**BACKGROUND**

Response effect on survival in older but not younger patients in the Phase I and II studies of devimistat in combination with chemotherapy for the AML cell line RHRAS (Dox=doxorubicin, CPI=devimistat). Bottom right, middle and left show dose of carbon metabolism with the devimistat targets shown in red. Top right is the effect of devimistat on sensitivity to CPI

**STUDY OBJECTIVES, STUDY DESIGN & PARTICIPATING COUNTRIES**

Spain, Italy, Australia, South Korea and other potential countries

**Secondary Objectives:**

- To explore biomarkers using diagnostic biopsies and blood/plasma samples
- To assess pharmacokinetics (PK) of devimistat and mitoxantrone
- To evaluate overall survival (OS) of devimistat and high dose cytarabine and mitoxantrone vs. high dose cytarabine
- To evaluate complete remission (CR) using standard response criteria by independent data monitoring committee

**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 CR 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 15 marrow) or
   c. No response after at least 3 cycles of a hypomethylating agent (azacitidine or decitabine)
3. Relapse is defined as development of recurrent AML (as described by DHah et al. 2010), after CR or CR 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 (azacitidine or decitabine) either alone or in combination with radiation is allowed. Targeted therapies including FLT3 or IDH1/2 inhibitors or hydrea-2 are allowed. Targeted therapies and hydrox may be taken until the day prior to starting CRAM or HAM therapy
2. Patients who are evidence of any other clinically significant disorders (e.g. symptomatic congestive heart failure, unstable angina, persistent myocardial infarction, uncontrolled cardiac arrhythmia, peripheral cardiac or heart failure New York Heart Association Class III or IV), or severe debilitating pulmonary disease, that would prevent the patient from receiving therapy, or the opinion of the investigators, 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 CSF)
4. Any active uncontrolled bleeding, or any patients with a bleeding diathesis (e.g. active peptic ulcer disease)

**TREATMENT SCHEMA**

**Induction (Up to 2 cycles):**

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<th>Day 1</th>
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**Maintenance (Until Progression):**

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**DEVIMISTAT** is a novel lipoate derivative

*Abstract No. 2658*

**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 institutions:

- Timothy S. Pardee (timothy.pardee@rafaelpharma.com), Sanjeev Luther (sanjeev.luther@rafaelpharma.com)

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

**ABSTRACT No. 2658**

**STUDY OBJECTIVES, STUDY DESIGN & PARTICIPATING COUNTRIES**

**Secondary Objectives:**

- To evaluate overall survival (OS) 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 evaluate pharmacokinetics (PK) of devimistat
- To evaluate reported patient-outcomes (POs) by EORTC QLQ-C30

**Experimenatal Objectives:**

- To explore biomarkers using diagnostic biopsies and blood/plasma samples
- To assess PK analysis for dose/exposure of response of devimistat on efficacy and safety
- Primary 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

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**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 RHAs (De-vitaminosis, CPI-devimistat). Bottom right, middle and left show dose 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 RHAs (De-vitaminosis, CPI-devimistat). Bottom right, middle and left show dose of carbon metabolism with the devimistat targets shown in red.