered at 400 mg once daily for 7 days did not alter the mean AUC of a single oral dose of sorafenib 50 mg in healthy volunteers.

**7.4.6** Storage and Stability: Sorafenib tablets do not need to be protected from light. They are sufficiently stable with regard to light, oxidation, thermal stress, and hydrolytic degradation. The formulation is presented as an immediate release (IR) dosage form, i.e., the active ingredient is completely dissolved under in vitro test conditions within a short period of time.

**7.4.7** Recommended Dose Adjustments for Organ Dysfunction: Mild renal and hepatic dysfunction does not affect the pharmacokinetics of sorafenib, and drug adjustment is not necessary (See Section 6.8.5 for Dose Reduction for Subsequent Cycles.)

# 8.0 EVALUATION AND END POINT DEFINITIONS

## 8.1 Treatment Response and Outcome

Treatment response (e.g. morphologic/cytogenetic/molecular complete remission, partial remission) or treatment failure (e.g. resistant disease, aplasia, morphological or molecular/cytogenetic relapse) as well as treatment outcome (e.g. overall survival, relapse-free survival, event-free survival, and remission duration) will be determine by peripheral blood count and bone marrow evaluation and categorized according to criteria recommended by International Working Groups [2, 33]. Patients are routinely assessed for the presence of minimal residual disease (MRD) as detected by multi-parameter flow cytometry and cytogenetic assessment, as per institutional practice.

## 8.2 Toxicity Criteria

This study will use the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5.0 for Toxicity and Adverse Event reporting. A copy of the CTCAE v5.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov).

## 8.3 Definition of Dose-limiting Toxicities (DLTs)

Reported adverse events and potential risks for G-CSF, cladribine, cytarabine, and mitoxantrone, are described in section 7. Dose-limiting toxicities (DLTs) used to guide dose escalation in this trial are defined as follows:

**8.3.1** Any Grade ≥3 non-hematologic toxicity lasting >48 hours that results in >7 day delay of the subsequent treatment cycle, with the exception of febrile neutropenia or infection.

**8.3.2** Any Grade ≥4 non-hematologic toxicity with the exception of febrile neutropenia/infection unless felt to be a direct consequence of treatment-related toxicity (e.g. intestinal infection following mucosal barrier breakdown), and with the exception of constitutional symptoms if no recovery to Grade ≤2 within 14 days.

**8.3.3** Hematologic toxicity with ANC <500/ μL or platelet count <50,000/μL for >49 days after initiation of G-CLAM, in conjunction with bone marrow showing no evidence of MRD or persistent AML.

### 8.4 Monitoring of Exploratory Endpoints

We will plan to assess QOL and healthcare resource utilization. Cost data will be obtained at the conclusion of study therapy

**8.4.1 QOL:** QOL will be assessed after each cycle of remission induction and post-remission therapy, then every 3 months if they remain on maintenance Sorafenib for up to 12 months, and at the conclusion of study treatment by the European Organization for Research and Treatment of Cancer QLQ-C30 questionnaire, a validated QOL measurement for oncology patients (Appendix C) [34]. These questionnaires will be distributed at clinic visits, which will be occurring at least monthly.

**8.4.2 Cost:** Cost records will be obtained at the conclusion of study treatment from the Financial Services Department.

**8.4.3 Healthcare resource utilization**: This will be a composite measure. These variables will be recorded (at the end of the study due to time constraints of the data coordinator) to capture the period from the start of treatment to first response assessment (e.g. remission induction). The following variables will be collected: total number of hospital admissions and duration of stays, days in the intensive care unit, number of blood product transfusions received, episodes of febrile neutropenia and days requiring antibiotic use, number of visits to the emergency department, and number of physician or advanced practice provider clinic visits.

### 8.5 Duration of Follow-up

Patients will be followed after completion of study treatment to determine EFS and RFS (for patients achieving CR) as well as overall survival (for all patients) for a maximum of 5 years. Follow-up may include periodic (e.g. every 3 months) review of medical records, and, if absolutely necessary, direct contact of the study participant.

## 9.0 RECORDS

Research data will be recorded in a study-specific, password protected database using a unique study ID for each patient to assure patient confidentiality. Data from source documents will be transcribed into this database. Source documents are documents where patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, quality of life assessments, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, X-rays, patient files, and records kept at the pharmacy, laboratories, and medico-technical departments involved in the clinical trial.

Any publication or presentation will refer to patients by this number and not by name. The licensed medical records department, affiliated with the institution where the patient receives medical care, maintains all original inpatient and outpatient chart documents. Patient research files will be maintained under control of the Principal Investigator and/or study team and kept in a locked office or file room within a secure building. Access to the study database will be restricted by electronic password protection and restricted access to computers (i.e., locked offices).

# 10.0 PROTOCOL ENROLLMENT AND SPECIAL CONSIDERATIONS

All eligible patients will be included in this study without regard to gender or ethnicity. The incidence of AML is slightly higher in men, so it is expected that the distribution of these patients will reflect a slight male predominance of the disease as well as the general demographic distribution of AML patients seen at our institution. Up to 84 patients with newly diagnosed AML/high-risk MDS/MPN will be enrolled in this study. This is an approximate number as it depends on the number of patients enrolled below the MTD in phase 1.

