

Phase II Study of Sorafenib Plus 5-Azacitidine for the Initial Therapy of Patients with Acute Myeloid Leukemia and High Risk Myelodysplastic Syndrome with FLT3-ITD Mutation
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Core Protocol Information

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- The Clinical Research Committee - (CRC)

Protocol Body



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**Phase II Study Of Sorafenib Plus
5-Azacitidine For The Initial Therapy Of Patients With Acute Myeloid
Leukemia And High Risk Myelodysplastic Syndrome With FLT3-ITD
Mutation**

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risk MS with FLT3-ITD mutation**

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1.0 Objectives

1.1 Primary objectives:

1. To determine the clinical activity (CR +CRi) of the combination of AZA and sorafenib in patients with untreated acute myeloid leukemia and High risk MDS with FLT3-ITD mutation.

1.2 Secondary objectives:

1. To determine the toxicity profile of the combination of AZA and sorafenib in patients with untreated acute myeloid leukemias and MDS with FLT3-ITD mutation.
2. To determine potential mechanisms of synergy with this combination and its correlation with response.

2.0 Background

Acute myeloid leukemia (AML) is a neoplasm involving immature granulocytes or monocytes. AML is characterized by accumulation of leukemic blasts and blockade of normal bone marrow hematopoietic cell production resulting in thrombocytopenia, anemia, and neutropenia. In the U.S., approximately 12,000 new cases of AML are diagnosed every year, with an estimated 9,000 deaths attributable to the disease. Almost all newly diagnosed cases, as well as deaths, will be in adults. Standard treatment for AML includes systemic combination chemotherapy to control bone marrow and systemic disease. Treatment is generally divided into an induction phase, to attain remission, and a consolidation phase. Approximately 60% to 70% of adults with AML can be expected to attain complete remission status following appropriate induction therapy. Remission rates in adult AML are inversely related to age, with an expected remission rate of >65% for those younger than 60 years. Increased morbidity and mortality during induction appear to be directly related to age (Sheinberg, 2005).

Signaling via receptor tyrosine kinases (RTKs) is frequently deregulated in hematological malignancies.¹ FLT3 (FMS-like tyrosine kinase III) is a transmembrane tyrosine kinase that belongs to the Class III family of RTKs. FLT3 is primarily expressed on immature hematopoietic progenitors and also on some mature myeloid and lymphoid cells.²⁻⁴ FLT3 is activated following binding of FLT3 ligand, which causes receptor dimerization leading to increased kinase activity and activation of downstream signaling pathways including Stat5, Ras, and PI3'kinase.⁵ FLT3 plays a normal role in the regulation of survival and proliferation of hematopoietic progenitor cells, in particular by synergy with other RTKs and cytokine receptors. FLT3 is also expressed in AML cells from approximately 90% of patients and stimulates survival and proliferation of leukemic blasts.⁶⁻⁸

Additionally, FLT3 is mutated in 30% of AML cases.⁹ The two leading types of mutations found in AML include internal tandem duplications in the juxtamembrane domain (ITD, 17-34%) and

mutations in the activation loop (approximately 7%).⁹ Patients with mutations in FLT3 have a worse prognosis when treated with conventional chemotherapy compared to patients with wild-type FLT3.¹⁰ Initial studies using small molecule FLT3 inhibitors have offered encouragement that when added to the conventional arsenal of AML treatments, patients with AML expressing mutated FLT3 may experience significant clinical benefit.¹¹

2.1 Sorafenib

Sorafenib (Nexavar, Bayer-Onyx) is an oral, small molecule kinase inhibitor that was initially developed as a Raf inhibitor. Subsequent laboratory characterization of sorafenib demonstrated that it is a multikinase inhibitor of several other targets including vascular endothelial growth factor receptor-2 (VEGFR-2), VEGFR-3, and platelet-derived growth factor receptor-beta (PDGFR-[beta]). Due to its inhibition of VEGFR, sorafenib has been classified as an antiangiogenic drug. Sorafenib garnered initial attention when its antitumor activity in renal cell cancer was noted in early clinical trials. More recently, on the basis of a phase III trial, sorafenib was approved by the Food and Drug Administration (FDA) for the treatment of metastatic renal cancer and hepatocellular cancer.

Sorafenib was initially identified through a library screen as a small molecule that inhibits C-Raf. In addition to C-Raf, sorafenib is a multikinase inhibitor of several other targets including wild type and mutant B-Raf, VEGFR-2, VEGFR-3, PDGFR-[beta], Flt-3, c-Kit, and fibroblast growth factor receptor-1. In contrast, Erk1, Erk2, insulin-like growth factor, c-met, EGFR, and protein kinase C are not inhibited by sorafenib.¹²

A series of phase I trials involving a range of sorafenib doses (50–800 mg) and schedules (intermittent and continuous) have been conducted. Plasma drug levels of 400 mg twice daily are well tolerated and higher than those necessary to inhibit Raf kinase, as well as VEGFR and PDFGR. Thus the recommended dose for single agent phase II testing is 400 mg twice daily.

In the phase I studies, sorafenib was well tolerated; the rate of grade 3 toxicities was low and no grade 4 toxicities were reported. The most common drug-related side effects were hand-foot syndrome (23%), rash (26%), fatigue (39%), diarrhea (55%), hypertension (35%), stomatitis (7%), neuropathy (22%) and alopecia (16%).

Based on results from preclinical and phase I studies, sorafenib was expected to cause growth arrest and clinical disease stabilization rather than tumor shrinkage. Assessment of cytostatic drugs and disease stabilization in phase II studies is challenging in that it is often difficult to distinguish drug effect versus prolonged natural history of the disease in any single patient. One proposed phase II design for cytostatic agents is the randomized discontinuation trial (RDT).

In the sorafenib RDT phase II trial, all patients initially received sorafenib 400 mg twice daily for 12 weeks; patients who experienced >25% tumor reduction in bidimensional measurements (modified WHO criteria) at the 12-week evaluation were continued on the drug. Patients with >25% tumor growth in bidimensional measurements after the 12-week run-in phase, were taken off the study. Patients with <25% reduction and <25% growth within the first 12 weeks were

classified as stable disease and were randomized in a placebo-controlled double-blind fashion to continue or discontinue sorafenib. The primary endpoint of the study was the fraction of randomized patients that maintained stable disease 12 weeks postrandomization.¹⁵ In this manner, the trial not only determines whether the observed stable disease is a drug effect, but also, and perhaps more importantly, selects (or enriches) the trial for patients most likely to experience the endpoint of disease stabilization.

The latter trial design characteristic is especially important as the trial was originally designed to evaluate activity of sorafenib in colorectal cancer based on its Raf inhibitory properties and the role of the Raf pathway in this disease. The trial also, however, allowed recruitment of patients with other malignancies. During the study, investigators noted tumor regression in renal cell cancer (RCC) patients and the protocol was thus amended to expand enrollment of this cohort. A total of 202 patients with RCC (502 total with all tumor types) were treated during the run-in phase, 73 had tumor shrinkage $\geq 25\%$; 66 patients with stable disease at 12 weeks were randomized to sorafenib or placebo. At 24 weeks, 50% of sorafenib-treated patients were progression-free in comparison with 18% of placebo-treated patients ($P = 0.007$). Additionally, median progression-free survival from randomization was significantly longer with sorafenib (24 weeks) than placebo (6 weeks; $P = 0.009$). Of note, only a small number of patients demonstrated objective tumor regressions that would qualify as partial responses according to RECIST criteria; thus the RDT design of this phase II trial allowed investigators to quickly identify an active therapy that may have been mistakenly classified as inactive in traditional phase II trial designs.

A large multicenter randomized phase III trial in patients with metastatic clear cell RCC was initiated.¹⁶ Eligibility was limited to patients with clear cell RCC who progressed on one prior systemic therapy within 6 months, Eastern Cooperative Oncology Group (ECOG) performance <2 , and no brain metastases. The primary end point was overall survival; secondary endpoints included progression-free survival toxicity and response rate. The progression-free survival analysis was designed to be evaluated after 363 events with a nominal one-sided P -value of 0.01. The survival analysis was designed to be evaluated after 540 events with a nominal two-sided P -value of 0.04 and with interim analyses after 270 events. 905 patients were randomized to receive either sorafenib 400 mg twice daily or placebo; no crossover to sorafenib was initially allowed on the trial. The preliminary results were presented at the 2005 American Society of Clinical Oncology annual meeting. Among the 335 patients who received sorafenib, only 2% achieved a partial response according to RECIST criteria, but 78% demonstrated stable disease, with a majority of these patients experiencing some tumor shrinkage. Progression-free survival, however, was significantly prolonged in the treatment arm, with those receiving sorafenib demonstrating a time to progression of 24 weeks versus 12 weeks ($P < 0.000001$). Due to this marked positive clinical benefit, the protocol was amended to allow patients on the placebo arm to receive sorafenib. In addition, sorafenib was approved by the FDA in December 2005 for the treatment of patients with advanced/metastatic RCC.

