Protocol ARO-011

Pilot study of Crenolanib Combined with Standard Salvage Chemotherapy in Subjects with Relapsed/Refractory Acute Myeloid Leukemia

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TABLE OF CONTENTS

List of Figures

List of Tables

LIST OF ABBREVIATIONS

Term	Definition
AE	Adverse Event
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
AST	Aspartate aminotransferase
AUC	Area under the curve
BID	Twice daily
CBC	Complete blood count
C_{max}	Maximum concentration of drug in serum
CMP	Complete metabolic panel
CR	Complete remission
CRi	Complete remission with incomplete count recovery
CRF	Case report form
CTCAE	Common terminology criteria for adverse events
DARF	Drug accountability record form
DLT	Dose limiting toxicity
DoR	Duration of response
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EFS	Event-free survival
EKG	Electrocardiogram
EOS	End of study
FLAG	Fludarabine, Ara-C, G-CSF
FLT3	FMS-like tyrosine kinase 3
FLT3-ITD	FMS-like tyrosine kinase 3 – internal tandem duplication
FLT3-TKD	FMS-like tyrosine kinase 3 – tyrosine kinase domain
GCP	Good clinical practice
GVHD	Graft versus host disease
HAM	High-dose cytarabine and mitoxantrone
HiDAC	High-dose cytarabine
HR	Hazard ratio
HSCT	Hematopoietic stem-cell transplant
IB	Investigator Brochure

ICF	Informed consent form
ICH	International Conference on Harmonisation
Ida	Idarubicin
IDAC	Intermediate-dose cytarabine
IMP	Investigational medicinal product(s)
IRB/IEC	Institutional review board/ Independent ethics committee
ITT	Intent-to-treat
IVRS	Interactive voice response system
KM curve	Kaplan-Meier curve
LFT	Liver function test
MEC	Mitoxantrone, Etoposide, Cytarabine
MTD	Maximum tolerated dose
MTZ	Mitoxantrone
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PDGFRα	Platelet-derived growth factor receptor alpha
PFS	Progression-free survival
PK	Pharmacokinetic
PR	Partial response
PS	Performance Status
RECIST	Response Evaluation Criteria In Solid Tumors
RFS	Relapse-free survival
R/R	Relapsed/Refractory
RR	Response Rate
RTK	Receptor tyrosine kinase
SAE	Serious adverse event
SD	Stable disease
SOC	Standard of care
SUSAR	Suspected Unexpected Serious Adverse Reactions
$t_{1/2}$	Half-life
TID	Three times daily
TKI	Tyrosine kinase inhibitor
t_{max}	Time that drug is at maximum concentration in serum
QD	Once daily

ULN	Upper limit of normal
WOCBP	Women of child-bearing potential

DEFINITION OF TERMS

Term	Definition
Adverse Drug Reaction	Any adverse event that is deemed to be at least possibly related to the study drug.
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).
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.
Compliance	Adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
Consent	The act of obtaining informed consent for participation in a clinical trial from subjects deemed eligible or potentially eligible to participate in the clinical trial. Individuals entered into a trial are those who sign the informed consent document directly or through their legally acceptable representatives.
Enrolled Subject	An enrolled subject is a subject who has signed the informed consent form, completed all screening evaluations, has been deemed eligible for the trial by the investigator and sponsor and has been enrolled.
Ethics Committee	All appropriate properly constituted committees or boards recognized by the appropriate regulatory agencies for approving clinical studies. Including the independent ethics committee and institutional review boards.
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/ Ethics 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 subjects participating in a clinical trial are protected.
Regulation	All appropriate regulations, laws and guidelines.
Screening Period	The screening period begins when the subject signs the Informed Consent Form and continues until randomization.
Screen Failure	A screen failure refers to subjects who have signed the Informed Consent Form but do not subsequently enroll in the trial. Data from these subjects will be recorded in the screening log, but not entered into the study database.
Treatment period	The time period from administration of the first dose of study drug through the end of the one month post-treatment discontinuation visit.