**Projected Target Accrual**
**ETHNIC AND GENDER DISTRIBUTION CHART**

| **TARGETED / PLANNED ENROLLMENT: Number of Subjects: 84** | | | |
|---|---|---|---|
| Ethnic Category | **Sex / Gender** | | |
| | **Females** | **Males** | **Total** |
| Hispanic or Latino | 1 | 2 | 3 |
| Not Hispanic or Latino | 33 | 48 | 81 |
| Ethnic Category Total of All Subjects* | 34 | 50 | 84 |
| Racial Categories | | | |
| American Indian / Alaska Native | 0 | 0 | 0 |
| Asian | 1 | 1 | 2 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 1 | 1 | 2 |
| White | 32 | 48 | 80 |
| Racial Categories: Total of All Subjects* | 34 | 50 | 84 |

**The "Ethnic Category Total of All Subjects" must be equal to the "Racial Categories Total of All Subjects."*

# 11.0 GUIDELINES FOR SERIOUS ADVERSE EVENT REPORTING

## 11.1 Expedited Reporting Requirements

In accordance with FHCRC/UW Cancer Consortium IRB policy, all adverse events (AEs; whether occurring on-site or off-site), which in the opinion of the principal investigator (PI) are (1) unexpected, and (2) related or possibly related to the research, and (3) serious or suggests that the research places research participants or others at a greater risk of physical or psychological harm than was previously known or recognized, will be submitted to the IRB within ten (10) calendar days of learning of the problem. Both the "Expedited Reporting Form for Unanticipated Problems or Noncompliance" and the "Adverse Event Reporting Form", or equivalent forms, will be completed for this reporting.

## 11.2 Definitions

**11.2.1** Adverse Event (AE): Any harm or untoward medical occurrence in a research participant administered a medical product, medical treatment or procedure even if it does not necessarily have a causal relationship with the product, treatment, or procedure. An adverse event can be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medical product, medical treatment, or procedure whether or not considered to be related. Mechanisms of obtaining information on AE include monthly transcripts, assessment forms obtained after each clinic visit, and hospital progress and discharge notes.

**11.2.2** Related or Possibly Related AE: An AE is "related or possibly related to the research procedures" if in the opinion of the principal investigator, it was more likely than not caused by the research procedures. AEs that are solely caused by an underlying disease, disorder or condition of the subject or by other circumstances unrelated to either the research or any underlying disease, disorder or condition of the subject are not "related or possibly related". If there is any question whether or not an AE is related or possibly related, the AE should be reported.

**11.2.3** Serious AE (SAE): An adverse event that results in any of the following outcomes:
- Death
- Life-threatening adverse event (real risk of dying)
- Prolongation of hospitalization*
- Persistent or significant disability/incapacity/or change in psychosocial status
- Congenital anomaly
- Requirement of intervention to prevent permanent impairment of damage

*Hospitalization itself will not be considered a serious adverse event if required for complications of AML or comorbid conditions. Hospitalization will be considered a SAE if it fulfills the criteria for a serious and unexpected adverse event as otherwise described.

**11.2.4** Unexpected AE: An AE is "unexpected" when its nature (specificity), severity, or frequency are not consistent with (a) the known of foreseeable risk of adverse events associated with the research procedures described in the protocol-related documents, such as the IRB-approved research protocol, informed consent document, and other relevant sources of information such as product labeling and package inserts.

**11.2.5** Management of Adverse Events. Please see Appendix D for prevention/management strategies for adverse events common with sorafenib.

Grade ≥3 adverse events other than hematologic toxicities will be recorded, graded, and reported as appropriate. AEs will be collected from the time of consent until 60 days after day 1 of each cycle or until the patient receives an alternative anti-cancer therapy, whichever date comes first. AEs that do not meet the requirement for expedited reporting will be reported to the IRB as part of the annual renewal of the protocol. Myelosuppression and associated complications are expected events during leukemia therapy; therefore, myelosuppression and associated simple complications such as fever,

infections, bleeding, and related hospitalizations will not be reported as individual AE but will be summarized in the annual report to the IRB.

