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A Phase 1b/2 Study of Pivekimab Sunirine (PVEK, IMGN632) in Combination With Venetoclax/Azacitidine or Magrolimab for Patients With CD123-Positive Acute Myeloid Leukemia (AML)

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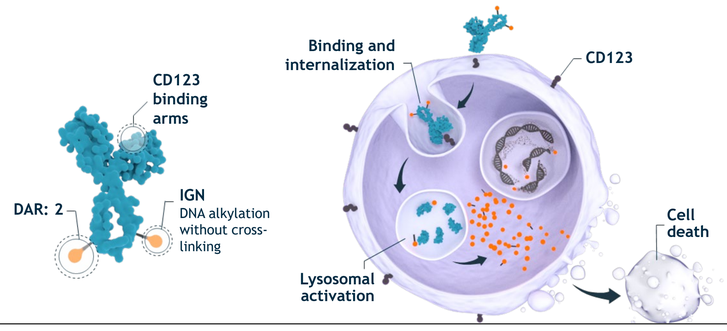
BACKGROUND

- Despite improved outcomes with azacitidine (AZA) and venetoclax (VEN) in frontline unfit AML (CR 37% and CR/CRi 66%), long-term survival remains inadequate (mOS, <15 mo)[1]
- CD123 is expressed on most AML blasts and leukemic stem cells (LSCs) while being minimally expressed on normal hematopoietic stem cells[2]
- Preclinical data have demonstrated the therapeutic synergy of PVEK combined with AZA and VEN, including in AZA/VEN-resistant murine AML models[3]
- Clinical data reported at ASH 2022 (Daver et al.) in relapsed/refractory (R/R) AML supported the continued clinical exploration of triplet therapy with PVEK+AZA+VEN[4,5]
  - Expansion cohorts (Regimen C; Cohorts 1 and 2) in frontline AML will evaluate antileukemic activity and MRD levels with the combination of PVEK+AZA+VEN[6]
- An earlier phase 1 study of patients with R/R AML who received magrolimab monotherapy at doses up to 30 mg/kg twice weekly found that magrolimab was well tolerated, with no DLTs or an MTD observed[7]
  - An expansion cohort (Regimen E) in R/R AML will evaluate the safety and antileukemic activity of PVEK+magrolimab[6]

Mechanism of Action: PVEK and Magrolimab

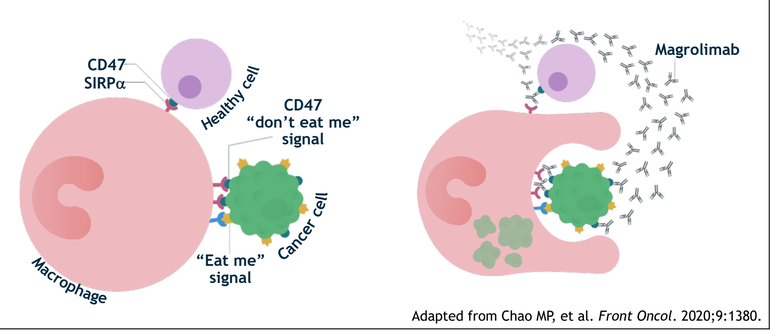
PVEK Structure and MOA[2,8]

- PVEK is a first-in-class antibody-drug conjugate (ADC) comprising a high-affinity CD123 antibody, cleavable linker, and an indolinobenzodiazepine pseudodimer (IGN) payload
- The IGN payload alkylates DNA and causes single-strand breaks without crosslinking. IGNs are designed to have high potency against cancer cells, while demonstrating less toxicity to normal marrow progenitors compared with other DNA-targeting payloads



Magrolimab MOA[9,10]