The analysis of this trial was updated recently after 367 survival events occurred: patients on the sorafenib arm had a continued improvement in overall survival of 19.3 months versus 15.9 months for placebo arm ($P = 0.015$; hazard ratio 0.77), despite the fact that 48% of patients

initially randomized to the placebo arm crossed over to receive sorafenib. In the final report, the OS of patients receiving sorafenib was comparable with that of patients receiving placebo (17.8 v 15.2 months, respectively; hazard ratio [HR] = 0.88; P = .146); however, when post-cross-over placebo survival data were censored, the difference became significant (17.8 v 14.3 months, respectively; HR = 0.78; P = .029).¹⁷

Again, sorafenib was well tolerated with very few grade 3 or 4 toxicities seen. Toxicities experienced in the treatment arm included hand–foot syndrome, hypertension, rash, and fatigue.

In preclinical studies, sorafenib induced dephosphorylation of MEK1/2 and ERK and induced apoptosis in AML cells.¹² Furthermore, sorafenib was 1000- to 3000-fold more potent in inducing apoptosis in Ba/F3 cells with FLT3-ITD or D835G mutations than those with WT FLT3.¹² In a mouse model of AML with mutant FLT3, sorafenib reduced the leukemic burden and prolonged survival.¹³ It has been approved by the FDA for the treatment of renal cell and hepatocellular carcinoma at a standard dose of 400 mg twice daily. In phase I studies and used anecdotally in patients with advanced AML, sorafenib was capable of producing significant clinical responses. The objectives of this study were to determine the feasibility, safety and efficacy of combining sorafenib with induction chemotherapy.

2.2 Azacitidine

Azacitidine (AZA), an analog of the pyrimidine nucleoside cytidine, has effects on cell differentiation, gene expression, and deoxyribonucleic acid (DNA) synthesis and metabolism. Since the early 1970s, azacitidine has been investigated primarily in the US for the treatment of acute leukemia. Clinical studies have focused mainly on patients with disease refractory to conventional chemotherapy. Results of these investigations demonstrated activity of azacitidine in the treatment of AML. Clinical studies subsequently evaluated the effects of azacitidine in a variety of other malignant and hematologic disorders, including solid tumors, hemoglobinopathies (eg, thalassemia and sickle cell anemia), and MDS. In 1984, the Cancer and Leukemia Group B (CALGB) began a series of clinical studies with azacitidine in patients with MDS. These studies, in addition to other supportive data, led to the approval of Vidaza® (azacitidine) in May 2004 for the treatment of MDS.

Azacitidine inhibits the methylation of newly synthesized DNA by inhibiting DNA methyltransferase (DNMT). Increased methylation of DNA (hypermethylation) may result in the silencing of critical genes responsible for cell growth control and differentiation. Hypermethylation of CpG islands spanning the promoter regions of tumor suppressor genes is commonly associated with cancers. It is now widely recognized that hypermethylation of DNA is frequently associated with myelodysplastic syndromes and other cancers, such as renal, melanoma, breast, colorectal, non-small cell lung and hematologic malignancies. Azacitidine is believed to exert its antineoplastic effects through hypomethylation and cytotoxicity on abnormal hematopoietic cells in the bone marrow. Hypomethylation may restore normal function to genes that are critical for differentiation and proliferation. The cytotoxic effects of azacitidine cause the death of rapidly dividing cells, including cancer cells that are no longer responsive to normal growth control mechanisms.

The cytotoxicity of azacitidine is proportional to dose and exposure time. Although the mechanisms of cytotoxicity are complex and multifaceted, there is general agreement that incorporation of azacitidine into DNA and ribonucleic acid (RNA), and inhibition of protein synthesis, are critically important. Cytotoxicity is greatest in cells that are proliferating (S phase) and metabolically active. Cytotoxic effects may also be mediated through induction of the DNA damage response pathways. Non-proliferating cells are relatively insensitive to azacitidine.

Toxicology studies have been conducted in mice, rats, dogs, and Rhesus monkeys. Most of the studies were performed during the 1970s and early 1980s according to existing guidelines and standards in place during that period. The preclinical studies identified the bone marrow, liver, kidneys, and lymphoid tissues (spleen, lymph nodes, and thymus) as the main target organs of toxicity for azacitidine. In single-dose studies, the lethal dose of azacitidine after intravenous (IV) administration in mice, rats, and dogs was approximately 250 mg/m². Repeated daily dosing appears to increase the toxicity of azacitidine. The genotoxicity of azacitidine is consistent with that of other nucleoside analogs that interact with nucleic acids. Likewise, similar to other agents with cytostatic properties, azacitidine was embryotoxic and reduced the reproductive performance in mice and rats.

Limited azacitidine pharmacokinetic data are currently available. Based on human plasma concentrations of total radioactivity (which represents parent drug plus circulating metabolites), azacitidine is rapidly absorbed when given subcutaneously (SC), with maximum plasma concentrations found 0.5 to 2 hours after dosing. Azacitidine and/or its by-products are then rapidly cleared by the kidneys. The half-lives and percent radioactivity recovered in urine are similar following IV and SC routes of administration. The effects of renal or hepatic impairment, gender, age, or race on the pharmacokinetics of azacitidine have not been studied. A single dose (75 mg/m²) SC versus IV crossover study in 6 MDS subjects revealed an approximate bioavailability of 89% for the SC dose (range 52% to 128%) with mean half-lives of 0.69 hour and 0.36 hour after SC and IV administration, respectively. These results demonstrated that azacitidine is rapidly and nearly completely absorbed after SC administration and that elimination is also rapid. The apparent SC clearance (167 L/h or 2791 mL/min) and systemic IV clearance (147 L/h) of azacitidine exceeded the glomerular filtration rate (approximately 125 mL/min) and total renal blood flow (1200 mL/min) in healthy subjects. This indicates that non-renal elimination (eg, metabolism, hydrolysis, and/or degradation) plays a role in the elimination of parent azacitidine. In addition, azacitidine 75 mg/m² was generally well-tolerated after single SC injection or IV infusion over 10 minutes.

A number of studies have looked at different parenteral doses and schedules of azacitidine, finding maximum tolerated doses of up to 500 mg/m² when administered weekly.

During the two decades between the start of the CALGB studies and the approval of azacitidine, a new understanding of MDS has developed, such as the World Health Organization (WHO) diagnostic criteria, the International Prognostic Scoring System (IPSS), and the International Working Group (IWG) response criteria. Silverman et al. reevaluated the combined data (N = 309) from 3 of the CALGB studies using the WHO classification system for MDS and

AML and the IWG response criteria. Using the IWG response criteria in MDS patients, response rates were between 40% and 70% in azacitidine treated patients. Ten to 17% of patients achieved a complete remission; partial remission was rare; and 23% to 36% of patients had a hematologic improvement. In patients with AML (N = 103), 35% to 48% had hematologic improvement or better responses. The median survival time for 27 patients assigned to azacitidine was 19.3 months compared with 12.9 months for the 25 patients assigned to observation.

A randomized international Phase III trial (Study AZA PH GL 2003 CL 001) for higher-risk MDS patients, classified by FAB as RAEB, RAEB-T, or CMML with 0-29% marrow blasts, with an IPSS of Intermediate -2 or High by central pathology/cytogenetic review was recently reported. Patients were randomized to azacitidine (75 mg/m²/day x 7days in 28 day cycles) or conventional care regimens (CCR) , where CCR was pre-selected by the Investigator as best supportive care (transfusions, antibiotics, and G-CSF for neutropenic infection), low-dose cytarabine (20 mg/m²/day x 14 days in 28 day cycles); or standard chemotherapy (conventional induction/consolidation). Patients were stratified by FAB/IPSS and randomized 1:1 to azacitidine or CCR. This trial did not allow erythropoietin. Three-hundred fifty eight patients (70% male) were randomized at 79 centers to azacitidine (N=179) or CCR (N=179): best supportive care only (N=105, 59%), low-dose cytarabine (N=49, 27%), or standard chemotherapy (N=25, 14%). Median age was 69 years (range 38-88 years). The azacitidine and CCR groups were comparable for baseline patient characteristics. At baseline, 95% of patients were higher risk: RAEB (58%), RAEB-T/WHO AML (34%), CMML (3%), and other (5%). By IPSS, 87% were higher risk: Intermediate -2 (40%), High (47%), and 13% Indeterminate/other. Azacitidine was administered for a median of 9 cycles; low-dose cytarabine for 4 cycles. Median follow-up for the survival analysis was 21.1 months. Azacitidine demonstrated statistically superior overall survival compared to CCR, with a median overall survival of 24.4 months vs. 15 months for CCR (stratified log-rank p=0.0001, hazard ration 0.58). Two-year survival approximately doubled in the azacitidine arm compared to CCR: 51% vs. 26% (p<0.0001). Azacitidine was well tolerated with safety data consistent with previous reports.

