A Study of Crenolanib and Chemotherapy with Cytarabine and Anthracyclines in Patients with Newly Diagnosed Acute Myeloid Leukemia with FLT3 Activating Mutations

PROTOCOL ARO-006

VERSION 2.0

Date: January 4, 2017

AROG PHARMACEUTICALS, INC.
TWO LINCOLN CENTRE
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DALLAS TX 75240

SIGNATURE PAGES

Protocol Lead responsible for designing the clinical trial:

I approve the design of the clinical trial.

_____ _____

Signature Date of Signature

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Trial Title	A Study of Crenolanib and Chemotherapy with Cytarabine and Anthracyclines in Patients with Newly Diagnosed Acute Myeloid Leukemia with FLT3 Activating Mutations
IND Number	118,143
Clinical Trial Protocol Version Date	4 January, 2017
Center Number	

_____

Principal Investigator

_____

I, the undersigned, am responsible for the conduct of the trial at this site and affirm that:

- I understand and will conduct the trial according to the clinical trial protocol, any approved protocol amendments, ICH Good Clinical Practice (ICH Topic E6 GCP) and all applicable Health Authority requirements and national laws.
- I will not deviate from the clinical trial protocol without prior written permission from the Sponsor and prior review and written approval from the Institutional Review Board or Independent Ethics Committee, except where necessary to prevent immediate danger to the subject.
- I understand that some Health Authorities require the Sponsors of clinical trials to obtain and supply, when required, details about the Investigators' ownership interests in the Sponsor or Investigational Medicinal Product and information regarding any financial ties with the Sponsor.
- The Sponsor will use any such information that is collected solely for the purpose of complying with the regulatory requirements. I therefore agree to supply the Sponsor with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children), and to provide updates as necessary.

_____ _____

Signature Date of Signature

Name, academic qualifications _____

Position (job title) _____

Address of Institution _____

Phone and fax _____

E-mail _____

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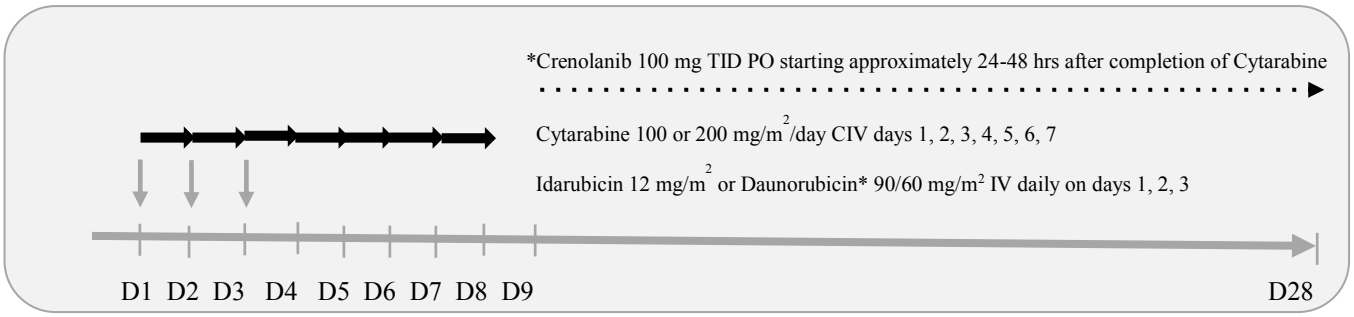
1. OVERVIEW OF THE TREATMENT PLAN

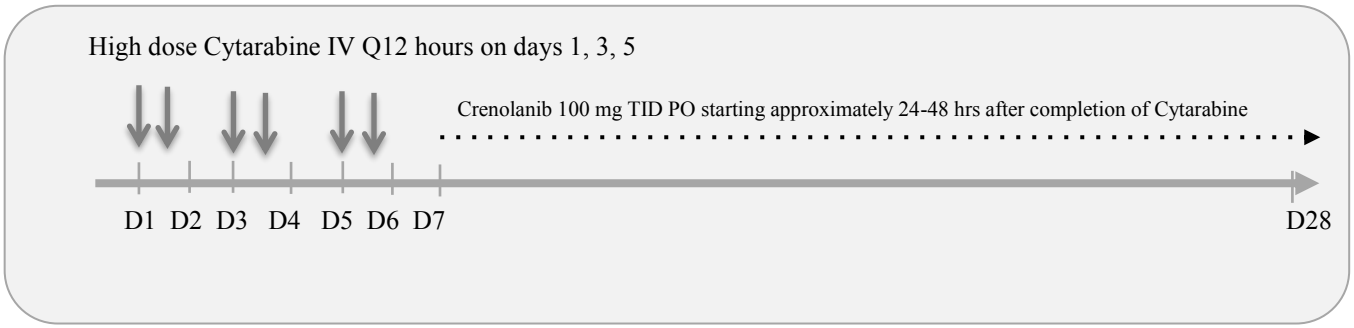
INDUCTION



* Daunorubicin dose:
  - 90 mg/m^2: Age < 60
  - 60 mg/m^2: Age ≥ 60 or for patients who are <60 and receiving a second cycle of induction (per physician's discretion)

- Crenolanib starts approximately 24-48 hours after completion of Cytarabine (+7-day window). **Normal total bilirubin and ALT and AST ≤2.0x ULN are required within 24 hours prior to crenolanib commencement. Crenolanib can be delayed until these criteria are met.** (If crenolanib will be delayed longer day 16, a discussion with PI and sponsor should be conducted to determine the best options for the patient)
- On first day of crenolanib, only one 100 mg dose given; from second day on, all three doses given (100 mg TID)
- A total of two cycles of induction will be allowed.
- Crenolanib should be held 72 hours prior to subsequent chemotherapy

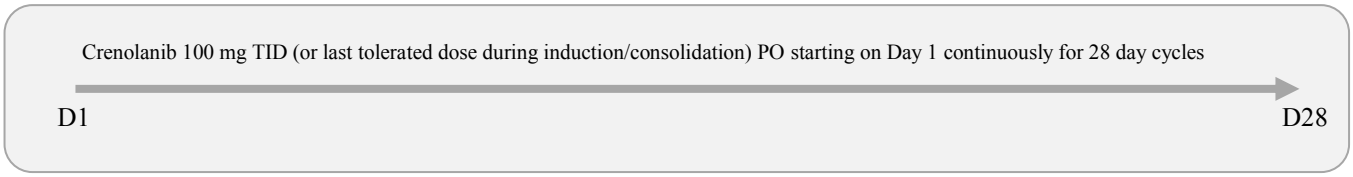
CONSOLIDATION



- Cytarabine dose:
  - Age < 60: 3000 mg/m^2 (3g/m^2)
  - Age ≥ 60: 1000 mg/m^2 (1 g/m^2)
- On days 1,3,5 every 12 h (total of 6 doses)
- Up to 4 cycles of consolidation allowed with HiDAC

- Crenolanib starts approximately 24-48 hours after completion of cytarabine (+7-day window)**.**
- **Normal total bilirubin and ALT and AST ≤2.0x ULN are required within 24 hours prior to crenolanib commencement. Crenolanib can be delayed until these criteria are met.** (If crenolanib will be delayed longer day 14, a discussion with PI and sponsor should be conducted to determine the best options for the patient)
- Crenolanib should be held 72 hours prior to subsequent chemotherapy

MAINTENANCE



- A total of 12 cycles of maintenance will be allowed.
- During maintenance, patients will take continuous crenolanib. Cycles will be 28 days long.
- Patients who have received HSCT and remain in remission may receive crenolanib maintenance therapy. Crenolanib should be restarted no sooner than 30 days post-HSCT and should be administered at the same dose of crenolanib last taken by the patient.
- Patients not undergoing hematopoietic stem cell transplant who are in remission may continue on crenolanib after induction and/or HiDAC consolidation.

2. SPONSOR CONTACT INFORMATION

Protocol Number:	ARO-006
Version	2.0
Version Date:	January 4, 2017
Investigational Product:	Crenolanib Besylate
Development Phase:	Phase II
Sponsor:	Arog Pharmaceuticals, Inc. 5420 LBJ Freeway, Suite 410, Dallas TX 75240 O: (214) 593-0500 F: (214) 594-0002 Email: info@arogpharma.com
Medical Monitor:	John Eckardt, MD O: (214) 451-4520 M: (314) 614-5124 F: (214) 594-0002 Email: jeckardt@arogpharma.com

3. SYNOPSIS

3.1. Rationale for the Proposed Study

This study is designed to evaluate the safety and clinical benefit of oral crenolanib besylate given sequentially during standard induction and consolidation chemotherapy in patients with newly diagnosed AML with FLT3 activating mutations. Acute myelogenous leukemia (AML) has a significant resistance to primary chemotherapy with a cure rate of only 30-40%.[1] The prognosis varies according to cytogenetic status. Activating mutations of FLT3 including internal tandem duplication (ITD) mutations within the juxtamembrane domain and single base pair mutations within the tyrosine kinase domain (TKD) of the receptor are the most frequent mutations described in AML, with a prevalence of approximately 24-30%.[2, 3] Despite the presence of these mutations, there is no approved target specific therapy for AML patients who harbor them.

Crenolanib besylate (AR-868,596-26) is an orally bioavailable benzimidazole that was designed to be a selective and potent inhibitor of type III receptor kinases FLT3, PDGFRα and PDGFRβ. Molecular binding data support that crenolanib is a type I kinase inhibitor that binds preferentially to the active kinase conformation of FLT3.[4] As a result of this property, crenolanib potently inhibits both wild type and constitutively active mutant FLT3 kinase. In vitro studies in cell lines and a xenograft model have shown that crenolanib has higher binding affinity (K_d) for and potency (IC_{50}) against FLT3 kinase with internal tandem duplication (ITD) and tyrosine kinase domain (TKD) mutations.[2, 4, 5] A saturation mutagenesis screen of FLT3-ITD failed to recover any resistant colonies in the presence of crenolanib at a concentration significantly lower than what has been safely achieved in patients.[4] This high affinity of crenolanib allows it to inhibit aberrant FLT3 signaling at clinically achievable concentrations in AML patients.

Two phase II clinical trials administered single-agent crenolanib to a total of 69 patients with FLT3 mutant AML. Encouraging single-agent activity, safety and PK was observed with crenolanib in this patient population. Amongst 18 evaluable who had relapsed AML patients after chemotherapy or allogeneic stem cell transplant (but who had not received prior FLT3 inhibitors), crenolanib therapy resulted in an overall response rate of 50% (39% CR/CRi and 11% PR). Median overall survival was almost eight months (234 days). The overall response to crenolanib monotherapy was 31% in 36 patients who progressed after a median of three prior regimens (including chemotherapy and FLT3 inhibitors like sorafenib, midostaurin and quizartinib). Crenolanib had a half-life of 7.5hrs and no crenolanib accumulation seen with repeated dosing. Common adverse events (AEs) included nausea/vomiting, transaminitis and fluid retention (majority Grade 1/2) and only 2 patients discontinued crenolanib due to related AEs (fatigue and nausea). No patient acquired a secondary FLT3 mutation at the time of relapse following crenolanib.

For patients with newly diagnosed AML, the standard chemotherapy induction regimen used in this study (7+3, cytarabine and anthracyclines) is considered universally as effective as any other regimen.[8] For this trial, crenolanib will be added to standard induction and consolidation chemotherapy regimens. This study will initially have a safety phase with two cohorts designated by anthracycline: in cohort A daunorubicin will be given at 90 mg/m^2 for patients younger than 60 years of age and 60 mg/m^2 for patients ≥60 and in cohort B idarubicin will be given at 12 mg/m^2. Once the safety of the combination has been established an expansion of an additional 72 patients will be initiated. During the expansion, patients will be eligible for either anthracycline regimen per physician's discretion.

3.2. Study Synopsis

Title of Study: A Study of Crenolanib and Chemotherapy in Patients with Newly Diagnosed Acute Myeloid Leukemia with FLT3 Activating Mutations

Number of Planned Subjects: 120

Approximately 48 patients will be enrolled into two cohorts during an initial safety phase:

Cohort A: 24 patients receiving cytarabine/daunorubicin followed by crenolanib
Cohort B: 24 patients receiving cytarabine/idarubicin followed by crenolanib

Once safety of adding crenolanib to cytarabine/daunorubicin and cytarabine/idarubicin has been established, an expansion phase of 72 additional patients will be treated with either cytarabine/daunorubicin or with cytarabine/idarubicin induction chemotherapy followed by crenolanib to further assess the safety and clinical benefit of the combination.

Length of Study: 2-3 years

Primary Objectives

- To determine the safety and tolerability of crenolanib given sequentially with chemotherapy for newly diagnosed AML
- To determine the response rate to induction therapy in newly diagnosed AML subjects with FLT3 activating mutations when crenolanib is given sequentially with standard induction/consolidation chemotherapy, including the rates of complete remission (CR), CR with incomplete blood count recovery (CRi), and partial response (PR).

Secondary Objectives

- To determine the overall survival (OS) in newly diagnosed AML subjects with FLT3 activating mutations when crenolanib is given sequentially with standard induction/consolidation chemotherapy
- In those patients achieving response, assess parameters of response including: remission duration and relapse-free survival (RFS)
- Pharmacokinetic analysis of crenolanib when given with chemotherapy

Exploratory Objectives

To evaluate the impact of crenolanib given in combination with chemotherapy:

- Determine steady-state serum crenolanib concentration
- Identify and correlate specific molecular markers with clinical outcomes
- Determine changes in molecular markers during treatment and their correlations with clinical outcomes
- Measure minimal residual disease (MRD) and correlate with post-remission outcomes

Inclusion Criteria:

1. Unequivocal diagnosis of AML based on the WHO classification, excluding acute promyelocytic leukemia
2. No prior therapy for AML, except for hydroxyurea and/or leukapheresis, in this setting is allowed.
3. Subjects with AML evolving from MDS with or without prior MDS therapy with demethylating agents will be allowed in the ***safety phase only***.
4. Subjects must have tested positive for FLT3-ITD and/or other FLT3 activating mutations.
5. Age ≥18 years will be allowed in the ***safety phase***; during the ***expansion phase,*** subjects must be ≥18 - ≤70 years of age.

