Phase III Multicenter Open-Label Randomized Trial to Evaluate Efficacy and Safety of CPI-613® (devimistat) in Combination with High Dose Cytarabine and Mitoxantrone (CHAM) Compared to High Dose Cytarabine and Mitoxantrone (HAM) therapy and control sub-groups: combination of Mitoxantrone, Etoposide and Cytarabine (MEC) and combination of Fludarabine, Cytarabine, and Filgrastim (FLAG) in Older Patients (≥ 50 years) with Relapsed/Refractory Acute Myeloid Leukemia (AML)

RAFAEL
Pharmaceuticals, Inc.

"To Save A Life Is To Save A Universe"

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LIST OF ABBREVIATIONS

AE	Adverse Events
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
ATP	Adenosine Triphosphate
AUC	Area Under the Plasma Concentration-Time Curve
AUC_{inf}	Area Under the Plasma Concentration-Time Curve from Time Zero Extrapolated to Infinite Time
AUC_{0-t}	Area Under the Plasma Concentration-Time Curve from Time Zero to the Time of the Last Quantifiable Concentration
BM	Bone Marrow
BP	Blood Pressure
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CCAAT	Cytosine-cytosine-adenosine-adenosine-thymidine
CEBPα	CCAAT Enhancer Binding Protein A
CFR	Code of Federal Regulations
CHAM	CPI-613® (devimistat) in Combination with High Dose Cytarabine and Mitoxantrone
CI	Confidence Interval
CL	Apparent Total Body Clearance
CrCl	Creatinine Clearance
C_{max}	The Maximum (Peak) Plasma Drug Concentration
C_{min}	The Minimum (Trough) Plasma Drug Concentration
CMH	Cochran-Mantel-Haenszel
CNS	Central Nervous System
CR	Complete Remission
CRh	CR (Complete Remission) with Partial Hematologic Recovery
Cri	CR (Complete Remission) with Incomplete Recovery
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTnT	Cardiac Troponin T
D5W	Dextrose 5% in Water
DEHP	Diethylhexyl Phthalate
DMC	Data Monitoring Committee
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EF	Ejection Fraction
EORTC QLQ	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire

EOS	End-of-Study
EOT	End-of-Treatment
FDA	Food and Drug Administration
FLAG	Fludarabine, Cytarabine, and Filgrastim
Flt3	FMS-Like Tyrosine Kinase 3
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HAM	High Dose Cytarabine and Mitoxantrone
HAMA or HM	High Dose Cytarabine + Mitoxantrone + Asparaginase
hERG	The Human Ether-À-Go-Go-Related Gene
HiDAC	High Dose Cytarabine
HM	High Dose Cytarabine + Mitoxantrone + Asparaginase
HR	Heart Rate
HSCT	Hematopoietic Stem Cell Transplantation
5-HT	5-Hydroxytryptamine
IB	Investigator's Brochure
IC_{50}	The Half Maximal Inhibitory Concentration
ICF	Informed Consent Form
ICH	International Council for Harmonization
IDH1/2	Isocitrate Dehydrogenase 1 and 2
IHC	Immunohistochemistry
INR	International Normalized Ratio
IRB	Institutional Review Board
ITD	Internal Tandem Duplication
ITT	Intent-To-Treat
IUD	Intrauterine Device
IUS	Intrauterine Hormonal-Releasing System
IV	Intravenous
IWRS	Interactive Web Response Systems
KGDH	Alpha-Ketoglutarate Dehydrogenase
L-T	Long-Term
LVEF	Left Ventricular Ejection Fraction
MAP	Mean Arterial Pressure
MEC	Mitoxantrone, Etoposide and Cytarabine
MedDRA	Medical Dictionary for Regulatory Activities
MID	Minimal (Clinical) Important Difference
MLFS	Morphological Leukemia-Free State
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
MUGA	Multigated Acquisition Scan
NA	North American
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NOS	Not Otherwise Specified
ORR	Overall Response Rate

OS	Overall Survival
PDH	Pyruvate Dehydrogenase
PK	Pharmacokinetic(s)
pKa	Dissociation Constant
PP	Per Protocol
PR	Partial Remission
PRO	Patient-Reported Outcome
PS	Performance Score
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
Q12h	Twice a Day with 12 hours Interval
QC	Quality Control
QD	Once a Day
QTc	Corrected QT Interval
RNA	Ribonucleic Acid
ROW	Rest of the World
RR	Respiratory Rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SFU	Safety Follow-up
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SUSAR	Suspected Unexpected Serious Adverse Reaction(s)
$T_{1/2}$	Elimination half-life
TEA	Triethanolamine
TF	Treatment Failure
TKD	Tyrosine kinase domain
T_{max}	Time to Reach the Maximum (Peak) Plasma Concentration following Drug Administration
TTE	Transthoracic Echocardiogram
ULN	Upper Limit of Normal
USP	United States Pharmacopeia
V_d	Apparent Volume of Distribution
WBC	White Blood Cells

