#P563

VIALE-M: A Randomized, Double-Blind, 2-Arm, Multicenter, Phase III Study of Venetoclax and Oral Azacitidine Versus Oral Azacitidine as Maintenance Therapy for Patients With Acute Myeloid Leukemia in First Remission After Intensive Chemotherapy

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STUDY OVERVIEW

Randomized | Multicenter, International | Phase III | Approx. 486 Patients Overall | NCT04102020

OBJECTIVES

1. The primary objective for the dose-escalation phase of the trial is to identify the recommended Phase 3 dose of Venetoclax in combination with oral Azacitidine
2. The primary objective for the randomization phase of the trial is to evaluate the relapse-free survival as assessed by an independent review committee
3. The secondary objective for the randomization phase of the trial is to evaluate key secondary endpoints, including overall survival, minimal residual disease conversion, and improvement in quality of life

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INTRODUCTION

Acute myeloid leukemia (AML) is an aggressive, heterogenous hematologic malignancy with poor prognosis

- AML is one of the most common forms of acute leukemia in adults, has the lowest survival rate, and accounts for the largest number of deaths[1]
- While patients who are fit to receive intensive treatment will often achieve remission, more than 50% of these patients will ultimately relapse[2, 3, 4]
- There is a critical and unmet need for strategies that decrease the risk of relapse and improve the survival of patients with AML

Venetoclax (Ven) combined with azacitidine (Aza) leads to prolonged OS, rapid and durable remissions (CR+CRi) in patients newly diagnosed with AML and ineligible for intensive chemotherapy.

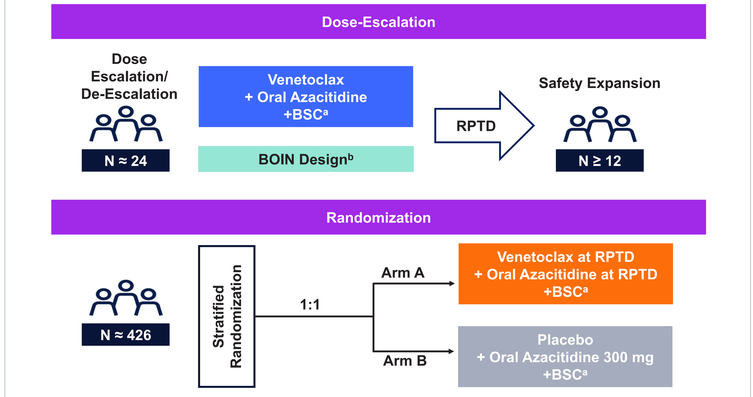
This combination is approved for the treatment of AML in this patient population.

- Ven is a first-in-class, highly selective, potent, oral BCL-2 inhibitor that induces apoptosis in AML cells. Aza is a hypomethylating agent. Combining Ven with Aza has been shown to induce apoptosis in AML malignant cells
- Oral Aza is approved for continued maintenance treatment of patients with AML who achieved first CR or CRi following intensive induction chemotherapy and were unable to complete intensive curative therapy

VIALE-M is a Phase III randomized, double-blind trial in progress evaluating the safety and efficacy of Ven + oral Aza versus placebo + oral Aza as maintenance therapy for patients 18 years and older with newly diagnosed AML in first CR or CRi following intensive

METHODS

Study Design



a. BSC (best supportive care) excluding any AML-directed therapy, will be determined for each patient by the investigator and institutional guidelines.
b. Dose-finding will follow a BOIN design to guide dose-escalation and de-escalation decisions.
RPTD, recommended Phase III dose; BOIN, Bayesian optimal interval.

