TPS6587: A Phase 1 Single-Arm, Open-Label Study of Emavusertib (CA-4948) in Combination with Azacitidine and Venetoclax in Acute Myeloid Leukemia Patients in Complete Response with Measurable Residual Disease

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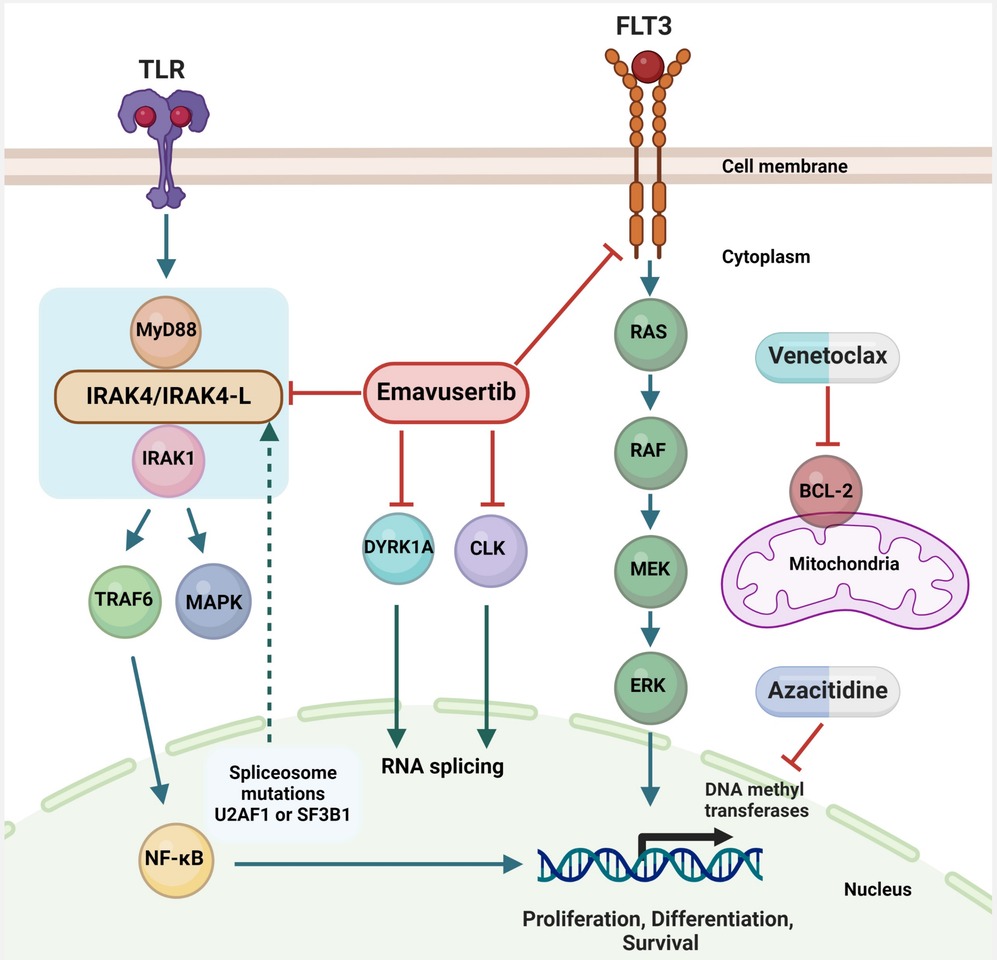
INTRODUCTION

Acute myeloid leukemia (AML) is a heterogenous disease and exhibits a dynamic mutational landscape as the disease progresses.[1] In the VIALE-A study, composite complete response (CRc), which includes complete response (CR) or CR with incomplete hematological recovery (CRi) in association with measurable residual disease (MRD) of <1 residual blast/1000 leukocytes or MRD negative (MRD−) resulted in longer duration of response, event-free survival, and OS than patients who achieved CRc but were MRD positive (MRD+).[2] Single cell sequencing performed in older AML patients showed that primary and adaptive resistance in venetoclax-based combinations was commonly characterized by acquisition or enrichment of clones with FMS-like tyrosine kinase 3 (FLT3)-internal tandem duplication (ITD) mutations.[3] There is no established role for a FLT3 inhibitor in front-line setting for patients who are unsuitable for intensive chemotherapy. The current standard of care is the combination of azacitidine plus venetoclax; however, FLT3-driven relapses are common.[4,5]

