Protocol ARO-010

Phase I-II Study of Crenolanib Combined with Standard Salvage Chemotherapy and Crenolanib Combined with 5-Azacitidine in Acute Myeloid Leukemia Patients with FLT3 Activating Mutations

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PHASE I-II STUDY OF CRENOLANIB COMBINED WITH STANDARD SALVAGE CHEMOTHERAPY AND CRENOLANIB COMBINED WITH 5-AZACITIDINE IN ACUTE MYELOID LEUKEMIA PATIENTS WITH FLT3 ACTIVATING MUTATIONS

Core Protocol Information

Short Title	ARO-010: Crenolanib in AML
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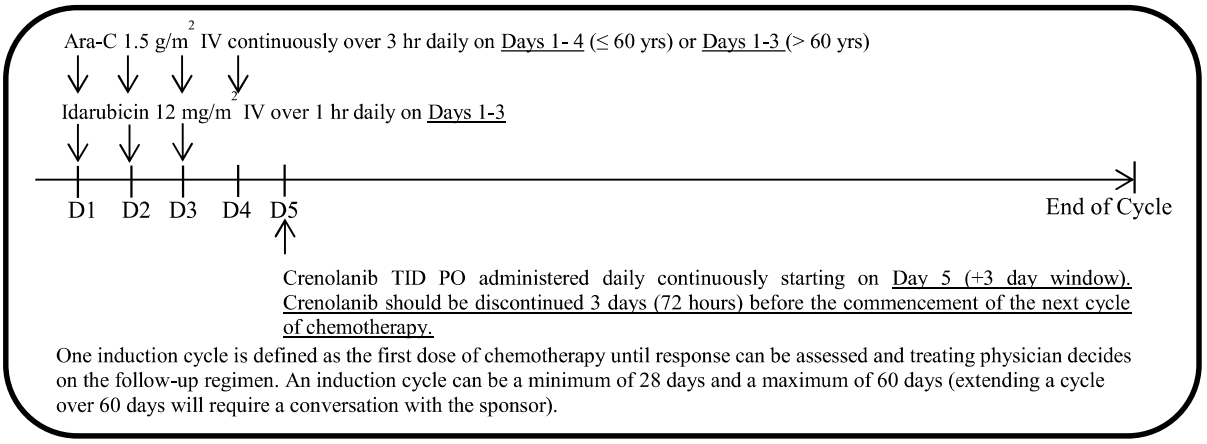
STUDY SCHEME

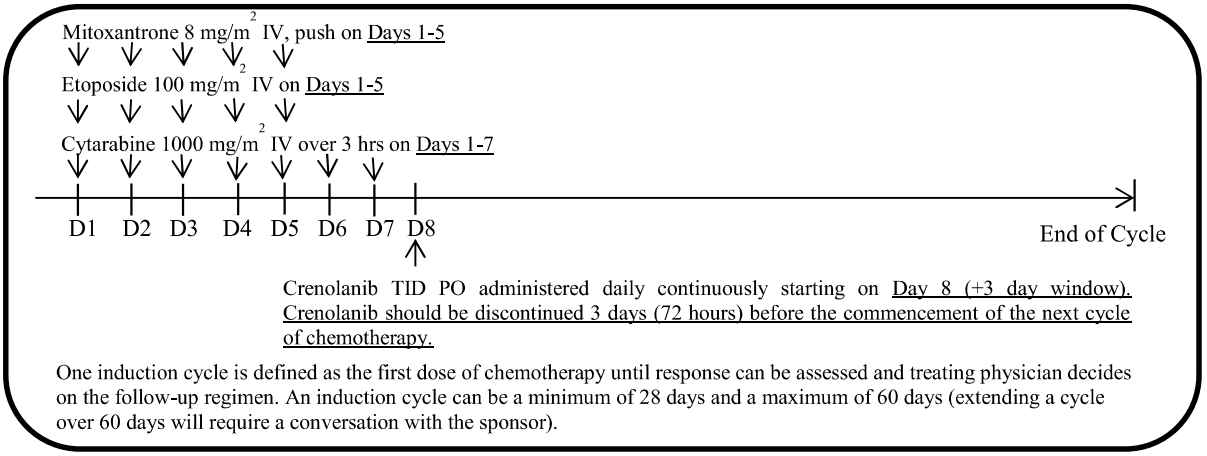
Arm 1: INDUCTION (Up to 2 cycles)

Idarubicin/cytarabine



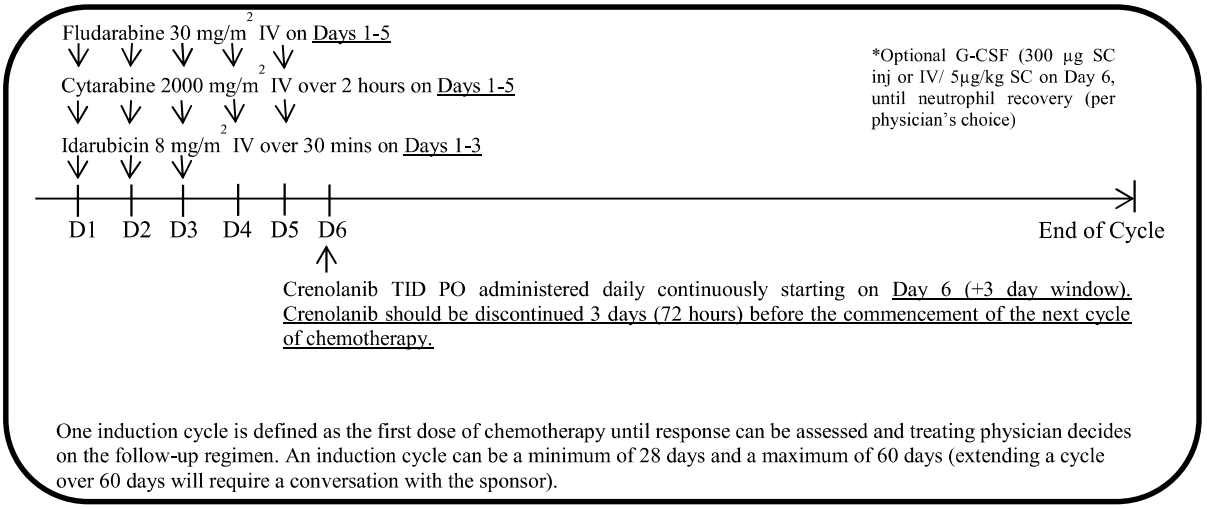
One induction cycle is defined as the first dose of chemotherapy until response can be assessed and treating physician decides on the follow-up regimen. An induction cycle can be a minimum of 28 days and a maximum of 60 days (extending a cycle over 60 days will require a conversation with the sponsor).

MEC



One induction cycle is defined as the first dose of chemotherapy until response can be assessed and treating physician decides on the follow-up regimen. An induction cycle can be a minimum of 28 days and a maximum of 60 days (extending a cycle over 60 days will require a conversation with the sponsor).

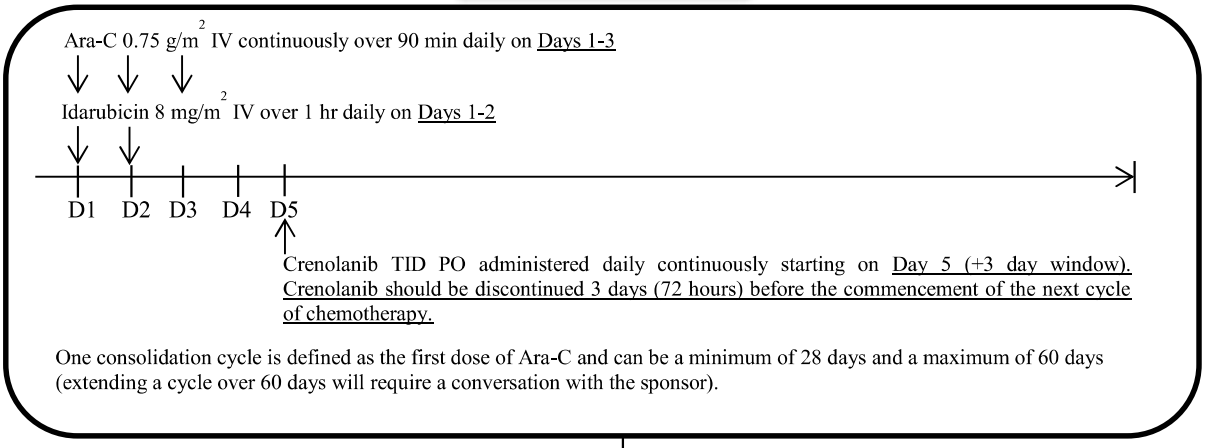
FLAG-Ida



One induction cycle is defined as the first dose of chemotherapy until response can be assessed and treating physician decides on the follow-up regimen. An induction cycle can be a minimum of 28 days and a maximum of 60 days (extending a cycle over 60 days will require a conversation with the sponsor).

Patients in CR or CRi/CRp may receive consolidation or maintenance
(physician's discretion)

CONSOLIDATION (Up to 6 cycles)



Patients in CR or CRi/CRp may receive maintenance
(physician's discretion)

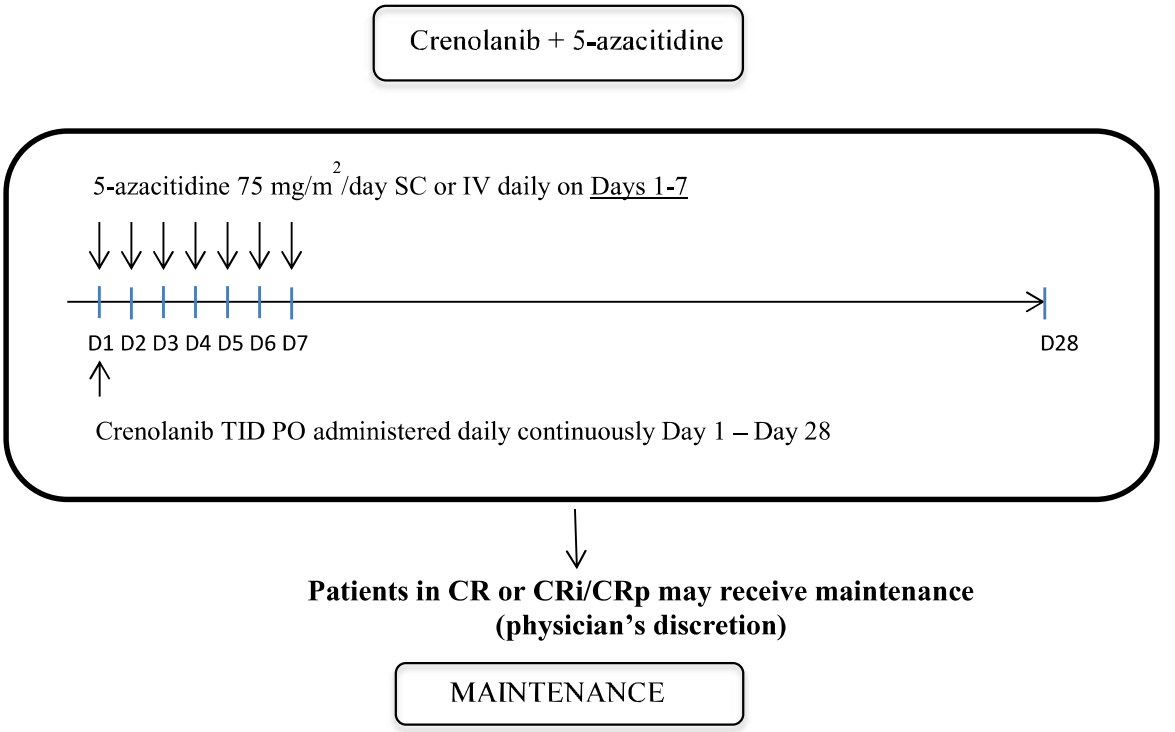
MAINTENANCE

*Crenolanib administered daily continuously for up to 365 days (1 cycle = 28 days)

*Crenolanib will be given orally in 3 dose levels:

Dose Level	Crenolanib
0	60 mg BID
1 (Starting dose)	60 mg TID
2	80 mg TID
3	100 mg TID

Arm 2:



*Crenolanib will be given orally in 3 dose levels:

Dose Level	Crenolanib
0	60 mg BID
1 (Starting dose)	60 mg TID
2	80 mg TID
3	100 mg TID

SYNOPSIS

Name of Investigational Product	Crenolanib besylate (CP-868,596-26)
Title of Study	Phase I-II study of Crenolanib Combined with Standard Salvage Chemotherapy and Crenolanib Combined with 5-Azacitidine in Patients with Acute Myeloid Leukemia with Activating FLT3 Mutations
Number of Planned Patients	Phase I: Arm 1 (18), Arm 2 (18) Phase II: Arm 1 (26), Arm 2 (26)
Length of Study	2 years
Primary Objectives	Phase I: a. To determine the dose limiting toxicity and maximal tolerated dose of the combination of crenolanib with standard salvage chemotherapy (arm 1) or with 5-azacytidine (arm 2) in patients with refractory/relapsed AML or high-risk MDS with FLT3 mutations. b. To determine the safety of the combination of crenolanib with standard salvage chemotherapy (arm 1) or with 5-azacytidine (arm 2) in patients with refractory/relapsed AML or high-risk MDS with FLT3 mutations Phase II: To determine the response rate (including the rates of complete remission (CR), CR with incomplete blood count recovery (CRi), and partial remission (PR)) with the combination of crenolanib with standard salvage chemotherapy (arm 1) or with 5-azacytidine (arm 2) in patients with AML or high-risk MDS with activating FLT3 mutations.
Secondary Objectives	Response rate, Duration of response, PFS, OS, pharmacokinetics and pharmacodynamics of crenolanib with chemotherapy
Study Design	Open label, dose escalation, two-arm, Phase I-II trialInvestigator to determine treatment assignment Arm 1: crenolanib with standard salvage chemotherapy Arm 2: crenolanib with 5-azacitidine For each arm: Phase I with dose-limiting toxicity (DLT) determination using the Rolling-6 design. Cohort 1 will start with crenolanib at 60 mg TID. Dose escalations to 80 mg TID and 100 mg TID are planned for subsequent cohorts dependent on DLTs. Phase II total of 26 patients in each arm treated at established phase I dose. Enrollment to be simultaneous to each arm.
Eligibility Criteria	**Inclusion Criteria** 1. Confirmed diagnosis of refractory/relapsed AML or high-risk MDS (IPSS intermediate-2 risk and high risk, see Appendix VIII) that is refractory or has relapsed after prior therapy. Patients with secondary leukemia (i.e., evolving from MDS or MPN, or secondary to therapy for other malignancies) are eligible

- Arm 1: Subjects must have received at least one prior therapy and a maximum of three prior therapies
- Arm 2: Subjects must have received at least one prior therapy and a maximum of three prior therapies. No prior treatment with 5-Azacitidine is allowed in this arm.

2. Presence of FLT3 ITD and/or other FLT3 activating mutations
3. Extramedullary disease is allowed except for active CNS disease
4. Prior use of hydroxyurea or isolated doses of cytarabine for palliation (i.e., control of WBC) are allowed but should be discontinued at least 24 hrs prior to study start. Other agents used strictly with palliative intent might be allowed during this period after discussing with principal investigator
5. Age ≥18 years
6. ECOG PS 0-2
7. Adequate liver function tests will be required within 72 hours of enrollment. Adequate liver function will be defined as:
   - Normal total serum bilirubin
   - ALT and AST ≤ 2.0 x ULN
8. Adequate renal function, defined as serum creatinine ≤1.5x ULN
9. Negative pregnancy test, within 72 hours of enrollment, for women of childbearing potential

   "Woman of childbearing potential" is defined as any woman who has not undergone a hysterectomy and who has had menses at any time in the preceding 24 consecutive months

10. Able and willing to provide written informed consent

Exclusion Criteria

1. Absence of FLT-3 activating mutations at time of study screening
2. < 5% blasts in blood or marrow at screening, except if measurable extramedullary AML is confirmed
3. Subjects with Acute promyelocytic leukemia (APL)
4. Known clinically active CNS leukemia
5. Clinically active or unstable graft-versus-host disease requiring treatment which precludes administration of chemotherapy as defined in this protocol
6. Therapy with curative intent for relapsed AML or high-risk MDS prior to the first dose of crenolanib as follows: within 14 days of study enrollment for classical cytotoxic agents and for 5x the half-life for FLT3 targeting TKI, hypomethylating agents or MEK inhibitors
7. Patient with pre-existing liver diseases (i.e. cirrhosis, chronic hepatitis B or C, nonalcoholic steatohepatitis, sclerosing cholangitis)
8. Patients with known HIV infection
9. "Currently active" second malignancy (other than non-melanoma skin cancer, carcinoma in situ of the cervix or prostatic intraepithelial neoplasia within 1 year). Subjects are not considered to have a "currently active" malignancy if they have completed therapy and are considered by their physician to be at less than 30% risk of relapse within 1 year
10. Subject with concurrent severe and/or uncontrolled medical conditions that in the opinion of the investigator may impair the participation in the study or the evaluation of safety and/or efficacy.