6. ECOG PS 0 – 2
7. Adequate liver function, defined as normal total bilirubin, ALT ≤2.0x ULN, and AST ≤2.0x ULN.
8. Adequate renal function, defined as serum creatinine ≤1.5x ULN or GFR >50 mL/min
9. Negative pregnancy test (serum or urine) for women of childbearing potential (WOCBP).
    - Women considered not of childbearing potential include any of the following: no menses for at least 2 years or menses within 2 years but amenorrheic for at least 2 months and luteinizing hormone (LH) and follicular stimulating hormone (FSH) values within normal range (according to definition of postmenopausal for laboratory used) or bilateral oophorectomy or radiation castration and amenorrheic for at least 3 months or with bilateral tubal ligation.
10. WOCBP must practice contraception. Acceptable methods of contraception are double barrier methods (condoms with spermicidal jelly or foam and diaphragm with spermicidal jelly or foam), oral, depo provera, or injectable contraceptives, intrauterine devices, tubal ligations, and abstention.
11. Male patients (except those with prior surgical contraceptive procedures) with female partners who are of childbearing potential: Recommendation is for male and partner to use effective contraceptive methods, such as latex condoms, during the study.
12. Able and willing to provide written informed consent

Exclusion Criteria:

1. Pre-existing liver diseases (i.e., cirrhosis, chronic hepatitis B or C, nonalcoholic steatohepatitis, and sclerosing cholangitis, etc.)
2. Known active CNS leukemia
3. ***During the expansion phase*** subjects with therapy-related AML, AML with prior history of MDS with or without prior HMA therapy or AML in the setting of antecedent hematologic disorder.
4. Subject with concurrent severe and/or uncontrolled medical conditions that may impair the participation in the study or the evaluation of safety and/or efficacy
5. NYHA Class III-IV heart failure, myocardial infarction <6 months prior to study entry, and/or serious arrhythmia requiring anti-arrhythmic therapy
6. Major surgical procedures within 14 days of enrollment (does not include line placement as needed for chemotherapy administration).
7. Unwillingness or inability to comply with protocol.
8. Concurrent use of other investigational agents.
9. Subjects who are not eligible for standard chemotherapy

Test Product, Dosage and Mode of Administration:

Crenolanib besylate will be taken at a starting dose of 100 mg TID, orally. Patient, nursing or research staff will complete documentation to record the date, time and amount (number of tablets) of crenolanib taken.

Drug Information:

Crenolanib besylate will be provided in 100 mg and/or 20 mg tablets by Arog Pharmaceuticals, Inc.

Study Design:

Patients will initially be enrolled to the safety phase of the study. During the safety phase, patients will be enrolled to either cohort A: cytarabine/daunorubicin or cohort B: cytarabine/idarubicin. Each cohort will enroll independently and patients will be treated with crenolanib following either cytarabine/daunorubicin or cytarabine/idarubicin.

Once safety of adding crenolanib to cytarabine/daunorubicin and cytarabine/idarubicin has been established, an expansion phase of an additional 72 patients will be treated with standard 7+3 (either cytarabine/daunorubicin or with cytarabine/idarubicin, per physician's discretion) induction chemotherapy followed by crenolanib.

Per physician's discretion, patients may receive up to 2 cycles of the same induction therapy. Following induction, eligible patients can receive up to four cycles of consolidation with HiDAC followed by crenolanib. Following either

induction or consolidation, eligible patients may receive maintenance therapy with crenolanib up to an additional 12 cycles.

Eligible patients should receive allogeneic stem cell transplant following induction and/or consolidation with HiDAC. Those who have received transplant may receive maintenance therapy with crenolanib following transplant.

Planned Duration of Treatment:
If patients receive all available therapy options, patients may stay on trial for approximately 20 months. Information for survival and disease status (until progression of disease) on patients who have discontinued study drug for any reason should be obtained at least every 6 months for a maximum of 24 months or until the end of the study, whichever is later.

Statistical Plan:
During the initial safety phase, there will be two cohorts (based on chemotherapy regimen). Each cohort will enroll independently. To confirm the safety of each combination (cytarabine/daunorubicin with crenolanib and cytarabine/idarubicin with crenolanib), approximately 24 patients will be enrolled onto each cohort, if early stopping criteria are not met. Following analysis of the initial safety phase, an expansion phase of an additional 72 patients will be initiated to further assess safety and clinical benefit of this combination.

Safety analysis:
During the initial safety phase, twelve patients will be enrolled onto each cohort and if the early stopping rule criterion are not met than approximately 12 additional patients will be enrolled onto each cohort. Safety monitoring will be performed separately for each cohort and enrollment will be halted within a cohort if stopping rules are met for early mortality due to any cause, increase in expected non-hematologic crenolanib-related grade 4 adverse events, or any unexpected non-hematologic crenolanib-related grade 4 adverse events.

Stopping rules during the initial safety phase are the following: If the observed mortality rate exceeds 10 % and 20% at day 30 and 60, respectively, enrollment will be halted pending Protocol Safety Committee review. If an observed increase of expected non-hematologic crenolanib-related grade 4 adverse events exceeds 20% during the first 60 days of treatment further enrollment will be halted pending Protocol Safety Committee review. If an observed increase of unexpected non-hematologic crenolanib-related grade 4 adverse event exceeds 15% during the first 60 days of treatment further enrollment will be halted pending Protocol Safety Committee review.

During the expansion phase, safety monitoring will be performed for the entire per protocol patient population (defined as those who receive at least one dose of study drug) and in a separate analysis dictated by chemotherapy agent used.

Response rate analysis:
This study will enroll approximately 120 patients with the following confidence intervals based on projected response rate. A response rate of 90% will have a 95% CI of ±5%. That is to say that if we treat 120 patients and observe a 90% response rate, we are 95% sure that the true response rate is between 85% to 95%.

Analysis method:
Descriptive statistics will be used to summarize the safety and efficacy data for this study. Categorical data will be summarized by number and percentage of patients in each category. Time – to – event endpoints will be summarized using the cumulative incidence and Kaplan-Meier methodology.

4. ABBREVIATIONS AND DEFINITIONS

Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally occurring during the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
Audit	A systematic and independent examination of the trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, applicable standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s).
Compliance	Adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
Complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
Confirmation	A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that AROG is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be retested at some defined time point, depending on the steps required to obtain confirmed results.
Case Report Form (CRF)	Sometimes referred to as clinical report form: a printed or electronic form for recording study participants' data during a clinical study, as required by the protocol.
Consent	The act of obtaining informed consent for participation in a clinical trial from patients deemed eligible or potentially eligible to participate in the clinical trial. [Patients/Subjects] entered into a trial are those who sign the informed consent document directly or through their legally acceptable representatives.
End of Study (trial)	The date of the last visit or last scheduled procedure shown in the Study Schedule for the last active subject in the study.
Enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.
Investigator	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.
Institutional Review Board/Ethical Review Board (IRB/ERB)	A board or committee (institutional, regional, or national) composed of medical and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the patients participating in a clinical trial are protected.

Legal Representative	An individual, judicial, or other body authorized under applicable law to consent on behalf of a prospective patient, to the patient's participation in the clinical trial.
Patient	A study participant who has the disease or condition for which the investigational product is targeted.
Screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical trial. In this study, screening involves invasive or diagnostic procedures and/or tests (for example, radiology and blood draws). For this type of screening, informed consent for these screening procedures and/or tests shall be obtained.
Treatment-Emergent Adverse Event (TEAE)	Any untoward medical occurrence that either occurs or worsens at any time after treatment baseline and which does not necessarily have to have a causal relationship with this treatment (also called treatment-emergent signs and symptoms [TESS]).

ALT	alanine aminotransferase
AML	acute myeloid leukemia
Ara-C	cytarabine
ASCO	American society of clinical oncology
AST	aspartate aminotransferase
BMA	bone marrow aspiration
BUN	blood urea nitrogen
CALGB	cancer and leukemia group b
CBC	complete blood count
CIV	continuous intravenous therapy
CNS	Central nervous system
CR	complete response
CRi	complete remission with incomplete blood count recovery
CYP3A4	Cytochrome P450 3A4
DNA	deoxyribonucleic acid
ECOG -PS	Eastern Cooperative Oncology Group performance status
EFS	Event free survival
EKG	Electrocardiogram
FLT3	FMS-like Tyrosine Kinase 3
GCP	good clinical practice
GVHD	Graft versus host disease
HI	Hematologic improvement
HiDAC	High dose cytarabine
HSCT	Hematologic stem cell transplant
IC_{50}	Half maximal inhibitory concentration
ICD	informed consent document
ICH	International Conference on Harmonization
IRB	Internal review board
ITD	internal tandem duplication
IV	Intravenous therapy
K_d	Dissociation constant
KIT	Stem cell growth factor receptor

LDH	Lactate dehydrogenase
MDS	Myelodysplastic syndrome
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.03
NYHA	New York Heart Association
OS	Overall survival
PD	progressive disease
PIA	Pharmacologic inhibitory assay
PK	Pharmacokinetics
PO	By mouth
PR	Partial response
RFS	relapse-free survival
SAE	Serious adverse event
TID	Three times a day
TKD	tyrosine kinase domain
TKI	tyrosine kinase inhibitor
ULN	upper limit of normal
UPIN	Unique patient identification number
WBC	White blood count
WOCBP	Woman of child bearing potential

5. BACKGROUND

5.1. Crenolanib inhibits wild-type FLT3 and its constitutively active mutations

Crenolanib besylate (also known as AR-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. [4, 5]

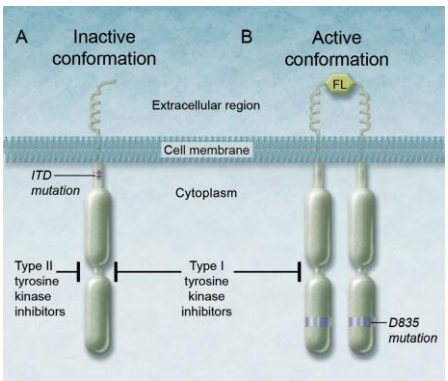
Crenolanib has heightened binding affinity against the FLT3-ITD mutation (the most frequent FLT3 aberration in AML) and TKD point mutations FLT3 (D835H), FLT3 (D835Y) and FLT3 (D835V). Crenolanib binds to FLT3-ITD and FLT3-TKD D835H with K_d values of 0.43 and 0.4 nM, respectively. Similarly, crenolanib also binds to FLT3-TKD D835Y with a K_d 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.[4] Crenolanib inhibitory activity has been verified in human AML cell lines. [4]

Table 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 1 tyrosine kinase inhibitor that binds to both the active and inactive conformation of FLT3.

Figure 1 Schematic of inactive and active FLT3 with most common resistance mutations in AML.[8]



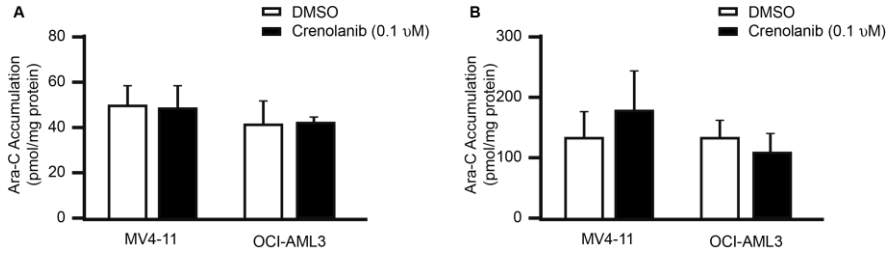
5.2. Crenolanib has reduced activity against KIT

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 [9] 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.

5.3. 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 uM of radiolabeled cytarabine combined with DMSO control or in combination with crenolanib at 0.1 uM for 5 minutes and 2 h (Figure 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.[5]

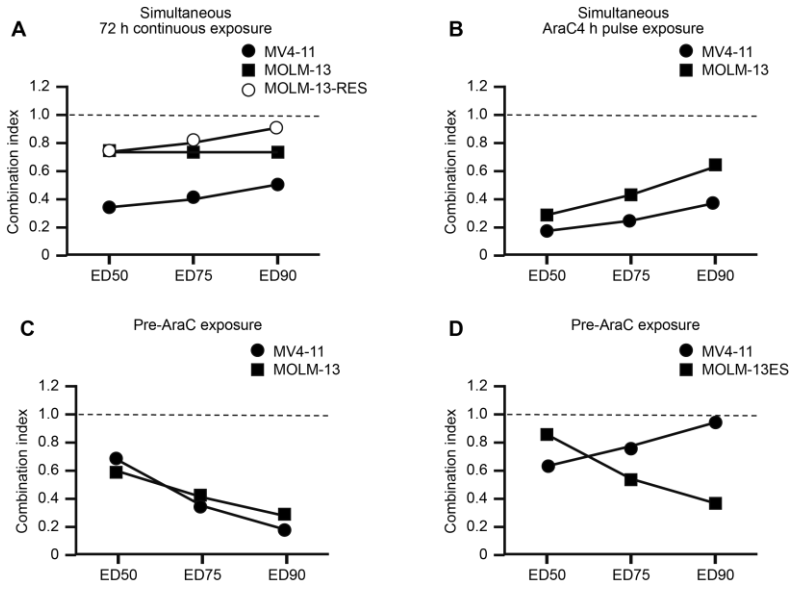
Figure 2 Effects of crenolanib on uptake of cytarabine in AML cells.



(A) 5 minute incubation; (B) 2 hour incubation. 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 3). Results suggested synergistic activity with the combination [5].

Figure 3 Crenolanib and cytarabine combination synergistically inhibit FLT3-ITD-positive cell viability in vitro.