Emavusertib is a novel potent oral inhibitor of interleukin-1 receptor-associated kinase 4 (IRAK4) with additional inhibitory activity against FLT3 and CDC-like kinases (CLK1/2/4). Clinical studies with emavusertib monotherapy have demonstrated a significant reduction in blasts, along with CR, in patients who received prior therapy with an hypomethylating agent (HMA) and FLT3 inhibitor. Additionally, emavusertib in combination with azacitidine and venetoclax demonstrated significant anti-leukemic effects in all AML cell lines, including azacitidine- or venetoclax-resistant cell lines.[6] MCL-1 is a prime driver of resistance to venetoclax and targeting IRAK4 has been shown to affect transcription and post translational regulation of MCL-1.[7,8] Given the significant role of FLT3 mutations and MCL-1 in conferring resistance to the combination therapy of azacitidine and venetoclax, we designed this phase 1b study to assess the efficacy of emavusertib in combination with venetoclax and azacitidine in AML patients in CR with MRD. (EUCTR#2023-505828-58).



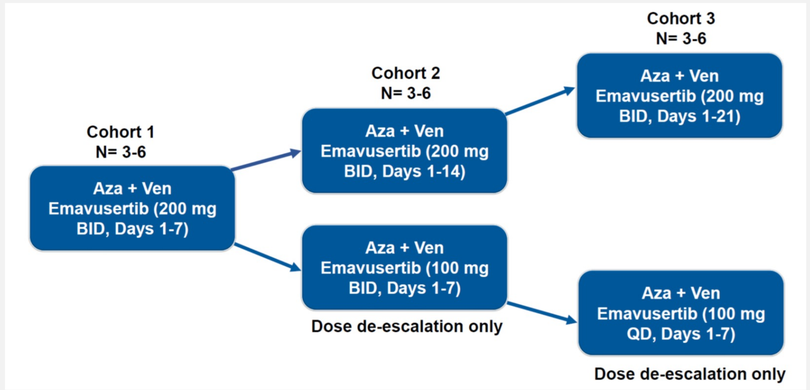
The mechanism of action of emavusertib in combination with azacitidine and venetoclax

STUDY OBJECTIVES

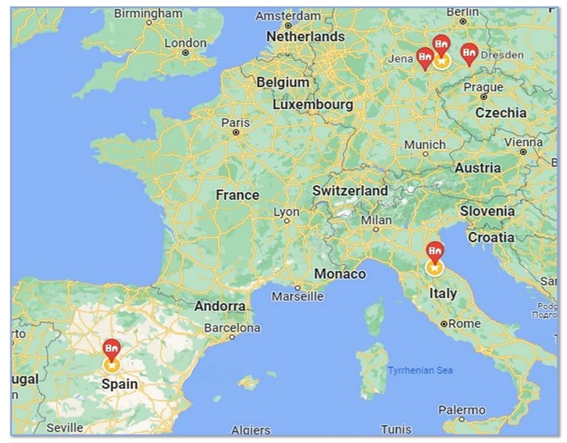
Primary	• Evaluate the safety and tolerability of different dosing schedules of emavusertib as an add-on agent to the combination of azacitidine and venetoclax
Secondary	• Conversion of MRD+ to MRD- status • Characterize the pharmacokinetic profiles of emavusertib, azacitidine, and venetoclax • Assess the effects of the triplet regimen (emavusertib + azacitidine + venetoclax) on dynamics of MRD status and the relationship to outcomes • Evaluate anti-cancer activity of the triplet regimen
Exploratory	• Evaluate the molecular profile of peripheral blood at baseline and following treatment with the triplet regimen

STUDY DESIGN

This is a Phase 1, single-arm, open-label study evaluating safety and tolerability, PK, and conversion of MRD status with emavusertib as an add-on agent in AML patients who have received azacitidine + venetoclax as first-line therapy after no more than 6 cycles and have achieved CR or CRh with MRD+ status.