# 12.0. DATA AND SAFETY MONITORING PLAN

The Principal Investigator will carry out ongoing trial oversight and will meet frequently with the study team to review recently acquired data and adverse events. The data recorded within the research charts and protocol database is compared with the actual data that is available from the medical record and/or clinical histories. All investigators on the protocol have received formal training in the ethical conduct of human research. The Principal Investigator will receive monitoring support as described below. Institutional support of trial monitoring will be in accordance with the FHCRC/University of Washington Cancer Consortium Institutional Data and Safety Monitoring Plan. Under the provisions of this plan, FHCRC Clinical Research Support coordinates data and compliance monitoring conducted by consultants, contract research organizations, or FHCRC employees unaffiliated with the conduct of the study. Independent monitoring visits occur at specified intervals determined by the assessed risk level of the study and the findings of previous visits per the institutional DSMP. In addition, protocols are reviewed at least annually and as needed by the Consortium Data and Safety Monitoring Committee (DSMC), FHCRC Scientific Review Committee (SRC) and the FHCRC/University of Washington Cancer Consortium Institutional Review Board (IRB). The review committees evaluate accrual, adverse events, stopping rules, and adherence to the applicable data and safety monitoring plan for studies actively enrolling or treating patients. The IRB reviews the study progress and safety information to assess continued acceptability of the risk-benefit ratio for human subjects. Approval of committees as applicable is necessary to continue the study. The trial will comply with the standard guidelines set forth by these regulatory committees and other institutional, state and federal guidelines.

# 13.0 ETHICAL AND REGULATORY CONSIDERATIONS

## 13.1 Institutional Review Board

In accordance with federal regulations (21 CFR 312.66), an Institutional Review Board (IRB) that complies with regulations in 21 CFR 56 must review and approve this protocol and the informed consent form prior to initiation of the study.

## 13.2 Consent

The Principal Investigator or her designee must explain verbally and in writing the nature, duration, and purpose of the study and possible consequences of treatment. Patients must also be informed that they may withdraw from the study at any time and for any reason without jeopardizing their future treatment. In accordance with federal regulations (21 CFR 50), all patients enrolled in the study must sign the IRB-approved consent form.

## 13.3 Confidentiality

Patient medical information obtained for the purposes of this study is confidential, and disclosure to third parties, other than those noted below, is prohibited. Upon the patient's request and written permission, medical information may be given to his/her personal physician or other appropriate medical personnel responsible for the patient's welfare. Data generated for this study

must be available for inspection on request to representatives of the national or local health authorities, and the associated IRB/IEC. Release of research results or data that reveal patient names or other identifiers, such as photographs, audio or videotapes, must be carried out in accordance with Department of Health and Human Services Final Standards for Privacy of Individual Health Information, 45 CFR 164.508. Written authorization must be obtained from the patient and IRB/IEC prior to the release of such information. Identifiable patient data may not be used for purposes of promoting any drugs used in this trial.

### 13.4 Publication Statement

The results of this clinical trial may be used for public dissemination in the form of papers, abstracts, posters, or other informational materials to be presented at scientific meetings, or published in professional journals, or as a part of an academic thesis by an investigator. Identifiable patient data may not be used for any of these presentations, manuscripts, or reports unless directed by law.

## 14.0 STATISTICAL CONSIDERATIONS

### 14.1 Phase 1

**14.1.1** General Considerations: DLTs are defined in Section 8.3. DLTs occurring during Cycle 1 will be used to guide dose escalation. However, before the phase 2 portion is begun, all grade ≥3 adverse events of all patients treated in the phase 1 portion will be reviewed to assess for late and cumulative toxicities that were not captured during the phase 1 portion of the trial. The Principal Investigator reserves the right to modify the protocol to reduce the drug doses identified in the phase 1 portion if this assessment suggests a significant risk of late/cumulative toxicities. Patients will be considered evaluable for DLT if they received at least 75% of the assigned doses of each chemotherapeutic during Cycle 1 or if they developed a DLT. If a patient does not develop a DLT but does not receive at least 75% of treatment during Cycle 1, the patient will be considered not evaluable for DLT and will be replaced. Maximum tolerated dose (MTD) is defined as the highest dose studied in which the incidence of DLT is <33% assuming at least 6 patients have been treated at this dose.

**14.1.2** Dose Escalation scheme:

Starting with dose level K=1:

A. Evaluate 6 patients at dose level K
    a. If 0 or 1 have DLT, increase dose to K+1 and go to A
    b. If 2 have DLT, stop dose escalation
    c. If >2 have a DLT, go to dose K-1

    The dose level below that which dose escalation was stopped is the potential MTD.

In order to better define safety and initial evidence of anti-leukemia activity while waiting for patients to complete their treatment cycles to assess the MTD, any dose level cohort may be expanded up to 12 patients, provided that

2 or fewer of 6 patients had DLT at that dose level (ie at last 4/6 have had no DLT). the cohort is expanded to 7-11 patients, these patients will not count toward DLT and MTD evaluation. If a cohort is expanded to 12 patients, the following rules will determine further dose escalation:
If 3 of fewer have DLT, increase dose to K+1 (go to A)
If 4 or more have DLT, stop dose escalation

Dose-finding for both mitoxantrone and sorafenib:

| | | |
|---|---|---|
| Level 1 | Mitoxantrone10 mg/m$^2$ | Sorafenib 200 mg BID |
| Level 2 | Mitoxantrone12 mg/m$^2$ | Sorafenib 200 mg BID |
| Level 3 | Mitoxantrone15 mg/m$^2$ | Sorafenib 200 mg BID |
| Level 4 | Mitoxantrone18 mg/m$^2$ | Sorafenib 200 mg BID |
| Level 5 | Mitoxantrone18 mg/m$^2$ | Sorafenib 400mg AM, 200 mg PM |
| Level 6 | Mitoxantrone18 mg/m$^2$ | Sorafenib 400 mg BID |
| Level -1 | Mitoxantrone10 mg/m$^2$ | Sorafenib 200 mg once daily |