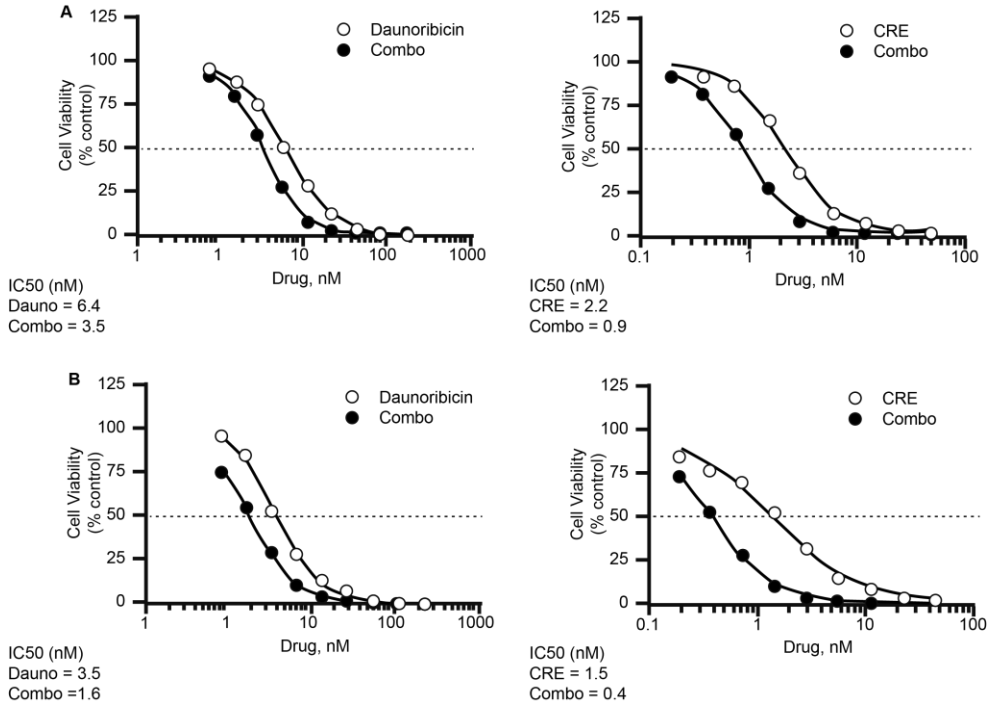


(A) simultaneous 72 h drug exposure; (B) simultaneous 4 h drug exposure followed by 68 h crenolanib exposure; (C) (pre-AraC) 4 h AraC exposure followed by 68 h crenolanib exposure; or (D) (pre-crenolanib) 24 h crenolanib exposure followed by 48 h AraC exposure. [5].

5.4. 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 4, unpublished data on file, Dr. Sharyn Baker).

Figure 4 Viability of FLT3 ITD cell lines treated with crenolanib and daunorubicin



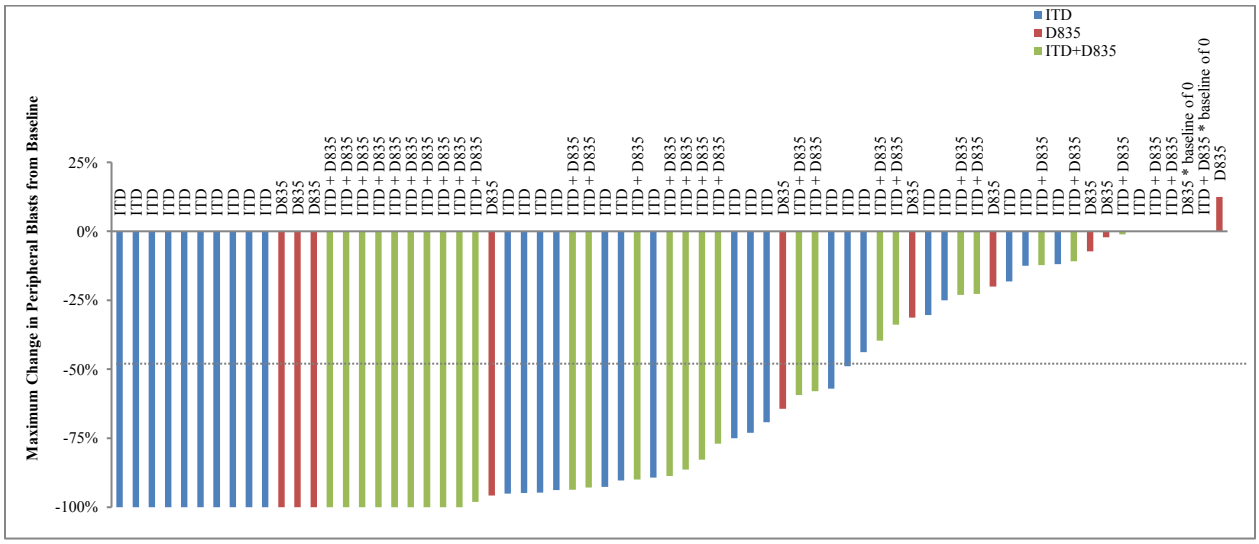
(A) Molm 13 cell line; (B) MV4-11 cell line

5.5. Clinical studies of crenolanib in AML

5.5.1. Clinical summary of crenolanib in relapsed/refractory FLT3 mutated AML

Crenolanib has been studied in relapsed/refractory FLT3 mutant AML (NCT01522469, NCT01657682). Crenolanib was administered as single-agent in 69 patients with relapsed/refractory FLT3 mutated AML in two clinical trials, NCT01522469/ARO-004 and NCT01657682/ARO-005. Encouraging single-agent activity, safety and PK was observed with crenolanib in this patient population. Amongst 18 evaluable who had relapsed AML patients after chemotherapy or allogeneic stem cell transplant (but who had not received prior FLT3 inhibitors), crenolanib therapy resulted in an overall response rate of 50% (39% CR and 11% PR). Median overall survival was almost eight months (234 days). The overall response to crenolanib monotherapy was 31% in 36 patients who progressed after a median of three prior regimens (including chemotherapy and FLT3 inhibitors like sorafenib, midostaurin and quizartinib). Crenolanib had a half-life of 7.5hrs and no crenolanib accumulation seen with repeated dosing. Common adverse events (AEs) included nausea/vomiting, transaminitis and fluid retention (majority Grade 1/2) and only 2 patients discontinued crenolanib due to related AEs (fatigue and nausea). No patient acquired a secondary FLT3 mutation at the time of relapse following crenolanib.

Figure 5 Peripheral blast clearance in FLT3 mutant AML patients treated with crenolanib.



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.

5.6. Tolerability of crenolanib in AML patients who had undergone prior allogeneic bone marrow transplant

A retrospective analysis of those patients who, following hematopoietic cell transplant (HCT), received monotherapy crenolanib on the relapsed/refractory AML studies (ARO-004 and ARO-005) was performed and reported at ASH 2015. This analysis showed that crenolanib at the full therapeutic dose of 100 mg TID was well tolerated in this heavily pre-treated patient population following HCT. A phase II clinical trial of crenolanib in the post-HCT maintenance setting (NCT02400255 / ARO-009) is on-going.

5.7. 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.

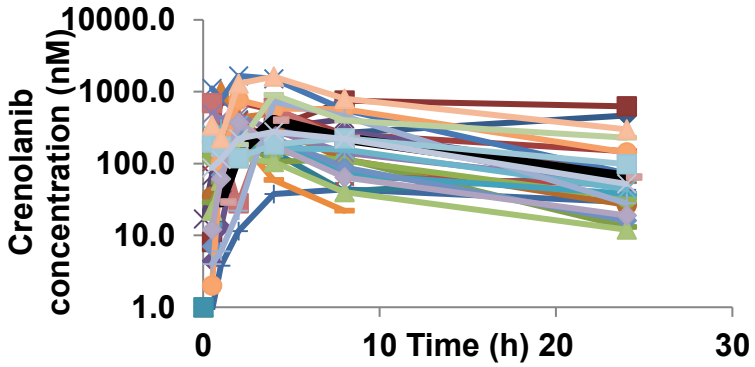
5.8. Rationale for Crenolanib Dose and Schedule

Crenolanib has been tested in 51 AML patients as single agent., Two dosing schedules have been studied: 100 mg TID (28 patients) and 200 mg/m^2/day (23 patients). Crenolanib was safe and well tolerated in this patient population. The most common adverse events were low-grade nausea, vomiting, diarrhea, and transaminitis.

To date, 28 AML patients have been treated with 100 mg TID crenolanib. Day 1 pharmacokinetics data is shown in Figure 6. Trough crenolanib levels were measured in 25 patients on Day 15 by which time steady state levels should have been achieved. Only 2 patients had > 1000 nM crenolanib, but neither required dose de-escalation due to adverse events. Thus, a fixed dose

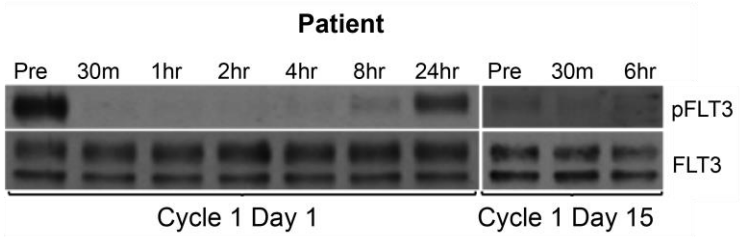
regimen of 100 mg TID will be utilized for this trial. Dose reductions to 80 mg TID and 60 mg TID will be applied should toxicities emerge in study individuals.

Figure 6 Pharmacokinetics analyses in AML patients on 100 mg crenolanib.



Previous plasma inhibitory assays have shown that FLT3 phosphorylation is inhibited for approximately 8 hours after each dose of crenolanib (see representative PIA assay below in Figure 7). Hence, crenolanib will be given in this protocol in a TID schedule.

Figure 7 Representative PIA analysis of patient plasma samples after taking crenolanib single agent.



The study by Robert J, et al. in 16 leukemia patients showed that the major metabolites of idarubicin or daunorubicin were the 13-dihydroderivative of each drug, idarubicinol or daunorubicinol. The elimination half-life of idarubicinol was two times higher than that of daunorubicinol (80.7 h versus 37.3 h). [6] During 7+3 induction in this protocol, idarubicin or daunorubicin will be administered on days 1, 2, and 3. By the time crenolanib is started (Day 9), idarubicinol level should have declined by 75% (2 half-lifes) and daunorubicinol levels will have dropped by 93.5% (4 half-lifes). Crenolanib will be discontinued 3 days (9 half-lifes) prior to initiation of subsequent chemotherapy.

6. STUDY OBJECTIVES

6.1. Primary Objective

- To determine the safety and tolerability of crenolanib given sequentially with cytarabine and anthracycline chemotherapy for newly diagnosed FLT3 mutant AML.
- To determine the response rate to induction therapy in newly diagnosed AML subjects with FLT3 activating mutations when crenolanib is given sequentially with standard induction/consolidation chemotherapy, including the rates of complete remission (CR), CR with incomplete blood count recovery (CRi) and partial remission (PR).

6.2. Secondary Objectives

- To determine the overall survival (OS) in newly diagnosed AML subjects with FLT3 activating mutations when crenolanib is given sequentially with standard induction/consolidation chemotherapy
- In those patients achieving response with crenolanib, assess parameters of response including remission duration and relapse-free survival (RFS)
- Pharmacokinetic analysis of crenolanib when given with chemotherapy

6.3. Exploratory Objectives

To evaluate the impact of crenolanib given in combination with chemotherapy:

- Determine steady-state serum crenolanib concentration
- Identify and correlate specific molecular markers with clinical outcomes
- Determine changes in molecular markers during treatment and their correlations with clinical outcomes
- Measure minimal residual disease (MRD) and correlate with post-remission outcomes

7. SUBJECT ELIGIBILITY

All patients must meet eligibility as defined. Clarifications of eligibility should be directed to the sponsor's medical monitor.

7.1. Inclusion Criteria

1. Unequivocal diagnosis of AML based on WHO classification, excluding acute promyelocytic leukemia.
2. No prior therapy for AML, except for hydroxyurea and/or leukapheresis, in this setting is allowed.
3. Subjects with AML evolving from MDS with or without prior MDS therapy with demethylating agents will be allowed in the ***safety phase only***.
4. Subjects must have tested positive for FLT3-ITD and/or other FLT3 activating mutations.
5. Age ≥18 years will be allowed in the ***safety phase***; during the ***expansion phase,*** subjects must be ≥18 - ≤70 years of age.
6. ECOG PS 0 – 2
7. Adequate liver function, defined as normal bilirubin, ALT ≤2.0x ULN, and AST ≤2.0x ULN measured within 24 hours prior to crenolanib commencement.
8. Adequate renal function, defined as serum creatinine ≤1.5x ULN or GFR >50 mL/min
9. Negative pregnancy test (serum or urine) for women of childbearing potential (WOCBP).
    - Women considered not of childbearing potential include any of the following: no menses for at least 2 years or menses within 2 years but amenorrheic for at least 2 months and luteinizing hormone (LH) and follicular stimulating hormone (FSH) values within normal range (according to definition of postmenopausal for laboratory used) or bilateral oophorectomy or radiation castration and amenorrheic for at least 3 months or with bilateral tubal ligation.
10. WOCBP must practice contraception. Acceptable methods of contraception are double barrier methods (condoms with spermicidal jelly or foam and diaphragm with spermicidal jelly or foam), oral, depo provera, or injectable contraceptives, intrauterine devices, tubal ligations, and abstention.
11. Male patients (except those with prior surgical contraceptive procedures) with female partners who are of childbearing potential: Recommendation is for male and partner to use effective contraceptive methods, such as latex condoms, during the study.
12. Able and willing to provide written informed consent.

7.2. Exclusion Criteria

1. Pre-existing liver diseases (i.e., cirrhosis, chronic hepatitis B or C, nonalcoholic steatohepatitis, and sclerosing cholangitis, etc.)
2. Known active CNS leukemia

3. ***During the expansion phase*** subjects with therapy-related AML, AML with prior history of MDS with or without prior HMA therapy or AML in the setting of antecedent hematologic disorder.
4. Subjects 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.
5. NYHA Class III-IV heart failure, myocardial infarction <6 months prior to study entry and/or serious arrhythmia requiring anti-arrhythmic therapy
6. Major surgical procedures within 14 days of enrollment (does not include line placement as needed for chemotherapy administration).
7. Unwillingness or inability to comply with protocol.
8. Concurrent use of other investigational agents.
9. Subjects who are not eligible for standard chemotherapy.

7.3. Protocol Registration

To register, a form 1572 listed physician involved in the care of the potential participant must contact either the Principal Investigator or the Study Coordinator to complete the Eligibility Checklist for the Sponsor (Appendix I). For registration, a completed Checklist is to be provided to the sponsor who will provide the site with a Confirmation of Enrollment form which will assign a patient study number (UPIN).

7.4. Discontinuations

7.4.1. Discontinuations of Study Drugs and Disease status/Survival Follow up of Patients

The criteria for enrollment must be followed explicitly. If a patient who does not meet enrollment criteria is inadvertently enrolled, that patient should be immediately discontinued from the study drug.

Study drug may be held for an extended period of time for comorbidities including but not limited to infections, ICU admissions, severe graft vs host disease, and other comorbidities typically seen in patients undergoing induction, consolidation or allogeneic transplant therapies for AML. Such prolonged drug hold will not require the patient to be taken off study. Study drug can be restarted, even after prolonged drug holds, at the same dose as was last received by the patient. Restart of study drug will require a discussion with the sponsor.