Further details can be found in the azacitidine Investigator's Brochure, which contains comprehensive pharmacology, toxicology, pharmacokinetics, pharmacodynamics, metabolism, preclinical, and clinical efficacy and safety data information.

A potential mechanism of resistance to FLT3 kinase inhibitors is high levels of FLT3 ligand (FL) which is commonly seen after treatment with myelosuppressive chemotherapy. We hypothesized that combining sorafenib with a less myelosuppressive agent, such as 5-azacytidine (AZA), may lead to higher and more durable responses. We have previously conducted a clinical trial combining azacytidine and sorafenib for the treatments of patients with relapsed AML. Patients received 5-azacytidine (AZA) 75 mg/m² intravenously daily for 7 days and sorafenib 400 mg orally twice daily continuously; cycles were repeated at ~1-month intervals. This trial was registered at clinicaltrials.gov as #NCT01254890. Overall, 57 patients with AML with a median age of 65 years (range, 21-87) were enrolled. They included 27 (47%) patients with normal cytogenetics, 12 (21%) with chromosome 5/7 or complex cytogenetic abnormalities, 15 (26%) with other miscellaneous abnormalities; 3 (5%) had insufficient metaphases. Prior to the initiation of treatment, *FLT3*-ITD was detected in 53/57 (93%) patients with a median allelic

ratio of 0.348 (range, 0.009 – 0.934). They had received a median of 2 prior treatments (range, 0 -7) including 13 previously untreated patients. Twenty (35%) patients had received ≥ 3 prior regimens and 12 had failed prior therapy with FLT3 kinase inhibitors (6 with AC220, 2 with PKC412, and 9 with sorafenib, either as monotherapy or with chemotherapy or plerixafor); 4 patients had failed 2 prior FLT3 inhibitors. The overall CR/CRi/PR rate among the 57 patients is 44%, including 16 (28%) with CRi and 8 (14%) with CR and 1 (2%) with PR. The response rate among the previously untreated patients was 62% and among relapsed patients 39%. Patients have received a median of 3 (range, 1 - 27) treatment cycles with the median number of cycles to response among the responders being 2 (range, 1 – 4) and the median time to achieving response, 2.1 months (range, 0.8 – 4.6 months). The median duration of CR/CRi is 2.4 months (range, 0.8 – 24.8 months). Seven patients have proceeded to allogeneic stem cell transplant. The most common study drug-related adverse events were rash and fatigue with no deaths attributable to study medications. One patient developed grade 3 cardiomyopathy. With a median follow-up of 8.6 months (range, 6.1 – 26.9), 13 patients remain alive, 5 still in remission. The median overall survival of the 57 patients was 6.3 months, and 12.4 months in the 25 responding patients. Mean FL levels at cycle 2, day 0 and cycle 2, day 10 were 27 pg/mL and 54 pg/mL, respectively, which is significantly lower than those seen previously in studies of FLT3 kinase inhibitor plus chemotherapy.¹⁸

3.0 Patient selection

3.1 Inclusion criteria:

1. Patients with untreated AML ($\geq 20\%$ blasts in bone marrow and/or peripheral blood) or high risk MDS ($\geq 10\%$ blasts in bone marrow) Patients with AML and history of MDS who have received prior therapy with a hypomethylating agent (including azacitidine) and/or with lenalidomide for prior MDS are eligible if the treating physician feels that participation in the study is in the patients' best interest. Patients should have molecular evidence of the presence of FLT3-ITD mutation with a molecular burden of at least 10%.
2. Age ≥ 60 years; patients younger than 60 who are unsuitable for or unwilling to receive standard cytotoxic chemotherapy are also eligible to be enrolled.
3. ECOG Performance Status ≤ 2
4. Adequate liver (bilirubin $\leq 1.5 \times$ ULN, ALT or AST $\leq 2.5 \times$ ULN and Alkaline phosphatase $\leq 4 \times$ ULN if not related to leukemic disease) and renal (creatinine $\leq 1.5 \times$ ULN) function.
5. Patients must provide written informed consent.
6. Patients must have been off therapy for MDS for 2 weeks prior to entering this study, and must have recovered from the toxic effects of that therapy to at least grade 1, unless there is evidence of rapidly progressive disease. Use of hydroxyurea (any dose) or ara-C (up to 1 g/m² x 2 doses) for patients with rapidly proliferative disease is allowed before the start of

study therapy; these should be stopped for 24 hours prior to the initiation of azacitidine and sorafenib.

7. Women of childbearing potential should be advised to avoid becoming pregnant with an adequate method of contraception (barrier or hormonal methods) and men should be advised to not father a child while receiving treatment with azacitidine. All men and women of childbearing potential must use acceptable methods of birth control throughout the study as described below: Women of childbearing potential must have a negative serum pregnancy test performed within 7 days prior to the start of treatment. Men should use adequate birth control for at least 30 days after the last administration of sorafenib. Post-menopausal women (defined as no menses for at least one year) and surgically sterilized women are not required to undergo a pregnancy test

Females of childbearing potential: Recommendation is for 2 effective contraceptive methods during the study. Adequate forms of contraception are double-barrier methods (condoms with spermicidal jelly or foam and diaphragm with spermicidal jelly or foam), oral, depo provera, or injectable contraceptives, intrauterine devices, and tubal ligation.

Male patients with female partners who are of childbearing potential:

Recommendation is for male and partner to use at least 2 effective contraceptive methods, as described above, during the study.

8. Ability to understand and the willingness to sign a written informed consent. A signed informed consent must be obtained prior to any study specific procedures.
9. $INR \leq 1.5$. Patients receiving anti-coagulation treatment with an agent such as warfarin or heparin **may** be allowed to participate. For patients on warfarin, the INR should be measured prior to initiation of sorafenib and monitored weekly, or as defined by the local standard of care, until INR is stable.

3.2 Exclusion criteria:

- ◆ Nursing and pregnant females.
- ◆ Patients with acute promyelocytic leukemia are excluded
- ◆ Patients with known allergy to sorafenib or azacitidine, mannitol or any of their components.
- ◆ Patients with known severe impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of sorafenib.
- ◆ Patients with any other known disease (except carcinoma in-situ) or concurrent severe and/or uncontrolled medical condition (e.g. uncontrolled diabetes, cardiovascular disease including congestive heart failure, myocardial infarction

within 6 months and uncontrolled hypertension, chronic renal disease (creatinine clearance < 20 ml/min using the Cockcroft and Gault formula), or active uncontrolled infection) which could compromise participation in the study.

- ◆ Patients with a known confirmed diagnosis of HIV infection or active viral hepatitis (B or C).
- ◆ Patients who have had any major surgical procedure within 28 days prior to Day 1.
- ◆ Patients unwilling or unable to comply with the protocol.
- ◆ Cardiac disease: Congestive heart failure > class II NYHA. Patients must not have unstable angina (anginal symptoms at rest) or new onset angina (began within the last 3 months) or myocardial infarction within the past 6 months.
- ◆ Uncontrolled hypertension defined as systolic blood pressure > 150 mmHg or diastolic pressure > 90 mmHg, despite optimal medical management.
- ◆ Active clinically serious infection > CTCAE v4. Grade 2 not controlled with antibiotics.
- ◆ Thrombotic or embolic events such as a cerebrovascular accident including transient ischemic attacks within the past 6 months.
- ◆ Pulmonary hemorrhage/bleeding event \geq CTCAE v4. Grade 2 within 4 weeks of first dose of study drug.
- ◆ Any other hemorrhage/bleeding event \geq CTCAE v4. Grade 3 within 4 weeks of first dose of study drug.
- ◆ Serious non-healing wound, ulcer, or bone fracture.
- ◆ Evidence of bleeding diathesis or coagulopathy within the past 6 months
- ◆ Known or suspected allergy to sorafenib or any agent given in the course of this trial.
- ◆ Substance abuse, medical, psychological or social conditions that may interfere with the patient's participation in the study or evaluation of the study results including known non-compliance issues on study trials.
- ◆ Use of strong CYP3A4 inducer

4.0 Treatment Plan

4.1 General

All patients will be registered through CORE. The objective will be to administer azacitidine and sorafenib at full dose.