In addition to safety stopping rules in phase 1, we will also employ efficacy stopping rules to make sure that the regimen does not have lower response rates than our current standard. Among the first 57/61 evaluable patients treated with G-CLAM alone in our ongoing phase 1/2 study, the MRDneg CR rate was 68%. We will assume that the G-CLAM+sorafenib regimen will not be of further interest if the true MRDneg CR rate is 60% or less (null hypothesis) and that that an MRDneg CR rate of 80% or more would be of interest for further investigation (alternative hypothesis). Therefore, if MRDneg CR is seen in < 5 of the first 11 patients, consideration will be given to stopping the study. An 80% confidence interval for an MRDneg CR rate of 4/11 is 0.17-0.60. Thus the upper bound of this limit is less than the current MRDneg CR rate with G-CLAM alone (68%). However, because the first 11 G-CLAM + sorafenib patients may differ with respect to cytogenetics/age etc. from the original 57 G-CLAM patients, a decision to stop would also depend on comparative examination of patient characteristics.

## 14.2 Phase 2

The study will be conducted in two sequential parts. The phase 1 portion ends once an MTD is identified or dose level 6 has been completed, whichever occurs first. Patients enrolled in the Phase 1 portion and treated at the MTD dose of sorafenib and mitoxantrone will be included in the analysis of the Phase 2 portion. The primary objective of the Phase 2 portion is to evaluate the MRDneg CR rate after up to 2 courses of induction chemotherapy.

A two-stage design will be used (Simon Optimal Two-Stage). As per the phase 1 section above, the MRDneg CR rate of our historical control of G-CLAM alone is 68%. G-CLAM+sorafenib will not be of further interest if the true MRDneg CR rate is 60% or less (null hypothesis) and that that an MRDneg CR rate of 80% or more would be of considerable interest for further investigation (alternative hypothesis). Therefore, in the first stage, 19 eligible patients will be accrued. If necessary, the study may be temporarily closed while remission data is collected. If at least 12 of the first 19 patients achieved an MRDneg CR (63%), we will move to the second stage. The second stage would enroll another 22 patients (for a total of 41), with G-CLAM + sorafenib considered of interest (at least 80% MRDneg CR rate) if at least 31/41 attained

MRDneg CR. The probability of declaring a therapy of interest when it is not is 10% (type-1 error), and not of interest when it is, is 20% (power 80%). Under the null hypothesis (true MRDneg CR rate 60%) the probability of termination before enrolling 41 patients is 51% and the average sample size is 29 patients. Note that patients treated at the recommended sorafenib and mitoxantrone doses during the Phase 1 part of the study would count toward the first 19 patients. Patients will be considered not evaluable if they received less than 75% of the assigned doses of each chemotherapeutic agent during Cycle 1, and they will be replaced. If a patient does not receive at least 75% of their assigned dose of sorafenib but discontinues the drug due to toxicity, they will be considered evaluable as we want to capture this essential toxicity data (and its potential downstream effect on efficacy) and not be replaced.

QOL scores, resource utilization, and cost variables will be recorded and summarized using descriptive methods including boxplots, histograms, and statistical summary measures (medians, means, standard deviation, N, and proportions). This study will not be powered to detect statistically significant differences between these endpoints for those with different responses; rather we will record these outcomes to inform a subsequent larger study, should follow up investigations be warranted.

## 15.0 STUDY TERMINATION

The study will terminate as described in section 15.0. The Principal Investigator, the IRB, and the FDA reserve the right to terminate this study at any time.

## 16.0 REFERENCES

1. Ferrara, F. and C.A. Schiffer, *Acute myeloid leukaemia in adults.* Lancet, 2013. **381**(9865): p. 484-95.

2. Dohner, H., et al., *Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet.* Blood, 2010. **115**(3): p. 453-74.

3. Rollig C, M.-T.C., Huttmann A, Noppeney R, Kunzmann V, Baldus CD, Brants CH, Kramer A, Schafer-Eckart K, Neubauer A, Krause SW, Giagounidis A, Aulitzky WE, Bornhauser M, Schaich M, Parmentier SB, Thied C, Von Bonin M, Schetelig J, Kramer M, Serve H, Berdel WE, Ehninger G. , *Sorafenib Versus Placebo in Addition to Standard Therapy in Younger Patients with Newly Diagnosed Acute Myeloid Leukemia: Results from 267 Patients Treated in the Randomized Placebo-Controlled SAL-Soraml Trial.* American Society of Hematology Annual Meeting, 2014. **Abstract #6**.

4. Burnett, A.K., et al., *Optimization of chemotherapy for younger patients with acute myeloid leukemia: results of the medical research council AML15 trial.* J Clin Oncol, 2013. **31**(27): p. 3360-8.