Study drug may be held for an extended period of time if requested by the patient without necessitating the patient to be taken off study. Study drug can be restarted, even after prolonged drug holds, at the same dose as was last received by the patient. Patients will be continued to be followed for survival and disease status per protocol. Safety will be followed as per section 14.

Patients, who for any reason, require treatment with another therapeutic agent for AML or investigational agent will be discontinued from the study drug prior to introduction of the new agent. Restart of study drug will require a discussion with the sponsor.

Patients who have disease refractory to induction or consolidation therapy will be taken off crenolanib but be followed for survival. Similarly, patients who relapse after achieving a response will be taken off crenolanib but be followed for survival.

7.4.2. Discontinuation of Study Sites

Study site participation may be discontinued if AROG, the investigator, or the ethical review board of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice. Sites may also be discontinued if unable to accrue an adequate number of patients on the trial.

7.4.3. Discontinuation of the Study

The study will be discontinued if the site IRB judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice. The study could also be discontinued at any time at the sole discretion of the sponsor, AROG Pharmaceuticals, Inc.

8. TREATMENT PLAN

8.1. Summary of Treatment

This is a non-randomized, open label, phase II study enrolling newly diagnosed AML subjects with FLT3 activating mutations. Along with chemotherapy, subjects will be treated with crenolanib divided in three divided doses (preferably every 8 h) continuously until they fulfill one of the criteria for study discontinuation (see Section 7.4).

Study subjects, nursing or research staff will complete documentation (i.e patient diary) during induction and first cycle of consolidation to record the date, time and amount (number of tablets) of crenolanib taken and when taken relative to food. While study subjects are hospitalized, medical records, such as Medication Administration Record, may be used to enter data requested. Once subject is discharged from the hospital, they must submit the crenolanib administration documentation as required during induction 1 (and 2 if applicable), consolidation 1 (Appendix III). All subjects will be assessed for efficacy and toxicity.

8.2. Study Design

This will be a Phase II multi-center study assessing the safety and clinical benefit of crenolanib given with standard 7+3 induction chemotherapy in newly diagnosed in FLT3 mutated AML.

Safety Phase: Patients will receive either daunorubicin/cytarabine (Cohort A) or idarubicin/ cytarabine (Cohort B) per the treating hospitals SOP.

Expansion Phase: Patients may receive either daunorubicin/cytarabine or idarubicin/cytarabine per physician's discretion. During the expansion phase, patients may receive their standard 7+3 chemo of either anthracycline with cytarabine.

8.2.1. Induction

Patients with newly diagnosed AML with FLT3 activating mutations will be treated with crenolanib following induction with either daunorubicin/cytarabine or idarubicin/cytarabine. During the initial safety phase the anthracycline options will be separated into Cohort A and B. Induction treatment schedules combining standard 7+3 chemotherapy with crenolanib are listed in Tables 2 (Cohort A) and 3 (Cohort B). During the expansion phase, the choice of anthracycline will not be separated into different cohorts.

Crenolanib will start approximately 24-48 hours after completion of cytarabine (+7 day window). Adequate liver function including normal total bilirubin ALT and AST ≤2.0x ULN are required within 24 hours prior to crenolanib commencement. Crenolanib can be delayed until this criterion is met. (If crenolanib will be delayed longer day 16, a discussion with PI and sponsor should be conducted to determine the best options for the patient)

Table 2 Cohort A: Cytarabine, daunorubicin induction

Drug	Dose	Mode	Days
Cytarabine	100 - 200 mg/m^2/day	IV continuous infusion over 24 hrs	Days 1-7
Daunorubicin	90 mg/m^2 (<60 years old)	IV bolus over 10-15 mins	Days 1-3

	60 mg/m^2 (≥60 years old or for patients who are <60 and receiving a second cycle of induction (per physician's discretion))		

Table 3 Cohort B: Cytarabine, idarubicin induction

Drug	Dose	Mode	Days
Cytarabine	100 - 200 mg/m^2/day	IV continuous infusion over 24 hrs	Days 1-7
Idarubicin	12 mg/m^2	intravenously daily over 10-15 mins	Days 1-3

If after induction 1, the bone marrow is hypoplastic (<10 % cellularity) on day 14-28 and contains less than 5 percent blast cells, further chemotherapy treatment can be deferred and the marrow examination repeated weekly until marrow recovery, or per the discretion of the treating physician. A repeat bone marrow should be performed at time of hematological remission or Day 42, whichever occurs first. Crenolanib treatment may be continued during this period as per the discretion of the treating physician.

If after induction 1, the bone marrow shows residual disease without a hypocellular marrow, a second course of the same induction remission therapy (or lower dose of anthracycline per Tables 2 and 3) can be given at the decision of the treating physician. Timing and/or necessity of bone marrow evaluation following second induction will follow the same schedule as induction 1. Crenolanib must be held for 72 hours prior to the start of the next chemotherapy.

8.2.2. Consolidation

Therapy with crenolanib will be held for 72 hours prior to the start of the first dose of cytarabine given for consolidation. Crenolanib treatment should be continued during the period of marrow recovery.

Subjects on both cohorts A and B may have up to 4 consolidation courses with:

- High dose cytarabine (HiDAC) given as 3 g/m^2 (<60 years old) or 1 g/m^2 (for ≥60) intravenously over 3 h every twelve hours on days 1, 3, 5 (total of 6 doses).

Crenolanib will start approximately 24-48 hours after completion of cytarabine (+7 day window). Adequate liver function including normal total bilirubin ALT and AST ≤2.0x ULN are required within 24 hours prior to crenolanib commencement. Crenolanib can be delayed until this criterion is met (If crenolanib will be delayed longer day 14, a discussion with PI and sponsor should be conducted to determine the best options for the patient).

- Dose of crenolanib will be the same as that given in induction(s).
- Dose modification of crenolanib is allowed based on treating physician discretion according to Section 8.4 of this protocol.

8.2.3. Maintenance

Subjects not undergoing hematopoietic stem cell transplant who are in remission may continue on crenolanib after induction and/or HiDAC consolidation. Following the last dose of cytarabine given for consolidation, crenolanib can be given continuously for an additional twelve cycles.

Patients who undergo allogeneic transplant may receive maintenance crenolanib after transplant if they fulfill prerequisites. Subjects in remission who are scheduled for allogeneic hematopoietic stem cell transplant (HSCT) should discontinue crenolanib at least 72 hours prior to start of conditioning therapy. Start of maintenance therapy is intended no sooner than 30 days after allogeneic HSCT.

Prerequisites for start of maintenance are:

- a stable dose of immunosuppressive drugs for management or prophylaxis of GVHD or
- no escalation of therapy for GVHD within 14 days of starting study drug
- have no more than grade 2 persistent non-hematological toxicity related to the transplant
- must have received crenolanib during induction for AML prior to HSCT to continue on to maintenance

Maintenance therapy, whether following transplant or not will start at the last dose tolerated during induction/consolidation therapy. For example, if the patient was taking 80 mg TID prior to proceeding with HSCT, maintenance therapy will resume at 80 mg TID. If well tolerated, crenolanib can be escalated to 100 mg TID. Crenolanib maintenance can be given for up to 12 cycles and additional therapy can be provided after discussion with the sponsor.

8.3. Treatment with Crenolanib (AR-868,596)

The investigator or his/her designee is responsible for explaining the correct use of the investigational agent(s) to the subject or other site personnel such as inpatient staff, verifying that instructions are followed properly, maintaining accurate records of study drug dispensing and collection, and returning all unused and unopened medication to AROG or its designee at the end of the study. Study medication that has been dispensed but remains unused at the end of each cycle is recorded by the site personnel and either safely discarded if opened or returned to AROG if unopened with intact packaging.

Subjects will be instructed to contact the investigator as soon as possible if they have a complaint or problem with the study drug so that the situation can be handled.

Missed Doses/Counting Cycle Days: If a subject vomits after drug ingestion, no replacement dose is to be taken; the subject can continue to take the remaining doses as planned. If drug is held or a dose is missed by more than 3 hours after the scheduled time, the missed/held dose should not be made up. Dosing will resume with the next scheduled dose. The subject/nursing or research staff should enter in the diary the doses as missed and reason for missed dose. If drug is held or missed for a day or more, treatment should continue as if uninterrupted. As pill count for compliance assessment will be performed at each patient follow up; leftover drug should be returned to the study site by the subject upon follow up.

During induction and consolidation, one cycle is defined by start of chemotherapy and will continue until the start of next chemotherapy (i.e. induction 1 = cycle 1 and may exceed 28 days)

regardless whether drug is held. During maintenance, cycles will be 28 days in maximum duration (28 days = 1 cycle = 1 month).

"Days" of a cycle are to be counted sequentially from start of chemotherapy (not study drug) until start of next chemotherapy cycle. During maintenance, the start of a cycle is denoted by ingestion of the first dose of crenolanib after evaluation of efficacy at the end of induction or consolidation. The scheduled procedures/visits should comply with the study calendar regardless of amount of study drug administered.

8.4. Dosing and Dose Modification of Crenolanib

Subjects will be given a starting dose of 100 mg TID. Crenolanib should be held starting 72 hours prior to start of next induction chemotherapy cycle.

Table 4 Crenolanib dose reduction schedule

Dose level	Crenolanib dosing
0	100 mg TID
-1	80 mg TID
-2	60 mg TID

Reductions below 60 mg TID are not planned; dose reductions beyond those mentioned in Table 4 should be discussed with the sponsor and documentation justifying the specified dose should be recorded.

8.4.1. Dose Reductions for Non-hematologic Toxicities

Dose reductions for non-hematologic toxicities attributed to crenolanib will be done as outlined in Table 5. The starting dose (dose level 0) of crenolanib will be 100 mg TID. A maximum of two (2) dose reductions are allowed in a single subject for toxicities related to crenolanib. Please refer to Table 6 and 7 for specific instructions for dose modifications for elevated bilirubin, ALT, AST and/or Alkaline Phosphatase.

Table 5 Crenolanib dose reduction for non-hematologic toxicities related to crenolanib

Toxicity (CTCAE v4.03)	Dose Modification
Grade 1 or 2	No dose modification
Grade 3 or 4 (except nausea, vomiting or diarrhea)	Hold drug until toxicity resolves to grade 1 or less. Restart drug at next lower dose level (see Table 4)
Grade 3 or 4 nausea, vomiting or diarrhea despite optimal therapy within 72 hours of onset	Hold drug until toxicity resolves to grade 1 or less. Restart drug at next lower dose level (see Table 4)

Table 6 Crenolanib dose reduction for bilirubin elevation

Worst toxicity (CTCAE Grade)	Recommended Dose Modifications
Grade 1 bilirubin elevation (ULN- 1.5 x ULN)	Continue crenolanib at current dose
Grade ≥2 or bilirubin elevation (>1.5 x ULN)	Stop crenolanib. Restart drug at next lower dose level (-1) (Table 4) once bilirubin returns to normal.
Following re-challenge:	
Grade ≥2 or bilirubin elevation (>1.5 x ULN)	Stop crenolanib. Restart drug at next lower dose level (-2) once bilirubin returns to normal.

Table 7 Crenolanib dose reduction for elevation of AST, ALT, Alk Phos

Worst toxicity (CTCAE Grade)	Recommended Dose Modifications
Grade 1 ALT or AST elevation (ULN - 3.0 x ULN) and/or Alk phos (ULN - 2.5 x ULN)	Continue crenolanib at current dose
Grade ≥2 ALT or AST elevation (>3.0 x ULN) and/or Alk phos (>2.5 x ULN)	Stop crenolanib. Restart drug at next lower dose level (-1) (Table 4) once ALT, AST and/or Alk Phos returns to ≤ grade 1
Following re-challenge:	
Grade ≥2 ALT or AST elevation (>3.0 x ULN) and/or Alk phos (>2.5 x ULN)	Stop crenolanib. Restart drug at next lower dose level (-2) once ALT, AST and/or Alk Phos returns to ≤ grade 1

8.4.2. Dose Reductions of Crenolanib for Hematologic Toxicities

Subjects with neutropenia or thrombocytopenia as a consequence of the disease or chemotherapy do not require treatment interruptions for myelosuppression. Drug hold or dose reduction in these subjects may be considered in an individual case and should be discussed with the medical monitor at AROG prior to the drug hold. All dose holds and reductions should be captured in CRFs. Dose re-escalation is not allowed on this protocol, any exception must be approved by the sponsor in writing.

8.5. Other Dose Hold and Dose Reduction

Dose hold due to toxicity unrelated to crenolanib or other medical interventions may be allowed on a case by case basis. Investigator should discuss with sponsor prior to any dose hold for reasons other than toxicity related to crenolanib. All dose hold should be captured in CRFs.

8.6. Concomitant Therapy

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented with source documents on CRFs as concomitant medication.

Supportive measures including blood and platelet transfusions, antimicrobials including prophylaxis, etc. are permitted. The use of growth factors is allowed per institutional practice guidelines or the preference of the attending physician.

Chemotherapy not specified on this protocol, investigational cytotoxic agents, radiation, or biologic therapy is prohibited while the subject is on study with the following exceptions during induction:

1. Leukapheresis is allowed within the first 10 days of induction of the study only. Please notify the study's medical monitor if leukapheresis is required beyond this specification.
2. Hydroxyurea (up to a maximum of 5 g/d) for a maximum of 10 days within the first 28 days on trial may be administered during induction.
3. Leukapheresis and hydroxyurea may be administered together according to the guidelines above.

The parameters of exposure to leukapheresis and/or hydroxyurea apply as of cycle 1, day 1 of first induction. Patients who commenced hydroxyurea and/or leukapheresis prior to enrollment are allowed to participate.

Except for the chemotherapy or hydroxyurea specified in this protocol no other anticancer therapy including immunotherapy, hormonal cancer therapy, or experimental medications will be permitted while patients are participating in this study. Any disease progression requiring other forms of specific antitumor therapy will be cause for discontinuation of study therapy.

In clinical trials, crenolanib caused nausea and vomiting in >60% patients (2-5% Grade 3/4 events, data unpublished, on file at AROG) and diarrhea in 50% of patients (4% Grade 3/4 events, data unpublished, on file at AROG). Therefore, the recommendation is made that standard anti-emetic premedication is given (see Table 8). Prophylaxis can be discontinued if subject tolerates crenolanib without significant nausea and vomiting. Infectious work-up for diarrhea will be left to the discretion of the Investigator, using institutional guidelines. Treatment with antidiarrheal drugs is recommended once the onset of the earliest signs of diarrhea is present (see Table 9).