4.2 Schedule

PROTOCOL SUMMARY/SCHEMA

SCHEDULE OF EVALUATIONS / STUDY CALENDAR

Parameter	Pre-study	Weekly *****	Before Each Cycle	Before Every 2 - 4 Cycles	Study Termination	Follow - Up
History	X				X	X
Physical examination	X		X	X	X	X
BP**	X	X	X	X	X	X
Weight	X		X	X	X	X
Measurement of extramedullary tumor*****	X		X	X	X	X
Performance status	X		X	X	X	X
CBC, differential, platelet count	X	X	X	X	X	X
Serum Chemistries (must include, Bilirubin, Alk Phos, ALT orAST)	X	X	X	X	X	X
Glucose and Electrolytes (Na, K, Cl, CO ₂)	X	X	X	X	X	X
PT/PTT/INR***	X		X	X	X	X
Bone marrow exam with cytogenetics and molecular studies for FLT3 and NPM1****	X			X	X	
Beta HCG	X					
Chest x-ray	X					
Brain CT or MRI scan *	X					

As appropriate

*Brain imaging (CT/MRI) should be performed only in patients with neurological signs and symptoms concerning for intracranial metastatic masses.

**Blood pressure should be monitored weekly during the first 4 weeks of sorafenib therapy and thereafter monitored and treated, if required, in accordance with standard medical practice. In cases of severe or persistent hypertension, despite institution of antihypertensive therapy, temporary or permanent discontinuation of sorafenib should be considered.

***Infrequent bleeding events or elevations in the International Normalized Ratio (INR) have been reported in some patients taking warfarin while on sorafenib therapy. Patients taking concomitant warfarin should be monitored weekly for changes in prothrombin time, INR or clinical bleeding episodes.

****Bone marrow exam should be performed at Screening the end of Cycle 1, every 2-3 cycles for the first year, then at the discretion of the treating physician. Any change to this schedule that the treating physician feels is in the best interest of the patient must be approved by the PI.

Molecular studies (FLT3 and NPM1) performed at baseline only and on patients with unknown status.

***** Labs will be collected once weekly for the first 2 cycles, then monthly thereafter (differential can be omitted if WBC is $\leq 0.5 \times 10^9/L$)

*****Any tumor masses will be measured before and after the treatment to assess their response to treatment.

4.2.1 Patients will be treated according to the following schedule:

- Azacitidine 75 mg/m^2 will be administered subcutaneously (SQ) or intravenously (IV) daily for 7 days per cycle. Cycles should be repeated every 4-8 weeks at the discretion of the treating physician. The next azacitidine course may be started before 4 weeks or after 8 weeks if felt to be in the best interest of the patient and only after discussion with the PI.
- Sorafenib will be administered orally at a dose of 400 mg twice daily every day continuously. Sorafenib will only be held for sorafenib-related toxicity.

Both agents will start on the same day of the first cycle. Sorafenib will be given continuously thereafter unless there is a Sorafenib-related toxicity. It will be re-started as soon as that toxicity has resolved to a Grade 1 or baseline status. The first dose of each course of Azacitidine will constitute the beginning of the next cycle of treatment.

Dose reductions for both agents are allowed but should be discussed with the PI and documentation of the justification recorded in the chart.

One cycle of therapy is defined 7 days of azacitidine and continuous dosing of sorafenib. Patients will receive one cycle of therapy every 4 weeks (with a desired dose schedule of 4 week cycles) and can be delayed up to 56 days. If the treating physician feels that one or both of the drugs must be held for a longer period of time, then it must have PI approval.

Subsequent courses of azacitidine will be given if the ANC is equal or greater than $1.0 \times 10^9/L$ (or lower if the treating physician feels in the best interest of the patient and after discussion with PI) and the platelets are equal to or greater than $30 \times 10^9/L$ (unless transfusion dependent), in the absence of residual leukemia in the bone marrow (for the first 3 cycles of therapy, it is intended that the azacitidine cycles are administered every 4 weeks despite cytopenias and even if full recovery to the above levels has not occurred). If prolonged myelosuppression (more than 60 days) with evidence of a hypocellular marrow (marrow cellularity less than 5% without evidence of leukemia) is observed subsequent courses of azacitidine may be given at a lower dose after discussion with the PI. If the peripheral counts do not recover (ANC $< 1 \times 10^9/L$ (or to baseline value) and/or platelets $< 30 \times 10^9/L$ (unless transfusion dependent) but there is evidence of residual leukemia in the bone marrow, subsequent cycles can be administered earlier than 4 weeks at the

discretion of the treating physician, but not earlier than 3 weeks after the previous cycle.

Sorafenib is supplied as an immediate-release film-coated, round, and salmon color tablet containing 200 mg of the free base, Sorafenib, and the excipient croscarmellose sodium, microcrystalline cellulose, hydroxypropyl methylcellulose, sodium lauryl sulfate, and magnesium stearate. The film-coat consists of hydroxypropyl methylcellulose, polyethylene glycol, titanium dioxide and red iron oxide. The film coating has no effect on the rate of release of the active sorafenib.

Sorafenib will be administered 400 mg twice daily for 28 days/or until next cycle of Azacitidine is administered in each cycle. Drug doses must be separated by intervals of approximately 12 hours (+/-3 hours).

If a dose is missed, the next dose should not be increased to account for missing a dose. The subject should take the next regular dose at the regularly scheduled time. If a dose is vomited, do not take another dose of medication. Wait until the next dose is due. Take the next regular dose and do not increase it to account for missing a dose.

Modifications to the schedule and/or dose of both/either drugs that are thought to be in the best interest of the patient are allowed after discussion with and approval by the PI.

It is recommended that patients receive at least 3 cycles of therapy (as long as they are not clearly progressing and are tolerating it without significant toxicity) before deciding on termination of treatment. Patients will be eligible for efficacy assessment if they have received at least one full cycle of therapy (7 days of azacitidine and 28 days of sorafenib).

4.3 Duration of Therapy:

In the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria applies:

1. Progressive disease
2. Intercurrent illness that prevents further administration of treatment,
3. Patient request or
4. General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

It is planned that up to a total of 24 cycles of therapy will be administered for patients deriving benefit from this regimen. Continuation of therapy for patients completing 24 cycles of therapy may be considered on a case by case basis after discussion with the PI.

A minimum of 1 full course (defined as the administration of azacitidine for 7 days and sorafenib for up to 28 days) will be required for a patient to be considered as having received an adequate trial to evaluate efficacy. All patients receiving at least one dose of any of the two drugs will be considered evaluable for toxicity.

4.4 Concomitant medications

In general, the use of any concomitant medication/therapies deemed necessary for patient supportive care and safety are permitted. Other anticancer agents including systemic chemotherapy, radiation therapy, or biologic response modifiers are not permitted during the study. No other investigational drug is allowed during the study. Patients must be off growth factors for five days in order to declare a neutrophil response. Prophylaxis may be used for the prevention of nausea and vomiting. Patients may be given ondansetron up to 3 times a day or granisetron up to 2 times a day. Ondansetron and granisetron are federally approved drugs and will not be supplied by Bayer/Onyx or Celgene. Patients who suffer from Grade 3 or 4 nausea and/or vomiting, should be withheld from treatment and only restart if recovery occurs when symptoms are controlled to a Grade 1 status. Other antibiotics may be used at the discretion of the investigator include, but are not limited to, metoclopramide, promethazine, cyclizine, and prochlorperazine.

In the event of severe anemia, thrombocytopenia or neutropenia, patients may receive appropriate supportive care (e.g., transfusions, prophylactic antibiotics, antifungals and/or antivirals, hematopoietic growth factors). In the event of high white blood cell (WBC) counts, patients may receive hydroxyurea or up to 2 doses of ara-C prior to start of study medication in order to keep their WBC at an acceptable level. During the trial they may undergo Leukapheresis or receive further doses of hydroxyurea for the same purpose (if necessary).

Concomitant administration of any other therapy specific for MDS, CMML or AML, including any use of systemic retinoids, is prohibited. Concomitant administration of any other anticancer therapy is prohibited. Intrathecal chemotherapy is allowed, when indicated.

Subjects may receive anti-infective prophylaxis including azoles according to institutional practices. Use of recombinant myeloid colony stimulating factors (CSF) is allowed, if patients have febrile neutropenia or documented infections. The use of strong CYP3A4 inducers are not allow.

5.0 Dosing Delays/Dose Modifications

Patients experiencing unacceptable toxicity directly attributable to the study drugs should temporarily stop treatment according to the guidelines in the dose adjustment schema.

Toxicity grading will be according to the NCI CTCAE, v4. To prevent unnecessary morbidity, the following guidelines for dose adjustment for drug-related toxicities are recommended.