1. PROTOCOL SUMMARY AND SCHEMATIC OF STUDY DESIGN

Name of Sponsor:	Rafael Pharmaceuticals, Inc.
Protocol Number:	AML003
Name and Description of Investigational Product:	CPI-613® (devimistat) **Mechanism of Action:** Targets altered metabolism in cancer cells [Pyruvate Dehydrogenase (PDH) and α-Ketoglutarate Dehydrogenase (KGDH) Inhibitor] **Dose:** 2,000 mg/m^2/day in Induction and Consolidation Cycles and 2,500 mg/m^2/day in Maintenance Cycles **Route of Administration:** Intravenous (IV) infusion, 2 hours
Title:	Phase III Multicenter Open-Label Randomized Trial to Evaluate Efficacy and Safety of CPI-613® (devimistat) in Combination with High Dose Cytarabine and Mitoxantrone (CHAM) Compared to High Dose Cytarabine and Mitoxantrone (HAM) therapy and control sub-groups: combination of Mitoxantrone, Etoposide and Cytarabine (MEC) and combination of Fludarabine, Cytarabine, and Filgrastim (FLAG) in Older Patients (≥50 years) with Relapsed/Refractory Acute Myeloid Leukemia (AML)
Study Duration:	Approximately 48 months
Participation Duration:	Approximately 12 months
Objectives:	**Primary Objective:** ▪ To determine efficacy of CHAM in terms of complete remission (**CR)** and compare with HAM (control). CR will be determined as per standard response criteria for AML (Döhner et al. 2017; 129[4]:424-447). **Secondary Objectives:** ▪ To determine efficacy of CHAM in terms of overall survival (**OS**) and complete remission + complete remission with partial hematologic recovery (**CR+CRh**) as the two key secondary objectives to compare with HAM (control). The OS and CR+CRh will be determined as per standard response criteria for AML (Döhner et al. 2017; 129[4]:424-447). ▪ Safety: The assessment of safety will be based mainly on the frequency of adverse events (AEs) based on the Common Terminology Criteria for AEs (version 5.0 or later) grade. Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MeDRA (version 22.0 or higher). The safety outcomes will include the occurrence of at least one serious AE, of at least one Grade 3/4 AE, and of at least one AE requiring the discontinuation of study treatment. Electrocardiogram QTc intervals and cardiac markers will also be evaluated. **Other Secondary Objectives:** ▪ **Pharmacokinetics (PK):** to evaluate C_{max}, C_{min}, AUC, $T_{1/2}$, T_{max}, CL and V_d for both CPI-613® (devimistat) and

	its metabolites CPI-2850 and CPI-1810. To evaluate Patient-Reported Outcome (PRO) among patients receiving CHAM compared to HAM as per European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30). ▪ **Cancer-associated mutations and/or genetic alterations in bone marrow aspirates/biopsies and/or peripheral blood.** Up to 10 unstained slides from baseline and time of disease progression will be collected. These slides will be used for immuno histochemistry staining for PDKs, PDH, KGDH, SOD2 and CD79a. and as a source of material for RNA and whole exome sequencing should the bone marrow aspirate/biopsy material be inadequate. **Exploratory Objectives:** ▪ Gene expression analysis by RNA sequencing for baseline bone marrow aspirate/biopsy samples to validate previously described response signature from the Phase I study (study CCCWFU 22112). Efficacy and safety analyses per gene mutations will also be assessed (may include FLT3, IDH1/2, TP53, CEBPα, NPM1, etc). ▪ PK/PD analyses for dose/exposure-response on efficacy and safety. ▪ Patient Survival: 30-day and 60-day mortality after first dose of study-related treatment.
Endpoints:	**Primary Endpoint:** ▪ CR **Secondary Endpoints:** ▪ OS (key secondary) ▪ CR+CRh (key secondary) ▪ Safety ▪ PK ▪ PRO by EORTC QLQ-C30 ▪ Cancer-associated mutations and/or genetic alterations in bone marrow aspirate/biopsy and/or peripheral blood **Exploratory Endpoints:** ▪ The determination of the positive and negative predictive value of the gene expression signature found from studying patients on study CCCWFU 22112. Efficacy and safety analyses per gene mutations. ▪ PK/PD analysis for dose/exposure-response will be explored for clinical efficacy and safety. ▪ Patient Survival: 30-day and 60-day mortality after first dose of study-related treatment. ▪ Collection of buccal swabs at Screening/Baseline as a source of germline DNA for comparison with DNA obtained from bone marrow aspirate/biopsy samples.