	11. Subject with uncontrolled cardiac disease including congestive heart failure class III or IV by the NYHA, unstable angina (anginal symptoms at rest) or new onset angina (began within the last 3 months) or myocardial infarction within the past 6 months 12. Pregnant or breastfeeding women 13. Inability to give an informed consent
Treatment	**Arm 1:** Induction (up to 2 cycles) Physician's choice standard salvage chemotherapy regimen: *Ida/Cytarabine* Idarubicin 12 mg/m^2 IV over 1 hr daily on Days 1-3 Cytarabine 1.5 g/m^2 IV continuously over 3 hr on Days 1-4 (≤ 60 yrs) or Days 1-3 (> 60 yrs) Crenolanib PO starting on Day 5 (+3 day window) continuously *MEC + crenolanib* Mitoxantrone 8 mg/m² IV, push on Days 1-5 Etoposide 100 mg/m^2 IV on Days 1-5 Cytarabine 1000 mg/m² IV, over 3 hours on Days 1-7 Crenolanib 100 mg TID starting on Day 8 (+3 day window) continuously *FLAG-Ida + crenolanib* Fludarabine 30 mg/m^2 IV on Days 1-5 Cytarabine 2 g/m2 IV over 2 hrs on Days 1-5 G-CSF 300 ug s.c. inj or IV/5ug/kg SC on Day 6, until neutrophil recovery *(G-CSF optional, per physician's choice) Idarubicin 8 mg/m2 IV over 30 min on Days 1-3 Crenolanib 100 mg TID starting on Day 6 (+3 day window) continuously Consolidation (up to 6 cycles) Idarubicin 8 mg/m^2 IV over 1 hr daily on Days 1-2 Cytarabine 0.75 g/m^2 IV continuously over 90 min on Days 1-3 Crenolanib PO starting on Day 5 (+3 day window) continuously **Arm 2:** 5-azacitidine 75 mg/m^2/day SC or IV daily on Days 1-7 Crenolanib PO starting on Days 1-28 continuously Both arms 1 and 2 may receive maintenance crenolanib for a maximum of 365 days after completion of cytotoxic therapy if remaining in remission.
Planned Duration of Treatment	Evaluable patients must have been on study for a minimum of 28 days.
Criteria for Evaluation	International Working Group for AML (Cheson et al. JCO 2003) International Working Group for MDS (Cheson et al, Blood 2000)
Statistical Method	Phase I: Determination of MTD of crenolanib with standard salvage chemotherapy or with 5-Azacytidine Phase II: Determination of safety and response rate of crenolanib with standard salvage chemotherapy or with 5-Azacytidine

1. OBJECTIVES

1.1. Primary Objectives

1. For phase 1 portion of the study:
    a. To determine the dose limiting toxicity and maximal tolerated dose of the combination of crenolanib with standard salvage chemotherapy (arm 1) or with 5-azacytidine (arm 2) in patients with refractory/relapsed AML or high-risk MDS with FLT3 mutations.
    b. To determine the safety of the combination of crenolanib with standard salvage chemotherapy (arm 1) or with 5-azacytidine (arm 2) in patients with refractory/relapsed AML or high-risk MDS with FLT3 mutations.
2. For the phase 2 portion of the study:
    a. To determine the response rate (including the rates of complete remission (CR), CR with incomplete blood count recovery (CRi), and partial remission (PR)) with the combination of crenolanib with standard salvage chemotherapy (arm 1) or with 5-azacytidine (arm 2) in patients with AML or high-risk MDS with activating FLT3 mutations.

1.2. Secondary Objectives

1. For phase 1 portion of the study:
    a. To determine response rates of the combinations of crenolanib with standard salvage chemotherapy or with 5-azacitidine among patients with refractory/relapsed AML or high-risk MDS with activating FLT3 mutations
    b. To determine the duration of response in patients with refractory/relapsed AML or high-risk MDS with activating FLT3 mutations treated with crenolanib + standard salvage chemotherapy (arm 1) or crenolanib + 5-azacytidine (arm 2).
    c. To determine the progression free survival and overall survival of patients with refractory/relapsed AML or high-risk MDS with activating FLT3 mutations treated with crenolanib + standard salvage chemotherapy (arm 1) or crenolanib + 5-azacytidine (arm 2)
    d. To characterize the pharmacokinetics of crenolanib when combined with standard salvage chemotherapy or with 5-azacitidine in adult patients with refractory/relapsed AML patients with AML or high-risk MDS, and relate crenolanib exposure to outcome (e.g., toxicity and/or FLT3 inhibition).
    e. To analyze phospho-FLT3 and other pharmacodynamic markers from serially collected circulating leukemic blasts and/or marrow blast samples after treatment with crenolanib-based combinations and correlate with response to therapy.
2. For the phase 2 portion of the study:
    a. To determine safety of the combinations of crenolanib with standard salvage chemotherapy or with 5-azacitidine among patients with refractory/relapsed AML or high-risk MDS with activating FLT3 mutations.
    b. To determine the duration of response in patients with refractory/relapsed AML or high-risk MDS with activating FLT3 mutations treated with crenolanib + standard salvage chemotherapy (arm 1) or crenolanib with 5-azacytidine (arm 2).
    c. To determine the progression free survival and overall survival in patients with refractory/relapsed AML or high-risk MDS with activating FLT3 mutations

treated with crenolanib + standard salvage chemotherapy (arm 1) or crenolanib with 5-azacytidine (arm 2).

d. To characterize the pharmacokinetics of crenolanib when combined with standard salvage chemotherapy or with 5-azacitidine in adult patients with refractory/relapsed AML and relate crenolanib exposure to outcome (e.g., toxicity and/or FLT3 inhibition).
e. To analyze phospho-FLT3 and other pharmacodynamic markers from serially collected circulating leukemic blasts and/or marrow blast samples after treatment with crenolanib-based combinations and correlate with response to therapy

2. BACKGROUND

2.1. Acute Myeloid Leukemia

Acute myeloid leukemia (AML), characterized by malignant granulocytes or monocytes, involves accumulation of leukemic blasts and blockade of normal bone marrow production. This leads to thrombocytopenia, anemia, and neutropenia. High levels of FLT3 expression have been detected in AML blasts (70%-100%) [1,2].

With standard AML regimens, including anthracyclines plus cytarabine, the complete remission (CR) rates for AML are 60% to 70%. Prognosis in AML involves a variety of components including karyotype, patient age, performance status, and organ function. In general, t(8;21), inversion 16 or t(15;17) are associated with CR rates of 90% and cure rates of 50% to 80%. Younger patients ($\leq$ 60 years), who have diploid karyotypes, can achieve CR rates of 70% to 80%. Conversely, older patients and those with adverse karyotypes have lower CR rates of only 35% to 50%. Elderly patients with AML are known to have a poor prognosis, which is often due to chemotherapy intolerance along with higher rates of poor risk cytogenetic abnormalities and multidrug resistance (MDR) phenotype. At MD Anderson, for patients 65 years or older, the CR rate was poor. Among 245 treated patients in this age group during this period, CR was achieved in only 118 (48%); induction-related mortality, within 7 weeks from chemotherapy initiation, occurred in 54 (22%). Only 38 patients (18%) were alive in CR after 1 year, and 16 (8%) at 2 years.

2.2. FLT3 Targeted Therapy in Acute Myeloid Leukemia

FMS-like tyrosine kinase 3 (FLT3) is a member of the class III receptor tyrosine kinase family that has important roles in hematopoietic stem/progenitor cell survival and proliferation [3,4]. Mutations in the FLT3 gene are one of the most frequent somatic alterations in AML, occurring in approximately one third of all patients [5]. FLT3 internal tandem duplication (ITD) and tyrosine kinase domain (TKD) mutations are the two major types of FLT3 mutations that result in ligand-independent activation that leads to hematopoietic transformation [5, 6].

FLT3ITD mutations are detected in 20%-25% of AML patients and TKD mutations, arising in the activation loop of the TKI domain II [7, 8], are present in approximately 8% of AML patients. Approximately 2% of patients have both mutations present [9, 10]. The presence of a FLT3-ITD is a poor prognostic factor. AML with FLT3-ITD has higher rates of relapse and inferior rates of relapse free survival, event free survival, and overall survival compared to AML with wild-type FLT3 [7, 10, 11].

Because activation of signal pathways via receptor tyrosine kinases plays a central role in the pathogenesis of AML, inhibition using small molecules represents an attractive therapeutic concept. A number of FLT3 inhibitors with *in vitro* and *in vivo* activity against the FLT3 ITD mutation are in clinical development [12, 13, 14, 15, 16, 17]. Unfortunately, the majority of AML patients who initially respond to these FLT3 TKIs ultimately relapse. In approximately 5-10% of relapsed AML patients, the drug resistance is due to development of the D835 FLT3 TKD secondary mutation. So far none of the FLT3 inhibitors currently in development have inhibited the FLT3 TKD mutation D835.

Crenolanib is a second generation TKI with high potency and selectivity against FLT3. Crenolanib also shows evidence of activity against acquired D835 TKD mutations known to be a mechanism of resistance to other TKIs [18, 19]. Since FLT3/D835 mutations can also be present at initial diagnosis of AML in the presence or absence of ITD mutations, a FLT3 TKI such as crenolanib with activity against FLT3/D835 point mutations is of great interest to evaluate in the AML setting.

2.3. Crenolanib Besylate (CP-868, 596-26)

2.3.1 Crenolanib inhibits wild-type FLT3 and its constitutively active mutations

Crenolanib besylate (also known as CP-868,596-26) is an orally bioavailable class III RTK inhibitor that potently targets FLT3. Crenolanib inhibits wild-type FLT3, and its constitutively active mutations at clinically achievable concentrations (Table 2.1) [20, 21].

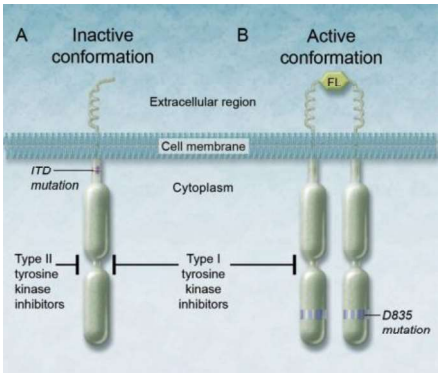
Crenolanib has heightened binding affinity against the FLT3-ITD mutation (the most frequent FLT3 aberration in AML) and TKD point mutations FLT3 (D835H), FLT3 (D835Y) and FLT3 (D835V). Crenolanib binds to FLT3-ITD and FLT3-TKD D835H with Kd values of 0.43 and 0.4 nM, respectively. Similarly, crenolanib also binds to FLT3-TKD D835Y with a Kd of 0.18 nM. A saturation mutagenesis screen of FLT3 ITD showed that crenolanib is a "pan-FLT3 inhibitor" that has the ability to successfully suppress all resistance-conferring TKD mutants. Crenolanib inhibitory activity has been verified in human AML cell lines [20].

Table 2.1 Dissociation constants of crenolanib with constitutively active FLT3 mutations

Gene Symbol	Crenolanib K_d (nM)
FLT3(ITD)	0.43
FLT3(D835H)	0.4
FLT3(D835Y)	0.18
FLT3 (D835V)	0.048

Crenolanib is a type I tyrosine kinase inhibitor that binds to both the active and inactive conformation of FLT3 (Figure 2.1) [22].

Figure 2.1 Schematic of inactive and active FLT3 showing Type I and Type II TKI binding



Blood 2013

2.3.2 Crenolanib has reduced activity against KIT

Crenolanib has been found to be approximately 100-fold more selective for FLT3 than for KIT and is therefore highly selective toward FLT3 relative to KIT [23] and elicits cytotoxicity in FLT3–mutant AML while largely sparing KIT inhibition (100-fold offset in both viability and biochemical assays) with limited activity against other kinases. As a result, crenolanib may be associated with less myelosuppression than the available type II FLT3 TKIs.

2.4. Correlative Studies

2.4.1. Pre-clinical Studies of Antileukemic Activity of Crenolanib in Combination with Cytarabine or Daunorubicin

(1) Synergistic activity of crenolanib in combination with cytarabine

The effect of crenolanib on nucleoside analogue uptake in AML cells was evaluated. Cells were incubated for 2 h with 1.25 μM of radiolabeled cytarabine combined with DMSO control or in combination with crenolanib at 0.1 μM for 5 minutes and 2 h (Figure 2.2). Combining cytarabine with crenolanib in FLT3 wild-type OCI-AML3 cells and FLT3-ITD MV411 cells showed that crenolanib does not decrease cytarabine accumulation in AML cells, despite length of crenolanib incubation time [21].

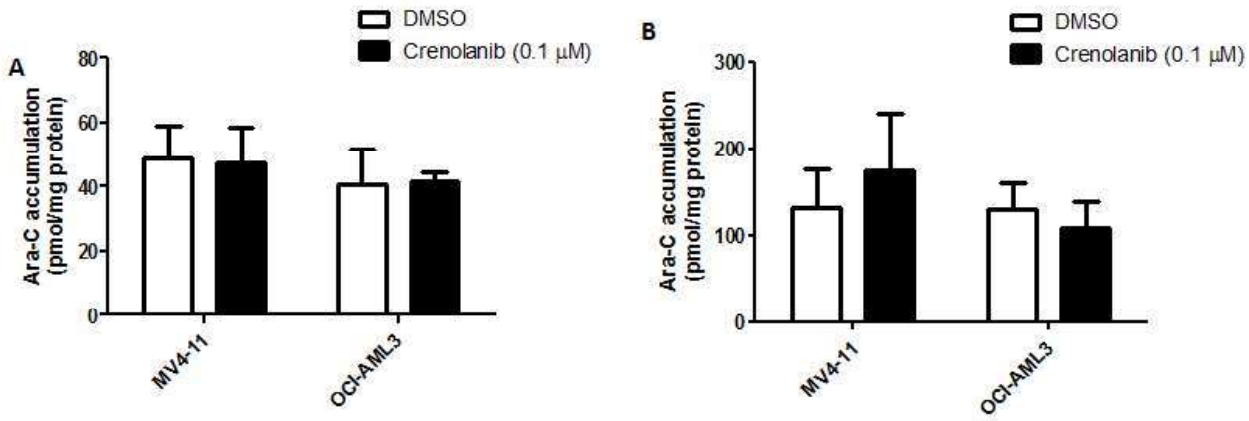


Figure 2.2 Effects of crenolanib on uptake of cytarabine in AML cells. Cytarabine uptake experiments performed in OCI-AML3 cells that are FLT3 wild type and MV4-11 cells that have a FLT3-ITD mutation show that crenolanib does not inhibit cytarabine accumulation in AML cells when exposed to 0.1 μM of crenolanib for (A) 5 minutes (B) or 2 hours. Histogram shows mean and SD.

Further combination experimentation was undertaken to give insight into the potential sequence of crenolanib and cytarabine administration in future clinical studies. Assays were performed to measure cell viability of FLT3 ITD cell lines (MOLM13 and MV4-11) that were incubated for

4 h with cytarabine followed by 68 h of crenolanib (Figure 2.3). Results suggested synergistic activity with the combination [21].

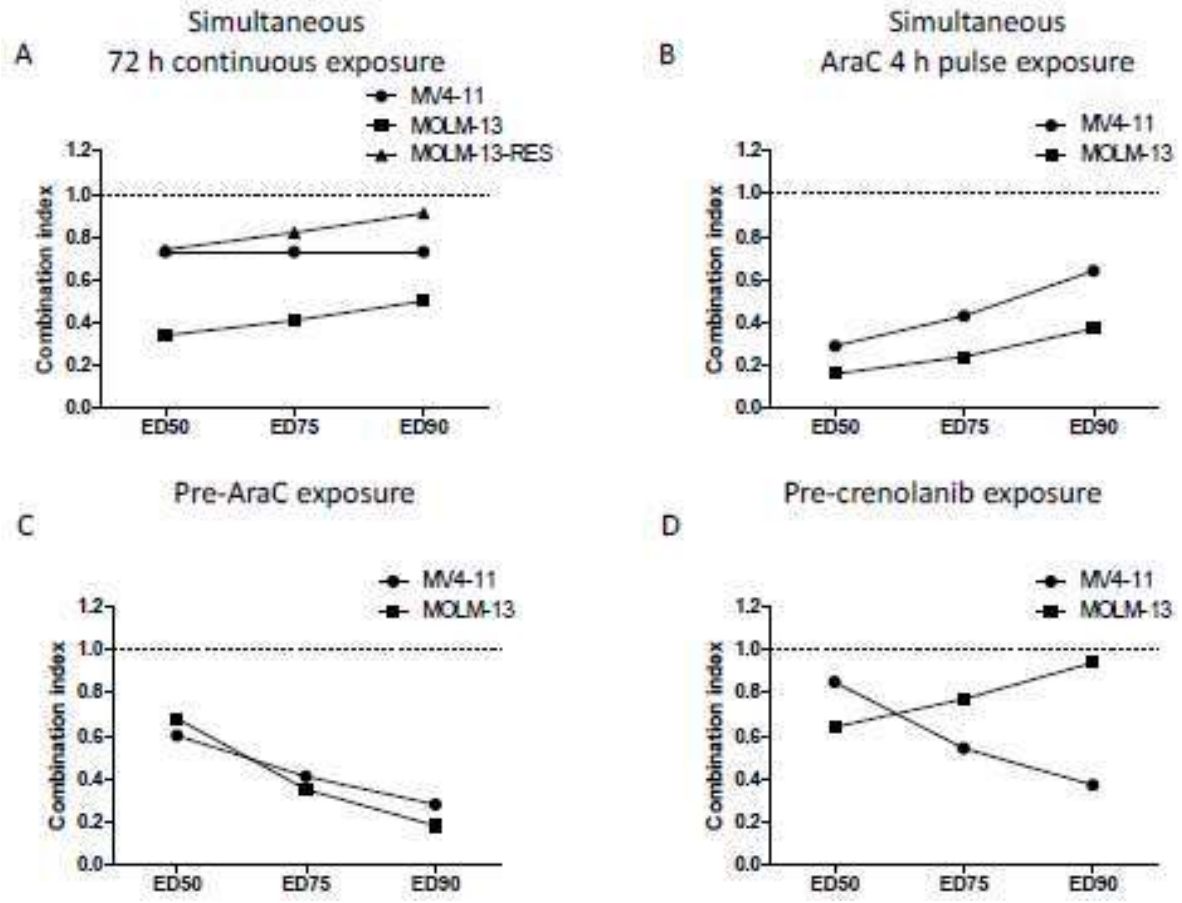


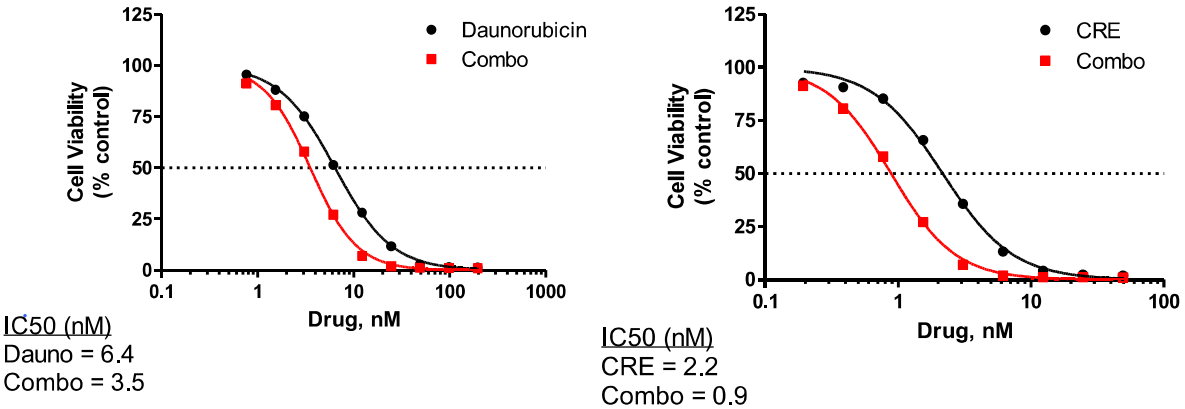
Figure 2.3 Crenolanib and cytarabine combination synergistically inhibit FLT3-ITD-positive cell viability in vitro. (A) simultaneous 72 h drug exposure; (B) simultaneous 4 h drug exposure followed by 68 h crenolanib exposure; (C) (pre-AraC) 4 h AraC exposure followed by 68 h crenolanib exposure; or (D) (pre-crenolanib) 24 h crenolanib exposure followed by 48 h AraC exposure.