Dose Reductions for non-hematologic toxicity possibly related to study drugs should be performed according to the following table:

Toxicity	Grade	Actions
Non-hematological (excludes myalgia/arthralgia responding to treatment, inadequately treated vomiting and diarrhea, or electrolyte abnormalities unless not responding to optimal supplementation)	3 or 4	Hold therapy until recovery to Grade ≤ 1 , then re-start and reduce one dose level unless approved by PI on case to case basis. If toxicity recurs again, hold therapy until recovery to grade ≤ 1 , then re-start and reduce one dose level. Dose reductions below dose level -2 will be considered on an individual basis after discussion with the PI. For grade 4, the recommendation is to discontinue Sorafenib
Non-hematological (excludes myalgia/arthralgia responding to treatment, inadequately treated vomiting and diarrhea, or electrolyte abnormalities unless not responding to optimal supplementation)	Persistent 2-considered clinically significant or upon patient's request	Hold therapy until recovery to Grade ≤ 1 , then re-start and reduce one dose level unless approved by PI on case to case basis. If toxicity recurs again, hold therapy until recovery to grade ≤ 1 , then re-start and reduce one dose level. Dose reductions below dose level -2 will be considered on an individual basis after discussion with the PI.

Patients in whom the toxicity occurs or persists beyond the planned completion of drug administration for the cycle will have the dose reductions implemented in subsequent cycles provided the toxicity has resolved as specified in the table above.

5.1 Myelosuppression:

Patients with leukemias and MDS usually present with abnormal peripheral blood counts at the time therapy is started and myelosuppression is an expected event during the course of therapy for acute leukemias and myelodysplastic syndromes. Thus, no dose adjustments or treatment interruptions for myelosuppression will be planned for the first 4 weeks of therapy. After this time, treatment interruptions and dose adjustments may be considered according to the following guidelines:

Patients with neutropenia or thrombocytopenia as a consequence of the disease, do not require treatment interruptions for myelosuppression. Dose-reductions in these patients should be considered in an individual case after discussion with the PI. The following guidelines can be used for these patients:

Patients with a response and pre-cycle counts of neutrophils $> 1 \times 10^9/L$ and platelets $>30 \times 10^9/L$ who have sustained low counts of neutrophils $<0.5 \times 10^9/L$ or a platelet count $<20 \times 10^9/L$ for more than 2 consecutive weeks in the current cycle, may receive a subsequent course. A reduction of up to 2 dose levels may be considered if the myelosuppression was deemed severe and life threatening by the treating physician, and if it is in the patient's best interest after discussion with the PI.

If there are persistent peripheral blood blasts, or the bone marrow shows $>5\%$ blasts, continue treatment regardless of neutrophil and platelet count and give supportive care as needed. After 3 cycles, there should be clear evidence of benefit (reduction in bone marrow blasts, improving counts with reduction in transfusion requirement or other clinical improvement in the opinion of the treating physician) in order to continue treatment regardless of the counts.

If no marrow evidence of leukemia, may hold therapy with azacytidine until recovery of granulocytes to $\geq 1 \times 10^9/L$ and platelets $\geq 30 \times 10^9/L$, then resume at same or 1 lower dose level according to guidelines mentioned above. In general, in the absence of other toxicity, it is recommended that therapy with sorafenib is not interrupted in a responding patient even in the presence of cytopenias (unless discussed with PI).

5.2 Dose escalation:

Dose escalation of sorafenib to 600 mg twice daily will be permitted provided:

- Patient has not experienced any grade 3 or higher non-hematologic toxicity, and
- Patient has not experienced hematologic grade 4 toxicity believed to be treatment related, and
- This has been discussed and approved by the PI and recorded in the patient's clinical records

Dose reductions/modifications/delays:

Dose reductions for sorafenib-specific non hematologic toxicity during subsequent cycles should be performed according to the table in section 5.3 above. Dose modification suggestions for specific toxicities can be found below.

Dose reduction to 200 mg twice daily, 200 mg once daily, and then 200 mg every other day will be allowed depending on the type and severity of toxicity encountered, provided that criteria for patient withdrawal from study treatment have not been met. The following tables describe the recommended dose modifications for sorafenib-associated toxicities:

Variation in the dosing schedules discussed may be allowed if thought to be in the best interest of the patient and after discussing with the study PI.

Suggested dose levels for each drug (adjustments to the dose of each drug can be done independently of the other):

Dose level	Sorafenib	Dose level	Azacytidine
-2	200 mg po daily	-2	50 mg/m ² SC/IV daily x 3
-1	200 mg po bid	-1	50 mg/m ² SC/IV daily x 5
0	400 mg po bid	0	75 mg/m ² SC/IV daily x 7
+1	600 mg po bid	+1	None

Proposed Dose modification for Sorafenib Associated toxicity

Table 1: Suggested Dose Modifications for Sorafenib for Hand-Foot Skin Reaction

Skin Toxicity Grade	Occurrence	Suggested Dose Modification
Grade 1 Numbness, dysesthesia, paresthesia, tingling, painless swelling, erythema or discomfort of the hands or feet which does not disrupt the patient's normal activities	Any Occurrence	Continue treatment with Sorafenib and consider topical treatment for symptomatic relief.
Grade 2 Painful erythema and swelling of the hands or feet and/or discomfort affecting the patient's normal activities	1 st Occurrence	Continue treatment with Sorafenib and consider topical treatment for symptomatic relief. If no improvement within 7 days see below
	No improvement within 7 days or 2 nd or 3 rd occurrence	Interrupt Sorafenib until toxicity resolves to Grade 0-1. When resuming treatment, decrease by 1 dose level
	4 th occurrence	Discontinue Sorafenib treatment
Grade 3 Moist desquamation, ulceration, blistering or severe pain of the hands or feet, or severe discomfort that causes the patient to be unable to work or perform activities of daily living	1 st or 2 nd occurrence	Interrupt Sorafenib treatment until toxicity resolves to Grade 0-1. When resuming treatment decrease Sorafenib by 1 dose level
	3 rd Occurrence	Discontinue Sorafenib treatment

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.

Table 2: Dose Modifications for Sorafenib-Associated Toxicity¹

Toxicity	Grade 1	Grade 2	Grade 3*	Grade 4*
Non-hematologic	Continue at the same dose level.	Reduce and Continue at the same dose level.	Withhold ^b dose until toxicity is grade ≤ 1 , then resume treatment decreasing by 1 dose level. If patient experiences a second grade 3 toxicity, withhold ^b dose until toxicity is grade ≤ 1 , then reduce dose by an additional dose level	Discontinue protocol therapy
a. Also excludes nausea/vomiting that has not been pre-medicated, and diarrhea b: If no recovery after 60 day interruption, treatment should be discontinued unless subject is deriving clinical benefit c: If more than 2 dose reductions are required, treatment should be discontinued.				
Toxicity	Grade 1	Grade 2	Grade 3*	Grade 4*
Hematologic	Continue at the same dose level.	Continue at the same dose level.	Withhold dose until toxicity is grade ≤ 2 , then resume treatment decreasing by 1 dose level ^b . If patient experiences a second grade 3 toxicity, withhold dose until toxicity is grade ≤ 2 , then reduce dose by an additional dose level	Withhold ^a dose until toxicity is grade ≤ 2 , then reduce dose by 2 dose levels ^b and resume treatment, or discontinue at the discretion of the principal investigator after discussion with study supporter.

a. If no recovery after 28 day delay, treatment should be discontinued

b. If more than 2 dose reductions are required, treatment should be discontinued.

Hypertension:

Hypertension is a known and potentially serious adverse event associated with Sorafenib treatment. Patients will have their blood pressure monitored and recorded weekly during the first cycle of therapy, either at the doctor's office or by using any calibrated electronic device (such as those found at a local drug store or pharmacy). Patients will have a Blood Pressure Diary on which to record the measurements, which will be kept with research chart. If the patient's blood

pressure is sustained at an elevated level at any time (>150/100), they should contact their treating physician.

Blood pressure measurements considered out of the normal range are diastolic pressure > 90 mm Hg and/or systolic pressure > 150 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-induced hypertension is outlined in Table 3. **The choice of anti-hypertensive medication to be used in cases of treatment-induced 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 eCRF.

