Phase 1/2, Open-Label, Multi-Center Study Assessing the Safety, Tolerability and Preliminary Efficacy of CD123 Natural Killer Cell Engager (NKCE), SAR443579, in Combination With Venetoclax and Azacitidine in Patients With Newly Diagnosed Acute Myeloid Leukemia (AML) Who Are Ineligible for Intensive Chemotherapy

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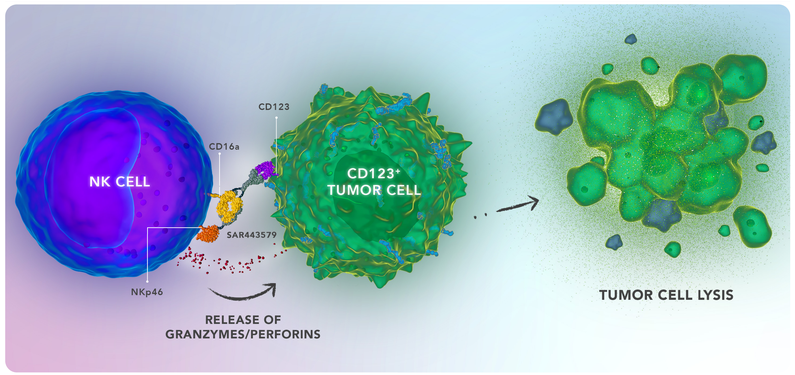
BACKGROUND

- Acute myeloid leukemia (AML) is an aggressive type of leukemia, accounting for 80% of adult cases. It is characterized by the clonal expansion of myeloid precursor cells in the bone marrow and peripheral blood[1,2]
- First-line treatment for AML involves intensive chemotherapy (IC) combined with targeted therapy[3]
- Patients with newly diagnosed AML (ND-AML) who are unfit for IC receive venetoclax in combination with azacitidine (VEN/AZA) as the standard of care treatment[4]
- Overall response rate (ORR; complete response/complete response with incomplete hematologic recovery/morphological leukemia-free state [CR/CRi/MLFS]) is 76.9% with VEN/AZA. Disease-free survival (DFS) and overall survival (OS) rates, however, are still poor, therefore, the need remains to improve the CR rate and durability of response by addressing the mechanisms of relapse and resistance that are common in AML[4-6]

Natural Killer Cell Engager, SAR443579

- Cluster of differentiation 123 (CD123) is overexpressed on AML cells and is correlated with poor prognosis, offering a potential target for AML treatment[7,8]
- Natural killer cell engagers (NKCEs) promote anti-tumor killing activity by engaging activating receptors on natural killer (NK) cells and tumor-specific antigens[7]
- SAR443579 is an NKCE that consists of 3 separate binding domains, designed to co-engage CD123 on tumor cells and the activating receptors NKp46 and CD16a on NK cells[9] (**Figure 1**)
- SAR443579 facilitates NK cell activation and tumor cell death by forming a cytolytic synapse between NK cells and CD123-positive leukemic cells, while reducing the risk of off-target activation[9,10]

Figure 1: Mechanism of Action of SAR443579



CD, cluster of differentiation; NK, natural killer.