1. SYNOPSIS

Name of Investigational Product
Crenolanib Besylate

Title of Study
Pilot study of Crenolanib Combined with Standard Salvage Chemotherapy in Subjects with Relapsed/Refractory Acute Myeloid Leukemia

Version and Date of Protocol
Version 3.0, June 7, 2016

Planned number of subjects and investigational sites
Approximately 72 subjects (~24 in each cohort) will be enrolled across approximately 10 sites in the U.S.

Study Rationale
Treatment of newly-diagnosed acute myeloid leukemia (AML) with standard chemotherapy regimens, such as anthracyclines and cytarabine, can lead to high complete remission (CR) rates (ranging from 60-70%). Unfortunately, the majority of these patients will relapse.

Upon relapse, the prognosis for a second remission or response in these patients significantly worsens. Currently, patients who are refractory or relapsed following standard induction therapy have no standardized treatment options. Several combinations have been suggested and each achieve similar outcome. High-dose cytarabine combined with mitoxantrone (HAM) has been shown to be associated with high CR rates in relapsed/refractory (R/R) AML. Two additional aggressive salvage chemotherapies, as per National Comprehensive Cancer Network (NCCN) guidelines, are also common options for relapsed/refractory patients: the combination of mitoxantrone, etoposide, and cytarabine (MEC) and the combination of fludarabine, cytarabine, G-CSF and idarubicin (FLAG-Ida). However, it has been proven difficult to achieve full prolonged responses with these chemotherapy agents alone.

Recent studies have shown that in AML, the addition of a tyrosine-kinase inhibitor (TKI) to standard chemotherapy in a sequential manner is feasible and associated with anti-leukemic efficacy. A randomized study (SORAML) has shown that the addition of a sorafenib to standard chemotherapy resulted in a significantly prolonged event-free survival (EFS) and relapse-free survival (RFS). This data has also suggested that this treatment regimen can be beneficial and effective in both FLT3 (Fms-related tyrosine kinase 3) wild-type and FLT3 ITD (FLT3 – Internal Tandem Duplication) AML.

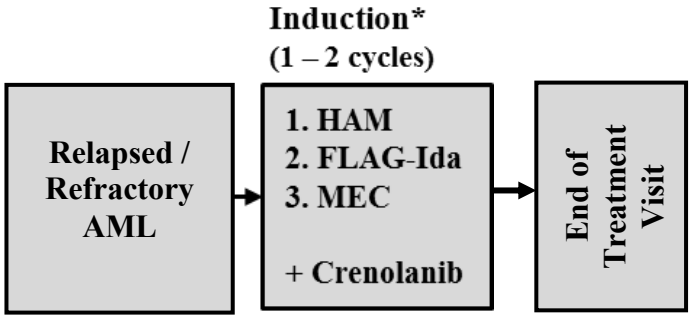
Crenolanib besylate is a second generation TKI with high potency and selectivity against both wild-type FLT3 and its constitutively active mutant isoforms including FLT3-ITD mutation and also tyrosine kinase domain (TKD) point mutations including the D835 TKD mutation. Clinical safety data of crenolanib is available for over 200 patients. Specifically, there are data in 66 patients with R/R FLT3 ITD and/or TKD mutant AML, which demonstrates clinical benefit in approximately 50% of these AML patients with responses that included complete remission (CR), complete remission with incomplete blood count recovery (CRi) and partial remission (PR).

The proposed study is designed combine crenolanib with salvage chemotherapies, including HAM, MEC or FLAG-Ida to treat patients with R/R AML irrespective of FLT3 status. The rationale for this study is as follows:
(1) There is clinical evidence for improved event-free survival in AML with the combination of a TKI and chemotherapy;
(2) HAM, MEC, and FLAG-Ida have been shown to improve the outcome in patients with R/R AML;

(3) Sequential administration of chemotherapy followed by a TKI is feasible and can achieve synergistic cytotoxicity.