(2) Antileukemic activity of crenolanib in combination with daunorubicin

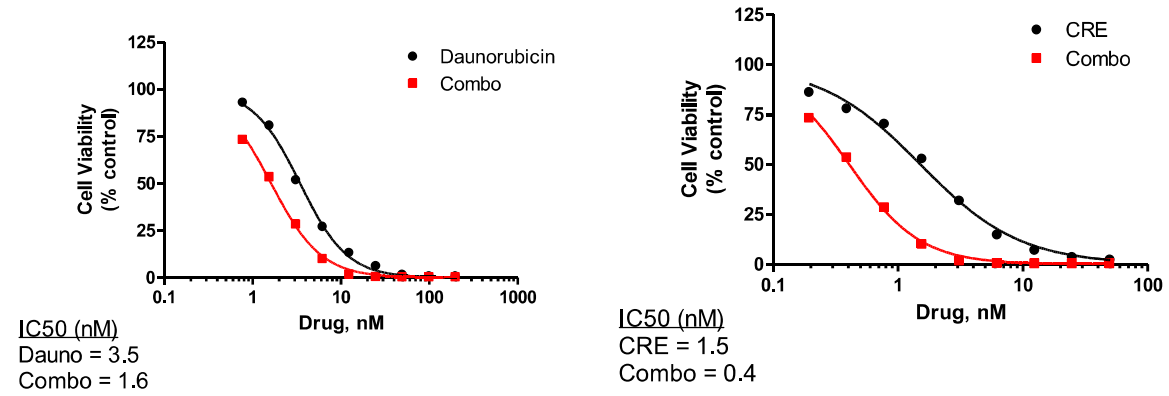
In vitro combination studies with crenolanib and daunorubicin also suggest antileukemic synergy in AML cell lines with mutant FLT3 (Figure 2.4, unpublished data on file, Dr. Sharyn Baker).

Figure 2.4 Viability of FLT3 ITD cell lines treated with crenolanib and daunorubicin

A.



B.



(A) Molm 13 cell line; (B) MV4-11 cell line

2.4.2. Clinical studies of Crenolanib in Relapse/Refractory FLT3 Mutated Acute Myeloid Leukemia

Crenolanib has been studied in relapsed/refractory FLT3 mutant AML (NCT01522469, NCT01657682). As of July 30, 2014, a total of 51 AML patients have been treated with single-agent crenolanib. Among those, 28 patients received fixed dose of crenolanib (300 mg) given as 100 mg TID; the other 23 patients received crenolanib using a body surface area (BSA) dosing schedule at 200 mg/m^2/d. Patients had received a median number of 3 prior therapies for AML (range 1-7) including prior transplant and TKI therapy.

Of the 51 AML patients (FLT3 ITD, or FLT3 D835, or FLT3 ITD/D835) treated with crenolanib, 49
patients were eligible for efficacy evaluation. Crenolanib has demonstrated clinical activity in this heavily treated population. Several patients showed peripheral blast clearance after crenolanib therapy (Figure 2.5). Twenty-seven (27) patients demonstrated response, including 1 complete remission (CR) with full count recovery, 8 CR with incomplete hematological recovery

(CRi), 7 partial remissions (PR) and 11 blast responses as defined by adaptive Cheson criteria [10]. Clinical benefit rate was 55 %. Five (11 %) of these heavily pre-treated patients were bridged to transplant. Of the 25 patients with FLT3-D835 AML, 14 patients achieved a clinical benefit (56 %): 6 CR/CRi (24%), 4 PR (16 %), and 4 blast response (16 %).

Figure 2.5 Peripheral blast clearance in FLT3 mutant AML patients treated with crenolanib

* Patients entered trials without peripheral blasts, † patients were not evaluable at cut off

Toxicity data from 38 patients is available. Commonly observed side effects included nausea (76 %), vomiting (52 %), diarrhea (47%), and transaminase elevations (8-11%). Two patients went off study due to toxicities, one due to nausea vomiting and one due to fatigue. Dose reduction occurred in 2 patients due to nausea and another due to transaminitis, respectively.

As of yet, QT prolongation has not been reported in 51 patients with AML treated with crenolanib. Most patients had received concomitant medication including antifungal medicine throughout crenolanib therapy; nonetheless no QT prolongation has been observed when EKG has been performed.

In conclusion, crenolanib is a FLT3 TKI showing preliminary clinical activity in a heavily pretreated population with FLT3-ITD, FLT3-D835, and compound FLT3-ITD/D835 mutant AML. Importantly, crenolanib is the first agent to demonstrate clinical activity in patients with FLT3-D835 activating mutations [24, 25].

(1) Tolerability of crenolanib in AML patients who had undergone prior allogeneic bone marrow transplant

Among the 51 AML patients who received crenolanib, 13 patients had prior stem cell transplant (1 patient had 2 prior transplants). Crenolanib at 100 TID and 200 mg/m^2/day was well tolerated even in patients who had undergone prior allogeneic bone marrow transplant. Three of these patients had dose reductions. One patient, who had received a transplant after being on study and continued on crenolanib for maintenance, had a dose reduction due to pancytopenia. Hyperbilirubinemia on crenolanib was observed in one patient. Liver biopsy showed reactivation of GVHD.

(2) Long-term Safety Data of Crenolanib

In a Phase I pediatric glioma study conducted at the St. Jude Children's Research Hospital, 6 children received crenolanib for at least 12 cycles. Four children have stayed on study for more than 24 cycles. No dose reduction was required. Long-term exposure to crenolanib seems to be tolerable and safe.

2.5. Rationale for combining a TKI with standard salvage chemotherapy and 5-azacytidine

Published data [26, 27] have demonstrated the clinical activity of the combination of the TKI sorafenib given with salvage chemotherapy (idarubicin and cytarabine) for previously untreated AML and in combination with 5-azacytadine for relapsed/refractory AML patients. The latter regimen is particularly of interest for those older patients or patients with poor performance status may not tolerate conventional chemotherapy.

The hypotheses of the study are: (1) The combination of crenolanib with cytotoxic agents, such as standard salvage chemotherapies, or a hypomethylating agent, such as 5-azacitidine, will generate a synergistic effect and target against the aberrant signal transduction of the leukemic blasts. (2) The combination of crenolanib with 5-azacitidine instead of with traditional chemotherapy regimens may trigger less treatment resistance by promoting lower levels of FLT3 ligand thus sustaining the response duration.

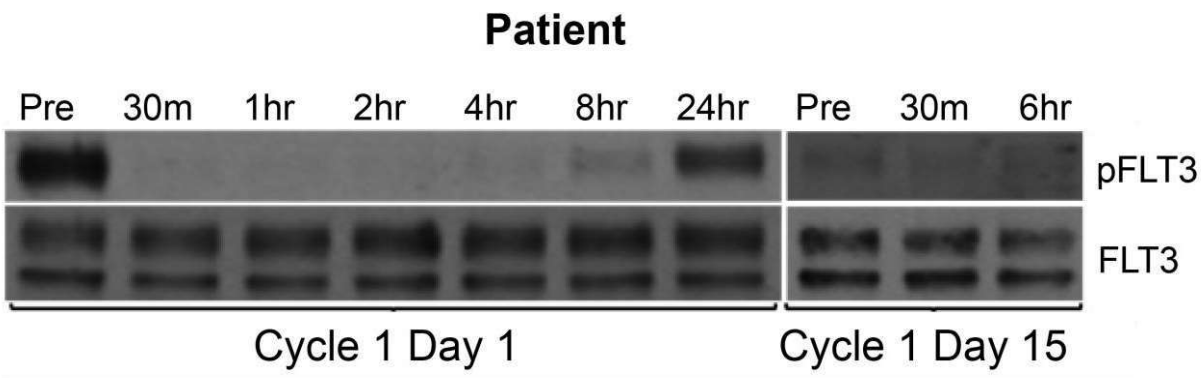
We propose to investigate the combination of standard salvage chemotherapies and crenolanib or 5-azacitidine with crenolanib in patients with relapsed AML or high-risk MDS as re-induction/consolidation therapy, followed by the use of crenolanib in a maintenance fashion for patients achieve response.

The phase I portion of the trial will define the safety and tolerability of the combination of crenolanib with other agents. The phase II portion of the trial will assess the efficacy of therapy in AML patients and compare to historical controls.

2.6. Rationale for Baseline Dose Selection

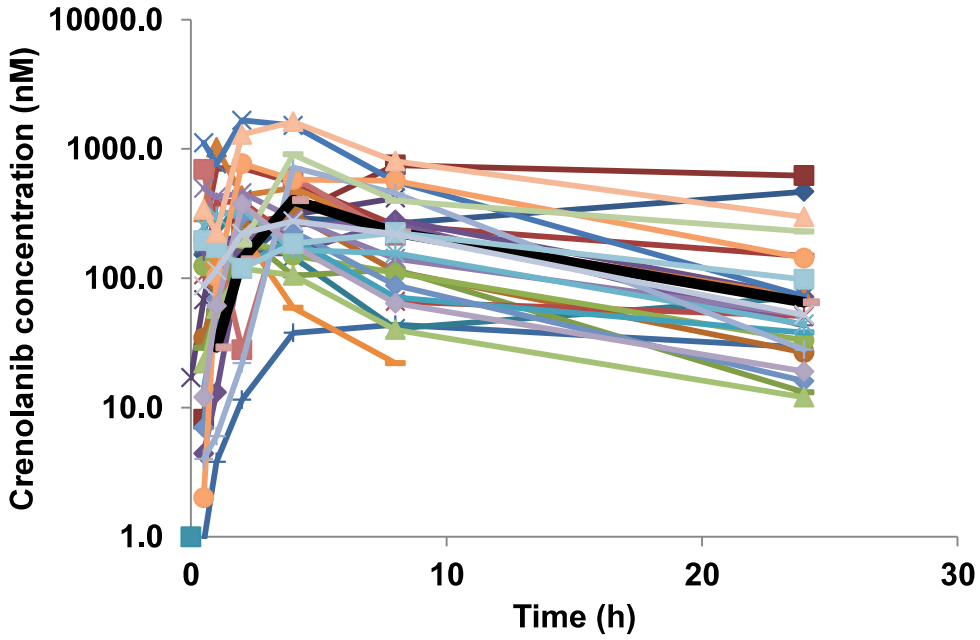
Among 51 AML patients on crenolanib monotherapy, 28 patients have received 100 mg TID and the rest at higher dose of 66 mg/m^2 TID. Most common adverse events were nausea, vomiting and diarrhea and LFT elevations. As crenolanib will be given in combination with standard salvage chemotherapy or with 5-Azacytidine, a dose escalation schedule will be utilized for this trial. The starting dose of crenolanib at 60 mg TID is 40% less than the dose (100 mg TID) that has been found to be well tolerated in previous phase II studies. If the 60 mg TID is proved to be safe and tolerable in the combination regimen, dose escalations to 80 mg TID and 100 mg TID will be studied. Representative plasma inhibitory activity (PIA) assay from single-agent crenolanib studies showed this dose schedule effectively inhibited the phosphorylated FLT3 (Figure 2.6).

Figure 2.6 Representative PIA result of AML patient samples after single dose crenolanib



To date, 28 AML patients have been treated with 100 mg TID crenolanib. Day 1 pharmacokinetics data is shown in Figure 2.7.

Figure 2.7 Serum concentrations of crenolanib following single dose (100 mg) in AML patients



3. STUDY DESIGN

This is a Phase I/II, two arm, open label study in FLT3 mutation positive AML of treatment given as either:

Arm 1: crenolanib with standard salvage chemotherapy
Arm 2: crenolanib with 5-azacitidine

Assignment to treatment arm will be determined by the Investigator with enrollment to each arm to occur simultaneously.

Crenolanib will be administered for the phase 1 portion as described according to dose levels in Table 6.2. Phase I will use a rolling-6 design and plan for a total of 18 patients on each arm. The starting dose will be 60 mg TID (dose level 1). Dose escalations will proceed to 80 mg TID (dose level 2) and 100 mg TID (dose level 3) based on DLTs (as defined in section 6.3). DLTs will be evaluated during the first cycle of crenolanib treatment. Patients who experience crenolanib related DLTs at dose level 1 will receive a dose reduction to dose level 0 (60 mg BID). Patients who encounter DLTs at dose levels 2 and 3 will receive dose reduction at 1 dose level lower.

Phase II total of 26 patients in each arm treated at established phase I dose.

4. PATIENT SELECTION

Patients must have baseline evaluations performed within 28 days prior to enrollment (unless otherwise specified in the schedule of events) and must meet all inclusion and exclusion criteria. Results of all baseline evaluations must be reviewed by the Principal Investigator or his/her designee prior to enrollment of that patient. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained from the patient prior to initiating treatment. The following criteria apply to all patients enrolled onto the study unless otherwise specified.

4.1. Inclusion Criteria

1. Confirmed diagnosis of refractory/relapsed AML or high-risk MDS (IPSS intermediate-2 risk and high risk, see Appendix VIII) that is refractory or has relapsed after prior therapy. Patients with secondary leukemia (i.e., evolving from MDS or MPN, or secondary to therapy for other malignancies) are eligible
    - Arm 1: Subjects must have received at least one prior therapy and a maximum of three prior therapies
    - Arm 2: Subjects must have received at least one prior therapy and a maximum of three prior therapies. No prior treatment with 5-Azacitidine is allowed in this arm.
2. Presence of FLT3 ITD and/or other FLT3 activating mutations
3. Extramedullary disease is allowed except for active CNS disease
4. Prior use of hydroxyurea or isolated doses of cytarabine for palliation (i.e., control of WBC) are allowed but should be discontinued at least 24 hrs prior to study start. Other agents used strictly

with palliative intent might be allowed during this period after discussing with principal investigator

5. Age ≥18 years
6. ECOG PS 0-2
7. Adequate liver function tests will be required within 72 hours of enrollment. Adequate liver function will be defined as:
    - Normal total serum bilirubin
    - ALT and AST ≤ 2.0 x ULN
8. Adequate renal function, defined as serum creatinine ≤1.5x ULN
9. Negative pregnancy test, within 72 hours of enrollment, for women of childbearing potential "Woman of childbearing potential" is defined as any woman who has not undergone a hysterectomy and who has had menses at any time in the preceding 24 consecutive months
10. Able and willing to provide written informed consent

4.2. Exclusion Criteria

1. Absence of FLT-3 activating mutations at time of study screening
2. < 5% blasts in blood or marrow at screening, except if measurable extramedullary AML is confirmed
3. Subjects with Acute promyelocytic leukemia (APL)
4. Known clinically active CNS leukemia
5. Clinically active or unstable graft-versus-host disease requiring treatment which precludes administration of chemotherapy as defined in this protocol
6. Therapy with curative intent for relapsed AML or high-risk MDS prior to the first dose of crenolanib as follows: within 14 days of study enrollment for classical cytotoxic agents and for 5x the half-life for FLT3 targeting TKI, hypomethylating agents or MEK inhibitors
7. Patient with pre-existing liver diseases (i.e. cirrhosis, chronic hepatitis B or C, nonalcoholic steatohepatitis, sclerosing cholangitis)
8. Patients with known HIV infection
9. "Currently active" second malignancy (other than non-melanoma skin cancer, carcinoma in situ of the cervix or prostatic intraepithelial neoplasia within 1 year). Subjects are not considered to have a "currently active" malignancy if they have completed therapy and are considered by their physician to be at less than 30% risk of relapse within 1 year
10. Subject with concurrent severe and/or uncontrolled medical conditions that in the opinion of the investigator may impair the participation in the study or the evaluation of safety and/or efficacy.
11. Subject with uncontrolled cardiac disease including congestive heart failure class III or IV by the NYHA, unstable angina (anginal symptoms at rest) or new onset angina (began within the last 3 months) or myocardial infarction within the past 6 months
12. Pregnant or breastfeeding women
13. Inability to give an informed consent

5. TREATMENT PLAN

5.1. General

Patients will be assigned to treatment arm by physician's choice and according to the availability of slots.

The study will enroll patients with relapsed/refractory AML with FLT3 activating mutations. There will be two parallel two arms. In Arm 1 patients will be treated with standard salvage chemotherapy combined with crenolanib. In Arm 2 patients will receive azacitidine combined with crenolanib. Arms 1 and 2 will enroll simultaneously. For both arms, patients will be treated with crenolanib at a starting dose level of 1 (60 mg TID) as defined in the Table 6.2. De-escalation to dose level 0 (60 mg BID) is possible in the event that dose level 1 is found to be too toxic. The dose escalation will proceed independently in each arm. In arm 1 a cycle of induction or consolidation can last for a minimum of 28 days and a maximum of 60 days (extending a cycle for more than 60 days would require a conversation with the sponsor); maintenance cycles will be defined as 28 days. In arm 2 a cycle is defined as 28 days. The first cycle of treatment (in arm 1 and arm 2 independently) will constitute the dose-limiting toxicity (DLT) evaluation period. Study drug will be taken continuously until one of the criteria for study discontinuation is fulfilled.

For each arm of the study, the first 6 patients will be treated at a dose level of 1(60 mg TID). Patients will be entered sequentially to subsequent dose levels, dose level 2 (80 mg TID) and dose level 3 (100 mg TID) after DLTs have been assessed and it is safe to dose escalate. The Rolling-6 design will be used. The Rolling-6 design aims to shorten the duration of Phase I trials by minimizing the time the trial would be closed to accrual for toxicity monitoring. This is achieved by enrolling anywhere from 2 to 6 patients at a dose level without requiring that the DLT status of the patients already assigned to the same dose level are known.