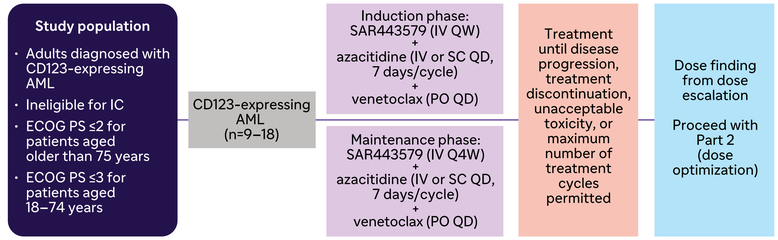
- Preclinical *in vitro* studies of SAR443579 demonstrate strong antitumor activity against AML cell lines[7]
- Preclinical *ex vivo* studies show a decrease in CD123-positive AML blasts upon exposure to SAR443579[7]
- Early clinical results of SAR443579 tested as monotherapy in patients with relapsed/refractory AML (NCT05086315) demonstrated a manageable toxicity profile at doses up to 6.0 mg/kg/infusion and complete response (CR or CRi) in 5 of 15 (33%) patients treated at the maximum target dose of 1.0 mg/kg/infusion, with durable responses (>10 months) in over half of responders[11,12]
- *In vitro* studies underscore the potential for VEN to enhance NK-mediated killing of AML by modulating the NKG2D pathway[13]
- The ability of NKCEs to mediate their therapeutic effects may rely on a sufficient pool of functional immune cells to clear malignant cells. Importantly, no changes in the abundance of peripheral NK cells were observed in patients with AML who received short-term treatment with VEN[14]
- Here, we describe the design of a sub-study of a Phase 1/2, randomized, open-label, multi-cohort, multicenter trial (NCT06508489) evaluating SAR443579 in combination with different agents for treatment of adult patients with CD123-expressing hematologic malignancies. The objective of this sub-study is to assess the safety, tolerability, and preliminary efficacy of SAR443579 in combination with VEN/AZA in patients with ND-AML who are ineligible for IC

METHODS

Study Design and Treatments

- Described here is sub-study 1 of the Phase 1/2 trial. Sub-study 1 will investigate SAR443579 in combination with VEN/AZA in adult patients with CD123-expressing ND-AML who are ineligible for IC in 3 parts:
  - Part 1: Dose finding (**Figure 2**)
    - Dose escalation will proceed according to the incidence of dose-limiting toxicities (DLTs)
  - Part 2: Dose optimization
  - Part 3: Dose expansion
- SAR443579 will be administered intravenously (IV) at the initial dose level weekly for induction and every 4 weeks for maintenance
- Oral VEN and IV or subcutaneous AZA will be administered at the recommended doses
- Duration of each treatment cycle will be 28 days
- Treatment will continue until disease progression, treatment discontinuation, unacceptable toxicity, or maximum number of treatment cycles permitted
- Approximately 9–18 patients will be enrolled in the dose escalation portion of the study, which is expected to last approximately 5 years with a follow-up period of 2 years after treatment

Figure 2: Trial Design (Part 1: Dose Finding)



A cycle duration is 28 days.
AML, acute myeloid leukemia; CD, cluster of differentiation; ECOG PS, Eastern Cooperative Oncology Group performance status; IC, intensive chemotherapy; IV, intravenous; PO, oral; QD, once daily; QW, once weekly; Q4W, once every 4 weeks; SC, subcutaneous.

TRIAL POPULATION

Table 1: Key Inclusion Criteria

- Aged ≥18 years
- Confirmed diagnosis of CD123-expressing AML who are ineligible for IC as defined by the following criteria:
  - Patients aged ≥75 years OR
  - Patients aged 18–74 years meeting at least one of the following:
    1. ECOG PS 2–3
    2. Cardiac history of CHF requiring treatment, LVEF of ≤50%, or confirmed symptomatic coronary heart disease
    3. DCLO ≤65% or FEV_1 ≤65%
    4. Creatinine clearance ≥30 to ≤45 mL/min
    5. Moderate hepatic impairment with total bilirubin >1.5 to ≤3.0 x ULN
- ECOG PS
  - ≤2 for patients aged ≥75 years
  - ≤3 for patients aged 18–74 years
- Adequate renal function for patients aged ≥75 years
- Patients with adequate liver function
  - 18–74 years: AST ≤3.0 x ULN, ALT ≤3.0 x ULN, bilirubin ≤3.0 x ULN, unless due to leukemic organ involvement <5 x ULN
  - ≥75 years: AST ≤1.5 x ULN, ALT ≤3.0 x ULN, bilirubin ≤3.0 x ULN, unless due to leukemic organ involvement <5 x ULN

ALT, alanine aminotransferase; AML, acute myeloid leukemia; AST, aspartate aminotransferase; CD, cluster of differentiation; CHF, congestive heart failure; DCLO, diffusing capacity of the lungs for carbon monoxide; ECOG PS, Eastern Cooperative Oncology Group performance status; FEV_1, forced expiratory volume in 1 second; IC, intensive chemotherapy; LVEF, left ventricular ejection fraction; ULN, upper limit of normal.