Study Design

Open label, dose de-escalation, phase 1b pilot trial of crenolanib with standard salvage chemotherapy. Subjects may receive up to 2 cycles of induction with standard salvage chemotherapy followed by crenolanib. Each arm will enroll approximately 24 patients (72 total); stratification to each arm will be per physician's choice.



Arm A (HAM + crenolanib)

Subjects 18-60 years of age who have not undergone a prior allogeneic hematopoietic stem cell transplant (HSCT):

- Mitoxantrone 10 mg/m² IV, over ≤ 30 mins days 1-3
- Cytarabine 1000 mg/m² IV, over 3 hours days 1-6
- Crenolanib 100 mg TID p.o. starting day 7 (+3 day)

For subjects > 60 years, or subjects who have undergone a prior allogeneic HSCT, or subjects who need a second re-induction HAM cycle, the following reduced doses will be used:

- Mitoxantrone 8 mg/m² IV, over ≤ 30 mins days 1-3
- Cytarabine 500 mg/m² IV, over 3 hours days 1-6
- Crenolanib 100 mg TID p.o. starting day 7 (+3 day)

Arm B (MEC + crenolanib)

Patients >18 years of age:

- Mitoxantrone 8 mg/m² IV, push days 1-5
- Etoposide 100 mg/m^2 IV days 1-5
- Cytarabine 1000 mg/m² IV, over 3 hours days 1-5
- Crenolanib 100 mg TID starting day 7 (+3 day)

Arm C (FLAG-Ida + crenolanib):

Patients >18 years of age:

- Fludarabine 30 mg/m^2 IV day 1-5
- Cytarabine 2 g/m^2 IV over 2 hrs day 1-5
- G-CSF 300 ug s.c. inj or IV/5ug/kg SC day 6 - neutrophil recovery
- Idarubicin 8 mg/m^2 IV over 30 min day 1-3
- Crenolanib 100 mg TID starting day 7 (+3 day)

Primary Objective

- To determine the safety, dose limiting toxicities and maximum tolerated dose (or confirm the target dose of 100 mg TID) of crenolanib given sequentially following standard salvage chemotherapy regimens in subjects with refractory/relapsed AML

Secondary Objectives

- To determine the response rate, duration of response, progression-free survival, and overall survival of crenolanib when given sequentially following standard salvage chemotherapy regimens in subjects with refractory/relapsed AML
- To determine the pharmacokinetics of crenolanib when given sequentially following standard salvage chemotherapy regimens in subjects with refractory/relapsed AML

Inclusion Criteria

1. Confirmed diagnosis of AML, including treatment-related secondary AML (except prior MDS) according to World Health Organization (WHO) 2008 classification at treating institution
2. Subjects who are refractory* or who have relapsed** following first line AML therapy with cytarabine/anthracycline based chemotherapy, with or without a tyrosine kinase inhibitor.

   *Refractory to induction therapy is defined as never achieving CR, CRi or CRp (according to International Working Group criteria) after one line of intensive regimen for AML (re-induction, consolidation and/or transplant allowed) including at least one cytarabine containing induction block with a total dose no less than 700mg/m² per cycle and 3 days of an anthracycline with or without a TKI.

   or

   **First relapse is defined as untreated hematologic relapse (according to International Working Group criteria) after one line of intensive regimen for AML (re-induction, consolidation and/or transplant allowed) including at least one cytarabine containing induction block with a total dose no less than 700mg/m² per cycle and 3 days of an anthracycline with or without a TKI that induced a CR/CRi/CRp. Subjects are allowed to receive induction, consolidation, transplant and/or maintenance prior to achieving their first CR/CRi/CRp.

3. Subjects considered eligible for intensive chemotherapy
4. ECOG performance status ≤ 2
5. Age ≥ 18 years
6. Adequate liver function within 72 hours of enrollment, defined as:
   - Normal total serum bilirubin
   - ALT and AST ≤ 2.0 x ULN
7. Adequate renal function, defined as serum creatinine ≤ 1.5x ULN
8. Women of childbearing potential must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL within 72 hours prior to enrollment

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

9. Women of child-bearing potential must either commit to continued abstinence from heterosexual intercourse or begin one acceptable method of birth control (IUD, tubal ligation, or partner's vasectomy) while on crenolanib and for 3 months following the last dose of crenolanib.