Dose Escalation/De-Escalation Rules in phase I

The following table enumerates all possible scenarios and describes escalation/de-escalation rules that will be applied during dose-finding, separately in each arm:

Table 5.1. Dose escalation/de-escalation rules for the Rolling-6 design

Dose Escalation/De-Escalation Rules for the Rolling-6 Design					
				Decision when Next Patient is Enrolled	
# Pats Enrolled	# Pats with DLTs	# Pats w/o DLT	# Pats with Toxicity Data Pending	Not at the Highest Dose Level	At the Highest Dose Level
2	0, 1	Any	Any	Stay	
2	2	0	0	De-escalate	
3	0	0, 1, 2	3, 2, 1	Stay	
3	0	3	0	Escalate	

3	1	0, 1, 2	2, 1, 0	Stay	
3	≥ 2	Any	Any	De-escalate	
4	0	0, 1, 2, 3	4, 3, 2, 1	Stay	Stay
4	0	4	0	Escalate	Stay
4	1	0, 1, 2, 3	3, 2, 1, 0	Stay	Stay
4	≥ 2	Any	Any	De-escalate	De-escalate
5	0	0, 1, 2, 3, 4	5, 4, 3, 2, 1	Stay	Stay
5	0	5	0	Escalate	Stay
5	1	0, 1, 2, 3, 4	4, 3, 2, 1, 0	Stay	Stay
5	≥ 2	Any	Any	De-escalate	De-escalate
6	0	0, 1, 2, 3, 4	6, 5, 4, 3, 2	Suspend	Suspend
6	0	5, 6	1, 0	Escalate	MTD not determined
6	1	0, 1, 2, 3, 4	5, 4, 3, 2, 1	Suspend	Suspend
6	1	5	0	Escalate	MTD not determined
6	≥ 2	Any	Any	De-escalate	De-escalate

The MTD is empirically defined as the highest dose level at which 6 patients have been treated with at most 1 patient experiencing a crenolanib related DLT and the next higher dose level has been determined to be too toxic. The maximum tolerated dose (MTD) may be further defined based on incidence of delayed or cumulative toxicity.

Approximately 88 patients (a maximum of 18 patients in each arm for determination of MTD and 26 patients each arm for phase II portion) will be enrolled in the study. In the dose finding phase I, a maximum of 6 patients at each dose level will be enrolled to establish the proper dose for phase II. As a result, as few as 6 patients and as many as 18 patients can be enrolled in phase I. The recommended dose of crenolanib for testing in the expansion phase will be tentatively identified in the dose escalation phase and will be that which is at or below the MTD, that can be delivered safely in multiple cycles with an acceptable incidence of on-time delivery, and that confers exposure consistent with that needed for efficacy based on the nonclinical models. Once the proper dose has been determined for phase II, an additional 26 patients will be enrolled in each arm.

Table 5.2. Dose levels of crenolanib (applies to both Arms 1 and 2)

Dose Level	Crenolanib mg PO daily during induction
0	60 mg BID
1 (Starting dose)	60 mg TID
2	80 mg TID
3	100 mg TID

Dose adjustments beyond those mentioned in this table or different to the doses specified may be acceptable after discussion with the PI and notification of the sponsor and documentation of the justification recorded in the chart.

5.2. Treatment Schedule

Crenolanib will be administered for the phase 1 portion as described according to dose levels in Table 6.2. The starting dose is 60 mg TID (dose level 1). Dose escalations will proceed to 80 mg TID (dose level 2) and 100 mg TID (dose level 3) based on DLTs. DLTs will be evaluated during the first cycle of crenolanib treatment. Patients who experience crenolanib related DLTs at dose level 1 will receive a dose reduction to dose level 0 (60 mg BID). Patients who encounter DLTs at dose levels 2 and 3 will receive dose reduction at 1 dose level lower.

5.2.1. Arm 1: Crenolanib combined with Standard Salvage Chemotherapy
5.2.1.2 Induction

ARM 1 Induction Dosing Schedule:
Physician's choice standard salvage chemotherapy regimen:

Ida/Cytarabine
Idarubicin 12 mg/m^2 IV over 1 hr daily on Days 1-3
Cytarabine 1.5 g/m^2 IV continuously over 3 hr on Days 1-4 (≤ 60 yrs) or Days 1-3 (> 60 yrs)
Crenolanib PO starting on Day 5 (+3 day window) continuously

MEC + crenolanib
Mitoxantrone 8 mg/m² IV, push on Days 1-5
Etoposide 100 mg/m^2 IV on Days 1-5
Cytarabine 1000 mg/m² IV, over 3 hours on Days 1-7
Crenolanib 100 mg TID starting on Day 8 (+3 day window) continuously

FLAG-Ida + crenolanib
Fludarabine 30 mg/m^2 IV on Days 1-5
Cytarabine 2 g/m2 IV over 2 hrs on Days 1-5
G-CSF 300 ug s.c. inj or IV/5ug/kg SC on Day 6, until neutrophil recovery
*(G-CSF optional, per physician's choice)
Idarubicin 8 mg/m2 IV over 30 min on Days 1-3
Crenolanib 100 mg TID starting on Day 6 (+3 day window) continuously

Crenolanib will be administered continuously until 72 hours prior to next induction cycle or in the case of CR/CRi/CRp, consolidation. If patient achieves a CR/CRi/CRp and will proceed to maintenance following induction, crenolanib does not need to be held 72 hours prior to starting first cycle of maintenance.

Induction cycles can be a minimum of 28 days or a maximum of 60 days (extending a cycle for more than 60 days would require a conversation with the sponsor). A maximum of 2 induction cycles may be given.

If a patient achieves a CR/CRi/CRp after induction cycle 1, this patient will be eligible (at the physician's discretion) to continue to consolidation or maintenance therapy with crenolanib. If a patient is to receive transplant following induction cycle 1, he/she must be discontinued from study treatment prior to transplant.

If a patient has not achieved a CR/CRi/CRp following induction cycle 1, they will not be eligible to start consolidation or maintenance. For a patient who does not achieve CR/CRi/CRp at the end of one induction cycle, a second cycle of induction may be given (per physician's discretion). The same maximum of 60 days duration will be used for the second induction. If a patient achieves a CR/CRi/CRp after induction cycle 2, this patient will be eligible (at the physician's discretion) to continue to consolidation or maintenance therapy with crenolanib. If a patient is to receive transplant following induction cycle 2, he/she must be discontinued from study treatment prior to transplant.

If a patient does not achieve CR/CRi/CRp by the end of the second induction cycle, he/she must be discontinued from crenolanib. Within 30 days of discontinuing crenolanib, prior to new treatment regimen, an end of treatment visit is strongly recommended. At the end of the study, patient's survival status will be assessed.

5.2.1.2. Remission Consolidation

ARM 1 Consolidation Dosing Schedule:

- Idarubicin 8 mg/m^2 IV over 1 hr daily on Days 1-2
- Cytarabine 0.75 g/m^2 IV continuously over 90 min on Days 1-3
- Crenolanib will be given Day 5 (+3 day window) continuously until 72 hours prior to next consolidation cycle. If patient remains in CR/CRi/CRp and will proceed to maintenance, crenolanib does not need to be held 72 hours prior to starting first cycle of maintenance.

Consolidation cycles can be a minimum of 28 days or a maximum of 60 days (extending a cycle for more than 60 days would require a conversation with the sponsor). A maximum of 6 consolidation cycles may be given.

A patient must maintain CR/CRi/CRp to be eligible for a second cycle of consolidation. If a patient is in a CR/CRi/CRp at any time, he/she is eligible for maintenance therapy with crenolanib (per physician's discretion). If a patient is to receive transplant, he/she must be discontinued from study treatment prior to transplant.

If at any time during consolidation a patient relapses or is taken off study for any other reason (such as transplant), an end of treatment visit is strongly recommended. This visit will occur within 30 days of discontinuing crenolanib and prior to new treatment regimen or transplant. At the end of the study, patient's survival status will be assessed.

5.2.1.3. Crenolanib Maintenance

ARM 1 Maintenance Dosing Schedule:

Patients achieving a remission following induction cycles or patients remaining in remission after consolidation therapy may receive crenolanib for maintenance therapy for up to 365 days. Maintenance therapy will be with single-agent crenolanib and cycles will be defined as 28 days.

If a patient is to receive transplant, he/she must be discontinued from study treatment prior to transplant. If at any time during maintenance a patient relapses or is taken off study for any other reason (such as transplant), an end of treatment visit is strongly recommended. This visit will occur within 30 days of discontinuing crenolanib and prior to new treatment regimen or transplant. At the end of the study, patient's survival status will be assessed.

5.2.2. Arm 2: Crenolanib plus 5-azacitidine

ARM 2 Dosing Schedule:

- 5-azacitidine 75 mg/m^2 will be administered subcutaneously (SQ) or intravenously (IV) at 75 mg/m^2/d for 7 days of every cycle (Days 1-7). The choice of SQ or IV administration will be selected by the treating physician and can be switched from one to another throughout the therapy as both SQ and IV forms of administration are FDA approved and considered interchangeable.
- Crenolanib will be given Days 1-28 (crenolanib will be given continuously unless toxicity occurs)

Cycles will be defined as 28 days. Patient may continue on combination crenolanib + 5-azacytidine per physician's discretion or until transplant, progression of disease, withdrawal, unacceptable toxicity, etc. (per Section 6.5).

If a patient achieves a CR/CRi/CRp, he/she will be eligible for maintenance therapy with single agent crenolanib (per physician's discretion). Crenolanib, in the maintenance setting, may be given for up to 365 days per physician's discretion.

If a patient is to receive transplant, he/she must be discontinued from study treatment prior to transplant. If at any time during maintenance a patient relapses or is taken off study for any other reason (such as transplant), an end of treatment visit is strongly recommended. This visit will occur within 30 days of discontinuing crenolanib and prior to new treatment regimen or transplant. At the end of the study, patient's survival status will be assessed.

5.2.3. General Principles for Both Arms

For arms 1 and 2, patients should be given prophylactic anti-emetics from the time of enrollment to be taken prior to each dose of crenolanib and as needed as per ASCO guidelines for moderately emetogenic therapy. Oral HT3 antagonists such as ondansetron are quite effective in mitigating crenolanib associated nausea. Prophylactic antiemetic administration may be adjusted (including discontinuation of prophylactic antiemetics as appropriate) throughout the course of therapy as needed to minimize and manage nausea and/or vomiting.

The following bullet points are exceptions allowed following discussion with and approval by the sponsor and PI.

- Cycles may be started early (but not earlier than cycle day 21) for patients with active disease if judged in the best interest of the patient by the treating physician and PI.
- Subsequent cycles may be delayed for recovery of toxicity. Delays in start of subsequent cycles greater than 7 weeks will be acceptable only for patients who are deriving clinical benefit and after discussion with the principal investigator of potential risk/benefit ratio.
- Crenolanib therapy may continue even if there is a delay in the start of azacitidine or standard salvage chemotherapy provided the delay is not due to toxicity possibly related to crenolanib.

5.3. Study Conduct and Definitions of DLT and MTD

5.3.1. Definition of DLT

DLT is defined as any clinically significant adverse event or abnormal laboratory value occurring during the first cycle of therapy that is not related to concomitant medications, co-morbidities or underlying disease (leukemia), and that is not expected for the chemotherapy being used together with crenolanib.

- Non-hematologic DLT is defined as any grade 3 or 4 non-hematologic toxicities despite optimal supportive care. For example, grade 3 or 4 nausea, vomiting, or diarrhea that cannot be controlled with standard antiemetic or antidiarrheal medications used at optimal dose within 72 hours of onset are considered DLTs.
    - Tumor lysis syndrome is considered DLT. If 2 out of the 10 first patients are observed to experience the tumor lysis syndrome of Grade 4, the trial will be put on hold and a mitigation strategy will be implemented.
- Hematologic DLT is defined as grade ≥3 neutropenia and/or thrombocytopenia with a hypocellular bone marrow lasting for 6 weeks or more after the last dose of therapy in the absence of residual leukemia (i.e., with less than 5% blasts).
    - Anemia will not be considered for the definition of DLT.

5.3.2. Cohort Management

Patients will be treated in cohorts of 6 patients at each dose level starting at dose level 1 of 60 mg TID for each Arm.

- If DLT occurs in ≥2/6 patients at dose level 1 (60 mg TID), this dose level would exceed the MTD, and a dose level 0 (60 mg BID) will be used. If 0-1/6 patients experience DLT, an additional 6 patients will be enrolled at dose level 2 (80 mg TID).
- Patients who are removed from study before cycle 1 day 28 for any reason other than toxicity and have not experienced DLT will be replaced.
- DLT and MTD will be established independently for each treatment arm (i.e. arm 1: crenolanib + standard salvage chemotherapy and arm 2: crenolanib + AZA).
- For arm 1: One induction cycle can continue for a minimum of 28 days and a maximum of 60 days from the start of induction chemotherapy, until the start of the second cycle of therapy (re-induction or consolidation) or achievement of CR/CRi/CRp. For arm 2: One cycle of crenolanib therapy is defined as 28 days from the first ingestion of study drug.

- During maintenance, one cycle of therapy is defined as 28 consecutive days of crenolanib therapy.
- Counting cycle days: If study drug is held or a dose is missed the missed/held dose should not be made up. Dosing will resume with the next scheduled dose. The patient should enter in his/her patient dosing diary the doses missed. If drug is held for one or more days, the counting of cycle days should continue as if uninterrupted. The start of cycle 1 is denoted by the start of chemotherapy. The scheduled procedures/visits should comply with the study calendar regardless of amount of study drug administered in a cycle.
- For arm 1: If myelosuppression persists more than 60 days from the day of the last dose of therapy with evidence of a hypocellular marrow (marrow cellularity less than 5%) without evidence of leukemia, standard salvage chemotherapy will be discontinued. Crenolanib might be continued or re-initiated in patients deriving benefit after discussion with the PI and the sponsor.
- For arm 2: If myelosuppression persists 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 the next lower dose. If the peripheral counts do not recover (ANC <1 x10^9/L and/or platelets <30 x10^9/L) but there is evidence of residual leukemia in the bone marrow, subsequent cycles can be administered at the discretion of the treating physician not earlier than 3 weeks (21 days) after the prior cycle.
- If the peripheral counts do not recover (ANC <1 x10^9/L and/or platelets <30 x10^9/L) but there is evidence of residual leukemia in the bone marrow after cycle 1, subsequent cycles of Azacitidine or standard salvage chemotherapy can be administered at the discretion of the treating physician (following discussion with the sponsor and PI) not earlier than 3 weeks (21 days) after the start of the prior cycle.
- For patients who discontinue therapy, the reason for treatment discontinuation will be captured.
- Patients who experience crenolanib-specific (defined as determined by the principal investigator) grade 3-4 extramedullary toxicities during induction cycle 1, and who are not in CR after cycle 1, may receive a second induction course at -1 dose level with respect to crenolanib (as defined in table above).
- Other dose modification schedules felt to be in the best interest of the patient may be permitted, after discussion with the principal investigator.
- If judged more beneficial for patient care and disease control, patients may have dose reductions to allow for continuation of therapy with acceptable myelosuppression.
- The dose of chemotherapy treatment in subsequent courses will be reduced by 25% for grade 3-4 extramedullary toxicities, or for severe life-threatening infections.
- In responding patients, courses will be given at 4 to 6 week intervals provided the granulocyte count has recovered to >1.0x10^9/L and the platelet count to >50x10^9/L. In patients with persistent disease, therapy could be restarted once counts recover to the pretreatment values.
- Dose adjustments for only one of the drugs can be made if, in the opinion of the treating physician, the toxicity is attributable to one of the drugs.

<u>Maintenance</u>–crenolanib may be continued in both arms until one of the criteria listed under the section 5.5 entitled "duration of therapy" applies.

For the maintenance phase the patient will remain on the same tolerable dose received during induction/consolidation.

5.4. Crenolanib Administration

- Prophylactic antiemetic therapy is recommended to be used as needed for nausea and/or vomiting as per ASCO Guidelines for "moderately emetogenic" therapy.
- If a dose is missed or vomited, it should **not** be taken again. The next dose should **not** be increased to account for missing a dose. The patient should take the next regular dose at the regularly scheduled time.

5.5. Duration of Therapy

Treatment may continue until one of the following criteria applies:

1. Clinically significant progressive disease
2. Intercurrent illness that in the opinion of the investigator prevents further administration of treatment
3. Patient request
4. General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
5. Unacceptable toxicity that in the opinion of the investigator makes it unsafe to continue therapy
6. Treatment interruption due to toxicity that has not recovered to at least grade 1 within 8 weeks
7. Patient is to receive HSCT

It is planned that up to 365 days of crenolanib maintenance therapy may be administered for patients deriving benefit from this regimen. This will be administered per physician's discretion or upon any of the criteria mentioned above for treatment discontinuation.

A minimum of 1 full course (defined as the administration of chemotherapy followed by crenolanib for a minimum of 28 days or at the time of protocol specified "pre-cycle 2" bone marrow) will be required for a patient to be considered as having received an adequate trial to evaluate efficacy. Patients who do not complete one cycle of crenolanib therapy will be replaced unless the reason is development of toxicity or progressive disease. All patients receiving at least one dose of study drug will be considered evaluable for toxicity.

5.6. 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, and/or biologic response modifiers are not permitted during the study, with the exception of intrathecal therapy which is allowed to prevent recurrence of CNS disease. No other investigational drugs are allowed during the study.

6. DOSING MANAGEMENT

6.1. Dosing Levels

Toxicities will be graded using the NCI CTCAE, Version 4.03 (Appendix IV).

- Dose reductions for non-hematologic toxicities due to crenolanib, will be done according to the schema outlined in Tables 6.1 and 6.2
- Reductions below 60mg BID are not planned; dose reductions beyond those mentioned in Table

6.2 or different than those specified, should be discussed with the PI and the sponsor and documentation of the justification recorded. If an appropriated dose is not identified, then it will lead to patients' withdrawal from the study drug, in which the patient will stop taking crenolanib, but will still be followed for outcomes.