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Study Design:	**Phase:** III **Study Design:** open label, multicenter, randomized trial **Sample Size:** approximately 500 **Study Groups:** ▪ **Arm 1:** CPI-613® (devimistat) + High Dose Cytarabine and Mitoxantrone (CHAM) ▪ **Arm 2:** Control group 1: High Dose Cytarabine and Mitoxantrone (HAM) o **Control sub-group 1:** Mitoxantrone, Etoposide and Cytarabine (MEC) o **Control sub-group 2:** Fludarabine, Cytarabine, and Filgrastim (FLAG) **Dosing Schedule of Interventions for CHAM arm (Arm 1):** **Induction Therapy** (up to 2 cycles, each cycle: 14 days): **Induction Cycle 1** (14-day cycle): ▪ CPI-613® (devimistat) (2,000 mg/m^2 over 2 hours as a central line IV infusion): 5 doses, once a day (QD) Days 1 to 5. Followed by: ▪ High Dose Cytarabine following completion of CPI-613® (devimistat) infusion (1 g/m^2 over 3 hours as a central line IV infusion): 5 doses, every 12 hours (Q12h) starting on Day 3 through Day 5. Time between completion of CPI-613® (devimistat) infusion and the start of Cytarabine infusion should be not more than 2 hours. Followed by: ▪ Mitoxantrone following completion of High dose Cytarabine infusion (6 mg/m^2 over 15 minutes as a central line IV infusion): 3 doses, QD following the 1st, 3rd and 5th doses of Cytarabine starting on Day 3 through Day 5 (3 doses). Mitoxantrone given as soon as possible, but no later than 2 hours, after completion of each Cytarabine administration. **Induction Cycle 2** (14-day cycle; based on Day 14 bone marrow aspirate/biopsy results): ▪ Patients are only eligible to receive full Induction Cycle 2 therapy if they are hemodynamically stable i.e. mean arterial pressure (MAP) > 60 mm Hg (not on pressors or fluid boluses), have maintained an ejection fraction (EF) sufficient to allow treatment with Mitoxantrone and are able to tolerate it in the opinion of the treating Investigator. ▪ If no nadir marrow is obtained or after full Induction Cycle 2 therapy, a recovery marrow will be obtained when peripheral blood counts are consistent with remission (absolute neutrophil count [ANC] > 1,000/μL, platelets > 100,000/μL and freedom from blood transfusions) or on

	Day 42 from the most recent chemotherapy, whichever comes first. If no Day 14 bone marrow aspirate/biopsy is obtained, no Induction Cycle 2 (Full or Abbreviated) will be given. Note: Sites that do not perform day 14 bone marrow will not perform induction cycle 2 (full or abbreviated) on any patients at that site. Induction Cycle 2 details: Same as Cycle 1 or an Abbreviated cycle (14-day cycle) as shown below: ▪ CPI-613® (devimistat) (2,000 mg/m^2): 3 doses, QD Days 1 to 3 Followed by: ▪ High Dose Cytarabine (1 g/m^2) following completion of CPI-613® (devimistat) infusion: 3 doses, Q12 h starting on Day 2 through Day 3 Followed by: ▪ Mitoxantrone (6 mg/m^2): 2 doses, QD following the 1st and 3rd doses of Cytarabine Cycle 2 is administered as soon as possible, but no later than 5 calendar days, following Day 14 bone marrow aspirate/biopsy results. **Consolidation Therapy** (for responders to induction): ▪ Abbreviated course as per Induction Cycles described above (up to 2 consolidation cycles). ▪ Patients must meet study eligibility criteria for organ function and performance status in order to be eligible for consolidation therapy. **Maintenance Therapy** (for responders to induction/ consolidation for **CHAM arm only**): ▪ CPI-613® (devimistat) (2,500 mg/m^2): 5 doses, QD Days 1 to 5 (28-day cycle); continued until disease recurrence, availability of stem cell transplant, the advent of intolerable side effects, or patient withdrawal of consent. NO administration of High Dose Cytarabine and Mitoxantrone in Maintenance Therapy. Patient may move directly into maintenance therapy if not eligible for re-induction or consolidation therapy. **Dosing Schedule of Interventions for HAM arm (Control group, arm 2):** HAM group is treated identically with the exception of the omission of CPI-613® (devimistat) and no Maintenance Therapy.

