AML-142

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# Patients at High Risk of Relapse Post-Transplant: A Phase 1 Study Design With a Novel Treatment Strategy Using the Estimand Framework

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## CONCLUSIONS

- Using the estimand framework, the safety and efficacy of a treatment strategy can be assessed as a whole, taking into account the different journeys of patients with AML following alloSCT
- The estimand framework [ICH E9 (R1)] is a structured framework for clinical trial planning, conduct, data collection, and interpretation of data. The definition of the treatment is an integral part of the estimand framework and requires a careful definition of the intervention of interest[11]
- Although clinical trial endpoints refer to events/outcomes that can be measured objectively,[12] an estimand summarizes, at a population level, what the outcomes would be in the same patients under different treatment conditions[11]

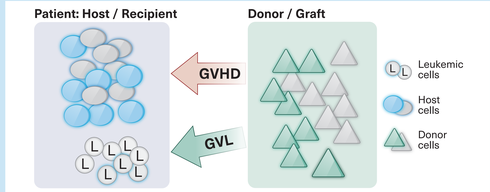
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## CLINICAL SUPPORT FOR STUDY TREATMENT STRATEGIES

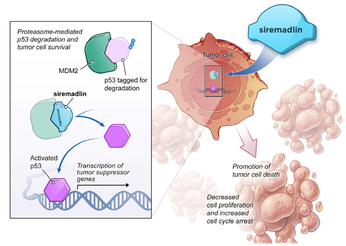
- The risk of disease relapse in patients who undergo allogeneic hematopoietic stem cell transplantation (alloSCT) for acute myeloid leukemia (AML) is high and remains the main cause of transplant failure[1,2]
- The great majority of patients destined to relapse post alloSCT will do so within the first 12 months, and survival after early relapse is dismal. Therefore, strategies to prevent relapse are urgently required[3]
- A potent graft-versus-leukemia (GVL) effect is exerted after alloSCT, and strategies that may augment a GVL effect have the potential to reduce relapse risk post alloSCT (**Figure 1**)[4,5]
- Siremadlin (HDM201) is an 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 (**Figure 2**)[6]
- An exploratory post hoc analysis from the first-in-human study (NCT02143635) shows antileukemic activity with single-agent siremadlin in patients with relapsed AML post-alloSCT[7]
- A report by Wang and colleagues demonstrated the immunomodulatory effects of siremadlin in vitro and in murine syngeneic models. Treatment with siremadlin led to upregulation of the costimulatory cluster of differentiation (CD) 80 molecule expression on tumor cells. This resulted in enhanced T-cell stimulation, increased CD8+ T-cell frequency, and promoted T-cell-mediated killing of tumor cells[8]
- MDM2 inhibitors, including siremadlin, possess potent immunomodulatory effects in murine solid tumor and AML models[6,9,10]
  - The post-alloSCT setting is ideal for investigating the immunomodulatory effects of MDM2 inhibition on enhancing GVL effect

**Figure 1. Clinical Treatment Objective of alloSCT**




alloSCT, allogeneic stem cell transplantation; GVHD, graft-versus-host disease; GVL, graft-versus-leukemia.

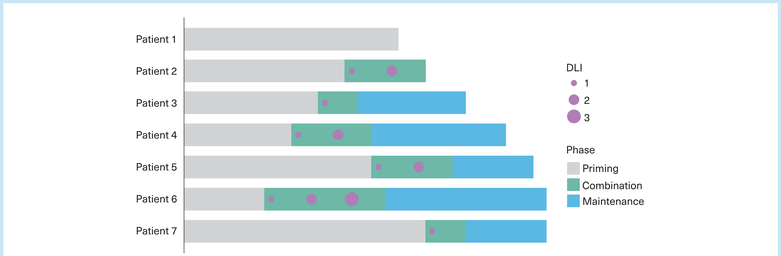
**Figure 2. Siremadlin Mechanism of Action**




MDM2, murine double minute-2.