Table 6.1 Crenolanib dose reduction for All Toxicities related to study drug

Toxicity (NCI Criteria)	Dose Modification
Grade 1 or 2	No dose modification
Clinically significant persistent grade 2 despite optimal therapy	May hold drug until toxicity resolves to grade 1 or less. Restart drug at same dose level (Table 6.2).
Grade 3 or 4	Hold drug until toxicity resolves to grade 1 or less. Restart drug at next lower dose level (Table 6.2).

Table 6.2 Crenolanib dose reduction schedule

Dose Level	Crenolanib Dosing
0	60 mg BID
1 (starting dose)	60 mg TID
2	80 mg TID
3	100 mg TID

6.2. Dose Reductions of Crenolanib for Hematologic Toxicities

Patients with leukemia 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 leukemia. 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:

The following guidelines can be used for these patients:

- Patients with a response (i.e., no residual leukemia) and pre-cycle counts of neutrophils >1x10^9/L and platelets >100 x10^9/L who have sustained low counts of neutrophils <0.5 x10^9/L or platelet counts <25 x x10^9/L for more than 4 consecutive weeks in the current cycle, may receive a subsequent course at 1 dose level reduction. A reduction of 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.

- If there are persistent peripheral blood blasts, or the bone marrow shows >5% blasts, may continue treatment regardless of neutrophil and platelet count and give supportive care as needed.

- If no marrow evidence of leukemia, consider holding therapy until recovery of granulocytes to ≥1 x10^9/L and platelets ≥ 60 x10^9/L, then resume at same or 1 lower dose level according to guidelines mentioned in Table 6.2.

- For prolonged myelosuppression, defined as delayed recovery of ANC to >= 1 x 10^9/L, platelets to >=50 x 10^9/L beyond 6 weeks, crenolanib will be withheld. Resume crenolanib at a lower dose level after ANC >= 1 x 10^9/L, platelets to >= 50 x 10^9/L. Discontinue crenolanib treatment upon a 2nd episode of myelosuppresion.

6.3. Other Modifications of Crenolanib Dose Schedules

- Further dose reductions can be made to keep clinically significant crenolanib-related toxicity grade $\leq$ 2. However, the lowest planned dose is 60 mg BID; dose reductions beyond those mentioned in this table or different than those specified, should be discussed with the PI and the sponsor notified, and documentation of the justification recorded.

- Dose adjustments by more than 1 dose level at a time can be considered when judged in the best interest of the patient (e.g., neutropenia with sepsis, bleeding requiring platelet transfusions) when toxicity has resolved. The reason for this reduction will be discussed with the PI or Co PI and documented in the medical record.

6.4. Dose Reduction for Standard Salvage Chemotherapy Regimens

- The dose of the chemotherapy regimens in subsequent courses may be reduced for grade 3-4 extramedullary toxicities, prolonged myelosuppression (e.g., delayed recovery of neutrophils to $\geq 1 \times 10^9$/L or platelets to $\geq 50 \times 10^9$/L), or for severe life-threatening infections at the discretion of the managing physician discretion.
- Dose reductions are to be documented with the justification recorded in the CRF.
- Dose reductions should follow the guidance of the package inserts for the individual chemotherapy regimens
- Dose reductions of only one drug may be considered for adverse events adjudicated to one of the agents (e.g., cardiotoxicity related to idarubicin).
    - In instances where adverse events suggest that it is unsafe to continue administration of one of these agents, treatment may be continued with only one or with crenolanib only.

6.5. Dose Reductions for Azacitidine

- Dose reductions of azacitidine in subsequent courses may be reduced according to dose levels suggested in Table 6.3 for grade 3-4 extramedullary toxicities, prolonged myelosuppression (e.g., delayed recovery of neutrophils to $\geq 1 \times 10^9$/L or platelets to $\geq 50 \times 10^9$/L), or for severe life-threatening infections.
- In instances where adverse events suggest that it is unsafe to continue administration of azacitidine, treatment may be continued with crenolanib only.
- Dose reductions are to be documented with the justification recorded in the CRF.

Table 6.3 Dose reduction and escalation for azacitidine

Dose Level	AZA (mg/m^2/d x 7 days)
1 (Starting dose)	75
-1	50
-2	25

6.6. Cycle Delays

- A cycle of therapy may be delayed for a maximum of 7 weeks to allow recovery from toxicities.
- Inability to re-start therapy within 7 weeks after a treatment interruption for toxicity may constitute grounds for removing the patient from protocol. Instances where continuation of therapy is considered in the best interest of the patient despite a delay of greater than 7 weeks should be discussed with and approved by the sponsor.

7. AGENT FORMULATION AND PROCUREMENT

7.1. Storage of Crenolanib

Crenolanib is supplied as 100 mg and/or 20 mg tablets for oral dosing, in 42-count bottles or 30-count bottles. Crenolanib tablets should be refrigerated at a temperature between 2°C and 8°C (35.6°F and 46.4°F). Standard household refrigeration is considered adequate for drug storage. Crenolanib should be stored in the vials provided by the pharmacy and kept out of the reach of children.

7.2. Supply of Crenolanib

Used and unused tablets and bottles should be returned to the treating physician before starting a new therapeutic cycle to assess treatment compliance. Study drug will be supplied by AROG Pharmaceuticals. Study drug may be packaged by a third party. Clinical trial materials will be labeled according to regulatory and institutional requirements.

8. CORRELATIVE/SPECIAL STUDIES

The study site will receive a laboratory kit containing blood collection tubes, labels, and a lab manual with collection instructions from AROG for the collection, processing and shipping of samples from consenting subjects. Site should contact AROG (Appendix V) to request lab kits in anticipation of each patient enrolled on the study.

Correlative studies to be evaluated include but are not limited to:

1. Pharmacokinetic analysis (PK)
2. Bone marrow aspirate (BMA) samples
3. Whole blood sample

Pharmacokinetic Assay

Sampling Schedule for PK

Serial blood samples for PK will be drawn. See Appendix V Laboratory Manual for details.

Please make sure that the time and dose of last four crenolanib administrations are captured on PK forms.

Peripheral blood (for pharmacokinetics) will be drawn at the following times:

Arm 1

a. Induction 1 cycle 1 day 5, 6, or 8 (**this will depend on the chemo regimen, this should be day 1 of crenolanib administration**, only 1 dose of crenolanib should be administered on this day to allow for PK testing)
    a. Pre-dose
    b. 2 hours (± 15 minutes)
    c. 4 hours (± 30 minutes)
    d. 8 hours (± 2 hours)

e. 24 hours (± 6 hours) (This PK will be drawn on the second day of crenolanib administration, regular TID dosing of crenolanib should begin after this PK)

b. Consolidation 1 cycle 1 day 5 (**this should be day 1 of crenolanib administration**, the second dose of crenolanib should not be taken until after the 8 hour pk is drawn)
    a. Pre-dose
    b. 4 hours (±30 minutes)
    c. 8 hours (±2 hours)

Arm 2
Peripheral blood (for pharmacokinetics) will be drawn at the following times:

a. Cycle 1 Day 1 (only 1 dose of crenolanib should be administered on this day to allow for PK testing)
    a. Pre-dose
    b. 2 hours (± 15 minutes)
    c. 4 hours (± 30 minutes)
    d. 8 hours (± 2 hours)
    e. 24 hours (± 6 hours) (This PK will be drawn on the second day of crenolanib administration, regular TID dosing of crenolanib should begin after this PK)

Bone Marrow Samples
Prior to start of first dose of crenolanib, a baseline sample of bone marrow or peripheral blood containing blasts should be obtained. If entry bone marrow aspiration is not available, obtain 1 green top tube of blood and process per bone marrow aspirate instructions in AROG Pharmaceuticals laboratory manual.

Sampling Schedule for Bone Marrow Aspirates
Samples of bone marrow aspirates for research purposes will be collected at each time of routine marrow sampling with 1 additional aspiration of 5 mL drawn for study purposes and placed in a heparinized cell preparation tube. After induction 1 bone marrow should be performed at the discretion of the treating physician per institutional SOC. See Appendix V for required form.

Arm 1

a. Induction 1: as per the institutional standard of care
b. During induction 2 and consolidations: as per the institutional standard of care
c. Maintenance: as per the institutional standard of care (criteria for CR must be maintained to continue on maintenance therapy).

Arm 2

a. Cycle 1 and during treatment: as per the institutional standard of care
b. Maintenance: as per the institutional standard of care (criteria for CR must be maintained to continue on maintenance therapy).

Sampling Schedule for Whole Blood Collection

Samples of 5-10 mL of whole blood are drawn and placed in heparinized cell preparation tubes for other correlative science research studies. See Appendix V for required form. Samples should be drawn at the following two time points:

a. Pre administration of first dose of therapy (standard salvage chemotherapy regimen in arm 1 or azacitidine in arm 2)
b. End of treatment visit prior to initiation of new treatment regimen or HSCT

Other Correlative Studies

Additional samples for correlative research may be collected at any time while the patient is on study, at the discretion of the investigator or as requested by the sponsor. These may include assays for resistance studies for cases in which responses are noted but not durable. Samples can be stored and collected and send at interim intervals. AROG may request the investigator obtain additional samples from the patients; the total blood drawn for these studies will be less than 200 mL in any month.

Samples will be stored at AROG or its designated facility for future correlative science research studies.

Sample Processing Instructions

See Appendix V lab manual for processing, storage, and shipment of samples.

9. PATIENT EVALUATION

STUDY SCHEDULE FOR ARMS 1 (CRENOLANIB AND CHEMOTHERAPY):

Induction (maximum 2 inductions allowed)									
Procedure	**Screening**[a] (Day -28 to Day -1)	**Induction 1** (Minimum of 28 days Maximum duration of 60 days)			**Induction 2** [o] (Minimum of 28 days Maximum duration of 60 days)			**End of Treatment** [p] (within 30 days post last dose of crenolanib)	**End of Study** [q]
		Day 1	**First day of crenolanib (Day 5, 6 or 8)**	**Weekly***	**Day 1**	**First day of crenolanib (Day 5, 6 or 8)**	**Every other week****		
Informed consent [b]	x								
Inclusion/Exclusion [c]	x								
Demographics [d]	x								
Relevant medical history [e]	x								
Evaluation of FLT3 (ITD, TKD, other) mutational status	x								
Concomitant medications [f]	x	x	x	x	x		x	x	
Physical examination [g]	x	x			x			x	
Vitals, ECOG PS, Weight, Height [h]	x	x			x			x	
Hematology [i]	x	x	x	x	x		x	x	
Blood chemistries [j]	x	x	x	x	x		x	x	
Pregnancy test [k]	x								
EKG	x								
Echocardiogram	x								
PK analysis [l]			x						
Blood for biomarker and genetic testing	x							x	
Bone marrow aspiration [m]	x	x [m]			x [m]				
Adverse events [n]		x	x	x	x		x	x	
Survival follow-up									x

Key

* Procedures and assessments to be performed weekly until end of cycle (cycle length cannot exceed 60 days)

**Procedures and assessments to be performed every other week until end of cycle (cycle length cannot exceed 60 days)

a. Screening procedures are to be performed ≤ 28 days prior to enrollment with the exception of the following: Hematology labs are to be drawn ≤ 7 days prior to enrollment, pregnancy test if applicable is to be performed ≤ 3 days prior to enrollment, and chemistry panel (with LFTs) is to be drawn ≤ 3 days prior to enrollment .

b. Written consent must be obtained prior to performing any protocol-specific procedure. Results of a test performed as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame.

c. All inclusion/exclusion criteria should be met and confirmed by the sponsor prior to enrollment.

d. Demographics should be assessed at screening and are defined as race, ethnicity, age, and gender

e. Relevant medical history should be recorded in the EDC at screening.

f. Concomitant medications are to be recorded in the source records and appropriately reported in the EDC at screening and each subsequent visit.

g. Complete physical examination should be performed at screening and on day 1 of each cycle. If patient discontinues drug and does not proceed to consolidation or maintenance, an End of Treatment visit is strongly recommended with a physical examination. Physical exams that are performed as per institutional standard of care will also be collected upon sponsor's request to assess safety.

h. Weight, PS and vital signs (temperature, blood pressure, pulse & respiratory rate) should be collected at each scheduled visit for physical examination. (For times of physical examination refer to description under [g]) Height will only be captured at screening.

i. Hematology assessments include complete blood count with differential and platelet count. Hematology labs should be drawn at screening and during induction 1 on day 1, first day of crenolanib (day 5, 6 or 8) and weekly until end of cycle. If patient continues to induction 2, hematology labs will be required on day 1 and every other week until end of cycle. If patient discontinues drug and does not proceed to consolidation or maintenance, an End of Treatment visit is strongly recommended with hematology labs. Labs should be drawn per study schedule; however, routine labs that are drawn as per institutional standard of care will also be collected upon sponsor's request to assess safety. (Local labs will be accepted, these labs must be sent to the central site)

j. Chemistry assessments include glucose, bicarbonate, protein, serum creatinine, creatinine clearance, sodium, potassium, calcium, blood urea nitrogen (BUN), albumin, total bilirubin, alkaline phosphatase, AST, ALT and LDH. Chemistry labs should be drawn for screening within ≤ 3 days prior to enrollment and **again within 24 hours prior to crenolanib commencement (This lab will be drawn to confirm patient has normal liver function prior to starting crenolanib as defined by eligibility criteria)**. Chemistry assessments will occur during induction 1 on day 1, first day of crenolanib (day 5, 6 or 8) and weekly until end of cycle. If patient continues to induction 2, chemistry labs will be required on day 1 and every other week until end of cycle. If patient discontinues drug and does not proceed to consolidation or maintenance, an End of Treatment visit is strongly recommended with chemistry labs. Labs should be drawn per study schedule; however, routine labs that are drawn as per institutional standard of care will also be collected upon sponsor's request to assess safety. (Local labs will be accepted, these labs must be sent to the central site)

k. Serum or urine pregnancy test (β-HCG) within 3 days of first dose of study drug for women of child-bearing potential.

l. Peripheral blood will be drawn to assess PK at these time points **at the first dose of crenolanib**: **Induction 1 at day 5, 6, or 8** (this will be dependent on the choice of chemo regimen, this should be day 1 of crenolanib administration) pre-dose and post-dose at 2 hours (± 15 minutes), 4 hours (±30 minutes), 8 hours (±2 hours), and 24 hours (±6 hours)

m. Bone marrow aspirate within the 28 days preceding study enrollment. Cytogenetics will be obtained prior to therapy (results from prior analysis can be used for this purpose, if done within 6 months). Bone marrow assessments on study will be done per institutional SOC.

n. Adverse events are to be assessed at each visit and recorded in the source records and appropriately reported in the EDC.

o. Induction 2 will be allowed (per physician's discretion) if patient does not achieve a CR or CRp and cannot proceed to consolidation or maintenance.

p. This visit will only take place following induction if patient does not continue to consolidation or maintenance. This visit is strongly recommended, all measures should be taken to ensure this visit occurs. An End of Treatment visit should be performed within 30 days post last dose of crenolanib (prior to initiation of new treatment regimen or HSCT). This visit will include physical exams, vitals, ECOG PS, weight, CBC and CMPs; concomitant medications and adverse events should also be assessed. This visit will also require a whole blood sample to be drawn for biomarker and genetic testing.

q. An End of Study assessment will be performed for all patients to record overall survival. (This assessment will occur upon the completion of the study)

Arm 1: Consolidation (maximum 6 consolidations allowed)						
Procedure	**Consolidation 1** (Minimum of 28 days Maximum duration of 60 days)			**Consolidation 2-N** [i] (Minimum of 28 days Maximum duration of 60 days)	**End of Treatment** [j] (within 30 days post last dose of crenolanib)	**End of Study** [k]
	Day 1	**Day 5**	**Every other week***	**Day 1**		
Concomitant medications [a]	x		x	x	x	
Physical examination [b]	x			x	x	
Vitals, ECOG PS, Weight, Height [c]	x			x	x	
Hematology [d]	x		x	x	x	
Blood chemistries [e]	x		x	x	x	
PK analysis [f]		x				
Bone marrow aspiration [g]	x [g]					
Adverse events [h]	x		x	x	x	
Blood for biomarker and genetic testing					x	
Survival follow-up						x

Key

* Procedures and assessments to be performed every other week until end of cycle (cycle length cannot exceed 60 days)

a. Concomitant medications are to be recorded in the source records and appropriately reported in the EDC at visit.

b. Complete physical examination should be performed on day 1 of each cycle. If patient discontinues drug and does not proceed to maintenance, an End of Treatment visit is strongly recommended with a physical examination. Physical exams that are performed as per institutional standard of care will also be collected upon sponsor's request to assess safety.

c. Weight, PS and vital signs (temperature, blood pressure, pulse & respiratory rate) should be collected at each scheduled visit for physical examination. (For times of physical examination refer to description under [b]) Height will only be captured at screening.

d. Hematology assessments include complete blood count with differential and platelet count. Hematology labs should be drawn at screening and during consolidation 1 on day 1 and every other week until end of cycle. If patient continues to consolidation 2 (or beyond), hematology labs will be required on day 1. If patient discontinues drug and does not proceed to maintenance, an End of Treatment visit is strongly recommended with hematology labs. Labs should be drawn per study schedule; however, routine labs will that are be drawn as per institutional standard of care will also be collected upon sponsor's request to assess safety. (Local labs will be accepted, these labs must be sent to the central site)

e. Chemistry assessments include glucose, bicarbonate, protein, serum creatinine, creatinine clearance, sodium, potassium, calcium, blood urea nitrogen (BUN), albumin, total bilirubin, alkaline phosphatase, AST, ALT and LDH. Chemistry labs should be drawn during consolidation 1 on day 1 and every other week until end of cycle. If patient continues to consolidation 2 (or beyond), chemistry labs will be required on day 1. If patient discontinues drug and does not proceed to maintenance, an End of Treatment visit is strongly recommended with chemistry labs. Labs should be drawn per study schedule; however, routine labs that are drawn as per institutional standard of care will also be collected upon sponsor's request to assess safety. (Local labs will be accepted, these labs must be sent to the central site)

f. Peripheral blood will be drawn to assess PK at these time points at **day 5 (of consolidation)** (depending on when patient starts crenolanib, **this should be first day of crenolanib administration**) pre-dose and post-dose at 2 hours (± 15 minutes), 4 hours (±30 minutes), and 8 hours (±2 hours).