It has not been established whether enzyme inducing drugs alter the dosing of crenolanib in patients. However, CYP3A4 is required for the metabolism of crenolanib in experiments done with hepatic microsomes. Therapeutic agents which are potential hepatic enzyme CYP3A4 inducing or inhibiting drugs should be used with caution in patient participation on the study, see Appendix VI.

Table 8 Suggested therapy for nausea and vomiting (ASCO 2011 guidelines)

Escalation of therapy	Drug or class	Directions
0	5-HT_3 receptor antagonist	30 minutes prior to crenolanib administration
1	Metoclopramide	
2	Dexamethasone	

Table 9 Suggested therapy for diarrhea

Escalation of therapy	Drug or class	Directions
0	Loperamide	As per investigators discretion, not to exceed maximum recommended dose
1	Lomotil	

These are suggested guidelines; subjects should be treated according to investigator/treating physician discretion.

9. DRUG FORMULATION, AVAILABILITY, AND PREPARATION

9.1. Crenolanib

Crenolanib besylate is supplied as 100 mg and/or 20 mg tablet for oral administration. Study drug will be supplied by AROG Pharmaceuticals, Inc. Study drug may be packaged by a third party. Clinical trial materials will be labeled according to regulatory requirements.

Crenolanib besylate 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. Used bottles, unused tablets and bottles and drug diaries should be returned to the study site.

9.1.1. Drug-Drug Interaction

It has not been established whether enzyme inducing drugs alter the dosing of crenolanib in patients. However, CYP3A4 is required for the metabolism of crenolanib in experiments done with hepatic microsomes. Therapeutic agents which are potential hepatic enzyme CYP3A4 inducing or inhibiting drugs should be used with caution in patient participation on the study, see Appendix VI.

9.2. Chemotherapy

Only qualified personnel familiar with procedures that minimize undue exposure to themselves or the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents in a self-contained, protective environment. Institutional protocols for preparation, dosing and discarding chemotherapeutic agents should be followed.

9.2.1. Cytarabine

Please see package insert for additional information.

9.2.2. Idarubicin

Please see package insert for additional information.

9.2.3. Daunorubicin

Please see package insert for additional information.

10. STUDY PROCEDURES

After providing informed consent, screening procedures may start with the patients assigned unique patient identification number (UPIN). The UPIN will consist of an eight-digit number where the first three digits will mark the protocol ID (006). The second two numbers will mark the site and will be determined by the sponsor. And the third will mark the patient sequentially. (ie. 00601001 will be the first patient enrolled from site 1 onto protocol ARO-006). The Sponsor should be provided with the complete "Enrollment Checklist" indicating the request to enroll the patient to the trial. After review, the sponsor will provide the site a "Confirmation of Enrollment" signifying enrollment of the patient to the trial and formal verification of the study unique patient identifier number (UPIN).

10.1. Screening

The following assessments will be performed after completion of the informed consent and within 28 days of enrollment except as otherwise specified. Any test or procedure performed as per standard of care can be used for screening purposes as long as done within the window required.

1. Medical history and physical exam (includes documentation of current medications, prior relevant surgeries or treatments, allergies and prior or existing relevant medical conditions)
2. Height, weight, vital signs
3. Demographics
4. ECOG Performance Status (Appendix II)
5. Serum or urine pregnancy test for women of child bearing capacity (within 7 days of enrollment)
6. Chemistry panel including creatinine, total bilirubin, ALT, and AST (within 7 days of enrollment)
7. CBC with differential (within 7 days of enrollment)
8. Bone marrow aspirate and biopsy (within 21 days of enrollment).
9. Evaluation of FLT3-D835, FLT3-ITD and other mutational status (within 21 days of enrollment).

10.2. Baseline

Baseline (first day of crenolanib) should be performed as follows:

1. Chemistry panel including total bilirubin, ALT and AST should be collected within 24 hours of initiation of crenolanib. Eligibility criteria (Section 7.1.7) should be reconfirmed at this time point. If patient does not have normal total bilirubin and ALT/AST $\leq$ 2x ULN at this time point, crenolanib can be delayed until these criteria are met (section 1 overview of treatment plan).
2. Baseline EKG should be collected after completion of chemotherapy (within 24 hours of start of crenolanib) and a second EKG should be performed 2 hour (± 30 minutes) post first dose of crenolanib
3. Active concomitant medications within 24 hours of initiation of crenolanib
4. CBC with differential collected after completion of chemotherapy and prior to initiation of crenolanib
5. PS, Physical exam with vitals after completion of chemotherapy and prior to initiation of crenolanib
6. Active toxicities or medical conditions after completion of chemotherapy and prior to initiation of crenolanib

7. Blood and marrow samples for translational research including pharmacokinetic analysis will be obtained as defined in Section 11 and lab manual. Every effort should be made to collect correlative studies at all time points for all patients; however, missing collection in one or more of these time points will not be considered a protocol deviation/violation.

10.3. Evaluation during treatment

Counting Cycle Duration: During induction and consolidation, one cycle is defined by start of chemotherapy and will continue until the start of next chemotherapy (i.e. induction 1 = cycle 1 and may exceed 28 days). During maintenance, cycles will be 28 days in maximum duration (28 days = 1 cycle).

It is assumed subjects will be in the hospital for chemotherapy (induction and consolidation). Required study patient evaluations should be performed as an inpatient or outpatient including:

1. Physical examination (with ECOG PS, vital signs and weight) and medical history update (including concomitant medications), and documentation of adverse events:
    a. During induction(s): Routinely per institutional standard of care , at response assessment visit (Day 14-28), and at count recovery (or day 42) whichever occurs first.
    b. During consolidation(s) Day 1 of crenolanib and then routinely per institutional standard of care
    c. During maintenance: Day 1 and then per site standard schedule but no less frequent than every 2 months (±1 month).
2. EKG measurements to be obtained during induction and consolidation therapy.
    a. EKG to be obtained 2 hour (± 30 minutes) post first dose of crenolanib in consolidation 1.
3. CBC with platelet count and differential (differential may be omitted if WBC is <0.5 $x10^9$/L) must be obtained at least
    a. During induction(s): Routinely per institutional standard of care (at least once weekly), at response assessment visit (Day 14-28), and at count recovery (or day 42) whichever occurs first.
    b. During consolidation(s): Routinely per institutional standard of care (at least once weekly).
    c. During maintenance: Day 1 of each cycle
4. Chemistry panel including creatinine, total bilirubin, ALT and AST must be obtained at least
    a. During induction(s): Routinely per institutional standard of care (at least once weekly), at response assessment visit (Day 14-28), and at count recovery (or day 42) whichever occurs first.
    b. During consolidation(s): Routinely per institutional standard of care (at least once weekly).
    c. During maintenance: Day 1 of each cycle
5. Bone marrow aspirations will be taken as follows:
    a. During induction (s): Between days 14-28, bone marrow is obtained per standard of care to evaluate for remission/response to therapy and at time of count recovery or Day 42 (whichever occurs first)
    b. Bone marrow sampling during consolidations should occur per institutional standard of care.

c. During maintenance: should occur per institutional standard of care (reference study calendar appendix IV).

6. Blood and marrow samples for translational research including pharmacokinetic analysis will be obtained as defined in Section 11 and lab manual. Every effort should be made to collect correlative studies at all time points for all patients; however, missing collection in one or more of these time points will not be considered a protocol deviation/violation.
7. Serum or urine pregnancy test for women of child bearing capacity should be done every six months while on study.

10.4. At time of progression or completion of study

1. Medical history and physical exam (includes documentation of current medications)
2. Weight, vital signs, ECOG Performance Status (Appendix II)
3. Adverse event documentation
4. CBC with platelet count, differential (differential may be omitted if WBC is $<0.5 \times 10^9$/L)
5. Chemistry panel including creatinine, total bilirubin, ALT, and AST
6. bone marrow and whole blood samples
7. Evaluation of FLT3-D835, FLT3-ITD and other mutational status when available

* Every effort should be made to collect optional procedures at all time points for all patients; however, missing collection in one or more of these time points will not be considered a protocol deviation/violation.

Procedures that are to be performed at the planned subject visits will be granted an exemption if the subject is hospitalized and unstable, or otherwise medically unstable as determined by investigator and unable to travel to the study sites. In the latter case, the investigator is responsible to ensure that the planned protocol procedures are performed at a local hospital and provide oversight. Appropriate documentation and source documents shall be obtained and information recorded onto study CRFs.

11. PHARMACOKINETIC AND CORRELATIVE STUDIES

The participating institution 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 VIII) to request lab kits in anticipation of each patient enrolled on the study.

Correlative samples to be collected include but are not limited to:

1. Serum for pharmacokinetic (PK) analysis (selected sites only)
2. Bone marrow aspirate (BMA) samples
3. Bone marrow smears
4. Whole blood sample

Sampling Schedule for PK (selected sites only)
Serial blood samples for PK will be drawn for correlative research. See lab manual for forms. During crenolanib treatment, PK will be drawn for the following time points:

Day 1 of crenolanib administration following Induction 1

a. pre-dose
b. post-dose 2 hours (± 15 minutes)
c. post-dose 4 hours (± 30 minutes)
d. post-dose 8 hours (± 2 h)
e. post-dose 24 hours (± 6 h) prior to first dose of the day

Day 15 of crenolanib administration following Induction 1

a. pre-dose
b. post-dose 4 hours (±30 minutes)

For patients who proceed to consolidation with HiDAC:

Day 1 of crenolanib administration following Consolidation 1

a. pre dose
b. post-dose 4 hours (±30 minutes)
c. post-dose 8 hours (± 2 h)

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

Sampling Schedule for Bone Marrow Aspirates
At the time of each routine marrow sampling, an additional aspiration of 2.5 mL should be drawn for research purposes and placed in a heparinized cell preparation tube. See lab manual for required form.

Scheduled bone marrow time points per protocol:

a. During induction(s): day 14-28 and at time of count recovery (or Day 42), whichever occurs first
b. During consolidations: as per the institutional standard of care

c. Maintenance: as per the institutional standard of care.
d. When patient is determined to have progressive disease by the treating physician (loss of CR/CRi).

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 lab manual for required form. Samples should be drawn at the following two time points:

a. Pre-administration of first dose of anthracycline in induction 1 (when applicable),
b. Upon progression

Sample Processing Instructions
See lab manual for processing, storage and shipment of samples.

Sampling Schedule for 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.

12. RESPONSE DEFINITIONS

12.1. Response Criteria

Response criteria will be adapted from the International Working Group for AML. [9] Responders are newly diagnosed patients receiving study drug 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):
    a. Peripheral blood counts:
        i. No circulating blasts
        ii. Neutrophil count $\geq 1.0 \times 10^9$/L
        iii. Platelet count $\geq 100 \times 10^9$/L
    b. Bone marrow aspirate and biopsy:
        i. < 5% blasts
        ii. No Auer rods
        iii. No extramedullary leukemia

2. Complete remission with incomplete blood count recovery (CRi):
    a. Peripheral blood counts:
        i. No circulating blasts
        ii. Neutrophil count $<1.0 \times 10^9$/L, or
        iii. Platelet count $<100 \times 10^9$/L
    b. Bone marrow aspirate and biopsy:
        i. < 5% blasts
        ii. No Auer rods
        iii. No extramedullary leukemia

3. Partial remission:
    a. All CR criteria except:
    b. ≥50 % reduction in bone marrow blast but within 5-25% or
    c. Marrow blasts < 5% with persistent Auer rods

4. Morphologic leukemia-free state:
    a. Bone marrow: <5% myeloblasts

5. Hematologic Improvement (HI):
   Hematologic response must be described by the number of positively affected cell lines.
    a. Blast response (B)
        i. At least a 50% reduction in blast percentage in peripheral blood (if > 5%) or bone marrow

13. STATISTICAL CONSIDERATIONS

13.1. Statistical and analytical plans

The statistical analysis of this study will be the responsibility of AROG Pharmaceuticals or its designees. The clinical research physician/scientist and statistician will jointly be responsible for the appropriate conduct of an internal review process for the final study report and any study-related material to be authorized for publication by AROG or its designees. A statistical analysis plan (SAP) will be prepared as a separate document that details the planned analyses and presentation of the study results.

13.1.1. General considerations

The statistical analyses will be performed by cohort and in some cases, with the cohorts combined. Descriptive statistics will be used to summarize the safety and efficacy data for this study. Continuous data will be summarized by the number of patients, mean, standard deviation, median, minimum, and maximum value. Categorical data will be summarized by the number and percentage of patients in each category. Time-to- event endpoints will be summarized using the cumulative incidence and Kaplan-Meier methodology, as appropriate.

13.1.2. Determination of sample size

A total of approximately 120 patients will be enrolled. The study consists of a safety phase and an expansion phase. The safety phase has two arms in which patients will receive cytarabine in combination with daunorubicin (Cohort A) or with idarubicin (Cohort B) during standard 7+3 therapy with Crenolanib. The safety of each arm will be evaluated separately and once the safety is established, an expansion phase will be opened in which patients can receive either chemotherapy regimens.

During the initial safety phase, the two cohorts, each consisting of approximately 24 patients, will be analyzed separately and initially enroll 12 patients to receive crenolanib with 1-2 courses of standard induction chemotherapy. If the early safety stopping criteria are not met for a cohort, then 12 additional patients may be enrolled in that cohort in order to further characterize the safety and tolerability of the combination.

Once the safety of the combinations is determined, a single arm expansion phase will be initiated to further confirm the safety and assess the clinical benefit of the combination of standard induction chemotherapy with crenolanib.

Historically, patients with newly diagnosed FLT3+ve AML achieve a 66% - 69% response rate with induction chemotherapy only. (Mandelli et al. J Clin Oncol. 2009;27(32):5397-403) In recent years, Midostaurin (a FLT3 TKI) has shown an improvement of response rate to 74-76% with the combination of Midostaurin to standard induction chemotherapy. (Schlenk et al. Blood 2016; 128(22): 449) This study will enroll approximately 120 patients with the following confidence intervals based on projected response rate. A response rate of 90% will have a 95% CI of ±5%. That is to say that if we treat 120 patients and observe a 90% response rate, we are 95% sure that the true response rate is between 85% to 95%.