	Induction Cycle 1 (14-day cycle): ▪ High Dose Cytarabine (1 g/m^2 over 3 hours as a central line IV infusion): 5 doses, Q12 hours starting on Day 1 through Day 3. Followed by: ▪ Mitoxantrone (6 mg/m^2 over 15 minutes as a central line IV infusion): 3 doses, QD following the 1st, 3rd and 5th doses of Cytarabine starting on Day 1 through Day 3. Mitoxantrone given as soon as possible, but no later than 2 hours, after completion of each Cytarabine administration. **Induction Cycle 2** (14-day cycle; based on Day 14 bone marrow aspirate/biopsy results [as described for CHAM Arm 1 above]). ▪ Patients are only eligible to receive Induction Cycle 2 therapy if they are hemodynamically stable i.e. MAP > 60 mm Hg (not on pressors or fluid boluses), have maintained an EF sufficient to allow treatment with Mitoxantrone and are able to tolerate it in the opinion of the treating Investigator. ▪ If no nadir marrow is obtained or after Induction Cycle 2 therapy, a recovery marrow will be obtained when peripheral blood counts are consistent with remission (ANC > 1,000/µL, platelets > 100,000/µL and freedom from blood transfusions) or on Day 42 from the most recent chemotherapy, whichever comes first. ▪ If no Day 14 bone marrow aspirate/biopsy is obtained, no Induction Cycle 2 (Full or Abbreviated) will be given. Abbreviated Induction Cycle 2: ▪ High Dose Cytarabine at 1 g/m^2 administered over 3 hours as a central line IV infusion (as per institutional guidelines or package insert instructions) Q12h starting on Day 1 through Day 2 (total of 3 doses). Followed by: ▪ Mitoxantrone at 6 mg/m^2 administered over 15 minutes as a central line IV infusion after the 1st and 3rd doses of Cytarabine (total of 2 doses). **Consolidation Therapy** (for responders to induction): ▪ Abbreviated course as per Induction Cycles described above (up to 2 consolidation cycles). **Dosing Schedule of Interventions for MEC (Control sub group, arm 2):** MEC sub-group will be treated as per below defined schedule and there is no Maintenance Therapy. **Induction Cycle 1 and 2 (2, 14 day-cycles)**: Induction cycle 2 based on Day 14 bone marrow aspirate/biopsy results. ▪ Etoposide 80mg/m^2 over 60 minutes as a central line IV infusion; 6 doses Day 1 though 6

	▪ Cytarabine 1000mg/m^2 over 3 hours as a central line IV infusion: 6 doses, Day 1 through 6 ▪ Mitoxantrone 6 mg/m^2 over 30 minutes as a central line IV infusion: 6 dose, Day 1 through 6 **Consolidation Cycle (1 and 2)** (for responders to induction): ▪ Etoposide 80mg/m^2 over 60 minutes as a central line IV infusion; 6 doses Day 1 though 6 ▪ Cytarabine 1000mg/m^2 over 3 hours as a central line IV infusion: 6 doses, Day 1 through 6 ▪ Mitoxantrone 6 mg/m^2 over 30 minutes as a central line IV infusion: 6 dose, Day 1 through 6 **Dosing Schedule of Interventions for FLAG (Control sub-group, arm 2):** FLAG sub-group will be treated as per below defined schedule and there is no Maintenance Therapy. **Induction Cycle 1 and 2 (2, 14-day cycles)**: Induction cycle 2 based on Day 14 bone marrow aspirate/biopsy results. ▪ Fludarabine 30mg/m^2/day over 30 minutes as a central line IV infusion; 5 doses Day 1 though 5 ▪ Cytarabine 2g/m^2 over 4 hours as a central line IV infusion; after Fludarabine: 5 doses, Day 1 through 5 ▪ Filgrastim 5µg/kg/day by SQ or as per institutional guidelines starting from Day 1 through Day 5 and can resume 7 days after completion of chemo until ANC ≥ 0.5mcL Note: Sites performing Day 14 bone marrow should not administer Filgrastim until the bone marrow is complete. **Consolidation Cycle 1 and 2 (2 cycles)**: ▪ Fludarabine 30mg/m^2/day over 30 minutes as a central line IV infusion; 5 doses Day 1 though 5 ▪ Cytarabine 2g/m^2 over 4 hours as a central line IV infusion: 4 hours after Fludarabine: 5 doses, Day 1 through 5 ▪ Filgrastim 5µg/kg/day by SQ or as per institutional guidelines starting from Day 1 through Day 5 and can resume 7 days after completion of chemo until ANC ≥ 0.5mcL Note: Sites performing Day 14 bone marrow should not administer Filgrastim until the bone marrow is complete. **Treatment Regimen Window:** ▪ For all treatment regimens (CHAM, HAM, MEC and FLAG) up to a 2 hour dosing window is allowed between the agents in each regimen.
Number of Sites Enrolling participants:	Approximately 90 sites