STUDY SITES



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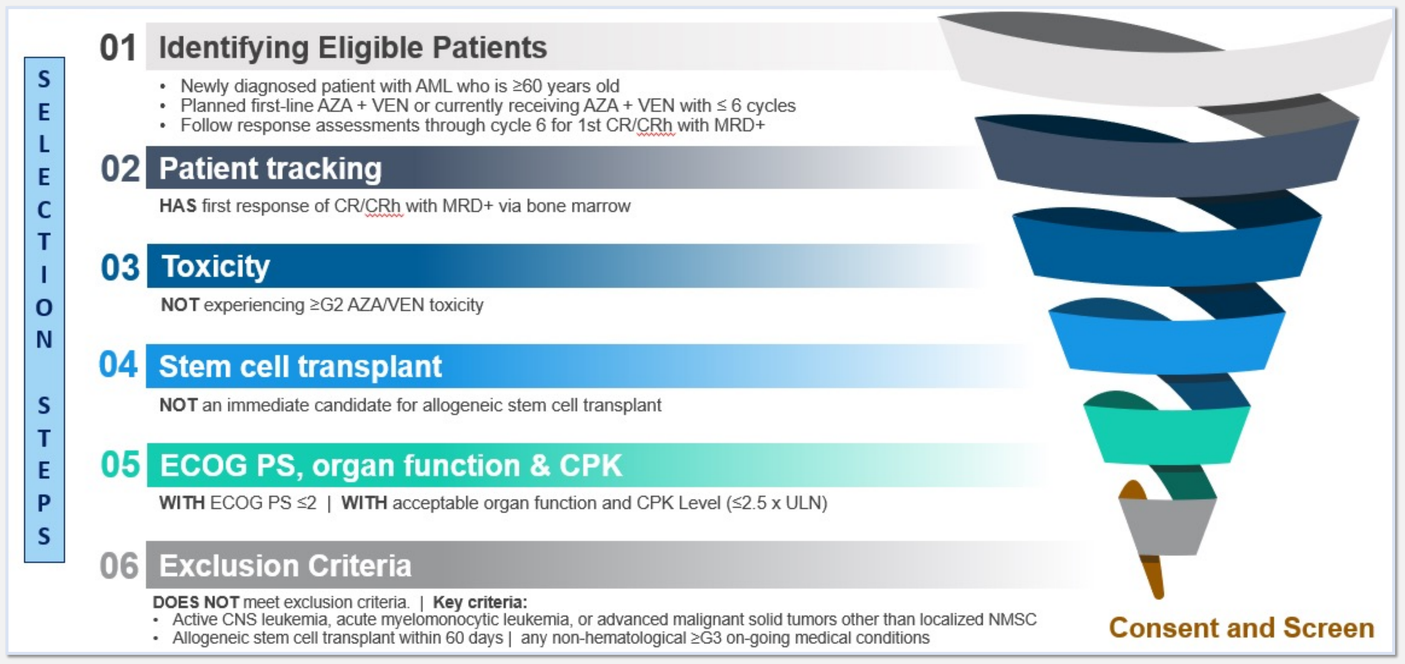
STUDY ELIGIBILITY



BIOANALYTICAL AND BIOMARKER PLAN

Pharmacokinetics	• Patient safety and drug clearance
Genomic analysis	• Genetic, epigenetic and mutational analysis of bone marrow and peripheral blood • MRD analysis by next generation sequencing (exploratory objective)
Transcriptomic analysis	• RNA-sequencing analysis of bone marrow and peripheral blood
Proteomic analysis	• MRD analysis by flow cytometry (secondary objective) • Cytokine/chemokine/growth factor quantification
Machine learning analysis	• Correlational analysis of biomarker and clinical data to determine predictive biomarkers of response.

SUMMARY

- Emavusertib monotherapy appears to be well tolerated in patients with relapsed or refractory AML, regardless of mutation status, previously treated with HMA, venetoclax, and FLT3 inhibitors.
- Emavusertib in combination with azacitidine and venetoclax demonstrated synergistic anti-leukemic effects in AML cell lines.
- Adding emavusertib to the azacitidine/venetoclax doublet in MRD+ patients at the time of CR may enable patients to achieve MRD negativity without significant toxicity.
- This triplet combination has a potential to become new regimen in front-line therapy for AML patients, regardless of mutation status.
- Exploratory biomarkers will be analyzed to determine predictive biomarkers of response.
- The study is currently enrolling patients.

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