Table 10 95% confidence interval based on response rate expected in approximately 120 patients

Response Rate	95% CI	True response rate interval
90%	±5%	85%-95%
85%	±6%	84%-96%
80%	±7%	83%-97%
75%	±8%	82%-98%

13.2. Safety monitoring during the initial safety phase

Adverse events, as defined in Section 14.1, 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 Protocol Safety Committee will review safety data from this trial on a periodic basis. The committee also will 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. For the first 6 patients, 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)
- Unexpected, non-hematologic, crenolanib-related toxicity (CTCAE Grade 4)

The criteria used to determine if enrollment will be halted are described in sections 13.2.1, 13.2.2 and 13.3.3.

13.2.1. Excessive early mortality

Early stopping rules for excessive mortality will be applied in the safety phase of the study. Early mortality is defined for this study as death due to any cause within 30 and 60 days of the initiation of study treatment. In the VALOR trial, all-cause mortality rates of 7.9% and 19.7% were reported, respectively, for patients with relapsed/refractory AML who received cytarabine and placebo as induction therapy. [14] The 30-day mortality rate of 7.9% from the VALOR trial is similar to the 28-day mortality rate of 10.3% that was reported from a retrospective analysis of more than 3000 patients with newly diagnosed AML, the majority of whom were treated with cytarabine-based regimens as induction therapy.[11]

Based on the above considerations, enrollment in a cohort will be halted if the observed 30- and 60-day early mortality rate exceeds 10% and 20%, respectively, as follows: if 1 or more of the first 6 patients enrolled within a cohort die prior to Day 30 then enrollment of additional patients within that cohort will be halted pending review by the Protocol Safety Committee. Additionally, enrollment will be halted within a cohort if 2 or more of the patients die prior to Day 60. Otherwise, 6 additional patients will be enrolled within the cohort provided none of the other stopping criteria have been met.

For the second group of 6 patients within a cohort, if 2 or more of the patients enrolled within a cohort die prior to Day 30, then enrollment of additional patients will be halted pending review by the Protocol Safety Committee. Similarly, if 3 or more of the patients enrolled within a cohort die

prior to Day 60, then enrollment of additional patients will be halted for that cohort. If these and the other early stopping criteria are not met, then the 12 additional patients will be enrolled within the cohort.

13.2.2. Excessive expected crenolanib-related toxicity

Early stopping rules for excessive expected crenolanib-related toxicity will be applied in the safety phase of the study. In clinical studies of crenolanib as single-agent therapy, the following treatment-related, non-hematologic, adverse events were the most frequently reported, irrespective of severity:

- hepatic dysfunction
- nausea, vomiting, and diarrhea
- ascites, edema, and effusions

The majority of these events were CTCAE severity grade 1-3, with grade 4 representing less than 5% of total cases reported. It's anticipated that these or similar adverse events also occur with relatively higher frequency for AML induction regimens that include cytarabine, idarubicin, or daunorubicin. Nonetheless, for purposes of monitoring enrollment in this study, the adverse events listed above represent the expected non-hematologic crenolanib-related toxicities. If the observed rate of expected, non-hematologic, crenolanib-related toxicity with CTCAE severity grade 4 exceeds 20% during the first 60 days of treatment, then enrollment will be halted as follows:

If 2 or more of the first 6 patients enrolled within a cohort experience a CTCAE grade 4, non-hematologic, expected crenolanib-related adverse event prior to Day 60 then enrollment of additional patients within that cohort will be halted pending review by the Protocol Safety Committee. Otherwise, 6 additional patients will be enrolled within the cohort provided none of the other stopping criteria have been met. Upon enrollment of the 6 additional patients within a cohort, if 3 or more of the patients enrolled within a cohort experience such an event prior to Day 60, then enrollment of additional patients will be halted pending review by the Protocol Safety Committee. If these and the other early stopping criteria are not met, then 12 additional patients will be enrolled to the cohort.

13.2.3. Excessive unexpected crenolanib-related toxicity

Early stopping rules for excessive unexpected crenolanib-related toxicity will be applied in the safety phase of the study. An unexpected crenolanib-related toxicity is defined as any non-hematologic, adverse event considered related to crenolanib (exclusive of those listed in Section 13.2.2). If the observed rate of unexpected, non-hematologic, crenolanib-related toxicity with CTCAE severity grade 4 exceeds 15% during the first 60 days of treatment then enrollment within a cohort will be halted as follows:

If 1 or more of the first 6 patients enrolled within a cohort experience a CTCAE grade 4, non-hematologic, unexpected crenolanib-related adverse event prior to Day 60 then enrollment of additional patients within that cohort will be halted pending review by the Protocol Safety Committee. Otherwise, 6 additional patients will be enrolled within the cohort provided none of the other stopping criteria have been met. Upon enrollment of the 6 additional patients within a cohort, if 2 or more of the patients enrolled within a cohort experience such an event prior to Day 60, then enrollment of additional patients will be halted pending review by the Protocol Safety Committee. If these and the other early stopping criteria are not met, then 12 additional patients will be enrolled to complete the cohort.

13.3. Assessments during the expansion phase

Once the safety of the combinations is determined, a single arm expansion phase will be initiated to further confirm the safety and assess the clinical benefit of the combination of standard induction chemotherapy with crenolanib.

13.3.1. Safety monitoring during the expansion phase

During the expansion phase, safety monitoring will be performed for the entire per protocol patient population (defined as those who receive at least one dose of study drug) and in a separate analysis dictated by chemotherapy agent used.

13.3.2. Response Rate Evaluation

At the expansion phase, the primary end-point is overall response rate. Patients must have received at least one dose of study drug and have at least one bone marrow disease assessment to be included in the complete response rate.

13.4. Subject Disposition

A summary of patient disposition will be provided for each cohort and will include the following:

- Number of patients enrolled
- Number of patients who participate in each study phase (induction, consolidation, maintenance)
- Reasons for discontinuation from study treatment and follow-up
- Summary of major protocol violations

13.5. Subject Characteristics

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

- Demographics
- Baseline disease characteristics
- Pre-existing conditions

Other characteristics will be summarized as deemed appropriate.

13.6. 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.

13.7. Response Outcome and Methodology

Response criteria will be adapted from the International Working Group for AML, as stated in section 12.1.

13.8. Safety Analyses

All subjects will be evaluable for safety. Adverse events that occur after a subject is entered (signs informed consent), but before the patient receives study drug, will not be recorded on the CRF unless the investigator believes that the events may have been caused by a protocol procedure. Safety analyses will include summaries of the incidence of adverse events by maximum CTCAE

grade (version 4.03; NCI 2010) that occur during the study treatment period or within 30 days of the last dose of study treatment or until alternate therapy is started, regardless of causality or relatedness to study drug. The safety-related outcomes that will be summarized include:

- Adverse events,
- TEAEs,
- SAEs,
- Deaths,
- Discontinuations due to adverse events,
- Extent of exposure to study drug treatment,
- Hospitalizations,
- Use of key concomitant medications.

Analyses for data with discrete dates (for example, death date and start/stop dates of concomitant medications) will be performed through 30 days after the patient has been discontinued from study treatment or until alternate therapy is started. Adverse events will also be analyzed in this time frame. After 30-day post-discontinuation follow-up, only those SAEs that are thought to be related to study treatment or protocol procedure should be reported immediately to AROG or its designee. For these events, the patient must be followed until the event has resolved or stabilized.

13.9. 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 subjects are continuing to benefit from study treatment, they will be allowed to continue receiving study treatment for up to one year as part of planned maintenance. Patient is considered "off therapy" when study drug stops for any reason and crenolanib therapy is not continued. Patient is considered "off study" after completion of the 30-day safety follow up, 2 year follow-up period or upon death or upon start of a new therapy, whichever comes first.

14. SAFETY EVALUATIONS AND APPROPRIATENESS OF MEASUREMENTS

14.1. Definitions of Adverse Events

14.1.1. Adverse Event (AE)

Any harm or untoward medical occurrence in a research participant administered a medical product, medical treatment or procedure even if it does not necessarily have a causal relationship with the product, treatment, or procedure. An adverse event can be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medical product, medical treatment, or procedure whether or not considered to be related. All adverse events regardless of grade must be recorded, graded, and reported to the Sponsor.

14.1.2. Serious AE (SAE)

An adverse event that results in any of the following outcomes:

- Death
- Life-threatening adverse event (real risk of dying)
- Hospital admission
- Prolongation of hospitalization
- Persistent or significant disability/incapacity/or change in psychosocial status
- Congenital anomaly
- Requirement of intervention to prevent permanent impairment or damage

14.2. Attribution to Study Drug

For reporting purposes, attribution is the assessment of the likelihood that an adverse event is caused by the research agent or protocol intervention. The attribution is assigned by the principal investigator after considering the clinical information, the medical history of the subject, and past experience with the research agent/intervention. This is recorded using one of the following four categories:

- Related
- Possibly Related
- Not Related
- Unknown

Related means that the adverse event was most certainly caused by the procedures involved in the research.

Possibly related means that there is reasonable possibility that the adverse events may have been caused by the procedures involved in the research.
Not related means that the adverse event was due to an underlying disease, disorder, or condition of the subject, or may have been caused by other circumstances unrelated to the research or any underlying disease, disorder, or condition of the subject.

Unknown means that it is unclear whether the adverse event was related to procedures involved in the research, either because more information is needed, and will be provided in follow-up, or because there is no way to make a determination.

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

14.3. Determination of Severity

The severity of AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03. If the AE is not defined in the CTCAE, the investigator will determine the severity based on the following definitions from the CTCAE:

- Grade 1 (Mild): Asymptomatic or mild symptoms, clinical or diagnostic observations only with no intervention indicated
- Grade 2 (Moderate): Minimal, local or noninvasive intervention indicated, limiting instrumental ADL
- Grade 3 (Severe): Medically significant but not immediately life-threatening, causing hospitalization or prolongation of hospitalization, disabling and limiting self-care AL
- Grade 4 (Life-Threatening): Urgent intervention indicated
- Grade 5 (Death)

14.4. Adverse Event Reporting

AROG has standards for reporting AEs that are to be followed regardless of applicable regulatory requirements that may be less stringent. Lack of drug effect is not an AE in clinical trials, because the purpose of the clinical trial is to establish drug effect.

Adverse Events (AEs) will be evaluated according to CTCAE version 4.03 and documented in medical record. After the Informed Consent Document (ICD) is signed, study site personnel will record the occurrence and nature of each patient's pre-existing conditions, including clinically significant signs and symptoms of the disease. During the study, site personnel will record any change in the pre-existing condition(s) and the occurrence and nature of any new adverse events.

All AEs related to protocol procedures are reported to AROG or designee. All AEs occurring after the patient receives the first dose of study drug must be reported to AROG or its designee via CRF. Investigators will be instructed to report to AROG or its designee their assessment of the potential relatedness of each AE to protocol procedure, studied disease state, study drug, and/or drug delivery system via CRF.

For all AEs, the investigator should specify:

1. ***Seriousness:*** Seriousness of an AE is defined by the criteria described in Section 10.1. A severe AE should not always be considered as serious.
2. ***Date of onset and its duration (start and end dates)***: The investigator should follow up the outcome of any AEs until they return to normal or consolidation of the subject's condition. All adverse events still evolving at the end of the study are to be followed up by the investigator until their resolution or stabilization.
3. ***Severity:*** (using NCI CTCAE v.4.03),

4. ***Action taken with respect to study drug:*** (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; hospitalization/prolonged hospitalization), corrective treatment/therapy given, additional investigations performed
5. ***Outcome:*** Resolved/Recovered, recovering/resolving, not recovered/resolved, recovered/resolved with sequelae, unknown
6. ***Relatedness*:** If an AE is related or not related to study drug

Follow-up of unresolved adverse events

Any AEs that are unresolved at the subject's last visit in the study are to be followed up by the investigator for as long as medically indicated. The sponsor retains the right to request additional information for any subject with ongoing AE(s) at the end of the study, if judged necessary.

CASE OF ROUTINE LABORATORY MEASUREMENTS

A value outside the normal or reference range in a routine safety assessment, such as clinical laboratory may be considered as an AE. However, laboratory, as well as vital signs abnormalities, are to be recorded into the eCRF as AEs only if they are considered medically relevant by the investigator: i.e. symptomatic, requiring corrective treatment, leading to IMP discontinuation/dose modification (reduction and/or delay), and/or fulfilling a seriousness criterion. Deterioration of a laboratory value that is unequivocally due to disease progression should not be reported as an AE. If the findings contribute to a clinical diagnosis (such as hepatitis in case of increased liver enzymes) this diagnosis should be recorded as an adverse event.

14.5. Serious Adverse Event Reporting

Serious adverse event collection begins after the patient has signed informed consent and has received a tablet or more of study drug. If a patient experiences an SAE after signing informed consent, but prior to receiving study drug, the event will NOT be collected unless the investigator feels the event may have been caused by a protocol procedure.

In case of a SAE, the investigator, within 24 hours of learning of the SAE or subject death, must notify the sponsor (Arog Pharmaceuticals by e-mail: SAE@arogpharma.com or Fax: 214-594-0002) and transmit the following information (within a signed SAE report form):

- Subject identification code, demographics and vitals
- Description of event with onset and duration (with CTCAE event term & severity)
- Dates, dose and frequency of study drug administered
- Assessment of the seriousness and causality of the event with the study drug using the causality criteria (EVCTM): related versus not related
- Study drug status (dose interrupted or discontinued)
- Date of death (if applicable)
- Concomitant therapy and interventions
- Pertinent laboratory data/diagnostic tests
- Pertinent medical history including underlying diagnosis

All SAEs must be followed by the investigator until resolution or stabilization until the subject's death. This may mean that follow-up will be extended beyond the subject's withdrawal from the trial. The investigator must provide follow-up information (outcome, more precise medical details, results of investigations, copy of discharge summary, etc…) within 24 hours of information becoming available to Arog Pharmaceuticals and to the study monitor, again using the SAE Report Form indicating follow-up. When this information is passed on, care must be taken to continue to respect subject anonymity. The study monitor may contact, or visit the investigator, in order to obtain details of the event.

The sponsor will report all SUSAR to the country specific regulatory authorities within the request period. The evaluation of expectedness is based on knowledge of the adverse reaction on the reference document: the current reference document is the latest version of the Investigator's Brochure of crenolanib.