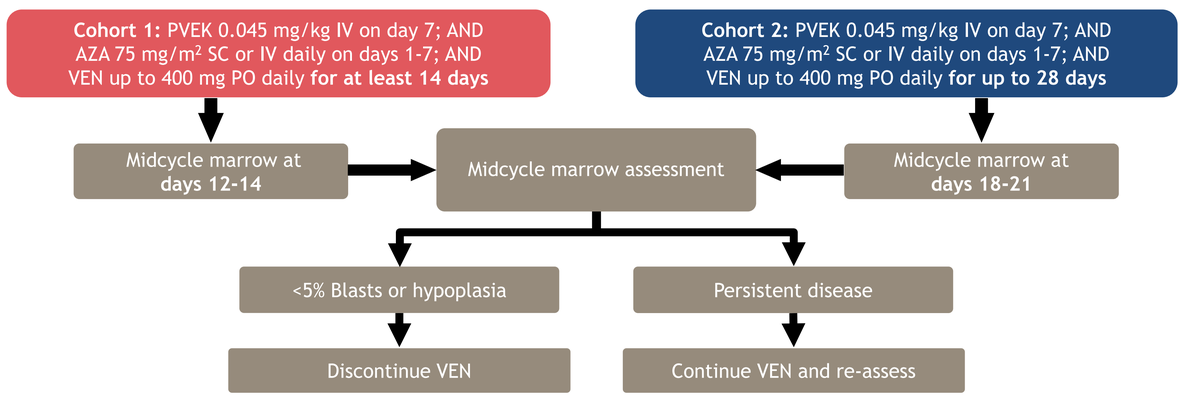
- Magrolimab is a monoclonal antibody that blocks the interaction between cell surface molecules CD47 and SIRPα, an interaction that normally prevents phagocytic elimination by providing a "don't eat me" signal
- CD47 expression is increased on some cancer cells, including AML LSCs
- Blockade of CD47 and the "don't eat me" signal by magrolimab has been shown to increase phagocytosis and reduce the frequency of cancer cells that overexpress CD47 or would be progeny from LSCs that overexpress CD47



Adapted from Chao MP, et al. *Front Oncol*. 2020;9:1380.

Cohort Design: PVEK+AZA+VEN Triplet (Regimen C)

PVEK+AZA+VEN Expansion Cohorts in Frontline AML; Phase 2[6]



- This is an open-label, multicenter, phase 1b/2 study of PVEK administered in combination regimens in patients with frontline CD123+ AML (NCT04086264)[5]
- Patients will receive the established recommended phase 2 dose (RP2D) of PVEK 0.045 mg/kg IV, as a <30-minute outpatient infusion[6]

Eligibility Criteria, Objectives, and Endpoints

Key Eligibility Criteria[5,6,a]

- Adults with newly diagnosed AML who are unfit for intensive induction therapy and appropriate for experimental therapy
- CD123+ AML as confirmed by local flow cytometry or IHC
- Patients with prior MPN-related secondary AML, active CNS AML, or prior use of hypomethylating agents for MDS are excluded

[a]List of eligibility criteria is not comprehensive.

Primary Objectives/Endpoints[5,6]

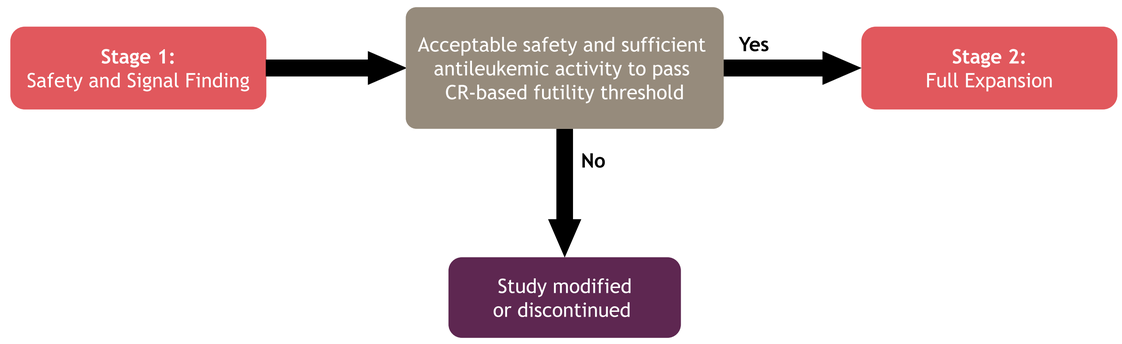
- Evaluate the antileukemic activity of PVEK when administered in combination with AZA and VEN in patients with untreated AML, as assessed by composite CR rate, overall response rate (ORR), and duration of remission (DOR)
- Assess MRD levels using central flow cytometry

