AML-143

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Trial in Progress: Phase Ib/II Study of Siremadlin in Combination With Venetoclax + Azacitidine in Patients With Acute Myeloid Leukemia (AML) Who Are Ineligible for Intensive Chemotherapy (IC)

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SUMMARY

- Siremadlin (HDM201) is an investigational, oral, small-molecule inhibitor of the p53-murine double minute-2 (MDM2) interaction, which results in the upregulation of the tumor-suppressive effect of p53
- This Phase Ib/II study (NCT05155709) assessing the safety and preliminary efficacy of siremadlin + venetoclax + azacitidine in AML patients who are unfit for IC is currently recruiting
- Approximately 56 patients are planned to be enrolled

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INTRODUCTION

Acute Myeloid Leukemia

- Acute myeloid leukemia (AML) is the most common form of acute leukemia in adults and is characterized by proliferation of undifferentiated hematopoietic stem cells which suppresses normal hematopoiesis[1]
- Intensive chemotherapy (IC) is the current standard of care treatment for AML but can be associated with severe toxicities[2,3]
- Patients who are elderly, have comorbidities, or have poor performance status may be unable to tolerate IC[2]
- Treatment options that provide durable clinical benefit and have tolerable safety profiles are needed for these patients[3]

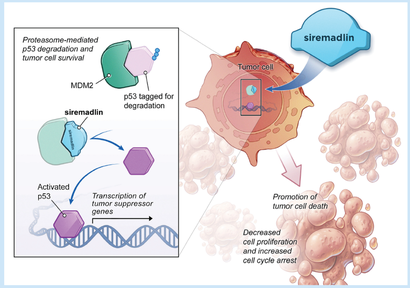
p53-MDM2: Myeloid Cell Target in Cancer

- MDM2 (also known as the human homologue HDM2) is an important negative regulator of protein p53 (**Figure 1**)[4]
  - p53 is normally activated when DNA is damaged so that the cell cycle can be halted for DNA repair. If repair does not ensue, the cell will undergo apoptosis[5]
  - p53 is therefore known as the "guardian of the genome"[7]
- MDM2 is frequently dysfunctional in AML[5]:
  - In AML samples with wild-type (wt) p53, there is a positive relationship between MDM2 levels and cell death triggered by MDM2 inhibition
  - This relationship is not observed in AML with mutant TP53 (encoding gene for protein p53)
- The p53-MDM2 interaction is therefore a potential drug target
- Siremadlin inhibits the interaction between p53 and HDM2 (a human ortholog of MDM2)

Siremadlin

- Siremadlin (HDM201) is an investigational, orally available inhibitor of the p53/MDM2 interaction protecting p53 from degradation, resulting in tumor growth inhibition and apoptosis (**Figure 1**)[7]
- Siremadlin has shown:
  - Potent single agent activity in various in vitro and in vivo tumor models with wt TP53[7]
  - Single agent activity in relapsed/refractory (R/R) AML
- In a Phase I study (NCT02143635), AML patients treated with siremadlin experienced a tolerable safety profile and preliminary antitumor activity[8]
- Initial results from a Phase Ib study (NCT03940352) exploring siremadlin+venetoclax showed promising antileukemic activity in patients with relapsed/refractory AML
- This Phase Ib/II study (NCT05155709) is designed to assess the safety and preliminary efficacy of siremadlin+venetoclax+azacitidine in AML patients unfit to receive IC

Figure 1. Siremadlin Mechanism of Action

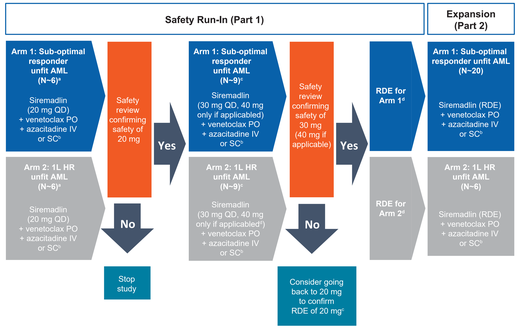


MDM2, murine double minute-2.

METHODS

- The study design for this Phase Ib/II study is described in **Figure 2**
  - Arm 1 and Arm 2 will open enrollment simultaneously
  - Patients will receive siremadlin in combination with venetoclax + azacitidine
  - Treatment dosing and schedule is explained in **Table 1**
  - The recommended dose for expansion (RDE) for Arm 1 and Arm 2 will be defined independently
- Study endpoints are shown in **Table 2**
- Key eligibility criteria are described in **Table 3**

Figure 2. Study Design



[a]At least 3 evaluable participants are needed to confirm safety. [b]Azacitidine IV or SC according to local standard of care. [c]At least 6 evaluable participants are needed to define RDE. [d]Selection of dose level for RDE will be based on totality of available data (i.e., pharmacokinetics, safety, tolerability, and preliminary efficacy data if available).
1L, first-line; AML, acute myeloid leukemia; HR, high-risk; IV, intravenous; QD, once daily; RDE, recommended dose for expansion; SC, subcutaneous.