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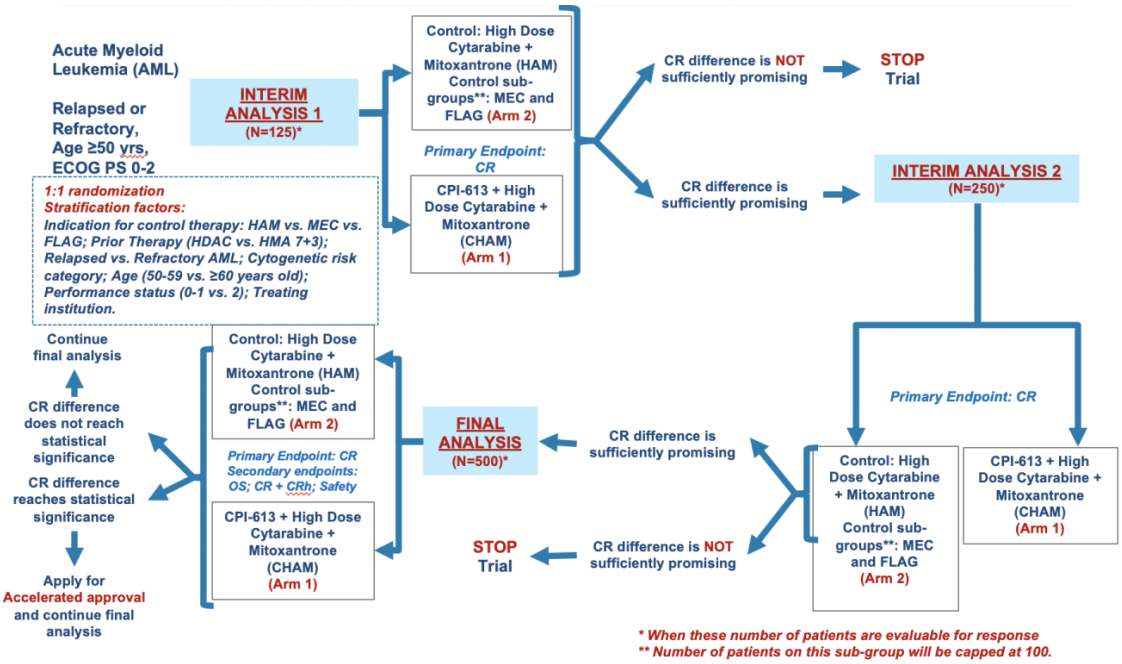
Population:	▪ **Sample Size:** approximately 500 ▪ **Gender:** Both male and female ▪ **Age:** ≥ 50 years ▪ **Demographic Group:** All ▪ **Eastern Cooperative Oncology Board Performance Score (ECOG PS):** 0-2 ▪ **Geographic Location:** United States, Canada, Austria, Belgium, Poland, France, Germany, Spain, Italy, Australia, South Korea, India and potentially other countries
Main Inclusion Criteria:	▪ Males and females age ≥ 50 years must have histologically documented AML that is relapsed from, or refractory to, prior standard therapies ▪ Refractory is defined as failure to achieve CR or complete remission with incomplete recovery (CRi) following: a. At least one cycle of any anthracycline, cytarabine or fludarabine containing induction regimen or persistence of disease on a nadir marrow following at least one cycle of any anthracycline, cytarabine or fludarabine containing induction regimen b. Persistent disease after at least 2 cycles of a hypomethylating agent (azacytidine or decitabine) with or without venetoclax ▪ Relapse is defined as development of recurrent AML (Döhner et al. 2017; 129[4]:424-447) after CR or CRi has been achieved with a prior chemotherapy or after disease progression on a hypomethylating agent with or without venetoclax ▪ ECOG PS (performance score) 0-2 ▪ Expected survival greater than 3 months
Main Exclusion Criteria:	▪ Patients who have received previous cytotoxic chemotherapy treatment for their relapsed or refractory AML. Treatment with hypomethylating agents (decitabine or azacytidine) either alone or in combination with Venetoclax are allowed until the day prior to starting of CHAM or HAM therapy or control sub-groups (MEC and FLAG). Targeted therapies including FLT3 or IDH1/2 inhibitors and/or Hydrea and/or venetoclax are allowed. Targeted therapies and Hydrea may be taken until the day prior to starting of CHAM or HAM therapy or control sub-groups (MEC and FLAG). ▪ Female patients who are pregnant or breastfeeding or planning to become pregnant or breastfeed during treatment and for an additional 6 months after the last dose