g. Bone marrow assessments on study will be done per institutional SOC.

h. Adverse events are to be assessed at each visit and recorded in the source records and appropriately reported in the EDC.

i. Subsequent consolidation cycleswill be allowed per physician's discretion. Up to 6 cycles of consolidation will be allowed.

j. This visit will only take place following induction if patient does not continue to maintenance. This visit is strongly recommended, all measures should be taken to ensure this visit occurs. An End of Treatment visit should be performed within 30 days post last dose of crenolanib (prior to initiation of new treatment regimen or HSCT). This visit will include physical exams, vitals, ECOG PS, weight, CBC and CMPs; concomitant medications and adverse events should also be assessed. This visit will also require a whole blood sample to be drawn for biomarker and genetic testing.

k. An End of Study assessment will be performed for all patients to record overall survival. (This assessment will occur upon the completion of the study)

Arm 1: Maintenance (maximum 365 days of crenolanib allowed)			
Procedure	**Maintenance Day 1 of Cycle N (1 cycle is 28 days)**	**End of Treatment** [i] (within 30 days post last dose of crenolanib)	**End of Study** [j]
Concomitant medications [a]	x	x	
Physical examination [b]	x	x	
Vitals, ECOG PS, Weight, Height [c]	x	x	
Hematology [d]	x	x	
Blood chemistries [e]	x	x	
Bone marrow aspiration [f]	x [f]		
Blood for biomarker and genetic testing		x	
Adverse events [g]	x	x	
Crenolanib administration [h]	x		
Survival follow-up			x

Key

a. Concomitant medications are to be recorded in the source records and appropriately reported in the EDC at each visit.
b. Physical exams may be performed on day 1 of every cycle (28 day cycles).
c. Weight, PS and vital signs (temperature, blood pressure, pulse & respiratory rate) should be collected at each scheduled visit for physical examination. (For times of physical examination refer to description under [c])
d. Hematology assessments include complete blood count with differential and platelet count. During maintenance, labs may be performed on day 1 of every cycle (28 day cycles). Labs should be drawn per study schedule; however, routine labs will that are be drawn as per institutional standard of care will also be collected upon sponsor's request to assess safety. (Local labs will be accepted, these labs must be sent to the central site)
e. Chemistry assessments include glucose, bicarbonate, protein, serum creatinine, creatinine clearance, sodium, potassium, calcium, blood urea nitrogen (BUN), albumin, total bilirubin, alkaline phosphatase, AST, ALT and LDH. Chemistry labs should be drawn during maintenance on day 1 of every cycle (28 day cycles). Labs should be drawn per study schedule; however, routine labs will that are be drawn as per institutional standard of care will also be collected upon sponsor's request to assess safety. (Local labs will be accepted, these labs must be sent to the central site)
f. Bone marrow should be drawn as per the institutional standard of care during maintenance
g. Adverse events are to be assessed at each visit and recorded in the source records and appropriately reported in the EDC.
h. Crenolanib will be administered continuously on days 1-28 during each cycle of maintenance. Patients and/or a caregiver will be trained for home administration of the study medication. For crenolanib training must include the use of the patient diary (Appendix II), study drug storage, management of missed doses, and emergency contact information.
i. This visit is strongly recommended, all measures should be taken to ensure this visit occurs. An End of Treatment visit should be performed within 30 days post last dose of crenolanib (prior to initiation of new treatment regimen or HSCT). This visit will include physical exams, vitals, ECOG PS, weight, CBC and CMPs; concomitant medications and adverse events should also be assessed. This visit will also require a whole blood sample to be drawn for biomarker and genetic testing.
j. An End of Study assessment will be performed for all patients to record overall survival. (This assessment will occur upon the completion of the study)

STUDY SCHEDULE FOR ARM 2 (CRENOLANIB AND AZACITIDINE):

	Screening [a]	**Cycle 1** (28 days)				**Cycle 2** (28 days)		**Cycle 3-N** (28 days)	**Maintenance**[b] (up to 365 days)	**End of Treatment** [c]	**End of Study** [d]
	Day -28 to Day -1	Day 1	Day 8	Day 15	Day 22	Day 1	Day 15	Day 1 of Cycle 3-N	Day 1 of Cycle N (1 cycle is 28 days)	Within 30 days post last dose of crenolanib	
Informed Consent [e]	x										
Inclusion/Exclusion [f]	x										
Demographics [g]	x										
Relevant medical history [h]	x										
Evaluation of FLT3 and other mutational status	x										
Concomitant medications [i]	x	x	x	x	x	x	x	x	x	x	
Physical examination [j]	x	x	x	x	x	x	x	x	x	x	
Vitals, ECOG PS, Weight, Height [k]	x	x	x	x	x	x	x	x	x	x	
Hematology [l]	x	x	x	x	x	x	x	x	x	x	
Blood chemistries [m]	x	x	x	x	x	x	x	x	x	x	
Pregnancy test [n]	x										
EKG	x										
Echocardiogram	x										
Blood for PK analysis [o]		x									
Blood for biomarker and genetic testing [p]	x									x	
Bone marrow aspirations [q]	x	x [q]									
Adverse events [r]		x	x	x	x	x	x	x	x	x	
Survival Follow-up											x

Key

a. Screening procedures are to be performed ≤ 28 days prior to enrollment with the exception of the following: Hematology labs are to be drawn ≤ 7 days prior to enrollment, pregnancy test if applicable is to be performed ≤ 3 days prior to enrollment, and chemistry panel (with LFTs) is to be drawn ≤ 3 days prior to enrollment .

b. Crenolanib may be administered for maintenance therapy for up to 365 days. Cycles of crenolanib will be 28 days. Physical exams, vitals, ECOG PS, weight, CBC and CMPs will be performed on Day 1 every cycle. At each visit concomitant medications and adverse events should be assessed.

c. This visit is strongly recommended, all measures should be taken to ensure this visit occurs. An End of Treatment visit should be performed within 30 days post last dose of crenolanib (prior to initiation of new treatment regimen or HSCT). This visit will include physical exams, vitals, ECOG PS, weight, CBC and CMPs; concomitant medications and adverse events should also be assessed. This visit will also require a whole blood sample to be drawn for biomarker and genetic testing.

d. An End of Study assessment will be performed for all patients to record overall survival. (This assessment will occur upon the completion of the study)

e. Written consent must be obtained prior to performing any protocol-specific procedure. Results of a test performed as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame.

f. All inclusion/exclusion criteria should be met and confirmed by the sponsor prior to enrollment.

g. Demographics should be assessed at screening and are defined as race, ethnicity, age, and gender.

h. Relevant medical history should be recorded in the EDC at screening.

i. Concomitant medications are to be recorded in the source records and appropriately reported in the EDC at screening and each subsequent visit.
j. Complete physical examination should be performed at screening, Cycle 1 day 1, 8, 15 and 22, Cycle 2 day 1 and 15 and on Day 1 of Cycle 3-N. Physical examination should be performed Day 1 of every cycle during maintenance. Physical examination should be performed at End of Treatment visit.
k. Weight, PS and vital signs (temperature, blood pressure, pulse & respiratory rate) should be collected at each scheduled visit for physical examination. (For times of physical examination refer to description under [j]) Height will only be captured at screening.
l. Hematology assessments include complete blood count with differential and platelet count. Hematology labs should be drawn at screening, Cycle 1 day 1, 8, 15 and 22, Cycle 2 day 1 and 15 and on Day 1 of Cycle 3-N. Hematology labs should be drawn Day 1 of every cycle during maintenance. Hematology labs should also be drawn at the End of Treatment visit. Labs should be drawn per study schedule; however, routine labs will that are be drawn as per institutional standard of care will also be collected upon sponsor's request to assess safety. (Local labs will be accepted, these labs must be sent to the central site)
m. Chemistry assessments include glucose, bicarbonate, protein, serum creatinine, creatinine clearance, sodium, potassium, calcium, blood urea nitrogen (BUN), albumin, total bilirubin, alkaline phosphatase, AST, ALT and LDH. Chemistry labs should be drawn for screening within ≤ 3 days prior to enrollment and **again within 24 hours prior to crenolanib commencement (This lab will be drawn to confirm patient has normal liver function prior to starting crenolanib as defined by eligibility criteria)**. Chemistry assessments will occur Cycle 1 day 1, 8, 15 and 22, Cycle 2 day 1 and 15 and on Day 1 of Cycle 3-N. Chemistry labs should be drawn Day 1 of every cycle during maintenance. Chemistry labs should also be drawn at the End of Treatment visit. Labs should be drawn per study schedule; however, routine labs will that are be drawn as per institutional standard of care will also be collected upon sponsor's request to assess safety. (Local labs will be accepted, these labs must be sent to the central site)
n. Serum or urine pregnancy test (β-HCG) within 3 days of first dose of study drug for women of child-bearing potential.
o. Peripheral blood will be drawn to assess PK at these time points at the first dose of crenolanib: **C1D1** pre-dose and post-dose at 2 hours (± 15 minutes), 4 hours (±30 minutes), 8 hours (±2 hours), and 24 hours (±6 hours)
p. Blood for biomarker and genetic testing should be drawn at baseline and at the end of treatment visit.
q. Bone marrow aspirations: at baseline (within 28 days) and as per the institutional standard of care.
r. Adverse events are to be assessed at each visit and recorded in the source records and appropriately reported in the EDC.

10. CRITERIA FOR RESPONSE

For AML, response criteria will be modified from the International Working Group for AML [28]. 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:

(1). Complete Remission (CR)

- **Peripheral blood counts:**
  - No circulating blasts
  - Neutrophil count ≥1.0 $x10^9$/L
  - Platelet count ≥100 $x10^9$/L
- **Bone marrow aspirate and biopsy:**
  - ≤5% blasts
  - No Auer rods
  - No extramedullary leukemia

(2). Complete Remission with Incomplete Blood Count Recovery (CRi)

- **Peripheral blood counts:**
  - No circulating blasts
  - Neutrophil count <1.0 $x10^9$/L, or
  - Platelet count <100 $x10^9$/L
- **Bone marrow aspirate and biopsy:**
  - ≤ 5% blasts
  - No Auer rods
  - No extramedullary leukemia

(3). Partial Remission (PR)

- 50 % reduction in bone marrow blast and to >5% and <20%.

(4). Morphologic Leukemia-Free State

- Bone marrow: ≤ 5% myeloblasts

(5). 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 $x10^9$/L)
  Absolute increase of ≥ 30 x 10^9/L for patients starting with > 20 x 10^9/L platelets
  Increase from < 20 x 10^9/L to > 20 x 10^9/L and by at least 100%
- **Neutrophil response (N)** (pretreatment ANC <1.0 $x10^9$/L)
  At least 100% increase and an absolute increase > 0.5 x 10^9/L
- **Blast response (B)**
  At least a 50% reduction in blast percentage in peripheral blood (if > 5%) or bone marrow

For high-risk MDS, response will use the International Working Group criteria [29].

11. ADVERSE EVENT REPORTING

Adverse event is any untoward medical occurrence that may present during treatment with a pharmaceutical product, but does not necessarily have a causal relationship with this treatment.

Adverse drug reaction is a response to a drug that is noxious and unintended, which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function.

Assessing causal connections between agents and disease is fundamental to the understanding of adverse drug reactions. In general, a drug may be considered a contributory cause of an adverse event if, had the drug not been administered, 1) the event would not have happened at all, 2) the event would have occurred later than it actually did, or 3) the event would have been less severe.

The Investigator or physician designee is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for each event for all subjects enrolled on the trial.

Adverse Events (AEs) will be evaluated according to the latest CTC version 4.03 and documented in medical record.

Captured AEs include:

1) Any new AE regardless of its grade or expectedness post study drug initiation
2) Worsening of any expected or unexpected AEs determined by the principal investigator as related to crenolanib

11.1. Disease Related Events

Adverse Events (AEs) will be evaluated according to the latest CTCAE version 4.03 and documented in medical record. Principal investigator should review and provide documentation of all baseline comorbidities related to the preexisting conditions and/or current medications prior to initiation of cycle one. These events will not be considered as related to crenolanib treatment. If these events continue during the treatment phase they do not need to be captured in the case report form.

Expected events during leukemia therapy are:

- Myelosuppression related events (due to disease or leukemia therapy)
- Febrile or infection episodes not requiring management in the intensive care unit
- Epistaxis or bleeding except for catastrophic CNS or pulmonary hemorrhage
- Anemia, neutropenia, lymphopenia, thrombocytopenia, leukopenia

11.1.1. Symptoms Associated with Anemia:

- Fatigue
- Weakness
- Shortness of breath
- Electrolyte abnormalities (sodium, potassium, bicarbonate, CO2, magnesium)
- Chemistry abnormalities (LDH, phosphorus, calcium, BUN, protein, albumin, uric acid, alkaline phosphatase, glucose)

- Coagulation abnormalities
- Disease specific therapy (induction, maintenance, salvage, or stem cell therapy)
- Alopecia
- Bone, joint, or muscle pain
- Liver function test abnormalities associated with infection or disease progression
- Disease progression
- Abnormal hematologic values

11.1.2. General Therapy Related Events:

- Catheter related events
- Renal failure related to tumor lysis syndrome or antibiotic/ antifungal therapy
- Rash related to antibiotic use
- Hospitalization for the management of any of the above expected events

Abnormal hematologic values will not be recorded on the case report form. For abnormal chemical values, the apogee or nadir (whichever is appropriate) will be reported per course on the case report form.

11.2. Serious Adverse Event (SAE) Reporting

A serious adverse event is – any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity – a substantial disruption of a person's ability to conduct normal life functions.
- A pregnancy or congenital anomaly/birth defect.
- Important medical events that do not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

Any important medical event may be reported as an SAE if deemed appropriate by the Principal Investigator, the IND Sponsor, or the Office of Research Education and Regulatory Management (ORERM) for MDACC held INDs.

All serious adverse events must be reported to the sponsor within 24 hours of the site becoming aware of the event. All serious adverse events will be recorded in the case report form.

All serious adverse events occurring during the conduct of a protocol will be reported (either via expedited report or log) to the IRB in accordance with the timeframes and procedures outlined in "University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy on Reporting Serious Adverse Events" For MDACC held INDs, these events will also be reported to ORERM and to AROG (Sponsor) following the same reporting guidelines in the policy above.

- All life-threatening or fatal events, expected or unexpected, and regardless of attribution to the study drug, must have a written report submitted within 24 hours (next working day) of knowledge of the event to the Safety Project Manager in ORERM and to AROG.
- The MDACC "Internal SAE Report Form for Prompt Reporting" will be used for reporting to ORERM and to AROG.
- Serious adverse events will be captured from the time the patient signs consent until 30 days after the last dose of drug. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- Additionally, any serious adverse event that occur after the 30 day time period that is related to the study treatment must be reported to IRB, ORERM, and to AROG. This may include the development of a secondary malignancy.

11.3. Reporting to FDA

Serious adverse events will be forwarded to FDA by the IND Sponsor (AROG) according to 21 CFR 312.32.

It is the responsibility of the PI and the research teams to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

12. STATISTICAL CONSIDERATIONS

12.1. General Considerations

There will be two parallel arms for the study: one for Crenolanib Combined with standard salvage chemotherapy; the other is for Crenolanib Combined with 5-Azcytadine in Patients with Acute Myeloid Leukemia with Activating FLT3 Mutations. Arm 1 is for the AML or high-risk MDS patients who are refractory or has relapsed after prior therapy. Patients will be treated with standard salvage chemotherapy combined with crenolanib. Arm 2 is for the AML or high-risk MDS with no more than one prior salvage therapy or previously untreated. Patients will receive azacitidine combined with crenolanib. For each arm, there will be a phase I part to identify the MTD of crenolanib combined with either standard salvage chemotherapy or 5-Azcytidine.

Phase I

Table 12.1. Dose levels of Crenolanib (applies to both Arms 1 and 2)

Dose Level	Crenolanib mg PO daily
0	60 mg BID
1 (Starting dose)	60 mg TID

2	80 mg TID
3	100 mg TID

First, phase I study is performed to assess the safety of different dosing regimens. Three combination dose levels are defined; the starting dose is dose 1. Dose levels of crenolanib apply to both arm 1 and 2. A Rolling-6 design will be used to for dose escalation and de-escalation. A maximum of 18 patients will enroll in the phase I study. Patients will be entered sequentially to each dose level. The DLT in phase I is based on the 1st cycle adverse event. If at least 2 of 3 or 2 of up to 6 patients experience a DLT at the starting dose level, then deescalate to the next lower dose. The MTD is defined as the highest dose level in which <2 patients of 6 develop first cycle DLT.

Phase II

The method of Thall, Simon and Estey [30] will be used for futility and toxicity monitoring for each arm. The 6 patients treated in the phase I MTD dose will be included in the phase II part. The primary endpoint is the response rate (CR+CRi+CRp+PR) after one or two cycles of treatment. The historical data suggested the response rate is 10%. With the assumption that the improved response rate to be 25%, it is estimated that a total of 32 evaluable patients including the 6 patients from phase I will yield 79% power at a significance level of 10% (two-sided) based on chi-square test (nQuery software version 7.0).

The response (CR+CRi+CRp+PR) denoted as RR, and toxicity (grade 3 or 4 non-hematologic toxicity not expected from chemotherapy alone), denoted as TOX, will be monitored simultaneously by Bayesian stopping boundaries calculated based on beta-binomial distribution. Independence is assumed between RR and TOX. There are no historical data available. The current regimen will be considered promising if the RR rate is at least 25% and the TOX rate is below 30%. The prior probabilities of RR and TOX for the regimen are modeled by beta distributions (*Beta*(0.5, 1.5) and *Beta*(0.6, 1.4), respectively). Denoting the probabilities of the RR rate and TOX by $\{\theta_{RR}, \theta_{TOX}\}$, the following decision criteria will be applied:

1) stop if Prob$\{ \theta_{RR} < 0.25 \mid \text{data}\} > 0.98$, and
2) stop if Prob$\{ \theta_{TOX} > 0.3 \mid \text{data}\} > 0.85$

Patients will be monitored by a cohort size of 4 according to the following stopping boundaries for RR and toxicity. If the number of responses required for moving the trial to next stage has not been achieved, the patient enrollment will be halted until enough responses observed. The design software Multc Lean Desktop (version 2.1) developed by the Department of Biostatistics at MD Anderson Cancer Center (MDACC) was used to generate the futility/toxicity stopping boundaries and the OC table.

