The Mitochondrial Metabolism Inhibitor CPI-613 in Combination with High Dose Ara-C (HDAC) and Mitoxantrone is Highly Active in High Risk Relapsed or Refractory AML

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Introduction

Acute myeloid leukemia (AML) is an aggressive malignancy of the bone marrow. Outcomes in relapsed disease are dismal especially in older patients and those with poor risk cytogenetics. New therapies are desperately needed. Glycolytic and mitochondrial metabolism are aberrant in cancers including AML. Altered mitochondrial function is associated with therapy-resistant leukemia cells. Pyruvate dehydrogenase complex (PDH) and α-Ketoglutarate dehydrogenase complex (KDH) are 2 key mitochondrial enzymes that require lipoate for their function. CPI-613 is a non-redox active lipoate derivative developed by Cornerstone Pharmaceuticals that inhibits lipoate dependent enzymes.

Lipoate Analogs are Preferentially Taken Up by AML Cells

CPI-613 Inhibits and Cytarabine Stimulates Mitochondrial Respiration. Top Left: Oxygen consumption rates (OCR) are shown for MEF2L cells treated with cytarabine and asparaginase, only 19% of patients with poor risk cytogenetics achieved a CR (19CR+4CRi out of 48 patients). In the intent to treat population the response rate was 48% (47CR+3CRi out of 60 patients).

CPI-613 Inhibits PDH and AMPK Phosphorylation in Patients

CPI-613 Induces Chemotherapy Sensitivity In p53 Suppressed AML Cells

Conclusions

CPI-613 is a first in class non-redox active lipoate derivative being tested in phase I clinical trial in combination with HDAC and Mitoxantrone for relapse or refractory AML.

- In the intent to treat population the response rate was 48% (19CR+4CRi out of 48 patients).
- In patients with poor risk cytogenetics the CR rate was 4% (1CR out of 23 patients).
- In a historical cohort of patients treated with HDAC, mitoxantrone and asparaginase, only 10% of patients with poor risk cytogenetics achieved a CR (15CR+5CRi out of 127 patients).
- Six patients (13%) died on or before day 30 compared to 13% in the historical cohort.

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