The sponsor will also inform the IRB of any SAE with the potential to modify the benefit/risk ratio of the present study. The sponsor will be responsible for reporting of New Safety Issues and Annual Safety Reports to IRBs.

The following events **are not** to be considered as a SAE:

- Any event requiring short consultation in a hospital
- An external treatment in a hospital emergency service
- Any event clearly related to disease progression
    - Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new, or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE or SAE. Events that are unequivocally due to disease progression should not be reported as AEs or SAEs during the study.
- Hospitalization (1 night or more) or hospitalization prolongation for one of the following reasons:
    - Planned hospitalization for routine intervention
    - Hospitalization or intervention requested by the protocol
    - Hospitalization for explorations not related to a modification of the subject's health
    - Hospitalization for comfort or for social reasons (for example: hospitalization of an elderly person due to dependence on his partner who was hospitalized)
    - Hospitalization not related to a subject's health worsening and not related to the study objectives (for example: plastic surgery)

14.6. Follow-up of Adverse Events

All adverse events will be followed up according to Good Clinical Practice.

During Treatment: During study, site personnel will track any change in the condition(s) and the occurrence and nature of any AEs and record the highest grade of the adverse event per cycle on the CRF. CTCAE grading will be assigned before each visit for any adverse events experienced during the previous visit period.

Preparation for transplant: Once patient enters conditioning prior to transplant, crenolanib will be held (72 hours prior to start of conditioning). Patients will not be followed for safety once conditioning starts. If patient receives maintenance crenolanib following transplant, safety will be assessed once patient restarts crenolanib (per protocol).

Discontinuation due to relapse:
Patients who have discontinued therapy due to relapse will be followed for safety for 30 days post last dose of crenolanib or until start of another therapy or death, whichever comes first.

Discontinuation due to toxicity:
Patients who have discontinued therapy due to toxicities attributable to study drug will be followed for safety for 30 days post last dose of crenolanib or until start of another therapy or death, whichever comes first.

Long-Term Follow-Up Period: Only new and ongoing serious adverse events (SAEs) thought to be related to study treatment or protocol procedures should be documented on the CRF and immediately reported to AROG or its designee via the designated transmission method. If drug-related toxicity is present beyond 30 days post-discontinuation, patients must be followed at least for 30 days or until the toxicity resolves.

14.7. Miscellaneous adverse events

New safety issues: Any new safety data that could lead to re-evaluate the ratio between the benefits and the risks of the research, or that could be sufficiently important to consider modifications of the research documents, the research management or, if need be, the drug utilization.

New cancers: The development of a new cancer should be regarded as an AE and will generally meet at least one of the serious criteria. New cancers are those that are not the primary reason for the administration of the study treatment and have been identified after the subject's inclusion in this study. They do not include metastases of the original cancer.

14.8. Deaths

All deaths that occur during the study should be reported as follows:

- Death, which is unequivocally due to disease progression, should be communicated to the study monitor at the next monitoring visit and should be documented in the CRF module, but should not be reported as a SAE during the study
- Where death is not clearly due to disease progression of the disease under study the AE causing the death should be reported to the study monitor as an SAE within 24 hours of becoming aware of the event. The report should contain a comment regarding the co-

involvement of progression of disease, if appropriate, and should assign a single primary cause of death together with any contributory causes

- Deaths with an unknown cause should always be reported as a SAE (within 24 hours of becoming aware of the event) but every effort should be made to establish a cause of death. A post-mortem may be helpful in the assessment of the cause of death, and if performed, a copy of the post-mortem results (with translation of important parts into English) should be reported in an expedited fashion to the sponsor within the usual timeframes

14.9. Pregnancy

Nothing is known about the effects of crenolanib on reproductive function. Women of reproductive potential and fertile men will be informed as to the potential risk of procreation while participating in this trial.

If the investigator has been informed that a female subject is pregnant during the study period:

1. The investigational product should be immediately discontinued and the planned safety assessments should be performed
2. The investigator must immediately notify the study monitor, complete the Pregnancy Report Form, and send it to Arog Pharmaceuticals by e-mail: SAE@arogpharma.com or Fax: 214-594-0002.
3. Follow-up of the pregnancy will be mandatory until the outcome has been determined.

Nota bene: In order to follow the pregnancy of the wife of a subject included in the study, consent or agreement of the subject's wife should appear in the medical file of the subject.

14.9.1. Maternal exposure

Pregnancy itself is not regarded as an adverse event. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of a pregnancy should be followed up and documented even if the patient was withdrawn from the study.

If a pregnancy occurs during exposure to investigational product or in the 30 days after discontinuing investigational product, then investigators or other site personnel must inform the sponsor immediately, or **no later than 24 hours** of when he or she becomes aware of it. The same timelines apply when outcome information is available.

14.9.2. Paternal exposure

Pregnancy of a patient's partner is not considered to be an adverse event. However, any conception occurring from the date of dosing until 16 weeks after dosing should be reported to the sponsor and followed up for its outcome.

14.10. Overdose

To date there have been no instances of patients who were inadvertently overdosed. Clinical studies have shown an apparent crenolanib half-life of approximately 8 hours. It is anticipated that

crenolanib would be metabolized and excreted within 5 half-lives of the drug. No specific antidote exists for the treatment of crenolanib overdose. Investigators will be advised that any patient who receives a higher dose than that intended should be monitored closely, managed with appropriate supportive care and followed up expectantly.

If an overdose occurs in the course of the study, then investigators or other site personnel must inform the sponsor immediately, or **no later than 24 hours** of when he/she becomes aware of it.

Such overdoses should be recorded as follows:

- An overdose with associated AEs/SAEs is recorded as the AE diagnosis/symptoms on the relevant AE/SAE modules in the eCRF.
- An overdose with no associated symptoms should be documented on the eCRF module for dosing of study drug.

15. DATA COLLECTION AND MANAGEMENT

To ensure accurate, complete, and reliable data, AROG or its representatives will do the following:

- Provide instructional material to the study site, as appropriate.
- Sponsor a start-up training session to instruct the investigators and study coordinators. This session will give instruction on the protocol, the completion of the CRFs, and study procedures.
- Conduct periodic teleconferences (approximately twice a month) with each study site to discuss current patients on trial, available pharmacodynamics/pharmacokinetic data, regulatory issues and other updates as applicable.
- Make periodic visits to the study site.
- Be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax.
- Review and evaluate CRF data and use audits to detect errors in data collection.
- Conduct a quality review of the database.

In addition, AROG or its representatives will periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by AROG or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

To ensure the safety of participants in the study, and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ethical review boards (ERBs) with direct access to original source documents.

15.1. Data Capture System

An electronic data capture system will be used in this trial. Case report form (CRF) data will be encoded and stored in a clinical trial database. Any data that will serve as the source document will be identified and documented in the site's study file.

15.2. Data Safety Monitoring Plan

AROG and Investigator, or his/her designee, will have periodic teleconferences (approximately twice a month) with each study site to discuss current patients on trial, available pharmacodynamics/pharmacokinetic data, regulatory issues and other updates as applicable.

AROG will have Data Safety Monitoring meetings at least every six months or for every 6 patients enrolled per cohort. At these meetings, compiled patient data including responses and safety analysis will be discussed.

16. INFORMED CONSENT, ETHICAL REVIEW, AND REGULATORY CONSIDERATIONS

16.1. Informed Consent

The Principal Investigator or designee is responsible for explaining verbally and in writing the nature, duration, and purpose of the study and possible consequences for treatment. In addition, the Principal Investigator or designee must ensure that the patient understands the potential risks and benefits of participating in the study, including answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the trial. Patients must also be informed that they may withdraw from the study at any time and for any reason without jeopardizing their future treatment. In accordance with federal regulations (21 CFR 50), all patients enrolled in the study must sign the IRB-approved consent form.

The informed consent document (ICD) will be used to explain the potential risks and benefits of study participation to the patient in simple terms before the patient is entered into the study, and to document that the patient is satisfied with his or her understanding of the risks and benefits of participating in the study and desires to participate in the study.

The investigator is responsible for ensuring that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the ICD prior to the performance of any protocol procedures and prior to the administration of study drug.

16.2. Document Review

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

Prior to IRB submission and review, AROG must review and approve all ICDs. All informed consent documents must be compliant with the International Conference on Harmonization (ICH) guideline on good clinical practice (GCP). Informed consent obtained under special circumstances may occur only if allowed by local laws and regulations and performed in accordance with a written process approved by AROG.

Any member of the IRB who is directly affiliated with this study as an investigator or as site personnel must abstain from the IRB's vote on the approval of the protocol.
As well as documentation required by the study site's IRB(s), the following will be provided:

- Current Study Protocol
- The current Investigator's Brochure or package labeling and updates during the course of the study
- Informed consent document

16.3. Confidentiality

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

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

16.4. Investigator Information

Physicians with a specialty in oncology will participate as investigators in this clinical trial.

16.5. Protocol Signatures

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to an AROG representative.

16.6. Final Report Signature

The clinical study report coordinating investigator, which may be the Principal Investigator, will sign the final clinical study report for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

The sponsor's responsible medical officer will sign the final clinical study report for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study. The final clinical study report will be written by the sponsor.

16.7. Publication Statement

The results of this clinical trial may be used for public dissemination in the form of papers, abstracts, posters, or other informational materials to be presented at scientific meetings, or published in professional journals, or as a part of an academic thesis by an investigator.

Identifiable patient data may not be used for any of these presentations, manuscripts, or reports unless directed by law.

17. REFERENCES

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9. Cheson, B.D., et al., Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 2003. 21(24): p. 4642-9.
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12. Mandelli et al. J Clin Oncol. 2009;27(32):5397-403
13. Schlenk et al. Blood 2016; 128(22): 449

Appendix I. Inclusion/Exclusion Criteria Checklist

All subjects enrolled must meet eligibility criteria based on the inclusion/exclusion criteria detailed in the application and approved by the IRB.

I. Study Information

Protocol Title:	A Study of Crenolanib and Chemotherapy with Cytarabine and Anthracyclines in Patients with Newly Diagnosed Acute Myeloid Leukemia with FLT3 Activating Mutations
Protocol Number:	ARO-006

II. Subject Information:

Subject Name/ID:
Gender: x Male x Female

III. Inclusion/Exclusion Criteria

Inclusion Criteria (From IRB approved protocol)	**Yes**	**No**	**N/A**	**Supporting Documentation***
1. Unequivocal diagnosis of AML based on the WHO classification, excluding acute promyelocytic leukemia.				
2. No prior therapy for AML, except for hydroxyurea and/or leukapheresis, in this setting is allowed.				
3. Subjects with AML evolving from MDS with or without prior MDS therapy with demethylating agents will be allowed in the ***safety phase only***.				
4. Subjects must have tested positive for FLT3-ITD and/or other FLT3 activating mutations.				
5. Age ≥18 years will be allowed in the ***safety phase***; during the ***expansion phase,*** subjects must be ≥18 - ≤70 years of age.				
6. ECOG PS 0 – 2				
7. Adequate liver function, defined as normal bilirubin, ALT ≤2.0x ULN, and AST ≤2.0x ULN measured within 24 hours prior to the induction chemotherapy.				
8. Adequate renal function, defined as serum creatinine ≤1.5x ULN or GFR >50 mL/min				

9. Negative pregnancy test (serum or urine) for women of childbearing potential (WOCBP). • Women considered not of childbearing potential include any of the following: no menses for at least 2 years or menses within 2 years but amenorrheic for at least 2 months and luteinizing hormone (LH) and follicular stimulating hormone (FSH) values within normal range (according to definition of postmenopausal for laboratory used) or bilateral oophorectomy or radiation castration and amenorrheic for at least 3 months or with bilateral tubal ligation.				
10. WOCBP must practice contraception. Acceptable methods of contraception are double barrier methods (condoms with spermicidal jelly or foam and diaphragm with spermicidal jelly or foam), oral, depo provera, or injectable contraceptives, intrauterine devices, tubal ligations, and abstention.				
11. Male patients (except those with prior surgical contraceptive procedures) with female partners who are of childbearing potential: Recommendation is for male and partner to use effective contraceptive methods, such as latex condoms, during the study.				
12. Able and willing to provide written informed consent.				
Exclusion Criteria (From IRB approved protocol)	**Yes**	**No**	**N/A**	**Supporting Documentation***
1. Pre-existing liver diseases (i.e., cirrhosis, chronic hepatitis B or C, nonalcoholic steatohepatitis, and sclerosing cholangitis, etc.)				
2. Known active CNS leukemia				
3. ***During the expansion phase*** subjects with therapy-related AML, AML with prior history of MDS with or without prior HMA therapy or AML in the setting of antecedent hematologic disorder.				
4. 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.				

5. NYHA Class III-IV heart failure, myocardial infarction <6 months prior to study entry and/or serious arrhythmia requiring anti-arrhythmic therapy				
6. Major surgical procedures within 14 days of enrollment (Does not include line placement as needed for chemotherapy administration)				
7. Unwillingness or inability to comply with protocol.				
8. Concurrent use of other investigational agents.				
9. Subjects who are not eligible for standard chemotherapy.				

*****All subject files must include supporting documentation to confirm subject eligibility. The method of confirmation can include, but is not limited to, laboratory test results, radiology test results, subject self-report, and medical record review.

IV. Statement of Eligibility

This subject is [x eligible / x ineligible] for participation in the study.