Table 3 Dose Modifications of Sorafenib for Hypertension

Grade (CTCAE v4.0)	Antihypertensive Therapy	Blood Pressure Monitoring	Sorafenib Dose
Grade 1 Pre-hypertension (systolic BP 120-139 mm Hg or diastolic BP 80-89 mm Hg)	None	Consider increased BP monitoring	No change
Grade 2 (asymptomatic) systolic BP 140-159 mm Hg or diastolic BP 90-99 mm Hg	Begin anti-hypertensive therapy as prescribed by the investigator based on site-specific treatment guidelines as applicable.	Increase frequency and monitor (by health professional) every 2 days until stabilized	No change
Grade 2 recurrent or persistent (> 24 hrs); symptomatic increase by 20 mm Hg(diastolic)/ OR Diastolic BP > 90 mm Hg and systolic > 140 mm Hg if previously WNL OR Grade 3	Add agent(s): as prescribed by the investigator based on site-specific treatment guidelines as applicable	Increase frequency and monitor (by health professional) every 2 days until stabilized; continue qod monitoring to stabilization after dosing restarted.	Hold ^a Sorafenib until symptoms resolve <u>and</u> diastolic BP < 90 mm/Hg. Resume treatment at 1 dose level lower ^b . If diastolic not controlled (< 90) on therapy, reduce another dose level ^c
Grade 4 Life Threatening			Off protocol therapy

- ^a Subjects requiring a delay of > 28 days should go off protocol therapy.
^b May be able to resume full dose later once blood pressure is adequately controlled.
^c Subjects requiring > 2 dose reductions should go off protocol therapy.

CTCAE v4.0 definitions

Grade 1: Prehypertension (systolic BP 120-139 mm Hg or diastolic BP 80-89 mm Hg)
Grade 2: Stage 1 HTN (systolic 140-159 mm Hg or diastolic BP 90-99Hg, medical intervention indicated; recurrent or persistent (>24 hrs) or symptomatic increase by >20 mmHg (diastolic) or to > 140/90if previously WNL; monotherapy indicated.
Grade 3: Stage 2 HTN (systolic BP > = 160 mm Hg or diastolic BP > = 100 mm Hg): medical intervention indicated; requiring more than one drug or more intensive therapy than previously
Grade 4: life threatening (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis)

Patients who develop GI perforation should discontinue therapy and be taken off study.

6.0 Agent Formulation and Procurement

Dose Preparation and Storage of azacitidine (VIDAZA): Azacitidine is commercially available and will not be provided for the study by Celgene. Standard procedures should be used for preparation and administration of azacitidine. The following guidelines are suggested:

VIDAZA is a cytotoxic drug and, as with other potentially toxic compounds, caution should be exercised when handling and preparing VIDAZA suspensions. (See Handling and Disposal.)

If reconstituted VIDAZA comes into contact with the skin, immediately and thoroughly wash with soap and water. If it comes into contact with mucous membranes, flush thoroughly with water.

The VIDAZA vial is single-use and does not contain any preservatives. Unused portions of each vial should be discarded properly. See **Handling and Disposal**. Do not save any unused portions for later administration.

Preparation for Subcutaneous Administration: VIDAZA should be reconstituted aseptically with 4 mL sterile water for injection. The diluent should be injected slowly into the vial. Vigorously shake or roll the vial until a uniform suspension is achieved. The suspension will be cloudy. The resulting suspension will contain azacitidine 25 mg/mL.

Preparation for Immediate Subcutaneous Administration: Doses greater than 4 mL should be divided equally into at least 2 syringes. The product may be held at room temperature for up to 1 hour, but must be administered within 1 hour after reconstitution.

Preparation for Delayed Subcutaneous Administration: The reconstituted product may be kept in the vial or drawn into a syringe. Doses greater than 4 mL should be divided equally into at least 2 syringes. The product must be refrigerated immediately, and may be held under refrigerated conditions (2°C–8°C, 36°F–46°F) for up to 8 hours. After removal from refrigerated conditions, the suspension may be allowed to equilibrate to room temperature for up to 30 minutes prior to administration.

Subcutaneous Administration: To provide a homogeneous suspension, the contents of the syringe must be re-suspended by inverting the syringe 2–3 times and vigorously rolling the syringe between the palms for approximately 30 seconds immediately prior to administration. VIDAZA suspension is administered subcutaneously. Doses greater than 4 mL should be divided equally into 2 syringes and injected into 2 separate sites. Rotate sites for each injection (thigh, abdomen, or upper arm). New injections should be given at least 1 inch from an old site and never into areas where the site is tender, bruised, red, or hard.

Suspension Stability: Azacitidine reconstituted for subcutaneous administration may be stored for up to 1 hour at 25°C (77°F) or for up to 8 hours between 2°C and 8°C (36°F and 46°F).

Preparation for Intravenous Administration: Reconstitute the appropriate number of VIDAZA vials to achieve the desired dose. Reconstitute each vial with 10 mL sterile water for injection. Vigorously shake or roll the vial until all solids are dissolved. The resulting solution will contain azacitidine 10mg/mL. The solution should be clear. Parenteral drug product should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Withdraw the required amount of VIDAZA solution to deliver the desired dose and inject into a 50-100 mL infusion bag of either 0.9% Sodium Chloride Injection or Lactated Ringer's Injection.

Intravenous Solution Incompatibility: VIDAZA is incompatible with 5% Dextrose solutions, Hespan, or solutions that contain bicarbonate. These solutions have the potential to increase the rate of degradation of VIDAZA and should therefore be avoided.

Intravenous Administration: VIDAZA solution is administered intravenously. Administer the total dose over a period of 10-40 minutes. The administration must be completed within 1 hour of reconstitution of the VIDAZA vial.

Solution Stability: VIDAZA reconstituted for intravenous administration may be stored at 25°C (77°F), but administration must be completed within 1 hour of reconstitution.

Storage: Store un-reconstituted vials at 25° C (77° F); excursions permitted to 15°-30° C (59°-86° F) (See USP Controlled Room Temperature). There is no need to protect azacididine from exposure to light.

Handling and Disposal: Procedures for proper handling and disposal of anticancer drugs should be applied.

Sorafenib is supplied as an immediate-release film-coated, round, and salmon color tablet containing 200 mg of the free base, Sorafenib, and the excipient croscarmellose sodium, microcrystalline cellulose, hydroxypropyl methylcellulose, sodium lauryl sulfate, and magnesium stearate. The film-coat consists of hydroxypropyl methylcellulose, polyethylene glycol, titanium dioxide and red iron oxide. The film coating has no effect on the rate of release of the active sorafenib.

Sorafenib 200 mg tablets are supplied in bottles of 120 tablets. Sorafenib is Commercially available.

Taken twice daily without food (at least 1 hour before or 2 hours after a meal)

Storage

Store at 25°C (77°F): excursions permitted to 15° - 30°C (59° - 86°F) (see USP controlled room temperature). Store in a dry place.

7.0 Correlative/Special studies

These studies are not mandatory for every patient and will be done when possible.

Molecular testing for cytogenetics, FLT3 and NPM1 will be performed on all bone marrow samples obtained during the study (unless normal at baseline or thought to not be needed by the treating physician).

Whenever feasible and through the MDACC Moonshot bone marrow procurement protocol, we will attempt to submit all patients' initial, pre-treatment bone marrow specimens as well as any follow-up specimens to the Cancer Genomics Laboratory (directed by Dr. Futreal) for comprehensive genomic evaluation to discern patterns of genomic evolution in responders versus non-responders.

Peripheral blood for correlative studies days (+/- 3 days) on days 0, 2, 7, 21 and 28 of the first cycle (done at MD Anderson, for Dr. Garcia-Manero's laboratory) will be optional. On subsequent courses samples will be obtained on day 0 (pretreatment), and day 7. All these samples can be obtained +/- 3 days. Peripheral blood samples for correlative studies (Plasma inhibitory assay and FLT3 ligand levels done at Johns Hopkins) will also be performed on days 0, 7 and 28 of the first course as well as days 0 and 7 of subsequent courses. Every effort will be made to collect these optional specimens – but any missed time point will not be considered a

deviation. Samples will be sent to: [Mark Levis MD PhD, Professor of Oncology, Johns Hopkins Medical Institutes, Cancer Research Building I, 1650 Orleans Street Room 230, Baltimore, MD 21287.](#)

8.0 Patient evaluation

8.1 Pre-treatment evaluation:

- All pretreatment studies should be obtained within 14 days of entry into the trial (except bone marrow that should be done within 28 days or 14 days if patient has received medication for their disease within that period of time).
- A complete history and physical, documentation of all measurable disease, and performance status should be performed within 48 hours before initiation of study.
 - CBC, platelet count, differential (differential can be omitted if WBC is $\leq 0.5 \times 10^9/L$)
 - Creatinine, total bilirubin, ALT or AST, electrolytes and chemistry, PT, PTT, INR, Pregnancy test (urine or serum) in females, should be performed 48 hours before initiation of study unless 12 months menopausal or surgically sterilized.
 - Bone marrow aspirate during the last 28 days preceding study initiation unless patient has received medication for their disease within that period of time. Cytogenetics and Molecular studies (FLT3 and NPM1) will be obtained prior to therapy (results from prior analysis can be used for this purpose). . Molecular studies (FLT3 and NPM1) performed at baseline only and on patients with unknown status.
 - Pretreatment optional correlative studies (see 8.2.5 below)

8.2 Evaluation during treatment:

- Physical exam at the start of each cycle (± 4 days) for the first 24 cycles, then every 2-3 cycles.
- CBC, platelet count, differential once weekly for the first 2 cycles, then monthly (differential can be omitted if WBC is $\leq 0.5 \times 10^9/L$)
- Creatinine, total bilirubin, ALT or AST, electrolytes and chemistry, weekly for the first 2 cycles, then monthly. PT, PTT, INR if greater than 1.5 at baseline if clinically indicated
- Bone marrow aspiration on Cycle 1 Day 28 (+/- 4 days), every 2-3 cycles for the first two years, and then at the discretion of the treating physician.
- Peripheral blood for correlative studies days (+/- 3 days) on days 0, 2, 7, 21 and 28 of the first course (done at MD Anderson) will be optional. On subsequent courses samples will

be obtained on day 0 (pretreatment), and day 7. All these samples can be obtained +/- 3 days-

9.0 Criteria for response

Criteria for response will be as per the international working group for MDS and AML.