Table 12.2. Stopping boundaries for response (RR) and toxicity

Number of patients evaluated	Stop the trial if there are this many response	Stop the trial if there are this many unacceptable toxicities
4	Never stop	3-4
8	Never stop	5-8
12	0	6-12

16	0	7-16
20	0-1	9-20
24	0-2	10-24
28	0-2	12-28

The operating characteristics are summarized in the following table.

Table 12.3. Operating characteristics of efficacy and safety monitoring

True Toxicity Rate	True RR Rate	Prob (stop the trial early)
0.1	0.05	0.90
	0.1	0.61
	0.15	0.33
	0.25	0.07
	0.35	0.01
0.2	0.05	0.9
	0.1	0.63
	0.15	0.37
	0.25	0.12
	0.35	0.07
0.3	0.05	0.93
	0.1	0.72
	0.15	0.52
	0.25	0.33
	0.35	0.29
0.4	0.05	0.96
	0.1	0.86
	0.15	0.76
	0.25	0.67
	0.35	0.65

Summary statistics will be provided for continuous variables. Frequency tables will be used to summarize categorical variables. The response (RR) rate will be estimated along with the exact 95% confidence interval.

Data from all subjects who receive any study drug will be included in the safety analyses. 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.

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

Justification for using a higher rate of serious toxicity for the early stopping criteria:
Refractory or relapsed AML remains among the most challenging scenarios in the management of AML due to lack of highly effective and standardized treatments for this situation. These patients are willing to take the risk of receiving an investigation drug to increase their chance of survival compared to average patients. Whenever possible, refractory/relapsed patients should be enrolled in clinical trials. The stopping boundary is set as such to make sure the trial will not get terminated prematurely due to serious toxicities which occurs if the boundary is too low.

12.2. Patient Disposition

A detailed description of patient disposition, broken by cohort, will be provided. It will include:

- Summary of patients entered
- Total number of patients entered
- Total number of patients enrolled
- Summary of reasons for patients entered, but not enrolled
- Summary of reasons for patient discontinuation from study treatment
- Summary of all identified important protocol violations

12.3. Patient Characteristics

Patient characteristics will be reported for each cohort, and include a summary of the following:

- Patient demographics
- Baseline disease characteristics
- Pre-existing conditions
- Prior therapies

Other patient characteristics will be summarized as deemed appropriate.

12.4. Determination of sample size

A total of 88 AML patients with FLT3 activating mutation will be enrolled. There are two study arms (44 patients per arm). Patients will receive crenolanib with chemotherapy. Arm 1 is for the AML or high-risk MDS patients who are refractory or has relapsed after prior therapy. Patients will be treated with standard salvage chemotherapy combined with crenolanib. Arm 2 is for the AML or high-risk MDS. Patients will receive azacitidine combined with crenolanib. For each arm, there will be 44 patients: in phase I, with 3 dose levels and Rolling-6 design, a maximum of 18 patients will be needed. With the 6 patients in the MTD dose enrolled in the following phase II part, for each arm, there will be 32 patients in total for phase II. In phase II, the primary endpoint is the response rate (CR+CRi+PR) after one or two cycles of treatment. The historical data suggested the response rate is 10%. With the assumption that the improved response rate to be 25%, it is estimated that a total of 32 evaluable patients

including the 6 patients from phase I will yield 79% power at a significance level of 10% based on chi-square test (nQuery software version 7.0).

12.5. Concomitant Therapy

Concomitant medication will be reported overall as well as summarized in a frequency table using the terms recorded on the CRF. If warranted, an attempt may be made to determine how concomitant medications are related to observed study outcomes.

12.6. Treatment Compliance

Treatment compliance information will be collected through pill counts at each tumor assessment visit and also by analyzing patient diaries where patients will record their daily drug intake. The estimate of percent compliance will be given by:

$$\text{Percent Compliance} = \frac{\text{Actual number of pills taken}}{\text{Number of pills expected to be taken}} \times 100$$

The number of tablets taken will be determined by counting the number of tablets returned at each visit and subtracting that number from the number of tablets dispensed. The number of tablets expected to be taken will be determined by the assigned dose and taking into account any prescribed dose reductions and omissions.

No minimal level of compliance will be defined for patient inclusion in efficacy analyses. An exploratory analysis of compliance may be performed by regressing percent compliance on selected efficacy endpoints. If significant results are indicated, analysis may be performed to determine the level of compliance that best delineates each endpoint.

12.7. Criteria for End of Study

This study will be considered complete following the data cut-off date for the final analysis. Documentation of the data cut-off will be included in the master study file.

After the final analysis, if patients are continuing to benefit from study treatment, they will be allowed to continue receiving study treatment. If patients continue on crenolanib beyond study closure, safety data must be collected. If further data are collected that are not included as part of the final locked database, the post hoc data will eventually be combined with the locked database and stored in a data library separate from the locked database.

13. DATA QUALITY MANAGEMENT

13.1. Data Quality Assurance

The quality of data will be ensured by the following:

· Creating, implementing, and upholding standard operating procedures (SOPs) for trial execution

· A quality scientific and medical design of the protocol: Changes to the protocol will be made only when protocol amendments have been signed by the principal investigator and approved by the sponsor and the IRB of the study center.

· Clinical investigator and site pre-assessment and selection
· Regulatory agency and ethics committee approval
· Developing and providing appropriate informed consent (language, transparency of benefits and risks) and obtaining ethics committee approval of the informed consent process
· Investigator meetings and training: Biweekly teleconferences with personnel at the study site will be set up to exchange key trial information and updates.
· Adequate recording and reporting of data: A robust electronic data capture system (MERGE eClinical OS) is being implemented. This will ensure timely capture and verification of safety information. All patient data (including source data) generated in connection with this study will be kept in the archives 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.
· Periodic monitoring and audits: Sponsor will perform periodic on-site visits by monitors monthly for the duration of the study. Significant findings identified as a result of monitoring will be escalated for review by the sponsor, which may then be managed as a suspected significant deviation. Risk assessments and evaluations are then conducted. Remedial actions may include notifying regulatory authorities and ethics committees of any significant regulatory and/or GCP requirements.

13.2. Data Safety Monitoring Plan

Adverse events will be monitored during the treatment and post-treatment follow up periods. Adverse events will be monitored on a continuous basis by the Sponsor.

The Sponsor will conduct a biweekly teleconference with the study site to review safety data from this trial. A more frequent evaluation will be performed if accrual is rapid. The Sponsor and its medical consultants will convene to analyze the safety data at least every six months, or at the completion of each dose level (to determine whether it is safe to proceed to the next dose level), or for every 6 patients enrolled on the expanded cohort, whichever occurs earlier. The Sponsor will also monitor the safety outcomes listed below for purposes of determining if enrollment in one or both cohorts should continue or be halted. Within each cohort, up to 6 patients will be initially enrolled and analyzed for safety. Patients will be enrolled in a sequential manner such that no more than 3 patients are within 30 days of starting induction 1 therapy. Enrollment will be halted within a cohort if an apparent increase is observed in the occurrence of one or more of the following outcomes:

· Early mortality due to any cause
· Expected, non-hematologic, crenolanib-related toxicity (CTCAE Grade 4.03)
· Unexpected, non-hematologic, crenolanib-related toxicity (CTCAE Grade 4.03)

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APPENDIX I. ADMINISTRATIVE PROCEDURES

Protocol Amendments, Other Changes to the Protocol

Any change or addition to this protocol requires a written protocol amendment that must be approved by the investigator before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation or the scientific quality of the study, require additional approval by the IRB/IEC/REB of all centers, and, in some countries, by the regulatory authority. A copy of the written approval of the IRB/IEC/REB, which becomes part of the protocol, must be given to all the monitors and supporters of the protocol. Examples of amendments requiring such approval are:

1. an increase in drug dosage or duration of exposure of subjects
2. a significant change in the study design (e.g. addition or deletion of a control group)
3. an increase in the number of invasive procedures to which subjects are exposed
4. addition or deletion of a test procedure for safety monitoring.

These requirements for approval should in no way prevent any immediate action from being taken by the investigator in the interests of preserving the safety of all subjects included in the trial. If an immediate change to the protocol is felt to be necessary by the investigator and is implemented by him/her for safety reasons, the sponsor should be notified and the IRB/IEC/REB at the center should be informed within 10 working days or per institutional policy.
Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB/IEC/REB approval but the IRB/IEC/REB of each center must be kept informed of such administrative changes. Examples of administrative changes not requiring formal protocol amendments and IRB/IEC/REB approval that can be treated as administrative amendments include:

1. changes in the staff used to monitor trials (e.g. AROG Pharmaceuticals staff versus a CRO)
2. minor changes in the packaging or labeling of study drug.

Publication of Results

Any formal presentation or publication of data from this trial will be considered as a joint publication by the investigator(s) and appropriate AROG Pharmaceuticals personnel. Authorship will be determined by mutual agreement. For multicenter studies it is mandatory that the first publication is based on data from all centers, analyzed as stipulated in the protocol, and not by the investigators. Investigators participating in multicenter studies agree not to present data gathered from one center or a small group of centers before the full publication, unless formally agreed to by all other investigators and AROG Pharmaceuticals.
AROG Pharmaceuticals must receive copies of any intended communication in advance of publication (at least 15 working days for an abstract or oral presentation and 45 working days for a journal submission). AROG Pharmaceuticals will review the communications for accuracy (thus avoiding potential discrepancies with submissions to health authorities), verify that confidential information is not being inadvertently divulged and provide any relevant supplementary information.

Disclosure and Confidentiality

The investigator agrees to keep all information provided by AROG Pharmaceuticals in strict confidence and to request similar confidentiality from his/her staff and the IRB/IEC/REB. Study documents provided by AROG Pharmaceuticals (protocols, investigators' brochures, case report forms and other

material) will be stored appropriately to ensure their confidentiality. The information provided by AROG Pharmaceuticals to the investigator may not be disclosed to others without direct written authorization from AROG Pharmaceuticals as applicable, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial.

Discontinuation of Study

AROG Pharmaceuticals reserves the right to discontinue any study under the conditions specified in the clinical trial agreement.

Ethics and Good Clinical Practice

This study must be carried out in compliance with the protocol and the principles of Good Clinical Practice, as described in AROG Pharmaceuticals standard operating procedures and:

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996.
   Directive 91/507/EEC, The Rules Governing Medicinal Products in the European Community.
2. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).
3. Declaration of Helsinki and amendments, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects).
4. The investigator agrees when signing the protocol to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

Institutional Review Board/Independent Ethics Committee

Before implementing this study, the protocol, the proposed informed consent form and other information to subjects, must be reviewed by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB). A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB must be given to AROG Pharmaceuticals before study initiation. Any amendments to the protocol, other than administrative ones, must be approved by this committee.

Informed consent

The investigator must explain to each subject (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it, and should be given a copy of the signed document. If the subject cannot read or sign the documents, oral presentation may be made or signature given by the subject's legally appointed representative, if

witnessed by a person not involved in the study, mentioning that the patient could not read or sign the documents. No patient can enter the study before his/her informed consent has been obtained.

The informed consent form is considered to be part of the protocol, and must be submitted by the investigator with it for IRB/IEC/REB approval. AROG Pharmaceuticals supplies a proposed informed consent form, which complies with regulatory requirements and is considered appropriate for the study. Any changes to the proposed consent form suggested by the Investigator must be agreed to by AROG Pharmaceuticals before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the AROG Pharmaceuticals monitor after IRB/IEC/REB approval.

Declaration of Helsinki

The investigator must conduct the trial in accordance with the principles of the Declaration of Helsinki. Copies of the Declaration of Helsinki and amendments will be provided upon request or can be accessed via the website of the World Medical Association at http://www.wma.net/e/policy/17-c_e.html

APPENDIX II. PATIENT CRENOLANIB ADMINISTRATION DIARY

Cycle No:_____ **This section to be completed by Site Study Staff ONLY**

Investigational Drug: Crenolanib Besylate (CP-868,596-26)
Protocol ID: ARO-010

Prescribed Dose:_____ mg TID, Dosing:_____100 mg tablets_____20 mg tablets

SUBJECT ID | | | | | | | | | SUBJECT INITIAL | | |

Day	Date ___/___/___ m d y	Time Taken (HR-MIN AM/PM	Number of Tablets Taken (100 mg Tablet)	Number of Tablets Taken (20 mg Tablet)	If Dose Skipped Please Provide the Reason/s	With Food	If Yes, please provide Description of Meal	Any Side Effects (Please Complete Adverse Events Form in Detail)
1		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
2		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
3		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
4		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
5		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
6		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
7		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		

Cycle No:_____ **This section to be completed by Site Study Staff ONLY**

Investigational Drug: Crenolanib Besylate (CP-868,596-26)
Protocol ID: ARO-010

Prescribed Dose:_____ mg TID, Dosing:_____100 mg tablets_____20 mg tablets

SUBJECT ID | | | | | | | | | SUBJECT INITIAL | | |

Day	Date ___/___/___ m d y	Time Taken (HR-MIN AM/PM	Number of Tablets Taken (100 mg Tablet)	Number of Tablets Taken (20 mg Tablet)	If Dose Skipped Please Provide the Reason/s	With Food	If Yes, please provide Description of Meal	Any Side Effects (Please Complete Adverse Events Form in Detail)
8		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
9		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
10		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
11		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
12		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
13		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
14		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		

Cycle No:_____ **This section to be completed by Site Study Staff ONLY**

Investigational Drug: Crenolanib Besylate (CP-868,596-26)
Protocol ID: ARO-010

Prescribed Dose:_____ mg TID, Dosing:_____100 mg tablets_____20 mg tablets

SUBJECT ID | | | | | | | | | SUBJECT INITIAL | | |

Day	Date ___/___/___ m d y	Time Taken (HR-MIN AM/PM	Number of Tablets Taken (100 mg Tablet)	Number of Tablets Taken (20 mg Tablet)	If Dose Skipped Please Provide the Reason/s	With Food	If Yes, please provide Description of Meal	Any Side Effects (Please Complete Adverse Events Form in Detail)
15		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
16		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
17		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
18		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
19		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
20		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
21		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		

Cycle No:_____ **This section to be completed by Site Study Staff ONLY**

Investigational Drug: Crenolanib Besylate (CP-868,596-26)
Protocol ID: ARO-010

Prescribed Dose:_____ mg TID, Dosing:_____100 mg tablets_____20 mg tablets

SUBJECT ID | | | | | | | | | SUBJECT INITIAL | | |

Day	Date ___/___/___ m d y	Time Taken (HR-MIN AM/PM	Number of Tablets Taken (100 mg Tablet)	Number of Tablets Taken (20 mg Tablet)	If Dose Skipped Please Provide the Reason/s	With Food	If Yes, please provide Description of Meal	Any Side Effects (Please Complete Adverse Events Form in Detail)
22		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
23		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
24		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
25		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
26		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
27		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
28		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		

APPENDIX III. COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE); VERSION 4.03

Investigations						
	Grade					
dverse Event	1	2	3	4	5	
unt decreased	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L	-	
A finding based on laboratory test results that indicate a decrease in number of platelets in a blood specimen.						
count decreased	<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L	-	
A finding based on laboratory test results that indicate a decrease in number of neutrophils in a blood specimen.						
	Loss of appetite without alteration in eating habits	Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated	Associated with significant weight loss or malnutrition (e.g., inadequate oral caloric and/or fluid intake); tube feeding or TPN indicated	Life-threatening consequences; urgent intervention indicated	De	
A disorder characterized by a loss of appetite.						
	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	De	
A disorder characterized by frequent and watery bowel movements.						
	Fatigue relieved by rest	Fatigue not relieved by rest; limiting instrumental ADL	Fatigue not relieved by rest; limiting self care ADL	-	-	
A disorder characterized by a state of generalized weakness with a pronounced inability to summon sufficient energy to accomplish daily activities.						
	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	-	-	
A disorder characterized by a queasy sensation and/or the urge to vomit.						
	1 - 2 episodes (separated by 5 minutes) in 24 hrs	3 - 5 episodes (separated by 5 minutes) in 24 hrs	>=6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	De	
A disorder characterized by the reflexive act of ejecting the contents of the stomach through the mouth.						
ninotransferase	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-	
A finding based on laboratory test results that indicate an increase in the level of alanine aminotransferase (ALT or SGPT) in the blood specimen.						
aminotransferase	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-	
A finding based on laboratory test results that indicate an increase in the level of aspartate aminotransferase (AST or SGOT) in a blood specimen.						
abin increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN	-	
A finding based on laboratory test results that indicate an abnormally high level of bilirubin in the blood. Excess bilirubin is associated with jaundice.						

APPENDIX IV. DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

Life threatening: "Life threatening" means that the patient was at immediate risk of death from the adverse event as it occurred or it is suspected that use or continued use of the product would result in the patient's death. "Life threatening" does not mean that had an adverse event occurred in a more severe form it might have caused death (i.e., hepatitis that resolved without hepatic failure).

Hospitalization: Outpatient treatment in an emergency room is not in itself a serious adverse event, although the reasons for it may be (e.g., bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered adverse events if the illness or disease existed before the patient was enrolled on the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention: Medical and scientific judgment should be exercised in deciding whether a case is serious in a situation where important medical events may not be immediately life threatening or result in death, hospitalization, disability or incapacity but may jeopardize the patient or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring intravenous hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (e.g., neutropenia or anemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

Disease progression: Any events or hospitalizations that are unequivocally due to progression of disease must not be reported as serious adverse events.

The following factors should be considered when deciding if there is a "reasonable possibility" that an adverse event may have been caused by the investigational product.

- Time course of events and exposure to suspect drug: Has the patient actually received the suspect drug? Did the adverse event occur in a reasonable temporal relationship to the administration of suspect drug?
- Consistency with known drug profile: Was the adverse event consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR could the adverse event be anticipated from its pharmacological properties?
- De-challenge experience: Did the adverse event resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause: The adverse event cannot be reasonably explained by another etiology, such as the underlying disease, other drugs, other host, or environmental factors.
- Re-challenge experience: Did the adverse event reoccur if the suspected drug was reintroduced after having been stopped? Laboratory tests: Has a specific laboratory

investigation confirmed the relationship?

