ARMADA 2000: 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) in Older Patients with Relapsed/Refractory Acute Myeloid Leukemia (AML)

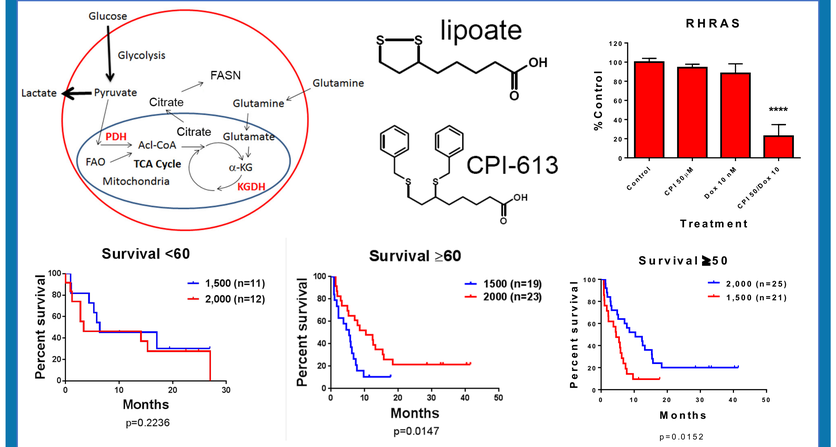
Abstract No. 2658

Timothy S. Pardee[1,3], Sanjeev Luther[1], Marc E. Buyse[2], Bayard L. Powell[3], Jorge Cortes[4];

[1]Rafael Pharmaceuticals, Cranbury, NJ; [2]International Drug Development Institute, Louvain-La-Neuve, Belgium; [3]Wake Forest Baptist Comprehensive Cancer Center, Department of Internal Medicine, Section on Hematology & Oncology, Winston-Salem, NC;
[4]Georgia Cancer Center, Augusta University, Augusta, GA

BACKGROUND

CPI-613® (DEVIMISTAT) IS A NOVEL LIPOATE DERIVATIVE



CPI-613® (devimistat) is a novel lipoate derivative that inhibits the citric acid (TCA) cycle and sensitizes AML to chemotherapy. The structure of lipoate and devimistat are shown on the top middle. On the top left is a simplified schematic of carbon metabolism with the devimistat targets shown in red. Top right is the effect of devimistat on sensitivity to chemotherapy for the AML cell line RHRAS (Dox=doxorubicin, CPI=devimistat). Bottom right, middle and left show dose response effect on survival in older but not younger patients in the Phase I and II studies of devimistat in combination with HiDAC and mitoxantrone. Median survival for both ≥50 and ≥60 years of age for 2,000 mg/m^2 dose is 10.4 months.

STUDY OBJECTIVES, STUDY DESIGN & PARTICIPATING COUNTRIES

STUDY OBJECTIVES:

Primary Objective:

- To evaluate complete remission (CR) using standard response criteria by independent data monitoring committee (DMC)

Secondary Objectives:

- To evaluate overall survival (OS) of devimistat and high dose cytarabine and mitoxantrone vs. high dose cytarabine and mitoxantrone
- To evaluate CR + CRh (complete remission + complete remission with partial hematologic response) of devimistat and high dose cytarabine and mitoxantrone vs. high dose cytarabine and mitoxantrone
- To evaluate safety of devimistat and high dose cytarabine and mitoxantrone vs. high dose cytarabine and mitoxantrone
- To assess pharmacokinetics (PK) of devimistat
- To evaluate patient-reported outcomes (PROs) by EORTC QLQ-C30

Exploratory Objectives:

- To explore biomarkers using diagnostic biopsies and blood/plasma samples
- To assess PK analyses for dose/exposure-response of devimistat on efficacy and safety
- Patient survival: 30-day and 60-day mortality after the first dose of the study

PARTICIPATING COUNTRIES: United States, Canada, Austria, Belgium, Netherlands, Poland, France, Germany, Spain, Italy, Australia, South Korea and other potential countries

KEY ELIGIBILITY CRITERIA

Key Inclusion Criteria:

1. Males and females age ≥ 60 years must have histologically documented AML that is relapsed from, or refractory to, prior standard therapies
2. Refractory is defined as failure to achieve CR or CRi following:
   a. Two standard dose cytarabine based induction cycles or one HiDAC based cycle, or
   b. Failure to respond to one cycle of either standard dose or HiDAC (defined as no decrease in marrow blast percentage from diagnosis on day 14 marrow), or
   c. No response after at least 3 cycles of a hypomethylating agent (azacytidine or decitabine)
3. Relapse is defined as development of recurrent AML (as described by Döhner et al, 2010) after CR or CRi has been achieved with a prior chemotherapy or after disease progression on hypomethylating agent
4. ECOG performance status 0-2; Expected survival >3 months

Key Exclusion Criteria:

1. Patients who have received previous cytotoxic chemotherapy treatment for their relapsed or refractory AML. Previous treatment with hypomethylating agents (decitabine or azacytidine) either alone or in combination with venetoclax is allowed. Targeted therapies including FLT3 or IDH1/2 inhibitors or hydrea are allowed. Targeted therapies and hydrea may be taken until the day prior to starting CHAM or HAM therapy
2. History or evidence of any other clinically significant disorder (e.g. symptomatic congestive heart failure, unstable angina pectoris, symptomatic myocardial infection, uncontrolled cardiac arrhythmia, pericardial disease or heart failure New York Heart Association Class III or IV), or severe debilitating pulmonary disease, that would potentially increase patients' risk for toxicity and in the opinion of the investigator, would pose a risk to patient safety or interfere with the study evaluation, procedures or completion
3. Patients with active CNS involvement (leukemic infiltration, blast in the spinal fluid)
4. Any active uncontrolled bleeding, and any patients with a bleeding diathesis (e.g. active peptic ulcer disease)

TREATMENT SCHEMA

Induction (Up to 2 cycles):

Start of Cycle

Day 1	Day 2	Day 3	Day 4	Day 5
Devimistat	Devimistat	Devimistat HiDAC Mito	Devimistat HiDAC Mito	Devimistat HiDAC Mito

HiDAC: 1 gm/m^2 Q12hr for 5 doses
Mito: 6 mg/m^2 QD for 3 doses
Devimistat: 2,000 mg/m^2 QD for 5 doses
Can be repeated on D14 based on nadir marrow
14 Day Cycle

Consolidation (Up to 2 Cycles):

Start of Cycle

Day 1	Day 2	Day 3
Devimistat	Devimistat HiDAC Mito	Devimistat HiDAC Mito

HiDAC: 1 gm/m^2 Q12hr for 3 doses
Mito: 6 mg/m^2 QD for 2 doses
Devimistat: 2,000 mg/m^2 QD for 3 doses
14 Day Cycle

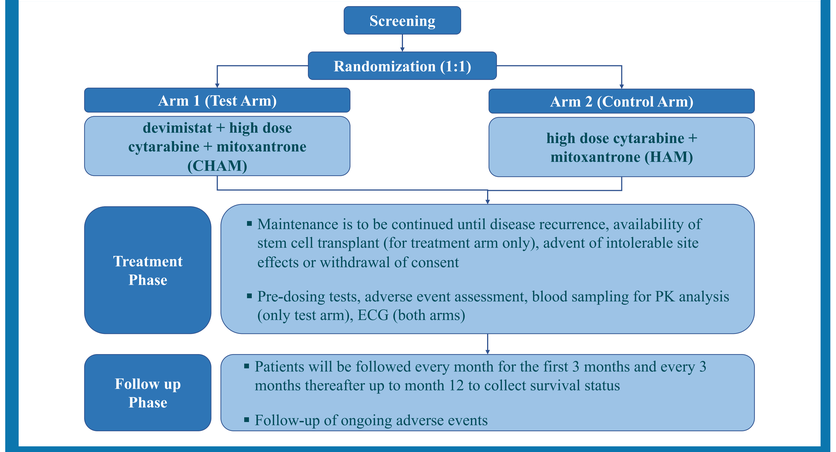
Maintenance (Until Progression):

Start of Cycle

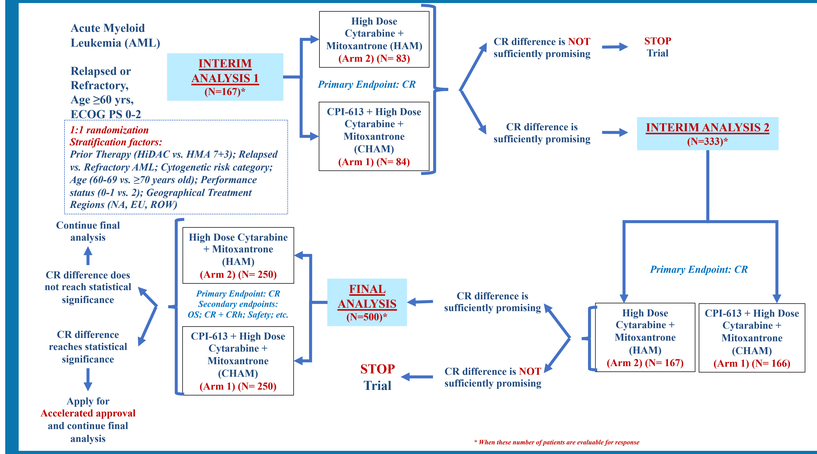
Day 1	Day 2	Day 3	Day 4	Day 5
Devimistat	Devimistat	Devimistat	Devimistat	Devimistat

Devimistat: 2,500 mg/m^2 QD for 5 doses
Every 28 days

STUDY DESIGN SCHEMA



STATISTICAL ANALYSIS PLAN



- **REGISTRATION:** ClinicalTrials.gov Identifier: NCT03504410
- **CONTACT INFORMATION:** For more information on qualification and enrollment, please contact one of the following individuals: Timothy S. Pardee (timothy.pardee@rafaelpharma.com); Sanjeev Luther (sanjeev.luther@rafaelpharma.com)