9.1 Response criteria for MDS: Response criteria will be according to the International Working Group (Blood 2006; 108: 419-425). Responders are patients who obtain a CR, CRi, or PR, with or without cytogenetic response, hematologic improvements, and morphologic leukemia-free state. Briefly, criteria are as follows:

9.1.1 Morphologic Complete Response (CR)

- ◆ **Peripheral blood counts:**
 - No circulating blasts
 - Neutrophil count $>1.0 \times 10^9/L$
 - Platelet count $>100 \times 10^9/L$
- ◆ **Bone marrow aspirate and biopsy:**
 - $< 5\%$ blasts
 - No extramedullary leukemia

9.1.2 Partial Response (PR)

- ◆ All CR criteria if abnormal before treatment except:
- ◆ $\geq 50\%$ reduction in bone marrow blast but still $>5\%$

9.1.3 Marrow CR

- ◆ Bone marrow: $\leq 5\%$ myeloblasts and decrease by $\geq 50\%$ over pretreatment
- ◆ Peripheral blood: if HI responses, they will be noted in addition to marrow CR

9.1.4 Hematologic Improvement (HI): Hematologic response must be described by the number of positively affected cell lines.

- ◆ **Erythroid response (E)** (pretreatment Hgb <11 g/dL)
 - Hgb increase by ≥ 1.5 g/dL
- ◆ **Platelet response (P)** (pretreatment platelets $<100 \times 10^9/L$)
 - Absolute increase of $\geq 30 \times 10^9/L$ for patients starting with $> 20 \times 10^9/L$ platelets
 - Increase from $< 20 \times 10^9/L$ to $> 20 \times 10^9/L$ and by at least 100%

- ◆ **Neutrophil response (N)** (pretreatment ANC <1.0 x10⁹/L)
At least 100% increase and an absolute increase > 0.5 x 10⁹/L

9.2 Response criteria for AML: Response criteria will be modified from the International Working Group for AML (JCO 2003; 21: 4642-9). Responders are patients who obtain a CR, CRi, or PR, with or without cytogenetic response, hematologic improvements, and morphologic leukemia-free state. Briefly, criteria are as follows:

9.2.1 Complete remission (CR):

- ◆ **Peripheral blood counts:**
No circulating blasts
Neutrophil count ≥1.0 x10⁹/L
Platelet count ≥100 x10⁹/L
- ◆ **Bone marrow aspirate and biopsy:**
< 5% blasts
No Auer rods
No extramedullary leukemia

9.2.2 Complete remission with incomplete blood count recovery (CRi):

- ◆ **Peripheral blood counts:**
No circulating blasts
Neutrophil count <1.0 x10⁹/L, or
Platelet count <100 x10⁹/L
- ◆ **Bone marrow aspirate and biopsy:**
< 5% blasts
No Auer rods
No extramedullary leukemia

9.2.3 Partial remission:

All CR criteria if abnormal before treatment except:
≥50 % reduction in bone marrow blast but still >5%

- ◆ **Morphologic leukemia-free state:**
Bone marrow: ≤5% myeloblasts

9.2.4 Hematologic Improvement (HI): Hematologic response must be described by the number of positively affected cell lines.

- ◆ **Erythroid response (E)** (pretreatment Hgb <11 g/dL)
Hgb increase by ≥1.5 g/dL

- ◆ **Platelet response (P)** (pretreatment platelets $<100 \times 10^9/L$)
 - Absolute increase of $\geq 30 \times 10^9/L$ for patients starting with $> 20 \times 10^9/L$ platelets
 - Increase from $< 20 \times 10^9/L$ to $> 20 \times 10^9/L$ and by at least 100%
- ◆ **Neutrophil response (N)** (pretreatment ANC $<1.0 \times 10^9/L$)
 - At least 100% increase and an absolute increase $> 0.5 \times 10^9/L$

10.0 Criteria for Removal from Study

- Progressive disease
- Intercurrent illness that prevents further administration of treatment,
- Patient request,
- Pregnancy or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

11.0 Background Drug Information

11.1 Sorafenib

Chemical Name:

4-{4-[3-(4-chloro-3-trifluoromethyl-phenyl) ureido]-phenoxy}-pyridine-2 carboxylic acid methanamide-4-methylbenzenesulfonate.

Other Names:

BAY 54-9085 is the tosylate salt of SORAFENIB

Classification:

Kinase inhibitor (Raf, VEGF-R, and PDGF-R)

Mechanism of Action:

The ras/raf signaling pathway is an important mediator of responses to growth signals and angiogenic factors. This pathway is often aberrantly activated in human tumors due to presence of activated ras, mutant b-raf, or over expression of growth factor receptors.

SORAFENIB is a potent inhibitor of c-raf, and wild-type and mutant b-raf in vitro. Additionally, further characterization of SORAFENIB revealed that this agent inhibits several receptor tyrosine kinases (RTKs) that are involved in tumor progression (VEGF-R, PDGF-R, Flt3, and c-KIT) and p38 α , a member of the MAPK family.

Molecular Formula:

$C_{12}H_{16}ClF_3N_4O_3 \cdot X \cdot C_7H_8O_3S$

M.W.:

SORAFENIB: 637 Daltons; SORAFENIB (free base): 465 Daltons

Approximate Solubility:

0.19 mg/100 mL in 0.1 N HCl, 453 mg/100 mL in Ethanol, and 2971 mg/100 mL in PEG 400.

How Supplied:

SORAFENIB is supplied as an immediate-release film-coated, round, and salmon color tablet containing 200 mg of the free base, SORAFENIB, and the excipients croscarmellose sodium, microcrystalline cellulose, hydroxypropylmethylcellulose, sodium lauryl sulfate, and magnesium stearate. The film-coat consists of hydroxypropylmethyl cellulose, polyethylene glycol, titanium dioxide and red iron oxide. The film coating has no effect on the rate of release of the active SORAFENIB .

SORAFENIB 200 mg tablets are supplied in bottles of 120 tablets.

Storage:

Store at controlled room temperature (15°C – 25°C). Storage conditions should not exceed 25°C.

Stability:

Stability studies with the 200 mg dosage form are ongoing. The current shelf life is 24 months when stored at controlled room temperature.

Route(s) of Administration:

Orally

Reported Adverse Events and Potential Risks:

Body as a whole:

fatigue, flu-like syndromes, fever, arthralgia

Gastrointestinal:

diarrhea, pancreatitis, elevated amylase/lipase, abdominal pain/cramping, nausea, flatulence, dyspepsia

Hepatic:

increased bilirubin, ALT, AST, GGT, LDH, and alkaline phosphatase

Metabolic and Nutritional:

anorexia

Skin:

hand-foot syndrome, characterized by palmar and plantar erythema; rash/desquamation, hypersensitivity reactions, dry skin, alopecia, nail changes, vitiligo

The following adverse events have been reported on trials but with the relationship to SORAFENIB still undetermined:

arthritis, brain stem stroke, dyspnea, hypertension, increase PT and PTT, and weight loss.

Method of Administration:

Patients will be instructed to take SORAFENIB on an empty stomach (1 hour before or 2 hours after eating).

Potential Drug Interactions:

SORAFENIB is metabolized by the P450 CYP3A enzyme and has been shown in preclinical studies to inhibit multiple CYP isoforms. Therefore, it is possible that SORAFENIB may interact with drugs that are metabolized by the P450 CYP isoenzymes or with drugs that inhibit CYP 3A. Close monitoring is recommended for patients taking agents with narrow therapeutic indices and metabolized by the liver, such as warfarin, phenytoin, quinidine, carbamazepine, phenobarbital, cyclosporine, and digoxin. Additionally, SORAFENIB is 97% to 99% protein bound; however, no drug interactions have been reported in studies, thus far.