   Hormonal contraception alone is not an acceptable method of birth control for the purpose of this trial.

10. Men must use a latex condom during any sexual contact with women of childbearing potential, even if they have undergone a successful vasectomy and must agree to avoid to father a child (while on therapy and for 3 month after the last dose of crenolanib).
11. Willing to adhere to protocol specific requirements
12. Following receipt of verbal and written information about the study, the subject must provide

signed informed consent before any study related activity is carried out.

13. Clinically significant toxic effects of prior therapy (expect hydroxyurea) resolved to Grade ≤ 1 before the start of study.

Exclusion Criteria

1. < 5% blasts in blood or marrow at screening, except if measurable extramedullary AML is confirmed
2. Acute promyelocytic leukemia (APL)
3. Known clinically active CNS leukemia
4. Clinically active or unstable graft-versus-host disease (GvHD) requiring treatment which precludes administration of chemotherapy as defined in this protocol
5. Prior anti-leukemia therapy within 14 days of enrollment for classical cytotoxic agents, and within 5x the half-life for other investigational agents
    - Prior use of hydroxyurea or isolated doses of cytarabine for palliation (i.e., control of WBC) are allowed but should be discontinued at least 24 hrs prior to enrollment.
    - Other agents used strictly with palliative intent might be allowed during this period after discussing with principal investigator
6. Pre-existing liver disease (e.g. cirrhosis, chronic hepatitis B or C, nonalcoholic steatohepatitis, sclerosing cholangitis)
7. Known HIV infection.
8. Evidence of ongoing, uncontrolled systemic infection or an uncontrolled local infection requiring therapy at the start of study.
9. "Currently active" second malignancy (other than non-melanoma skin cancer, carcinoma in situ of the cervix or prostatic intraepithelial neoplasia within 1 year). Subjects are not considered to have a "currently active" malignancy if they have completed therapy and are considered by their physician to be at less than 30% risk of relapse within 1 year.
10. Concurrent participation in another therapeutic clinical trial.
11. Pregnant or breastfeeding women
12. Subjects of childbearing potential not willing to use adequate contraception during study and 3 months after last dose of crenolanib
13. Subject with uncontrolled cardiac disease including congestive heart failure class III or IV by the NYHA, unstable angina (anginal symptoms at rest) or new onset angina (began within the last 3 months) or myocardial infarction within the past 6 months
14. Subject with concurrent severe and/or uncontrolled medical or psychiatric conditions that in the opinion of the investigator may impair the participation in the study or the evaluation of safety and/or efficacy
15. Inability to give an informed consent

Statistical Methods

Initially, the study will evaluate DLT and determine the maximum tolerated dose (or confirm the target dose of 100 mg TID) of crenolanib in combination with either HAM (Arm A), MEC (Arm B) or FLAG-Ida (Arm C) chemotherapy. Thereafter, the study will include a dose-expansion cohort.

For each arm, an initial 6 subjects will be enrolled at a crenolanib dose of 100 mg TID and will be evaluated for DLT, as follows:

- The DLT period will be 28 days
    - Assessment of potential hematologic DLTs that started during the DLT period will extend for up to 6 weeks following the start of the event (see definition of hematologic DLT)
- DLT will be defined as any clinically significant adverse event or abnormal laboratory value that

is not related to concomitant medications, co-morbidities or underlying disease (leukemia), and that is not expected for the chemotherapy being used together with crenolanib

The following will be considered to be DLT:

Non-hematologic DLT:

- Any grade 3 or 4 non-hematologic toxicity despite optimal supportive care
    - For example, grade 3 or 4 nausea, vomiting, or diarrhea that cannot be controlled with standard antiemetic or antidiarrheal medications used at optimal dose within 72 hours of onset
- Any tumor lysis syndrome