	of CHAM or HAM therapy or control sub-groups (MEC and FLAG) (the teratogenic potential of CPI-613® (devimistat) is unknown). Female patients of childbearing potential with a positive pregnancy test assessed by a serum pregnancy test at Screening. ▪ Patients receiving any other standard or investigational treatment for AML, or any other investigational agent for any indication within the past 1 week prior to initiation of CPI-613® (devimistat) treatment (the use of Hydrea and/or venetoclax, oral tyrosine kinase inhibitors FLT3 or IDH 1/2 inhibitors are allowed until the day prior to starting CHAM or HAM therapy or control sub-groups (MEC and FLAG). Previous exposure to a hypomethylating agents either alone or in combination with venetoclax is allowed until the day prior to starting of CHAM or HAM therapy or control sub-groups (MEC and FLAG). ▪ Patients who have received immunotherapy of any type within the past 1 week prior to initiation of CPI-613® (devimistat) treatment. ▪ Requirement for immediate palliative treatment of any kind including minor surgery. ▪ Patients who have received a chemotherapy regimen with autologous stem cell support (bone marrow transplantation) within 6 months of starting CHAM or HAM therapy or control sub-groups (MEC and FLAG). ▪ Patients who have had allogenic bone marrow transplantation within the last 6 months. Patients who have had an allogenic transplant more than 6 months ago are eligible provided they have no graft vs host disease.
Statistical Methods:	**Primary Endpoint – CR** The treatment arm will be compared with the control arm in terms of CR. The significance level will be determined using an O'Brien-Fleming type Lan-DeMets boundary for efficacy equal to 0.023, which will be reached if the difference in CR is larger than 8.3%. This requires 500 patients evaluable for response and will take 36 months after randomization. **Endpoint for the 1st Interim Analysis – CR** This will be performed when 125 patients are evaluable for response after randomization. The significance level for efficacy will be 0.0001 and it will be reached if the difference in CR is larger than 26.7%. The significance level for futility is 0.48 and it will be reached if the difference in CR is less than 0.5%.

	Endpoint for the 2nd Interim Analysis – CR This will be performed when 250 patients are evaluable for response and after randomization. The significance level for efficacy will be 0.006 and it will be reached if the difference in CR is larger than 12.8%. The significance level for futility is 0.21 and it will be reached if the difference in CR is less than 4.9%. Based on each of these interim analyses, if the CR difference is not sufficiently promising, consideration will be given to stopping the trial; otherwise, the trial will proceed. The final analysis will be performed when 500 patients are evaluable for response. This analysis will take place approximately 36 months after the first randomization. The number of events (deaths) required for secondary analysis is 394. For OS, the re-randomization will use a stratified Cox proportional hazard test-statistic. For CR+CRh, the CMH test-statistic will be used. A Data Monitoring Committee will review safety periodically during the study.

Figure 1 Schematic of Study Design



Abbreviations: CHAM: CPI-613® (devimistat) in Combination with High Dose Cytarabine and Mitoxantrone; CR: complete remission; CRh: complete remission with partial hematologic recovery; ECOG PS: Eastern Cooperative Oncology Group Performance Score; EU: European Union; HAM: High Dose Cytarabine and Mitoxantrone; HiDAC: High Dose Cytarabine; HMA: High Dose Cytarabine + Mitoxantrone + Asparaginase; NA: North American; OS: overall survival; ROW; Rest of the World; Mitoxantrone, Etoposide and Cytarabine (MEC); Fludarabine, Cytarabine and Filgrastim (FLAG).