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 (CR37% and CR/CRi66%), long-term survival remains inadequate (moS, ~15 mo)
- CD123 is expressed on most AML blasts and leukemic stem cells (LSCs) while being minimally expressed on normal hematopoietic stem cells
- Preclinical data have demonstrated the therapeutic synergy of PVEK combined with AZA and VEN, including in AZA/VEN-resistant murine AML models
- Clinical data reported at ASH 2022 (Davet et al.) in relapsed/refractory (R/R) AML supported the continued clinical exploration of triplet therapy with PVEK+AZA+VEN
- 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
- 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 MTD observed

Mechanism of Action: PVEK and Magrolimab

PVEK Structure and MOA1,2

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

Magrolimab MOA3,4

- 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 shown antileukemic activity, and upregulation of the frequency of cancer cells that overexpress CD47 or would be progeny from LSCs that overexpress CD47

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

PVEK+AZA+VEN Expansion Cohort in Frontline AML: Phase 2

Stage 1: Safety and Signal Finding

Acceptable safety and sufficient antileukemic activity to pass CR-based futility threshold

Stage 2: Full Expansion

- 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 to 30 mg/kg every 2 weeks, after the standard ramp up schedule

Eligibility Criteria, Objectives, and Endpoints

Key Eligibility Criteria1-4

- 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

Key Secondary Objectives/Endpoints1-4

- Patients with 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

Key Objectives/Endpoints1-4

- Evaluation of 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

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

For more information please contact: medicalinformation@immunogen.com

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Abstract TPS7073

American Society of Clinical Oncology 2023 Annual Meeting; June 2-6, 2023; Chicago, Illinois

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Acknowledgements: Studies described herein were sponsored by Immunogen, Inc. The authors would like to especially thank the patients who consented to be included in these trials, as well as their families. Editorial assistance and writing support in the preparation of this poster were provided by PRECISIONscientia, funded by Immunogen, Inc.


Abbreviations: ADC, antibody-drug conjugate; AE, adverse event; AML, acute myeloid leukemia; ASH, American Society of Hematology; AUC, area under the time-concentration curve; ASO4, asparaginase; CD, cluster of differentiation; Cmax, maximum plasma concentration; CHO, Chinese hamster ovary cells; CR, complete remission; CRi, complete remission with incomplete recovery; DAR, drug to antibody ratio; DOR, duration of remission; DLTs, dose-limiting toxicities; DNA, deoxyribonucleic acid; DOR, duration of remission; IGN, indolinobenzodiazepine pseudodimer; IHC, immunohistochemistry; IV, intravenously; LSC, leukemic stem cells; MDS, myelodysplastic syndromes; MRD, minimal residual disease; ORR, overall response rate; PK, pharmacokinetics; PVEK, phase 1 clinical trial; RCC, renal cell carcinoma; R/R, relapsed/refractory; SC, subcutaneously; SIRP, signal regulatory protein α; TEA, treatment-emergent adverse event; VEN, venetoclax.