5. Othus, M., et al., *Declining rates of treatment-related mortality in patients with newly diagnosed AML given 'intense' induction regimens: a report from SWOG and MD Anderson.* Leukemia, 2014. **28**(2): p. 289-92.

6. Anwar A, H.A., Scott BL, Becker PS, Othus M, Hendrie PC, Ranker EM, Perdue A, Chen TL, Buckley SA, Orlowski KF, Powell MA, Appelbaum FR, Estey EE, Walter RB. , *Phase 1 Trial of G-CSF, Cladribine, Cytarabine, and Dose-Escalated Mitoxantrone (G-CLAM) in Adults with Newly Diagnosed AML or High-Risk MDS.* European Hematology Association (EHA) Annual Congress 2015. **Abstract #P574**.

7. Halpern AB, A.A., Scott BL, Becker PS, Othus M, Hendrie PC, Ranker EM, Perdue A, Smith H, Chen TL, Buckley SA, Orlowski KF, Powell MA, Estey EE, Walter RB. , *Phase 1 Trial of G-CSF, Cladribine, Cytarabine, and Dose-Escalated Mitoxantrone (G-CLAM) in Adults with Newly Diagnosed AML or High-Risk MDS.* Society of Hematologic-Oncology Annual Meeting, 2015. **Abstract #208**.

8. Holowiecki, J., et al., *Cladribine, but not fludarabine, added to daunorubicin and cytarabine during induction prolongs survival of patients with acute myeloid leukemia: a multicenter, randomized phase III study.* J Clin Oncol, 2012. **30**(20): p. 2441-8.

9. Price, S.L., et al., *Salvage chemotherapy regimens for acute myeloid leukemia: Is one better? Efficacy comparison between CLAG and MEC regimens.* Leuk Res, 2011. **35**(3): p. 301-4.

10. Jaglal, M.V., et al., *Cladribine, cytarabine, filgrastim, and mitoxantrone (CLAG-M) compared to standard induction in acute myeloid leukemia from myelodysplastic syndrome after azanucleoside failure.* Leuk Res, 2014. **38**(4): p. 443-6.

11. Wierzbowska, A., et al., *Cladribine combined with high doses of arabinoside cytosine, mitoxantrone, and G-CSF (CLAG-M) is a highly effective salvage regimen in patients with refractory and relapsed acute myeloid leukemia of the poor risk: a final report of the Polish Adult Leukemia Group.* Eur J Haematol, 2008. **80**(2): p. 115-26.

12. Grimwade, D., et al., *Refinement of cytogenetic classification in acute myeloid leukemia: determination of prognostic significance of rare recurring chromosomal abnormalities among 5876 younger adult patients treated in the United Kingdom Medical Research Council trials.* Blood, 2010. **116**(3): p. 354-65.

13. Wilhelm, S., et al., *Discovery and development of sorafenib: a multikinase inhibitor for treating cancer.* Nat Rev Drug Discov, 2006. **5**(10): p. 835-44.

14. Escudier, B., et al., *Sorafenib in advanced clear-cell renal-cell carcinoma.* N Engl J Med, 2007. **356**(2): p. 125-34.

15. Llovet, J.M., et al., *Sorafenib in advanced hepatocellular carcinoma.* N Engl J Med, 2008. **359**(4): p. 378-90.

16. Ravandi, F., et al., *Phase I/II study of combination therapy with sorafenib, idarubicin, and cytarabine in younger patients with acute myeloid leukemia.* J Clin Oncol, 2010. **28**(11): p. 1856-62.

17. Ravandi, F., et al., *Final report of phase II study of sorafenib, cytarabine and idarubicin for initial therapy in younger patients with acute myeloid leukemia.* Leukemia, 2014. **28**(7): p. 1543-5.

18. Serve, H., et al., *Sorafenib in combination with intensive chemotherapy in elderly patients with acute myeloid leukemia: results from a randomized, placebo-controlled trial.* J Clin Oncol, 2013. **31**(25): p. 3110-8.

19. Fernandez, H.F., et al., *Anthracycline dose intensification in acute myeloid leukemia.* N Engl J Med, 2009. **361**(13): p. 1249-59.

20. Lowenberg, B., et al., *High-dose daunorubicin in older patients with acute myeloid leukemia.* N Engl J Med, 2009. **361**(13): p. 1235-48.

21. Walter, R.B., et al., *Shortcomings in the clinical evaluation of new drugs: acute myeloid leukemia as paradigm.* Blood, 2010. **116**(14): p. 2420-8.

22. Burnett, A.K., et al., *The addition of gemtuzumab ozogamicin to low-dose Ara-C improves remission rate but does not significantly prolong survival in older patients with acute myeloid leukaemia: results from the LRF AML14 and NCRI AML16 pick-a-winner comparison.* Leukemia, 2013. **27**(1): p. 75-81.

23. Burnett, A.K., et al., *Clofarabine doubles the response rate in older patients with acute myeloid leukemia but does not improve survival.* Blood, 2013. **122**(8): p. 1384-94.