Signature: _____ Date: _____

Printed Name: _____

Appendix II. ECOG Performance Status Criteria

Performance Status Criteria	
ECOG (Zubrod)	
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity, but ambulatory, and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of self-care, but unable to carry out any work activities, up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair for more than 50% of waking hours
4	Completely disabled; cannot carry on any self care; totally confined to bed or chair

Appendix III. Patient Diaries: Crenolanib

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

Investigational Drug: Crenolanib Besylate (AR-868,596-26)
Protocol ID: ARO-006

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 (AR-868,596-26)
Protocol ID: ARO-006

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 (AR-868,596-26)
Protocol ID: ARO-006

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 (AR-868,596-26)
Protocol ID: ARO-006

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		

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

Investigational Drug: Crenolanib Besylate (AR-868,596-26)
Protocol ID: ARO-006

Prescribed Dose:_____ mgTID, 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)
		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
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		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		
		___/___ AM/PM				___/___ YES/NO		

Appendix IV. Study Schedule

I. Induction

Assessment	Screening [a]	Baseline	On Treatment - Induction 1 and 2			
Day	-28 days of enrollment, unless otherwise specified	First day of crenolanib	Weekly following start of crenolanib	Day 14-28 (response assessment visit)	Day 42 ± (3 days) or at count recovery[+] (whichever is first)	Weekly until end of cycle (if cylce is extended past 42 days)
Demographics	X					
Relevant medical history, current medical conditions including AML-specific history	X					
Evaluation of FLT3 and other mutational status	X				X	
Prior/Concomitant medications and significant non-drug therapies	X	X	Per SOC	X	X	Per SOC
Physical examination with ECOG PS	X	X	Per SOC	X	X	Per SOC
EKG [b]		X**				
Vitals, Weight, and Height (only at screening)	X	X	Per SOC	X	X	Per SOC
Assessment of adverse events, toxicities		X	Per SOC	X	X	Per SOC
Hematology (CBC with differential)	X*	X	X [d]	X	X	X [d]
Serum Chemistries (CMP with bilirubin, ALT/AST and creatinine)	X*	X	X [d]	X	X	X [d]
Urine or serum pregnancy test	X		Every 6 months while patient is on study			
Blood collections for PK and correlative sciences [c]		X** (drawn per Section 11)				
Bone marrow biopsy and aspirate	X*			X [e]	X	

Key:

[+] count recovery is defined as : ANC ≥1000 and platelets ≥100,000

[a] Screening assessments should be performed within 28 days of enrollment with the following exceptions: CBC, CMP and pregnancy test (when applicable) should be performed within 7 days of enrollment, bone marrow biopsy and aspirate and evaluation of FLT3 and other mutational status should be performed within 21 days of enrollment

* If screening assessments were performed while patient was receiving induction chemotherapy, the following assessments performed prior to starting induction, if done per standard of care, may be requested by the sponsor: CBC with differential, CMP with bilirubin, ALT/AST, and bone marrow biopsy and aspiration

[b] EKG is to be performed pre-dose crenolanib (baseline on the first day of crenolanib) as well as 2 hours (± 30 minutes) post first dose of crenolanib during Induction 1

[c] Peripheral and whole blood samples for translation research (including PK analysis) should be collected as defined in Section 11.

** EKG, Peripheral blood for PK analysis and Whole blood sample will only be collected during Induction 1

[d] CBC with differential and CMP should be performed at least weekly while patients are receiving crenolanib during induction. Additional labs may be performed per SOC, for safety, the sponsor may request additional labs done per SOC be captured

[e] Bone marrow biopsy and aspirate performed on day 14-28 should have FLT3 testing and mutational status if available

Per SOC: Physician visits (with ECOG PS, vitals, weight, concomitant medication assessment and adverse events assessments) should be performed as per SOC while patients are receiving crenolanib during induction. At a minimum adverse events and concomitant medications should be reported to the sponsor (per EDC) monthly.

II. Consolidation

Assessment	Baseline - Consolidation 1-4		On Treatment - Consolidation 1-4
Day	First day of HiDAC consolidation	First day of crenolanib	Weekly following start of crenolanib
Prior/Concomitant medications and significant non-drug therapies	X	X	Per SOC
Physical examination with ECOG PS	X	X	Per SOC
EKG [a]		X*	
Vitals and Weight	X	X	Per SOC
Assessment of adverse events, toxicities	X	X	Per SOC
Hematology (CBC with differential) [c]	X	X	X
Serum Chemistries (CMP with bilirubin, ALT/AST and creatinine) [c]	X	X+	X
Urine or serum pregnancy test	Every 6 months while patient is on study		
Blood collections for PK and correlative sciences [b]		X*	
Bone marrow biopsy and aspirate [d]	Per SOC		

Key:
[a] EKG is to be performed 2 hours (± 30 minutes) post first dose of crenolanib during Consolidation 1
[b] Blood samples for translation research (including PK analysis) should be collected as defined in Section 11.
* EKG and blood for PK will only be collected during Consolidation 1
[c] CBC with differential and CMP should be performed at least weekly while patients are receiving crenolanib during induction. Additional labs may be performed per SOC, for safety, the sponsor may request additional labs done per SOC be captured
+ Prior to initiation of crenolanib (within 24 hours of first dose) following HiDAC consolidation, bilirubin, ALT and AST must meet eligibility criteria as depicted in section 1 treatment overview
[d] Bone marrow biopsy and aspirate performed should have FLT3 testing and mutational status if available
Per SOC: Physician visits (with ECOG PS, vitals, weight, concomitant medication assessment and adverse events assessments) should be performed as per SOC while patients are receiving crenolanib during induction. At a minimum adverse events and concomitant medications should be reported to the sponsor (per EDC) monthly.

III. Maintenance

Assessment	Maintenance 1-12	At time of progression or completion of study
Day within cycle	Day 1 (± 14 days)	
Prior/Concomitant medications, significant non-drug therapies	X [a]	X
Physical examination with ECOG PS	X [a]	X
Vitals and weight	X [a]	X
Assessment of adverse events, toxicities	X [a]	X
Hematology (CBC with differential)	X	X
Serum Chemistries (CMP with bilirubin, ALT/AST and creatinine)	X	X
Urine or serum Pregnancy test	Every 6 months while patient is on study	
Whole blood sample [b]		X
Bone marrow biopsy and aspirate [c]	Per SOC	X

Key:
[a] Day 1 and then per site standard schedule but no less frequent than every 2 months (±1 month).
[b] Whole blood samples for translation research should be collected as defined in Section 11.
[c] Bone marrow biopsy and aspirate performed should have FLT3 testing and mutational status if available

Appendix V. Common Terminology Criteria for Adverse Events; Version 4.03

Cardiac Disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Anorexia **Definition:** A disorder characterized by loss of appetite.	Loss of appetite 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); tube feeding or TPN indicated	Life-threatening consequences; urgent intervention indicated	Death
Diarrhea **Definition:** A disorder characterized by frequent and watery bowel movements	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	Death
Fatigue **Definition:** A disorder characterized by a state of generalized weakness with a pronounced inability to summon sufficient energy to accomplish daily activities.	Fatigue relieved by rest	Fatigue not relieved by rest, limiting instrumental ADL	Fatigue not relieved by rest, limiting self care ADL	–	–
Nausea **Definition:** A disorder characterized by queasy sensation and/or the urge to vomit.	Loss of appetite without altering in eating habits	Oral intake decrease without significant weight loss, dehydration or mainutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	–	–
Vomiting **Definition:** A disorder characterized by the reflexive act of ejecting the contents of the stomach throught the mount.	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	Death
Alanine aminotransferance increased **Definition:** A finding based on laboratory test results that indicate an increase in the level of alanine aminotransferance (ALT or SGPT) in the blood specimen.	>ULN-3.0 x ULN	>3.0-5.0 x ULN	>5.0-20.0 x ULN	>20.0 x ULN	–
Aspartate aminotransferance increased **Definition:** A finding based on laboratory test results that indicate an increase in the level of alanine aminotransferance (ALT or SGPT) in the blood specimen.	>ULN-3.0 x ULN	>3.0-5.0 x ULN	>5.0-20.0 x ULN	>20.0 x ULN	–
Blood bilirubin increased **Definition:** A finding based on laboratory test results that indicate an increase in the level of aspartate aminotransferance (AST or SGOT) in the blood specimen.	>ULN-1.5 x ULN	>1.5-3.0 x ULN	>3.0-10.0 x ULN	>10.0 x ULN	–

Cardiac Disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Pleural effusion **Definition:** A disorder characterized by an amounts of fluid within the pleural cavity. Symptoms include shortness of breath, cough and market chest discomfort	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; intervention indicated (e.g. diuretics or limited therapeutic thoracentesis	Symptomatic with respiratory distress and hypoxia; surgical intervention including chest tube or pieurodesis indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Pericardial effusion **Definition:** A disorder characterized by fluid collection within the pericardial sac, usually due to inflammation.	–	Asymptomatic effusion size small to moderate	Effusion with physiologic consequences	Life-threatening consequences; urgent intervention indicated	Death
Edema face **Definition:** A disorder characterized by swelling due to excessive fluid accumulation in face tissues.	Localized facial edema	Moderated localized facial edema; limiting instrumental ADL	Severe swelling; limiting self care ADL	–	–
Edema limbs **Definition:** A disorder characterized by swelling due to excessive fluid accumulation in the upper or lover extremities.	5-10% inter-limb discrepancy in volume or circumference at point of greatest visible difference; swelling or obscuration of anatomic architecture on close inspection	>10-30% inter-limb discrepancy in volume or circumference at point of greatest visible difference; readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour; limiting instrumental ADL	≥30% inter-limb discrepancy in volume; gross deviation from normal anatomic contour, limiting self care ADL	–	–
Edema trunk **Definition:** A disorder characterized by swelling due to excessive fluid accumulation in the trunk area.	Swelling or obscuration of anatomic architecture on close inspection	Readily apparent obscuration of anatomic architecture; obliteration of skin folds; deadly apparent deviation from normal anatomic contour, limiting instrumental ADL	Gross deviation from normal anatomic contour; limiting self care ADL	–	–

Appendix VI. CYP3A4 drugs potentially affecting crenolanib pharmacokinetics

The following are few examples of therapeutic agents which are potential hepatic enzyme (CYP3A4) inducing or inhibiting drugs and **should be used with caution in** patient participation on the study):

Strong Inducers

phenytoin (anticonvulsants and mood stabilizers)
carbamazepine (anticonvulsants and mood stabilizers)
oxcarbazepine (anticonvulsants and mood stabilizers)
phenobarbital (barbiturates)
rifampin (bactericidal)
modafinil (stimulant)
dexamethasone
hyperforin (constituent of St. John's Wort)
glucocorticoids
Rifabutin (antimycobiotic)
Troglitazone (anti-diabetic and anti-inflammatory drug)

Strong Inhibitors

telithromycin (macrolide antibiotics)
clarithromycin (macrolide antibiotics)
ketoconazole (azole antifungals)
itraconozole (azole antifungals)
nefadozone (antidepressant)
Saquinavir (HIV protease inhibitor)
Suoxone (analgesic)
Telithromycin (antibiotic)

Moderate Inducers

pioglitazone (Thiazolidinedione)

Moderate Inhibitors

erythromycin (macrolide antibiotics)
fluconazole (azole antifungals)
aprepitant (antiemetic)
bergamottin (constituent of grapefruit juice)
verapamil (calcium channel blocker)
Diltiazem (calcium channel blocker)

http://medicine.iupui.edu/clinpharm/ddis/table.aspx

Appendix VII. The WHO Classification of Acute Myeloid Leukemia[12]

Name	Description
Acute myeloid leukemia with recurrent genetic abnormalities	Includes: • AML with translocations between chromosome 8 and 21 - [t(8;21)(q22;q22);] RUNX1/RUNX1T1; • AML with inversions in chromosome 16 - [inv(16)(p13.1q22)] or internal translocations in it - [t(16;16)(p13.1;q22);] CBFB/MYH11; (ICD-O 9871/3); • Acute promyelocytic leukemia with translocations between chromosome 15 and 17 - [t(15;17)(q22;q12);] RARA/PML; (ICD-O 9866/3); • AML with translocations between chromosome 9 and 11 - [t(9;11)(p22;q23);] MLLT3/MLL; • AML with translocations between chromosome 6 and 9 - [t(6;9)(p23;q34);] DEK/NUP214; • AML with inversions in chromosome 3 - [inv(3)(q21q26.2)] or internal translocations in it - [t(3;3)(q21;q26.2);] RPN1/EVI1; • Megakaryoblastic AML with translocations between chromosome 1 and 22 - [t(1;22)(p13;q13);] RBM15/MKL1; • AML with mutated NPM1 • AML with mutated CEBPA

AML with myelodysplasia-related changes	This category includes patients who have had a prior documented myelodysplastic syndrome (MDS) or myeloproliferative disease (MPD) that then has transformed into AML, or who have cytogenetic abnormalities characteristic for this type of AML (with previous history of MDS or MPD that has gone unnoticed in the past, but the cytogenetics is still suggestive of MDS/MPD history). This category of AML occurs most often in elderly patients and often has a worse prognosis.
	Includes:
	• AML with complex karyotype
	• Unbalanced abnormalities
	  • AML with deletions of chromosome 7 - [del(7q);]
	  • AML with deletions of chromosome 5 - [del(5q);]
	  • AML with unbalanced chromosomal aberrations in chromosome 17 - [i(17q)/t(17p);]
	  • AML with deletions of chromosome 13 - [del(13q);]
	  • AML with deletions of chromosome 11 - [del(11q);]
	  • AML with unbalanced chromosomal aberrations in chromosome 12 - [del(12p)/t(12p);]
	  • AML with deletions of chromosome 9 - [del(9q);]
	  • AML with aberrations in chromosome X - [idic(X)(q13);]
	• Balanced abnormalities
	  • AML with translocations between chromosome 11 and 16 - [t(11;16)(q23;q13.3);], unrelated to previous chemotherapy or ionizing radiation
	  • AML with translocations between chromosome 3 and 21 - [t(3;21)(q26.2;q22.1);], unrelated to previous chemotherapy or ionizing radiation
	  • AML with translocations between chromosome 1 and 3 - [t(1;3)(p36.3;q21.1);]
	  • AML with translocations between chromosome 2 and 11 - [t(2;11)(p21;q23);], unrelated to previous chemotherapy or ionizing radiation
	  • AML with translocations between chromosome 5 and 12 - [t(5;12)(q33;p12);]
	  • AML with translocations between chromosome 5 and 7 - [t(5;7)(q33;q11.2);]
	  • AML with translocations between chromosome 5 and 17 - [t(5;17)(q33;p13);]
	  • AML with translocations between chromosome 5 and 10 - [t(5;10)(q33;q21);]
	  • AML with translocations between chromosome 3 and 5 - [t(3;5)(q25;q34);]

Name	Description
Therapy-related myeloid neoplasms	This category includes patients who have had prior chemotherapy and/or radiation and subsequently develop AML or MDS. These leukemias may be characterized by specific chromosomal abnormalities, and often carry a worse prognosis.
AML not otherwise categorized	Includes subtypes of AML that do not fall into the above categories • AML with minimal differentiation • AML without maturation • AML with maturation • Acute myelomonocytic leukemia • Acute monoblastic and monocytic leukemia • Acute erythroid leukemia • Acute megakaryoblastic leukemia • Acute basophilic leukemia • Acute panmyelosis with myelofibrosis

Appendix VIII. Contact Information AROG Pharmaceuticals

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