Eligibility Criteria*

Inclusion Criteria:

- Diagnosis of newly diagnosed AML
- Patient meets the following disease activity criteria:
  - Confirmation of AML by World Health Organization (WHO) criteria (2016) and have confirmed complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following completion of intensive induction and consolidation chemotherapies
  - Achieved first CR or CRi within 120 days of first dose of study drug or be no more than 75 days since last dose of intensive conventional chemotherapies
  - AML has intermediate or poor risk cytogenetics per National Comprehensive Cancer Network (NCCN) 2016 criteria
- Eastern Cooperative Oncology Group (ECOG) performance status <= 2
- Patient must have adequate hematologic, renal, and liver function laboratory values as described in the protocol

Exclusion Criteria:

- History of acute promyelocytic leukemia (APL)
- History of active central nervous system involvement with AML
- History of allogeneic stem cell transplantation or candidates for allogeneic stem cell transplantation

*For the complete list of eligibility criteria, please contact the study sponsor at 1-844-663-3742 or abbvieclinicaltrials@abbvie.com

Analysis Populations

The dose-escalation portion of the study will confirm the dose selection of Ven + oral Aza and ensure that the thresholds of safety will be met before expanding to the randomized portion

- The total enrollment is approximately 36 patients (each dose level will initially enroll at least 6 DLT-evaluable subjects; approximately 12 patients will be assigned to receive the preliminary RPTD identified during dose escalation; the safety expansion portion will enroll at least 12 additional patients
- Patients will receive Ven QD for up to 24 cycles and oral Aza QD on D1-14 of each 28-day cycle for up to 24 cycles to determine the RPTD
- For safety expansion, patients will receive Ven QD for up to 24 cycles and oral Aza QD on D1-14 of each cycle for up to 24 cycles at the RPTD

The randomization portion of the study will evaluate the efficacy of Ven + oral Aza when compared to placebo + oral Aza

- Approximately 426 patients will be randomized 1:1 to receive placebo or Ven QD at the RTPD and oral Aza QD on D1-14 of each cycle for 24 cycles

DLTs, dose-limiting toxicities; Ven, venetoclax; oral Aza, oral azacitidine; QD, once a day; RTPD, recommended Phase III dose

Dose Escalation | Primary Endpoint

Number of Patients With Dose-Limiting Toxicities (DLTs) of Ven + oral Aza

- Any of the following events during cycle 1, which are considered possibly or probably related to the administration of Ven, will be considered a DLT:
  - For hematologic toxicities, any Grade ≥ 3 neutropenia lasting more than 7 days, any Grade ≥ 3 thrombocytopenia lasting more than 7 days
  - For non-hematologic toxicities, any Grade 3 AE lasting ≥ 72 hours except for Grade 3 hypersensitivity reactions or Grade 3 localized injection-site toxicities, Grade ≥ 3 nausea, diarrhea, or vomiting despite adequate/maximal medical intervention lasting more than 7 days, any Grade ≥ 4 AE, any Hy's law cases
- Any AEs not meeting the above criteria but lead to omitting > 20% of the scheduled study drug doses within the first cycle
- To be considered DLT-evaluable, patients must complete at least 80% of assigned Ven dosing and oral Aza dosing in cycle 1 or experience a DLT in cycle 1

Randomization | Primary Endpoint

Relapse-Free Survival (RFS)

- Defined as the number of days from randomization to the date of relapse or the date of death from any cause, whichever comes first
- Disease relapse is defined as reappearance of ≥ 5% blasts after CR or CRi in peripheral blood or bone marrow or development of extramedullary disease

Randomization | Key Secondary Endpoints

Overall Survival (OS)

- Defined as the number of days from the date of randomization to the date of death

Minimal Residual Disease (MRD) Conversion

- Defined as the percentage of patients deemed MRD positive ($\geq 10^{-3}$) at study initiation who converted to MRD of $<10^{-3}$ in the bone marrow after randomization or initiation of treatment

Improvement in Health Related Quality of Life

- Measured by procedures outlined in the EORTC QLQ-C30 scoring manual. Fatigue will be evaluated using Patient-Reported Outcome (PRO) assessment of the Patient Reported Outcomes Measurement Information System (PROMIS) Fatigue Short Form (SF) 7a

~ 216 sites in 22 countries, enrolling ~426 patients in the randomization phase