24. Chen, X., et al., *Relation of clinical response and minimal residual disease and their prognostic impact on outcome in acute myeloid leukemia.* J Clin Oncol, 2015. **33**(11): p. 1258-64.

25. Appelbaum, F.R., et al., *End points to establish the efficacy of new agents in the treatment of acute leukemia.* Blood, 2007. **109**(5): p. 1810-6.

26. Alibhai, S.M., et al., *Quality of life beyond 6 months after diagnosis in older adults with acute myeloid leukemia.* Crit Rev Oncol Hematol, 2009. **69**(2): p. 168-74.

27. Swerdlow SH, C.E., Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW (Eds.), *WHO Classification of Tumours and Haematopoietic and Lymphoid Tissues.* . 4th Edition ed. 2008, Lyon.

28. Vardiman, J.W., et al., *The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes.* Blood, 2009. **114**(5): p. 937-51.

29. Estey, E., et al., *Effect of diagnosis (refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, or acute myeloid leukemia [AML]) on outcome of AML-type chemotherapy.* Blood, 1997. **90**(8): p. 2969-77.

30. Walter, R.B., et al., *Prediction of early death after induction therapy for newly diagnosed acute myeloid leukemia with pretreatment risk scores: a novel paradigm for treatment assignment.* J Clin Oncol, 2011. **29**(33): p. 4417-23.

31. Carton, E., A. Bellesoeur, and O. Mir, *Colony-stimulating factors for febrile neutropenia.* N Engl J Med, 2013. **369**(3): p. 285-6.

32. Reiss, A.L., et al., *Neuroanatomy of fragile X syndrome: the posterior fossa.* Ann Neurol, 1991. **29**(1): p. 26-32.

33. Cheson, B.D., et al., *Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia.* J Clin Oncol, 2003. **21**(24): p. 4642-9.

34. Aaronson, N.K., et al., *The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology.* J Natl Cancer Inst, 1993. **85**(5): p. 365-76.

# APPENDIX A: TREATMENT-RELATED MORTALITY (TRM) SCORE

## Calculation of Simplified Treatment-Related Mortality (TRM) Score

Includes covariates: performance status (PS), age, platelet count, albumin, secondary AML, white blood cell count (WBC), peripheral blood blast percentage, and creatinine

Score = $100/(1+e^{(-x)})$, with $x$ = -4.08 + 0.89*PS + 0.03*age - 0.008*platelet count - 0.48*albumin + 0.47*(have secondary AML) + 0.007*WBC - 0.007*(peripheral blood blast percentage) + 0.34*creatinine

## Probability of TRM Above and Below Various Simplified TRM Score Cut-offs

| TRM Score Interval | Patients below/ within/above TRM Score Interval (%) | TRM Probability if below TRM Score Interval (%) | TRM Probability if within TRM Score Interval (%) | TRM Probability if above TRM Score Interval (%) |
|---|---|---|---|---|
| 0 – 1.9 | 0/20/80 | - | 1 | 12 |
| 1.91 – 3.9 | 20/20/60 | 1 | 2 | 16 |
| 3.91 – 6.9 | 40/20/40 | 1 | 7 | 20 |
| 6.91 – 9.2 | 60/10/30 | 3 | 7 | 24 |
| 9.21 – 13.1 | 70/10/20 | 4 | 12 | 31 |
| 13.11 – 22.8 | 80/10/10 | 5 | 20 | 41 |
| 22.81 – 100 | 90/10/0 | 6 | 41 | - |

From: Walter RB, Othus M, Borthakur G, Ravandi F, Cortes JE, Pierce SA, Appelbaum FR, Kantarjian HM, Estey EH. Prediction of early death after induction therapy for newly diagnosed acute myeloid leukemia with pretreatment risk scores: a novel paradigm for treatment assignment. *J Clin Oncol*. 2011;29(33):4417-4424.

# APPENDIX B: CARDIOTOXICITY INDEX OF ANTHRACYCLINES

| Drug | Schedule | Relative Myelosuppressive Potency[1] | Approximate Relative Cardiotoxicity | Cardiotoxicity Index[2] |
|---|---|---|---|---|
| *Doxorubicin* | *Rapid infusion* | *1* | *1* | *1* |
| Doxorubicin | 24hr infusion | 1 | 0.62 | 0.62 |
| Epirubicin | Rapid infusion | 0.67 | 0.66 | 0.44 |
| Mitoxantrone | Rapid infusion | 5 | 0.5 | 2.5 |
| Daunorubicin | Rapid infusion | 0.67 | 0.75 | 0.5 |
| Idarubicin | Rapid infusion | 5 | 0.53 | 2.67 |

[1]Of single dose compared with doxorubicin administered by standard schedule. [2]The cardiotoxicity index represents a factor by which to multiply the cumulative dose of a drug administered to obtain an approximation of toxicity that might be expected had the resultant amount of doxorubicin been given by rapid infusion

Adapted from Holland J, et al. Cancer medicine, 5th ed. American Cancer Society. Hamilton and London: B.C. Decker, Inc. 2000.