Table 1. Treatment Dosing and Schedule

Treatment	Safety Run-In (Part 1)	Expansion (Part 2)
Siremadlin (PO)	• 20 or 30 mg once daily from D1 to D5 of every cycle (28-day cycles)	• RDE
Venetoclax (PO)	• Arm 1: Patients will continue receiving their tolerated dose prior to study enrollment • Arm 2: Increased over 3 days to reach target dose of 400 mg daily	
Azacitidine (IV or SC)[a]	• Arm 1: Patients will continue receiving their tolerated dose prior to study enrollment • Arm 2: 75 mg/m^2 [b] – From D1 to D7; OR – From D1 to D5 and D8 and D9	

[a]Formulation for azacitidine according to local standard of care. [b]Body surface area (BSA) in m^2=[height(cm) x weight(kg)/3600]$^{0.5}$
D, day; IV, intravenous; PO, by mouth; RDE, recommended dose for expansion; SC, subcutaneous.

Table 2. Study Endpoints

Primary Endpoints
- Proportion of patients with DLTs reported during Cycle 1
- Proportion of patients achieving a CR at RDE in Arm 1

Secondary Endpoints
- Incidence and severity of AEs and SAEs, changes in lab values and vital signs, incidence of notable ECG abnormalities
- Proportion of patients achieving a CR in Arm 2
- Duration of CR
- Proportion of patients achieving a CR/CRh or a CR/CRi
- Duration of CR/CRh and CR/CRi
- Overall survival
- Early mortality at Day 30 and Day 60
- PK parameters: AUC, C_{max} and T_{max} of siremadlin, venetoclax, and azacitidine
- Proportion of CR-MRD negative overall and in patients achieving a CR, CR/CRh, and CR/CRi

AE, adverse event; AUC, area under the curve; C_{max}, concentration maximum; CR, complete remission; CRh, complete remission with partial hematological recovery; CRi, complete remission with incomplete hematological recovery; DLT, dose limiting toxicity; ECG, electrocardiogram; MRD, measurable residual disease; PK, pharmacokinetic; RDE, recommended dose for expansion; SAE, serious adverse event; T_{max}, time to reach maximum concentration.

Table 3. Key Eligibility Criteria[a]

Inclusion Criteria
- Age ≥18 years
  - Patients with AML based on WHO 2016 classification who are ineligible for standard induction chemotherapy
  - Have received 2 to 4 cycles (1 cycle=28 days) of first-line venetoclax + azacitidine treatment and have not achieved CR, CRi, CRh, or MLFS (Arm 1)
  - Newly diagnosed AML with adverse ELN-2017 genetic risk stratification (except TP53 mutation) (Arm 2)
- Ineligible for standard-of-care intensive induction chemotherapy defined by the following:
  - ≥75 years of age; OR
  - ≥18 to 74 years of age with at least one of the following comorbidities:
    - » ECOG performance status of 2 or 3
    - » Cardiac history of congestive heart failure requiring treatment of ejection fraction ≤50% or chronic stable angina
    - » DLCO ≤65% or FEV_1 ≤65%
- ECOG performance status 0 to 2 (≥75 years of age) or 0 to 3 (18-74 years of age)
- WBC <25 x 10^9/L
- AST and ALT ≤3 x ULN
- eGFR ≥60 mL/min/1.73 m^2

Exclusion Criteria
- Prior exposure to MDM-inhibitor therapy at any time
- Patients positive for TP53 mutation
- Patients with del17p
- Previous treatment at any time with:
  - Checkpoint inhibitors
  - FLT3 inhibitors
  - Venetoclax and HMAs (except for as defined in the inclusion criteria for Arm 1)
  - Previous treatment for AML, MDS, myelofibrosis, essential thrombocythemia, or polycythemia vera (with the exception of hydroxyurea, growth factors, ruxolitinib, and supportive care)
- Patients with AML-M3/ APL with PML-RARA or with AML secondary to Down's syndrome
- Patients with concurrent or prior malignancy, except:
  - Patients with history of MDS, myelofibrosis, essential thrombocythemia, or polycythemia vera, aplastic anemia, or other antecedent hematologic disorder
  - Patients with history of adequately treated malignancy for which the participant has been disease free (absence of residual disease) for ≥1 year and no ongoing chemotherapy, radiotherapy or surgery required during the course of the study

[a]Other eligibility criteria apply.
AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; AST, aspartate aminotransferase; ALT, alanine transaminase; CR, complete remission; CRh, complete remission with partial hematological recovery; CRi, complete remission with incomplete hematological recovery; DLCO, diffusing capacity for carbon monoxide; ECOG, Easter Cooperative Oncology Group; eGFR, estimated glomerular filtration rate; FEV_1, forced expiratory volume in 1 second; HMA, hypomethylating agent; MDS, myelodysplastic syndrome; MLFS, morphologic leukemia-free state; PML-RARA, promyelocytic leukemia/retinoic acid receptor alpha; ULN, upper limit of normal; WBC, white blood cell.

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