Availability

SORAFENIB is commercially available.

Consult the package insert on www.nexavar.com for additional information

11.2 Azacitidine

Chemical Name:

4-amino-1-beta-D-ribofuranosyl-1,3,5-triazin-2(1H)-one

Other Names:

5-azacytidine, azacytidine, 5-AC, 5-AZC

Classification:

DNA methylation inhibitor

Mechanism of Action:

Azacitidine is a pyrimidine nucleoside analog of cytidine. Azacitidine is believed to exert its antineoplastic effects by causing hypomethylation of DNA and direct cytotoxicity on abnormal hematopoietic cells in the bone marrow. Hypomethylation may restore normal function to genes that are critical for differentiation and proliferation.

Molecular Formula:

C₈H₁₂N₄O₅

M.W.:

Azacitidine : 244 Daltons

How Supplied:

Azacitidine is supplied in a sterile form for reconstitution as a suspension for subcutaneous infection or reconstitution as a solution for further dilution for intravenous infusion. Vials of azacitidine contain 100 mg of azacitidine and 100 mg of mannitol as a sterile lyophilized powder.

Storage:

Store un-reconstituted vials at 25° C (77° F); excursions permitted to 15°-30° C (59°-86° F) (See USP Controlled Room Temperature). There is no need to protect azacitidine from exposure to light.

Stability:

Azacitidine reconstituted for subcutaneous administration may be stored for up to 1 hour at 25°C (77°F) or for up to 8 hours between 2°C and 8°C (36°F and 46°F). Azacitidine reconstituted for intravenous administration may be stored at 25°C (77°F), but administration must be completed within 1 hour of reconstitution.

Route(s) of Administration:

Subcutaneous or intravenous

Reported Adverse Events and Potential Risks:

Body as a whole:

weakness, rigors, fever, arthralgia, myalgia,

Gastrointestinal:

diarrhea, constipation, abdominal pain/cramping, nausea, vomiting

Hematologic:

Anemia, thrombocytopenia, neutropenia

Metabolism and Nutrition:

hypokalemia, anorexia

Renal:

Elevated serum creatinine, renal failure, renal tubular acidosis

Skin:

injection site erythema, petechiae, ecchymosis

Other:

hepatic coma, dizziness, headache, shortness of breath

Method of Administration:

See section 6.1 for complete details.

Potential Drug Interactions:

No formal assessments of drug-drug interactions between azacitidine and other agents have been conducted.

Availability

Azacitidine is commercially available.

Consult the package insert on www.vidaza.com for additional information

12.0 Adverse Event Reporting

Refer to **Appendix C** for Leukemia-Specific Adverse Event Recording and Reporting Guidelines. Only unexpected AEs will be recorded in the Case Report Form (CRF).

12.1 Pregnancies:

If a female subject or partner of a male subject becomes pregnant during the study dosing period or within 3 months from the discontinuation of dosing, the investigator should report the information to the MDACC IRB as if it is an SAE. The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated fertility date, pregnancy result and neonatal data etc., should be included in this information. The investigator will follow the medical status of the mother, as well as the fetus, as if the pregnancy is an SAE.

When the outcome of the pregnancy falls under the criteria for SAEs [spontaneous abortion, induced abortion, stillbirth, death of newborn, congenital anomaly (including anomaly in a miscarried fetus)], the investigator should respond in accordance with the report procedure for SAEs.

- "Spontaneous abortion" includes abortion and missed abortion.

- Death of an infant within 1 month after birth should be reported as an SAE regardless of its relationship with the study drug.

- If an infant dies more than 1 month after the birth, it should be reported if a relationship between the death and intrauterine exposure to the study drug is judged as "possible" by the investigator.

- In the case of a delivery of a living newborn, the "normality" of the infant is evaluated at the birth.

- "Normality" of the miscarried fetus is evaluated by visual examination unless test results which indicate a congenital anomaly are obtained prior to miscarriage.

13.0 Statistical Considerations

This is a single arm study using the dosage level recommended from a previously conducted and published phase I/II study in patients with relapsed AML. The sample size is 52. The trial will be continuously monitored for efficacy and toxicity (non-hematological \geq grade 3). The method of Thall, Simon, and Estey will be used to perform interim efficacy and safety monitoring.¹⁴

13.1 Efficacy

The primary endpoint is the overall response (CR+CRi) after three cycles of treatment. The historical data suggested the overall response rate is 45%. With the assumption that the improved overall response rate to be 65%, it is estimated that a total of 52 evaluable patients will yield 83% power at a significance level of 5% based on chi-square test. The trial will be continuously monitored. The study will be stopped early if the data suggest that:

$$\Pr(\pi > 0.45 | \text{data}) < 0.05$$

Here π is the overall response (OR) rate. That is, if at any time during the study we determine that there is a less than 5% chance that the average OR rate is greater than 45%, we will terminate the study. The OR rate is assumed to follow a non-informative prior of Beta (0.9, 1.1).

13.2 Monitoring Of non-hematological \geq grade 3 toxicities

With the concern of treatment related toxicity, the non-hematological toxicity (\geq grade 3) will also be closely monitored during the study.

Denote the probability of toxicity by P_E . We assume $P_E \sim \text{beta}(0.6, 1.4)$. Our stopping rule is given by the following probability statement:

$$\Pr(P_E > 0.3 | \text{data}) > 0.95 .$$

That is, we will stop the trial if, at any time during the study, we determine that there is more than 95% chance that the toxicity is more than 30%.

Patients will be monitored by a cohort size of 4 according to the following stopping boundaries for overall response and toxicity. The design software Multic Lean Desktop (version 2.1) developed by the Department of Biostatistics at M. D. Anderson Cancer Center (MDACC) was used to generate the futility/toxicity stopping boundaries and the OC table.

Table 13.1. Stopping boundaries for overall response and toxicity

Number of patients evaluated	Stop the trial if there are this many responses	Stop the trial if there are this many toxicities
4	0	4
8	0-1	5-8
12	0-2	7-12
16	0-3	9-16
20	0-5	10-20

24	0-6	12-24
28	0-8	13-28
32	0-9	15-32
36	0-11	16-36
40	0-12	18-40
44	0-14	19-44
48	0-15	20-48

Table 13.2. Operating characteristics of futility and safety monitoring

True Toxicity Rate	True overall response Rate	Prob (stop the trial early)	Average sample size
0.2	0.25	0.94	17.2
	0.35	0.59	31.9
	0.45	0.21	43.8
	0.55	0.07	48.8
	0.65	0.03	50.6
0.3	0.25	0.95	16.4
	0.35	0.64	29.7
	0.45	0.32	40.4
	0.55	0.2	44.9
	0.65	0.16	46.5
0.4	0.25	0.97	14.0
	0.35	0.82	23.1
	0.45	0.66	30.1
	0.55	0.61	33.2
	0.65	0.59	34.3
0.5	0.25	1.0	10.9
	0.35	0.97	15.1
	0.45	0.95	18.1
	0.55	0.94	19.5
	0.65	0.93	20

13.3 Analysis method

Data analysis will be performed using SAS or S-plus, as appropriate. All patients who received at least 1 dose of the combined agents will be included in the intent-to-treat analysis for efficacy. Demographic and disease characteristics of the patients at registration will be summarized using descriptive statistics such as mean, standard deviation (SD), median and range. Overall response rates will be presented with 95% confidence intervals. The association between response and patient and disease characteristics will be examined by two-sample t-test or Chi-square test.

The data from all patients who received the combined therapy during the study will be included for safety analysis. Subjects who entered the study and did not take any of the study drugs and had this confirmed will not be evaluated for safety. The severity of the toxicities will be graded according to the NCI CTCAE v4.0 whenever possible. We will follow standard reporting guidelines for adverse events. Safety data will be summarized by category, severity and frequency. The proportion of patients with AEs will be estimated, along with the Bayesian 95% credible interval. These descriptive summaries will be provided for all patients for each safety parameter by cycle, grade, and relationship to treatment.

This study will be conducted as described in this protocol, except for an emergency situation in which the protection, safety, and wellbeing of the patient requires immediate intervention, based on the judgment of the investigator or his/her designee. In the event of a significant deviation from the protocol, the investigator will notify the MDACC surveillance committee following the institutional guidelines.

14.0 Protocol Administration

14.1 Protocol amendments

Changes to the protocol will be made only when protocol amendments have been signed by the principal investigator, and by the ethical committee of the study center.

14.2 Archival of data

All patient data (including source data) generated in connection with this study will be kept in the archives of the MDACC for at least 15 years after the study has been completed. All data will be available for inspection by company representatives of the Medical Department and by regulatory authorities.

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