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Blood 142 (2023) 5975–5976

The 65th ASH Annual Meeting Abstracts

ONLINE PUBLICATION ONLY

616.ACUTE MYELOID LEUKEMIAS: INVESTIGATIONAL THERAPIES, EXCLUDING TRANSPLANTATION AND CELLULAR IMMUNOTHERAPIES

Trial in Progress: A Phase 1b 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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Background

Emavusertib is a novel potent oral inhibitor of interleukin-1 receptor-associated kinase 4 (IRAK4) with additional inhibitory activity against FMS-like tyrosine kinase 3 (FLT3) and CDC-like kinases (CLK1/2/4). Inhibition of these onco-proteins may induce remission thereby addressing a critical unmet need for novel therapies in acute myeloid leukemia (AML). Clinical studies with emavusertib monotherapy have demonstrated a significant reduction in AML blasts with clinical and molecular responses, including patients with relapsed or refractory AML, previously treated with an HMA and/or FLT3 inhibitors (Metzeler 2022). Azacitidine + venetoclax (aza+ven) has been approved in newly diagnosed, unfit patients with AML. In the VIALE-A study, composite complete response (CRc) (CR, CRh, or CRi) in the absence of measurable residual disease (MRD) of <1 residual blast/1000 leukocytes (MRD negative [MRD−]) resulted in longer duration of response (DOR), event-free survival, and overall survival (OS), and better HSCT outcome compared with patients who achieved CRc but were MRD+ (Pratz, 2022). In pre-clinical studies, emavusertib in combination with aza+ven demonstrated synergistic antileukemic effects in AML cell lines, including azacitidine- or venetoclax-resistant cell lines. Adding emavusertib to aza+ven in MRD+ patients at the time of CR may convert MRD status without adding significant toxicity and confirm that emavusertib can be safely added to aza+ven as a potential new regimen in front-line therapy.

Study Design:

This is a single-arm, open-label Phase 1b trial evaluating safety and tolerability, PK, and conversion of MRD status with emavusertib as an add-on agent to aza+ven in AML patients who achieved CR or CRh with MRD+ based on local testing (EU CT Number 2023-505828-58-00). The primary objective of the study is to determine a safe and tolerable dosing schedule for the triple combination. Secondary objectives include MRD conversion rate, DOR, OS, and pharmacokinetics. The study will enroll approximately 24 patients at 5 to 10 sites globally. Patients will have received azacitidine and venetoclax as first line therapy and achieved CR or CRh after 1-6 cycles of aza/ven. If MRD status remains positive, emavusertib will be added to the existing well tolerated aza+ven regimen. The starting emavusertib dose is 200 mg BID for 7 days per cycle of 28 days. If well tolerated, duration of emavusertib treatment will be extended to 14 and 21, respectively; no intra-patient change of emavusertib dosing duration is planned. The patients will continue triple treatment (emavusertib+aza+ven) until consent withdrawal, disease progression, intolerable toxicity, or not achieving MRD- within 6 cycles of triple treatment. In this Phase 1b trial, MRD can be evaluated by local testing of bone marrow. Key exclusion criteria include residual toxicities and significant comorbidities.

Disclosures Cerchione: *Janssen:* Consultancy, Honoraria, Speakers Bureau; *Servier:* Consultancy, Honoraria, Speakers Bureau; *Menarini:* Consultancy, Honoraria, Speakers Bureau; *Amgen:* Consultancy, Honoraria, Speakers Bureau; *Celgene:* Consultancy, Honoraria, Speakers Bureau; *AbbVie:* Consultancy, Honoraria, Speakers Bureau; *Sanofi Aventis:* Honoraria, Speak-

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https://doi.org/10.1182/blood-2023-190125