Hematologic DLT:

- Grade ≥ 3 neutropenia and/or thrombocytopenia with a hypocellular bone marrow lasting for 6 weeks or more after the last dose of therapy in the absence of residual leukemia (i.e., with less than 5% blasts)
    - Anemia will <u>not</u> be considered a DLT

For each arm, prior to determining the maximum tolerated dose (or confirming the target dose of 100 mg TID) of crenolanib based on DLT, subjects will be enrolled in a sequential manner such that no more than 6 subjects are within 30 days of starting induction 1 therapy. See Section 12.2.1 for dose de-escalation and stopping rules based on dose-limiting toxicity.

For each arm, following the determination of the maximum tolerated dose (or the target dose) of crenolanib, subject safety and early mortality will be monitored in cohorts of six throughout the study. Enrollment may be halted at any time based on safety reviews. See Section 12.2.2 for the study's stopping rules following the determination of the maximum tolerated dose (or the target dose) for crenolanib.

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 subjects in each category. Time-to-event endpoints will be summarized using the cumulative incidence and Kaplan-Meier methodology.

2. BACKGROUND AND STUDY RATIONALE

2.1 Unmet Medical Need in Relapsed or Refractory Acute Myeloid Leukemia

Treatment of newly-diagnosed acute myeloid leukemia (AML) with standard chemotherapy regimens, such as anthracyclines and cytarabine, can lead to high complete remission (CR) rates (ranging from 60-70%). Unfortunately, the majority of these patients will relapse. Upon relapse, the prognosis for a second remission or response in these patients significantly worsens.

Currently, there are multiple commonly used AML salvage regimens: high-dose cytarabine, multi-agent chemotherapy, hypomethylating agents, hydroxyurea, and supportive care. Roboz, et al conducted a large international, randomized Phase III clinical trial to investigate the efficacy of elacytarabine (a novel elaidic acid ester of cytarabine) versus investigator's choice of currently available salvage therapies. A total of 381 patients with relapsed/refractory (R/R) AML were enrolled in North America, Europe, and Australia.

The study results showed no significant differences in OS (3.5 v 3.3 months), response rate (23% v 21%), or relapse-free survival (RFS) (5.1 v 3.7 months) between the elacytarabine and control arms, respectively. As shown in Figure 1, overall survival (OS) in both study arms and for all treatments was extremely poor. [36] These results bring to light the need for new treatment options in this patient population.

Figure 1 Overall survival estimates in the intention-to-treat population of elacytarabine versus investigator's choice of current salvage therapies by Kaplan-Meier test