## PATIENT-FOCUSED TREATMENT CONSIDERATIONS

**Figure 3: Patients With AML in Remission Post Transplant Have Varied Treatment Needs**




AML, acute myeloid leukemia; DLI, donor lymphocyte infusion.

### Treatment decisions are guided by patients' status during each treatment phase (priming, combination therapy, and maintenance)

- A treatment strategy is defined as a treatment plan of several predefined parts. Depending on the treatment journey, patients may receive only a part of the interventions of the sequence (**Figure 3**)
- For determining the recommended dose of siremadlin we consider information separately from patients who received siremadlin during priming and during the combination phase
- For assessment of efficacy, we include all patients who started the priming phase at the recommended dose of siremadlin regardless of the actual journey the patient took. This approach addresses the clinical question on the outcome at the time of a treatment decision when it is unknown which parts of the treatment strategy the patient will actually receive. This approach might come closest to the patient's main interest to inform a treatment decision

## IMPLEMENTATION OF THE TREATMENT STRATEGY INTO A CLINICAL STUDY

### Treatment Strategy as a Sequence of Treatments: Clinical Considerations to Define the Intervention of Interest in a Clinical Trial as Motivated by the Estimand Framework

#### Primary Objectives

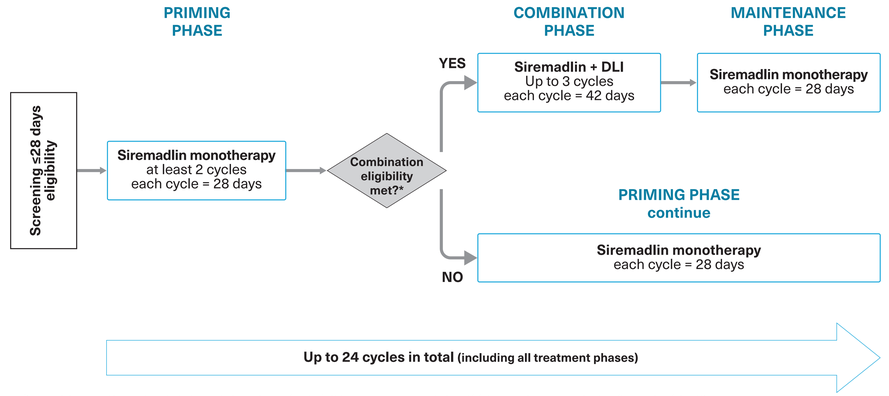
- To determine the safety of siremadlin monotherapy and in combination with donor lymphocyte infusion (DLI; incidence of DLT in priming phase and time to DLT in combination phase)
- To evaluate preliminary efficacy of study treatment strategy (siremadlin monotherapy, as priming and/or maintenance, with or without siremadlin in combination with DLI) on prevention of relapse

#### Patient Eligibility Criteria

- Adults with AML, Day 60-120 post-alloSCT (≥8/8 human lymphocyte antigen-matched related or unrelated donor), in compete remission (CR) or CR with incomplete hematological recovery (CRi)
- High risk for relapse based on pretransplant risk factors:
  - AML in CR1 with adverse-risk genetic abnormalities per ELN 2017, therapy-related AML, or AML secondary to myelodysplastic syndrome or myeloproliferative neoplasm
  - AML in ≥ CR2
- No active GVHD, and no history of grade III-IV acute GVHD and/or moderate to severe chronic GVHD
- Eastern Cooperative Oncology Group performance status 0-2
- Adequate engraftment and organ function

#### Secondary Objectives

- To assess relapse-free survival, overall survival, cumulative relapse at 1 and 2 years, minimal residual disease status within 6 months, safety and tolerability, incidence of grade III and grade IV acute GVHD and moderate to severe chronic GVHD, GVHD-free/relapse-free survival, pharmacokinetics




*The decision of DLI administration will be at the discretion of the treating investigator per standard of practice/institutional guidelines; however, patients must fulfill the combination phase eligibility criteria after completion of at least 2 cycles of priming.
DLI, donor lymphocyte infusion.

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