Key Secondary Objectives/Endpoints[5,6]

- Safety and tolerability (TEAEs)
- PK parameters (C_{max}, AUC)
- Immunogenicity (including the presence of antidrug antibodies)

Cohort Design: PVEK+Magrolimab Doublet (Regimen E)

PVEK+Magrolimab Expansion Cohort in R/R AML; Phase 2[6]



- The Regimen E arm of the study is an open-label multicenter investigation of PVEK administered in combination with magrolimab in patients with R/R CD123+ AML[6]
- Patients with R/R AML will receive PVEK IV on a dose-escalation schedule on day 1 of 28-day cycles in combination with magrolimab at 30 mg/kg every 2 weeks, after the standard ramp up schedule[6]

Eligibility Criteria, Objectives, and Endpoints

Key Eligibility Criteria[5,6,a]

- Adults with R/R CD123+ AML
- CD123+ AML as confirmed by local flow cytometry or IHC
- Hemoglobin ≥9 g/dL prior to initial dose of magrolimab
  - Transfusions are allowed to meet hemoglobin eligibility
- Pretreatment blood cross-match must be completed
- Patients who have been previously treated with a CD47- or SIRPα-targeting agent or have been previously enrolled in a magrolimab clinical study will be excluded

[a]List of eligibility criteria is not comprehensive.

Primary Objectives/Endpoints[6]

- Safety phase: evaluate DLTs with PVEK in combination with magrolimab
- Expansion phase: evaluate antileukemic activity (composite CR rate, ORR, duration of CR)
  - Including assessment of patients with prior VEN exposure

Key Secondary Objectives/Endpoints[6]

- Safety and tolerability (TEAEs)
- PVEK PK parameters (C_{max}, AUC)
- Immunogenicity (including the presence of antidrug antibodies)

802 Trial Status (PVEK+AZA+VEN Triplet and PVEK+Magrolimab Doublet Regimens)

- The PVEK+AZA+VEN triplet (Regimen C) is currently enrolling patients with frontline unfit AML across 29 sites in France, Germany, Italy, Spain, UK, and US
- The PVEK+magrolimab doublet (Regimen E) is planned to be open for enrollment mid-2023 at US sites
- This study is registered as ClinicalTrials.gov identifier: NCT04086264[5]
- For more information please contact: medicalinformation@immunogen.com

Abbreviations: ADC, antibody-drug conjugate; AE, adverse event; AML, acute myeloid leukemia; ASH, American Society of Hematology; AUC, area under the time-concentration curve; AZA, azacitidine; CD, cluster of differentiation; C_{max}, maximum plasma concentration; CNS, central nervous system; CR, complete remission; CRi, complete remission with incomplete recovery; DAR, drug to antibody ratio; DLTs, dose-limiting toxicities; DNA, deoxyribonucleic acid; DOR, duration of remission; IGN, indolinobenzodiazepine pseudodimer; IHC, immunohistochemistry; IV, intravenously; LSCs, leukemic stem cells; MDS, myelodysplastic syndromes; MOA, mechanism of action; mOS, median overall survival; MPN, myeloproliferative neoplasm; MRD, minimal residual disease; MTD, maximum tolerated dose; ORR, overall response rate; PK, pharmacokinetic; PO, given by mouth; PVEK, pivekimab sunirine; RP2D, recommended phase 2 dose; R/R, relapsed/refractory; SC, subcutaneously; SIRPα, signal regulatory protein α; TEAEs, treatment-emergent adverse events; VEN, venetoclax.

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