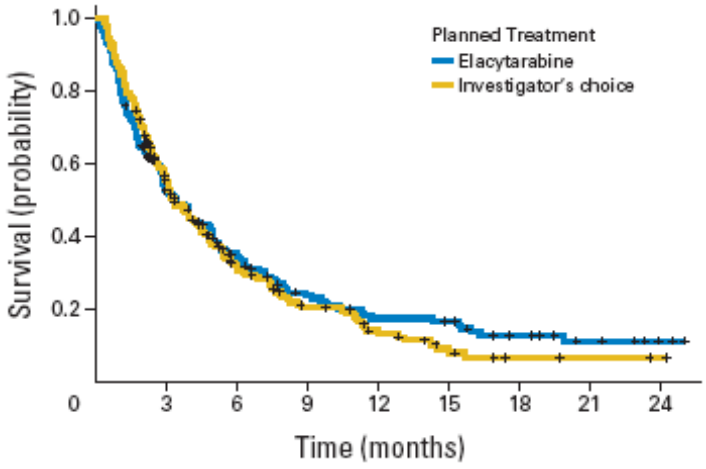


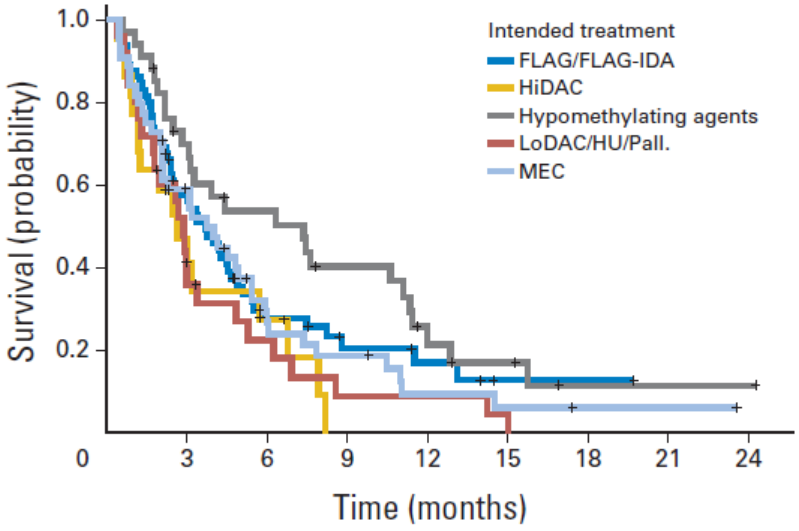
Table 1 30-day, 60-day mortality rates of elacytarabine and investigator's choice

	Total ITT Population (N=381)	
Parameter	**No. of patients**	**%**
Early mortality, days		
30	59	16
60	117	32

2.2 Physician's Choice of Salvage Chemotherapy Agents in Relapsed/Refractory AML

As mentioned above in section 2.1, Roboz et al showed that there is not a significant difference in OS, RR, or RFS between the elacytarabine and control arm of investigator's choice salvage regimen. Furthermore, figure below, shows the overall survival curves of different salvage regimens (including FLAG-Ida and MEC). These curves show the similarity of the effects of the different salvage regimens on overall survival. MEC and FLAG-Ida had 30 day mortality rates of 19% and 11% respectively. As these salvage regimens have shown similar outcomes, physician's choice of salvage regimen allows the treatment to be chosen based on the individual patient and disease characteristics/status.

Figure 2 Overall survival in the intention-to-treat population of investigator's choice of current salvage therapies by Kaplan-Meier test



2.3 Efficacy of HAM, MEC and FLAG-Ida in Relapsed/Refractory AML

MEC and FLAG-Ida have both been shown to provide responses in refractory or early relapse AML patients. In a single-center study, the combination of mitoxantrone, etoposide, and cytarabine (MEC) given as first salvage has shown to achieve a CR of 18% in 77 patients (median age: 54) who were refractory to conventional induction therapy or relapsed after achieving first CR [43]. The efficacy of FLAG-IDA was evaluated as first or second salvage in primary refractory or relapsed AML patients, and a CR/CRi of 73% was reported in 48 patients (median age: 50) [42].

High-dose cytarabine in combination with mitoxantrone (HAM) has also been shown to improve the outcome in patients with R/R AML. Results from a Phase I/II study conducted by the German AML Cooperative Group showed that HAM has high antileukemic activity in refractory AML. High-dose cytarabine with mitoxantrone was associated with a longer OS in patients with poor prognostic features. Of the 40 patients with refractory AML, 21 achieved a complete remission (53%) and 1 patient had a partial remission. [32]

Furthermore, in 2 prospective randomized studies, the high-dose cytarabine with mitoxantrone (HAM) regimen showed significant clinical activity in R/R AML patients (Table 2). In a

prospective randomized pivotal trial, Karanes C et al compared HiDAC (high-dose cytarabine) versus HiDAC + MTZ (mitoxantrone) in relapsed/refractory AML patients. 162 patients were evaluable for response to induction therapy, with 81 patients on each arm. There was trend toward a higher CR rate (from 32% to 44%) with combination HiDAC + MTZ compared to single agent HiDAC. [40]

Kern W et al. performed a randomized study comparing high-dose versus intermediate-dose cytarabine with mitoxantrone in patients with R/R AML. The remission rate and disease free survival were similar in patients getting 3 g/m^2 of cytarabine for 8 doses as compared to patients getting 1 g/m^2 of cytarabine for 8 doses. These data suggest that cytarabine at cumulative doses of 6-8 g/m^2 in combination with MTZ may provide effective complete remission rates in relapsed AML. [31] Hence, this pilot study is using cytarabine at a dose of 6 g/m^2 along with MTZ as salvage chemotherapy in patients with relapsed AML.