# APPENDIX C: EUROPEAN ORGANIZATION FOR RESEACH AND TREATMENT OF CANCER QLQ-C30 QUESTIONNAIRE

## EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Your birthdate (Day, Month, Year): ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Today's date (Day, Month, Year): 31 ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

| | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|
| 1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase? | 1 | 2 | 3 | 4 |
| 2. Do you have any trouble taking a long walk? | 1 | 2 | 3 | 4 |
| 3. Do you have any trouble taking a short walk outside of the house? | 1 | 2 | 3 | 4 |
| 4. Do you need to stay in bed or a chair during the day? | 1 | 2 | 3 | 4 |
| 5. Do you need help with eating, dressing, washing yourself or using the toilet? | 1 | 2 | 3 | 4 |

| **During the past week:** | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|
| 6. Were you limited in doing either your work or other daily activities? | 1 | 2 | 3 | 4 |
| 7. Were you limited in pursuing your hobbies or other leisure time activities? | 1 | 2 | 3 | 4 |
| 8. Were you short of breath? | 1 | 2 | 3 | 4 |
| 9. Have you had pain? | 1 | 2 | 3 | 4 |
| 10. Did you need to rest? | 1 | 2 | 3 | 4 |
| 11. Have you had trouble sleeping? | 1 | 2 | 3 | 4 |
| 12. Have you felt weak? | 1 | 2 | 3 | 4 |
| 13. Have you lacked appetite? | 1 | 2 | 3 | 4 |
| 14. Have you felt nauseated? | 1 | 2 | 3 | 4 |
| 15. Have you vomited? | 1 | 2 | 3 | 4 |
| 16. Have you been constipated? | 1 | 2 | 3 | 4 |

Please go on to the next page

| During the past week: | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|
| 17. Have you had diarrhea? | 1 | 2 | 3 | 4 |
| 18. Were you tired? | 1 | 2 | 3 | 4 |
| 19. Did pain interfere with your daily activities? | 1 | 2 | 3 | 4 |
| 20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television? | 1 | 2 | 3 | 4 |
| 21. Did you feel tense? | 1 | 2 | 3 | 4 |
| 22. Did you worry? | 1 | 2 | 3 | 4 |
| 23. Did you feel irritable? | 1 | 2 | 3 | 4 |
| 24. Did you feel depressed? | 1 | 2 | 3 | 4 |
| 25. Have you had difficulty remembering things? | 1 | 2 | 3 | 4 |
| 26. Has your physical condition or medical treatment interfered with your family life? | 1 | 2 | 3 | 4 |
| 27. Has your physical condition or medical treatment interfered with your social activities? | 1 | 2 | 3 | 4 |
| 28. Has your physical condition or medical treatment caused you financial difficulties? | 1 | 2 | 3 | 4 |

**For the following questions please circle the number between 1 and 7 that best applies to you**

29. How would you rate your overall health during the past week?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Very poor | | | | | | Excellent |

30. How would you rate your overall quality of life during the past week?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Very poor | | | | | | Excellent |



Aaronson, N.K., et al., *The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology.* J Natl Cancer Inst, 1993. **85**(5): p. 365-76.

# APPENDIX D: MANAGEMENT OF TOXICITIES SPECIFIC TO SORAFENIB

## I. Prevention/management strategies for diarrhea and fatigue

Diarrhea and fatigue are common side effects of sorafenib. The same dose-modification algorithm used for skin toxicities can be used to address these toxicities. However, the preventive/management strategies for diarrhea and fatigue should be consistent with local standards (e.g., anti-diarrheals and optimized hydration status for diarrhea).

### II. Hand-foot-skin reaction: Suggested sorafenib dermatologic toxicity modification

| **Recommended dose modification for hand foot skin reaction (HFSR)** | | |
|---|---|---|
| **Toxicity Grade** | | **Suggested dose modification** |
| Grade 1 | Any occurrence | Maintain dose level and consider topical therapy for symptomatic relief |
| Grade 2 | 1st occurrence | Maintain dose level and consider topical therapy for symptomatic relief<br>If no improvement within 7 days, see below |
| | No improvement within 7 days or 2nd occurrence | Interrupt until resolved to Grade 0-1<br>When resuming treatment, decrease dose by one dose level |
| | 3rd occurrence | Interrupt until resolved to Grade 0-1<br>When resuming treatment, decrease dose by two dose levels |
| | 4th occurrence | Discontinue treatment permanently |
| Grade 3 | 1st occurrence | Interrupt until resolved to Grade 0-1<br>When resuming treatment, decrease dose by one dose level |
| | 2nd occurrence | Interrupt until resolved to Grade 0-1<br>When resuming treatment, decrease dose by two dose levels |
| | 3rd occurrence | Discontinue treatment permanently |

**At first occurrence of HFSR, independent of grade, prompt institution of supportive measures such as topical emollients, low potency steroids, or urea-containing creams should be administered.**