Table 2: Key Exclusion Criteria

- Patients with a diagnosis of APL
- Cardiovascular disease of NYHA Class ≥2
- Malabsorption syndrome or other condition that precludes enteral route of administration
- Known active CNS involvement with AML upon enrollment
- QTc interval exceeding 470 msec
- Received at least one of the following:
  - A hypomethylating agent, venetoclax and/or chemotherapeutic agents, or other experimental therapies for AML
  - Strong or moderate CYP3A inducers 7 days prior to the initiation of study treatment
- Uncontrolled medical conditions
- Known second malignancy either progressing or requiring active treatment within the last 3 years (with exceptions)
- AIDS-related illness or HIV requiring antiretroviral treatment, hepatitis B or C, or SARS-CoV-2 infection (with exceptions)
- Autoimmune disease requiring systemic treatment in the past 2 years
- Predicted life expectancy of ≤3 months
- Medical conditions requiring treatment with medications with a narrow therapeutic index that are substrates of CYP enzymes and that cannot be closely monitored to allow for dose adjustment
- Ongoing adverse events of NCI CTCAE (v5.0) grade 2 severity or higher caused by prior anticancer therapy

AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; CNS, central nervous system; CYP, cytochrome P450; HIV, human immunodeficiency virus; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NYHA, New York Heart Association; QTc, heart rate–corrected QT interval; v, version.

ENDPOINTS

- The primary endpoint of Part 1 (dose escalation) is to establish the initial preliminary recommended dose for optimization of SAR443579 when combined with VEN/AZA by measuring the incidence of DLTs
- Part 2 will determine the recommended dose for expansion of SAR443579 with VEN/AZA by assessing overall safety and preliminary anti-tumor activity
- Part 3 will assess the anti-tumor activity of SAR443579 at the identified recommended dose for expansion with VEN/AZA by measuring the CR rate
- Secondary endpoints include the following:
  - Number of patients with treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), adverse events of special interest (AESIs), and laboratory abnormalities
  - Transfusion independence rate after treatment with SAR443579 in combination with VEN/AZA
  - Incidence of anti-drug antibody
  - Percentage of patients with minimal residual disease after achieving CR, CRh (CR with partial hematologic recovery), or CRi
  - Composite complete remission (CRc), ORR, alternative CR rate, event-free survival, OS, time to treatment failure
  - Duration of CR, CRc, overall response, alternative CR rate
  - Hematopoietic stem cell transplantation rate
  - Evaluation of pharmacokinetics parameters
  - Additional parameters of anticancer activity

SUMMARY

- We describe a Phase 1/2 trial (NCT06508489) investigating the safety, tolerability, and preliminary efficacy of SAR443579 administered in combination with VEN/AZA in patients with CD123-expressing ND-AML who are ineligible for IC
- The trial is currently open for enrollment in Australia and the United States and is recruiting patients

ACKNOWLEDGMENTS:
The authors thank the participating patients and their families, the study centers, and the investigators for their contributions to the study. This study was funded by Sanofi.
Medical writing support, under the direction of the authors, was provided by Sara Edwards, PhD, and Taryn Morash, PhD, of Envision Pharma Group, funded by Sanofi.

Poster presented at the 66th Annual Meeting of the American Society of Hematology (ASH); Dec 7-10, 2024; San Diego, CA

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