Table 2 Pivotal studies using the HAM regimen as salvage

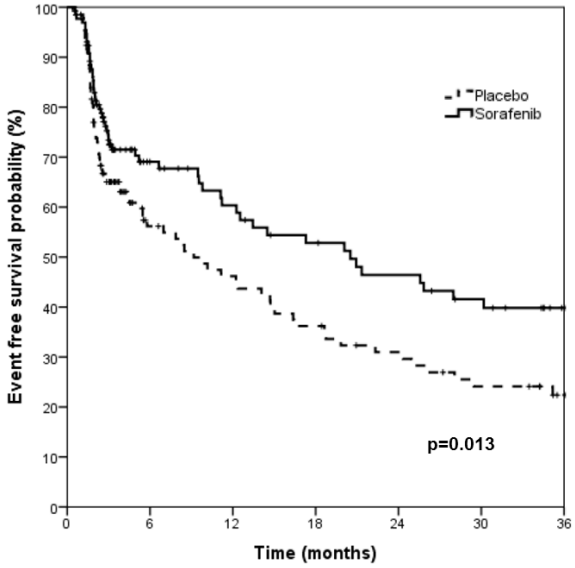
Reference	Study design	Regimens	Number of patients	Refractory/ relapsed	Median age (yrs)	% CR
Karanes C, et al. 1999 [40]	Phase 3, randomized	HiDAC vs HiDAC + MTZ	162 (81 on each arm)	56/106	48 vs 53	32 vs 44
Kern W, et al. 1998 [31]	Phase 3, randomized	HiDAC + MTZ vs IDAC + MTZ	186	27/159	50	47

2.4 Clinical Evidence of Combining a Tyrosine Kinase Inhibitor with Chemotherapy in AML Patients

Röllig, et al performed a randomized study (SORAML trial) of sorafenib versus placebo as add-on to standard induction in AML patients (irrespective of the Fms-like tyrosine kinase 3 (FLT3) mutation status). Two cycles of induction were allowed (initially with daunorubicin plus cytarabine; patients without response after 1 cycle received a 2nd induction with HAM). Consolidation treatment consisted of up to 3 cycles of high-dose cytarabine. 267 patients were enrolled on the study (134 patients received sorafenib and 133 received placebo). Only 46 of 267 (17%) were FLT3 internal tandem duplication (ITD) positive. [34]

Addition of sorafenib to cytarabine/anthracycline chemotherapy resulted in a statistically significant improvement in event-free survival (EFS) (the median EFS was 20.5 months in the sorafenib arm vs. 9.2 months in the placebo arm, p=0.013). These data suggest that in AML patients, the addition of a tyrosine kinase inhibitor (TKI) to standard chemotherapy in a sequential manner is feasible and associated with anti-leukemic efficacy in both FLT3 wild-type and FLT3 ITD AML patients. [34]

Figure 3 Event-free survival in the sorafenib arm vs. placebo



2.5 FLT3 Ligand Levels Increase Following Administration of Chemotherapy

It has been shown that plasma FLT3 ligand levels increase by 2-3 log order following intensive chemotherapy in patients with AML. In newly diagnosed AML patients, FLT3 ligand levels rose to 488 pg/mL after course one of chemotherapy and as high as 3251 pg/mL after the fourth course of chemotherapy. [35] These data suggest that the high level of FLT3 ligand in patients following intensive chemotherapy may actually be protective, or even stimulatory, to residual stem cells. Thus, it may be beneficial to add a selective FLT3 inhibitor following chemotherapy.

Figure 4 FLT3 ligand levels increase following multiple regimens of intensive chemotherapy