Recommended prevention/management strategies for skin toxicities consistent with HFSR are summarized below.

| Recommended Prevention/Management Strategies for Skin Toxicities Consistent with Hand-Foot-Skin-Reaction | |
|---|---|
| **Toxicity Grade** | **Practical Prevention / Management Strategies for HFSR** |
| **Grade 0** (Preventive strategies) | • Maintain frequent contact with trial physician to ensure early diagnosis of HFSR.<br>• Practical prevention strategies<br>o Pedicure[a] for subjects with pre-existing hyperkeratosis.<br>o Subjects should avoid hot water, and clothing or activities that can cause friction on the skin.<br>o Moisturizing cream should be applied sparingly.<br>• Padded gloves and open shoes with padded soles should be worn to relieve pressure points. |
| **Grade 1**<br>Any occurrence | • Continue preventive strategies and in addition:<br>o Soak hands in cool water.<br>o Apply petroleum jelly to moist skin.<br>• In the case of hyperkeratotic lesions, exfoliate the hands or feet and apply moisturizing cream immediately afterwards. |
| **Grade 2** Any occurrence or<br>**Grade 3** Any occurrence | • Continue supportive/management measures and add analgesic(s) for pain. |
| a: Pedicure should be done by a podiatrist. | |

## III. Treatment-emergent hypertension

Hypertension is a known and potentially serious AE associated with sorafenib treatment. Subjects will undergo brief physical examinations, including blood pressure monitoring, on a weekly basis through the first 6 weeks of therapy. Thereafter, blood pressure will be monitored on Day 1 of each cycle.

Blood pressure measurements considered out of the normal range are diastolic pressure > 90 mm Hg and/or systolic pressure > 140 mm Hg, or a 20 mm Hg increase in diastolic pressure if the previous measurement was within normal limits.

The dose-modification schedule to be followed in the event of treatment-emergent hypertension is outlined below. The choice of anti-hypertensive medication to be used in cases of treatment-emergent hypertension will be at the investigator's discretion and based on site-specific treatment guidelines as applicable. All anti-hypertensive medications used for the management of treatment-emergent hypertension should be recorded in the subject's records.

Once a dose-reduction modification has been made for treatment-emergent hypertension, NO dose re-escalation will be allowed.

| Management of Treatment-Emergent Hypertension | |
|---|---|
| **Grade of Event (NCI-CTCAE v4.0)** | **Management/ Next Dose** |
| **Grade 1** | Consider increasing blood pressure monitoring. Continue sorafenib dosing as scheduled. |
| **Grade 2** asymptomatic and diastolic pressure 90-99 mm Hg | Begin anti-hypertensive therapy. Continue sorafenib dosing as scheduled. |
| **Grade 2** (symptomatic/persistent)<br>**OR**<br>**Grade 2** symptomatic increase by > 20 mm Hg (diastolic) or to > 140/90 mm Hg if previously within normal limits<br>**OR**<br>**Grade 3** | Sorafenib should be held[a] until symptoms resolve and diastolic blood pressure < 90 mm Hg; also treat subject with anti-hypertensives and when sorafenib is restarted, reduce by 1 dose level.[b]<br>If diastolic blood pressure is not controlled (< 90 mm Hg) on anti-hypertensive therapy, reduce another dose level.[b] |
| **Grade 4** | Discontinue sorafenib |

a: Subjects requiring a delay of > 30 days (modify according to study specific cycle length) should discontinue sorafenib unless, in the opinion of the treating physician, the subject may benefit from continued treatment.

b: Subjects requiring dose reductions beyond 200 mg (1 placebo tablet) twice daily, every other day, should discontinue sorafenib.

# Appendix E: Study Medication Diary

| | | | |
|---|---|---|---|
| Principal Investigator: | Anna Halpern, MD | Sponsor: | Bayer Pharmaceuticals |
| Protocol Number: | 9510 | Sponsor Study #: | CC9510 |
| Title or Brief Description: | G-CLAM+Sorafenib in Newly Diagnosed AML/High-grade Myeloid Neoplasms | | |

**Subject Name** **Date of Birth** **Study ID**

**Study Medication** Sorafenib **Dose** 400 mg (2 tablets) twice daily **Date Dispensed**

**Patient instructions:**

- Check the box each time you take your pills every day on the diary below.
- Please bring all unused study medication, along with this drug diary, if you go to the hospital for any reason.
- Please return your sorafenib pill bottle (even if empty) and this drug diary to your doctor at your next appointment following your last dose of sorafenib.
- If you have any questions on your sorafenib dose or schedule, you can page us 24 hours a day through the UW paging operator at 206-598-6190. From 8 am – 5 pm Monday-Friday ask to page Kelsey-Leigh Garcia (research coordinator). For after hours and on the weekends, ask to page Dr. Anna Halpern.

| Day of the week/ Date | Check Column for Both AM Tablets Taken  | Check Column for Both PM Tablets Taken  | Comments |
|---|---|---|---|
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Patient Signature Date

****Do Not** sign the diary until you have returned to your doctor**