A “reasonable possibility” could be considered to exist for an adverse event when 1 or more of these factors exist.

In contrast, there would not be a “reasonable possibility” of causality if none of the above criteria apply, or if there is evidence of exposure and a reasonable time course, but any de-challenge (if performed) is negative or ambiguous, or there is another more likely cause of the adverse event.

In difficult cases, other factors could be considered such as the following:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Ambiguous cases should be considered as having a “reasonable possibility” of causal relationship, unless additional evidence becomes available to refute this.

If true progression is determined by subsequent imaging, then the date of progression returns to the earlier date with increasing mass.

APPENDIX V. LABORATORY MANUAL

Pharmacokinetic Assay

The study site will request a Pharmacokinetics (PK) Kit from AROG Pharmaceuticals to perform PK on each patient enrolled on the study. Site should contact Arog Pharmaceuticals at info@arogpharma.com or 1 214.593.0515 to request a Pharmacokinetics Kit.

Sampling Strategy: USE THE PK KIT PROVIDED BY THE SPONSOR
Peripheral blood for pharmacokinetic studies will be drawn at the following points:

Arm 1

a. Induction 1 cycle 1 day 5, 6 or 8 (**this will depend on the chemo regimen, this should be day 1 of crenolanib administration**), only 1 dose of crenolanib should be administered on this day to allow for PK testing)
    a. Pre-dose
    b. 2 hours (± 15 minutes)
    c. 4 hours (± 30 minutes)
    d. 8 hours (± 2 hours)
    e. 24 hours (± 6 hours) (This PK will be drawn on the second day of crenolanib administration, regular TID dosing of crenolanib should begin after this PK)
b. Consolidation 1 cycle 1 day 5 (**this should be day 1 of crenolanib administration**, the second dose of crenolanib should not be taken until after the 8 hour PK is drawn)
    a. Pre-dose
    b. 4 hours (±30 minutes)
    c. 8 hours (±2 hours)

Arm 2

Peripheral blood (for pharmacokinetics) will be drawn at the following times:

a. Cycle 1 Day 1 (only 1 dose of crenolanib should be administered on this day to allow for PK testing)
    a. Pre-dose
    b. 2 hours (± 15 minutes)
    c. 4 hours (± 30 minutes)
    d. 8 hours (± 2 hours)
    e. 24 hours (± 6 hours) (This PK will be drawn on the second day of crenolanib administration, regular TID dosing of crenolanib should begin after this PK)

Sampling Collection and Processing Instructions

- At the sampling time point, collect 10 mL of whole blood for each time point in an appropriately labeled red/orange-top tube containing thrombin and completely cover with aluminum foil to protect from light.
- The whole blood will remain at room temperature until clotted (approximately 5 minutes).
- The serum will be separated from whole blood by centrifugation at 1500xG for 10 minutes. Minimize light exposure during this process.

- Prepare screw-capped polypropylene collection tubes labeled with UPIN, date and time of collection. **For Day 5 (or day 6 or 8, depending on chemo regimen) of induction 1,** prepare an additional set of tubes containing tetrahydrauridine mark as cytarabine test (premade at -80C).
- The serum will be transferred to the appropriate tubes and covered with aluminum foil if not immediately frozen. Store at -80^{o}C within 1 hour of collection.
- Samples from each individual patient will be stored and batched for that patient. The date and time of sample collection, crenolanib dose, and **date and time of the last crenolanib dose** should be recorded on the appropriate Pharmacokinetics Data Collection Form (Forms 1, 2, and 3).

Sampling Handling and Shipping Instructions

- Samples should be shipped within **30 days** of the last sample collection, whenever feasible. Specimens collected should be shipped via **FedEx Priority Overnight** shipping for delivery Tuesday through Thursday. Weekend and holiday deliveries should be avoided.
- In preparation of shipping samples, contact AROG Pharmaceuticals at **samples@arogpharma.com** and Cynthia Gomez at **CGomez@microconstants.com** to notify of sample shipment and to provide the FedEx tracking number. AROG will provide a confirmation regarding receipt of email concerning the shipment to the site.
- Ship all pharmacokinetic samples on dry ice, along with a completed Pharmacokinetics Data Collection Form to:

Cynthia Gomez
Senior Project Coordinator
MicroConstants, Inc.
9050 Camino Santa Fe
San Diego, CA 92121
P 858.652.4600 . F 858.652.4699
E CGomez@microconstants.com
www.microconstants.com

Additional Information

If any additional information is needed for pharmacokinetic sampling, storage or shipment, please contact AROG Pharmaceuticals.
AROG Pharmaceuticals, Inc.
E: samples@arogpharma.com or aramachandran@arogpharma.com
O: +1 214-593-0515 (Abhijit Ramachandran)
F: +1 214.-594-0002

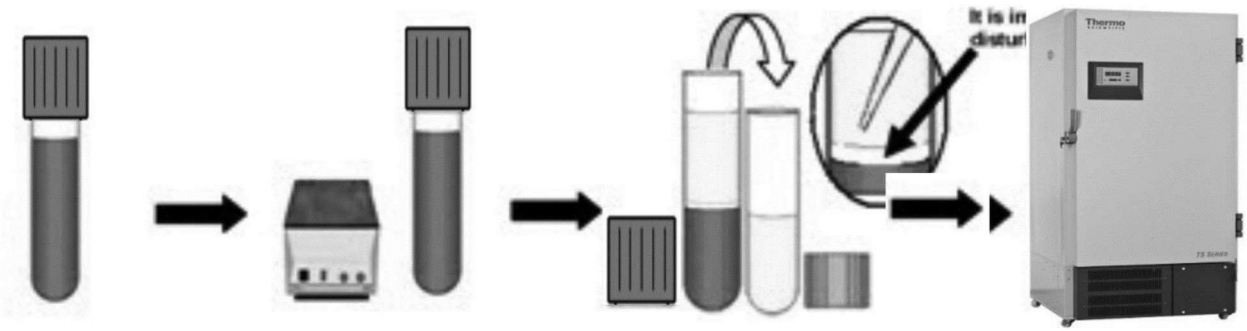

Figure 1: Sampling collection and processing instructions for Pharmacokinetic Assay

FORM 1 ARO-010 C_D_ (Induction or Consolidation) #__ Pharmacokinetics Data Collection Form

Study Accession #:	Study ID:	
Race:	Sex:	Date of Birth:
Height (cm):	Weight (kg):	
Total daily Crenolanib Dose (mg):	Today's Date:	

Fill in crenolanib dose date, time, and tolerance in the spaces below. **HOLD SECOND AND THIRD DOSE of crenolanib on the first day of crenolanib treatment during induction 1 or consolidation 1.** List the scheduled and actual times of the pharmacokinetic samples in the chart below. Scheduled time refers to the time that blood should be collected, and actual time refers to the actual time the blood was collected whether it is the same or different than the scheduled time. Blood should be collected as close to the scheduled time as possible.

Date of Dose: _____
Dose Administration Time:

_____
Describe Dose Tolerance:

_____

Course __ Day __ Samples	Date	Scheduled Time	Actual Time
Prior to crenolanib dose (pre)			
post crenolanib 2 hours (±15 minutes)			
post crenolanib 4 hours (±30 minutes)			
post crenolanib 8 hours (±2 h)			
post crenolanib 24 hours (±6 h)			

Name of person completing form: _____
Phone Number: _____
Email: _____
Date: _____

Please complete FORM 3 Pharmacokinetic Concomitant Medications with this form.

FORM 2 ARO-010 C_D_ in Consolidation # _ Pharmacokinetics Data Collection Form

Study Accession #:	Study ID:	
Race:	Sex:	Date of Birth:
Height (cm):	Weight (kg):	
Total daily Crenolanib Dose (mg):	Today's Date:	
Please mark cycle above		

Fill in crenolanib dose date, time, and tolerance in the spaces below. **Do not take second dose of crenolanib until 8h PK time point has been drawn.** List the scheduled and actual times of the pharmacokinetic samples in the chart below. Scheduled time refers to the time that blood should be collected, and actual time refers to the actual time the blood was collected whether it is the same or different than the scheduled time. Blood should be collected as close to the scheduled time as possible.

Date of Dose: _____

Dose Administration Time:

_____

Describe Dose Tolerance:

_____

Consolidation C_D_	Date	Scheduled Time	Actual Time
Prior to crenolanib dose (pre)			
post crenolanib 4 hours (±30 minutes)			
post crenolanib 8 hours (±2h) before next dose			

Name of person completing form: _____

Phone Number: _____

Email: _____

Date: _____

Please complete FORM 3 Pharmacokinetic Concomitant Medications with this form.

FORM 3 ARO-010 Pharmacokinetic / Concomitant Medications

This form accompanies Forms 1 and 2 for pharmacokinetic sampling.

List the name, dose, and regimen of other drugs the patient has received within 48 hours prior to PK sampling of crenolanib therapy, including any vitamins and herbal supplements (St. John's Wort, etc.) If more space is needed, please use an additional sheet:

Drug Name	Actual Dose	Date and Time Administered

List the type, quantity, and time of food/drink consumed 1 hour prior to crenolanib dose until 2 hours post crenolanib dose. Use an additional sheet if necessary.

_____

_____

Bone Marrow Aspiration and Whole Blood Collection

Sampling Schedule for Bone Marrow Aspirates

Bone marrow aspirates for research purposes will be collected at the time of routine marrow sampling with 1 additional aspiration of about 5 ml drawn for study purposes and placed in heparinized cell preparation tubes. The following are suggested time points, and after the first induction, bone marrow should be performed at the discretion of the treating physician. See FORMS 4 or 5.

Arm 1

a. Induction 1: as per the institutional standard of care
b. During induction 2 and consolidations: as per the institutional standard of care
c. Maintenance: as per the institutional standard of care (criteria for CR must be maintained to continue on maintenance therapy).

Arm 2

a. Cycle 1 and during treatment: as per the institutional standard of care
b. Maintenance: as per the institutional standard of care (criteria for CR must be maintained to continue on maintenance therapy).

Sampling Schedule for Whole Blood

One sample of 10 mL of whole blood for each time point is drawn and placed in heparinized cell preparation tubes for other correlative science research studies. See FORMS 4 or 5. Sample should be drawn at the following two time points:

a. Pre administration of first dose of therapy (standard salvage chemotherapy regimen in arm 1 or azacitidine in arm 2)
b. End of treatment visit prior to initiation of new treatment regimen or HSCT

Sampling collection and processing

- BMA/Blood will be done as per institutional bone marrow aspiration protocol. Sampling will consist of a minimum of 5 mL of aspirated BMA sample or 10 ml of whole blood placed in heparinized cell preparation tubes.
- After collection of bone marrow or whole blood, store tube upright at room temperature until centrifugation. BMA/Blood samples should be centrifuged within one hours of blood collection for best results.
- NOTE: Remix the BMA/blood sample immediately prior to centrifugation by gently inverting the tube 8 to 10 times. Also, check to see that the tube is in the proper centrifuge carrier/adapter.
- Centrifuge marrow/blood sample at room temperature (18-25ºC) in a horizontal rotor (swing-out head) for a minimum of 20 minutes at 1500 to 1800 RCF (Relative Centrifugal Force).
- After centrifugation, mononuclear cells and platelets will be in a whitish layer just under the plasma layer (see Figure 2 below). Aspirate approximately half of the plasma without disturbing the cell layer.
- Collect cell layer with a Pasteur pipette (provided by AROG) and transfer to 3 cryopreservation tubes (provided by AROG) and centrifuge at 3000 rpm for 5 min. Remove all liquid and either snap freeze cell pellet in liquid nitrogen or dry ice and then store -80ºC immediately.
- Samples from each individual patient will be stored and batched for that patient. Please complete appropriate Data Collection Form (FORMS 5 or 6).

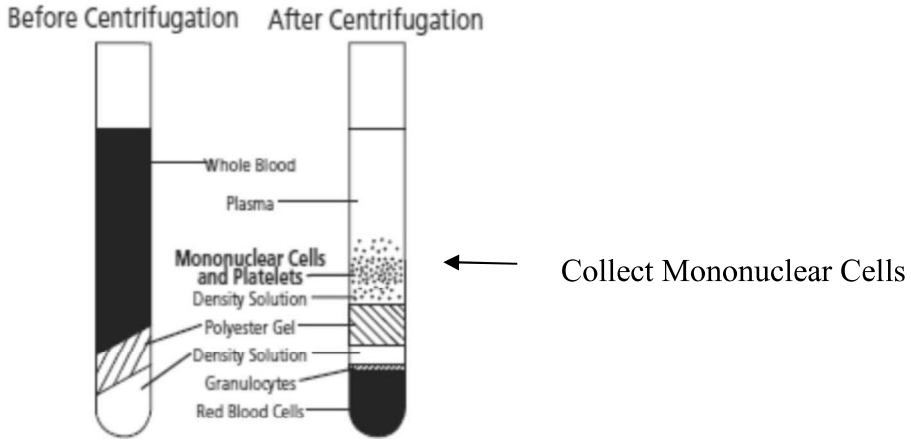

Figure 2 Layering of formed elements in the cell preparation tubes

Shipping of Samples

- In preparation of sample shipping, contact AROG Pharmaceuticals at **samples@arogpharma.com** and site at **debra.cohen@propath.com** to notify of sample shipment and to provide the FedEx tracking number. AROG Pharmaceuticals will provide a confirmation regarding receipt of email concerning shipment to the site.
- Samples can be shipped at intermediate times along with Data Collection Form to:

Debra Cohen
Cytogenetics and Molecular Laboratory Manager
ProPath
1355 River Bend Drive
Dallas TX 75247
214.237.1739
debra.cohen@propath.com
www.ProPath.com

Contact Information for notification of bone marrow aspiration samples:
AROG Pharmaceuticals, Inc.
E: aramachandran@arogpharma.com
O: +1 214-593-0515 (Abhijit Ramachandran)
F: +1 214.-594-0002

FORM 4 ARO-010 Whole Blood Collection Form

Study Accession #:	Study ID:	
Race:	Sex:	Date of Birth:
Height (cm):	Weight (kg):	
Crenolanib Dose (mg) and time of ingestion:		Today's Date:
Please indicate phase of therapy:	Screening	Follow up

List the name, dose, and regimen of other drugs the patient has received within 48 hours of crenolanib therapy, including any vitamins and herbal supplements (St. John's Wort, etc.).If more space is needed, please use an additional sheet:

Drug Name	Drug Dose	Date and Time Administered

List the type, quantity, and time of food/drink consumed 1 hour prior to crenolanib dose until 2 hours post crenolanib dose. Use an additional sheet if necessary.

_____

_____

_____

Fill in exact dose dates, times, and tolerances for the prior 4 crenolanib doses in the spaces below.

Crenolanib Date and Time Administered	Crenolanib Dose	Crenolanib Tolerance

List the scheduled and actual times of the collected samples in the chart below. List exact date and time of crenolanib administration. Scheduled time refers to the time that blood should be collected, and actual time refers to the actual time the blood was collected whether it is the same or different than the scheduled time. Blood should be collected as close to the scheduled time as possible.

Samples	Date	Scheduled Time	Actual Time

Name of person completing form: _____
Phone Number: _____
Email: _____
Date: _____

FORM 5 ARO-010 Bone Marrow Aspiration C_ D_ Data Collection Form

Study Acc #:	Study ID:	
Race:	Sex:	Date of Birth:
Height (cm):	Weight (kg):	
		Today's Date:
Please indicate phase of therapy: Induction	Consolidation	Maintenance

Please fill in crenolanib dose date, time, and tolerance in the spaces below. List sample volume or estimated mass, and note any collection issues in the chart below. Use an additional sheet if necessary.

Date of Dose: _____
Dose Administration Time:

_____
Describe Dose Tolerance:

_____

Bone Marrow Aspiration	**Sample Volume or Estimated Mass**	**Note any collection issues**	**Date**
Sample – 1			
Sample – 2			

Name of person completing form: _____
Phone Number: _____
Email: _____
Date: _____

APPENDIX VI. CONTACT INFORMATION AROG PHARMACEUTICALS

Contact Information of Medical Monitor

John Eckardt, MD
Chief Medical Officer
Phone (O): 214-451-4520
Email: jeckardt@arogpharma.com

Contact Information of Director of Clinical Operations

Abhijit Ramachandran
AROG Pharmaceuticals, Inc.
Email: aramachandran@arogpharma.com
Office: 214.593.0515
Mobile: 817.849.0175
Fax: 214.594.0002

Contact Information for notification of shipment of correlative studies samples

AROG Pharmaceuticals, Inc.
E: samples@arogpharma.com
Office: +1 214.593.0500
Fax: +1 214.594.0002

APPENDIX VII. SHIPPING ADDRESSES FOR SERUM AND TISSUE SAMPLES

A. Pharmacokinetics Samples

Cynthia Gomez
Senior Project Coordinator
MicroConstants, Inc.
9050 Camino Santa Fe
San Diego, CA 92121
P (858) 652-4600
F (858) 652-4699
CGomez@microconstants.com
www.microconstants.com

B. Bone Marrow Aspirate and Whole Blood samples

ProPath
1355 River Bend Drive
Dallas TX 75247
Attn: Debra Cohen, Cytogenetics and Molecular Laboratory Manager
214.237.1739
debra.cohen@propath.com
www.ProPath.com

APPENDIX VIII. DEFINITION OF HIGH-RISK MDS

High-risk MDS for this protocol includes Intermediate-2 risk and high risk per the International Prognostic Scoring System (IPSS).

Score value:

Percentage of Bone Marrow Blasts

☐< 5 percent (0 point)

☐5 to 10 percent (0.5 point)

☐11 to 20 percent (1.5 points)

☐21 to 30 percent (2.0 points)

Karyotype

☐Normal, Y-, 5q-, 20q- (0 point)

☐Abnormal chromosome 7 or 3 or more abnormalities (1.0 point)

☐All other cytogenic abnormalities (0.5 point)

Cytopenias (defined as hemoglobin < 10 g/dL, absolute neutrophil count < 1800/microL, platelet count < 100,000/microL)

☐No cytopenia or cytopenia of 1 cell type (0 point)

☐Cytopenia of 2 or 3 cell types (0.5 point)

Score	Risk Group
0 Point	Low risk
0.5 - 1 Point	Intermediate-1 risk
1.5 - 2.0 Points	Intermediate-2 risk
2.5-3.5 Points	High risk