Phase 1 Study of VIP943, an Anti-CD123 Antibody Drug Conjugate, in Patients with CD123+ Hematologic Malignancies: Trial in Progress

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BACKGROUND AND RATIONALE

VIP943 is a novel anti-CD123 antibody drug conjugate (ADC), binding to the IL3Ra chain (CD123). VIP943 combines the new payload class of kinesin spindle protein inhibitors (KSPi) with a novel legumain-cleavable linker, which is specifically cleaved in the lysosome and required to activate the payload. KSP inhibition results in the formation of characteristic monopolar spindles (monoasters) and subsequent mitotic catastrophe. Consequently, KSPi selectively acts on cells undergoing cell division. KSPi is a mitosis-specific drug optimized for significant retention in the tumor cell resulting in a favorable efficacy and safety profile[1, 2, 3].

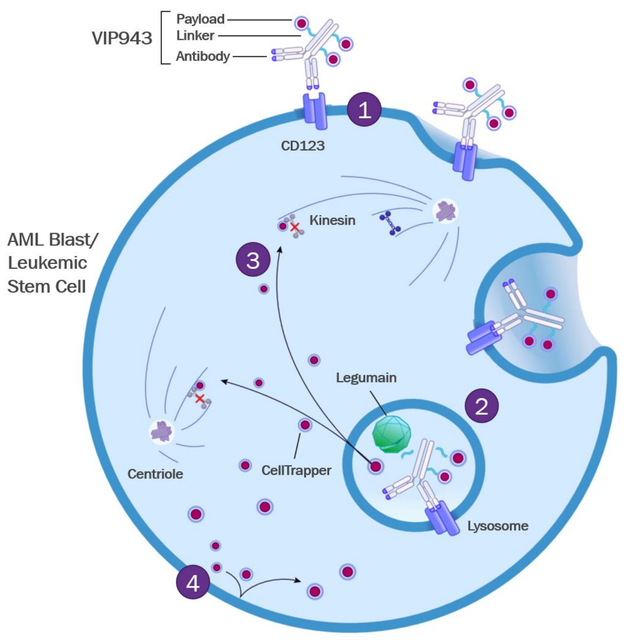


Figure 1. VIP943 mode of action.

1) The anti-CD123 mAb of the VIP943 ADC binds to the CD123 surface protein, a validated target in myeloid malignancies and a potential leukemic stem cell target.
2) VIP943 is internalized upon binding to CD123 and delivered to the lysosomes of the cancer cell. Here, legumain cleaves the linker and releases the KSPi payload.
3) KSPi inhibits the kinesin spindle protein and prevents the formation of the mitotic spindle, leading to mitotic catastrophe and cell death.
4) The CellTrapper™ modification of the KSPi payload prevents efflux of the KSPi, allowing for intracellular accumulation and preventing off-target activity of the payload after cell death.

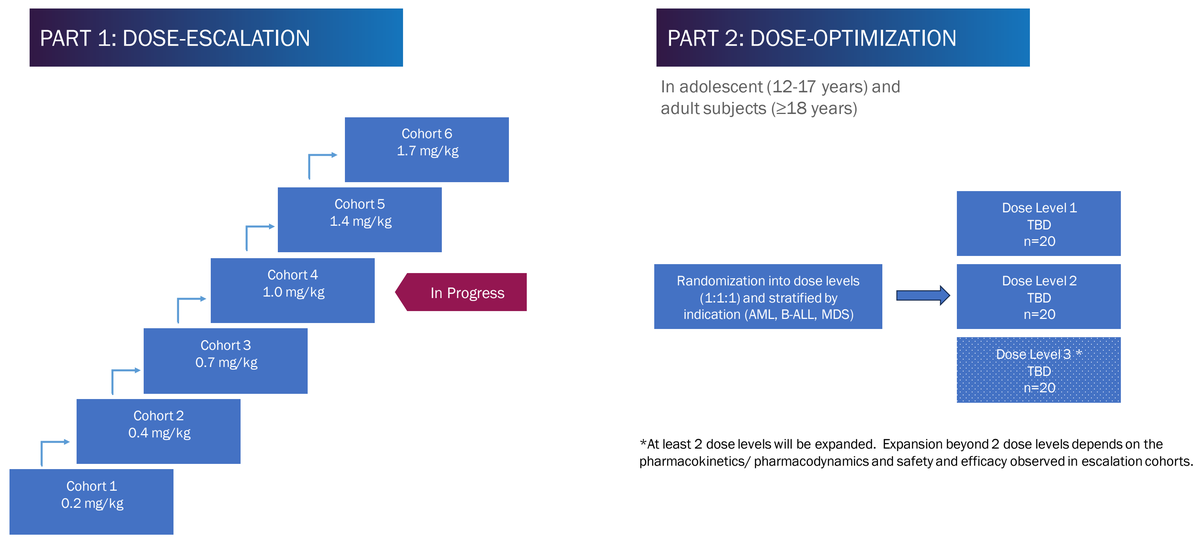
STUDY OBJECTIVES

PRIMARY	• For dose-escalation, to determine the maximum tolerated dose, if possible, or minimum optimal biologic dose, and evaluate the safety and tolerability of VIP943 in subjects with advanced CD123+ hematologic malignancies. • For dose optimization, to determine a recommended dose range (RDR) for Phase 2 in subjects with advanced CD123+ hematologic malignancies.
SECONDARY	• To evaluate anticancer activity by standard response criteria[3,4] • To assess duration of response (DOR), event-free survival (EFS), and progression-free survival (PFS). • To assess the pharmacokinetics (PK) of VIP943, total antibody, and payload. • To assess immunogenicity profile of VIP943 including development of neutralizing antidrug antibodies.
EXPLORATORY	• Evaluate the pharmacodynamic (PD) effect of VIP943 target engagement and/or payload activity. • Evaluate the effect of VIP943 on persistence, expansion or clearance of disease-specific tumor clones. • Evaluate PD effect of VIP943 on immune cell types including CD123 expressing cells. • Evaluate CD123 expression level as a potential selection biomarker for VIP943 treatment. • Evaluation of measurable residual disease (uMRD), as appropriate.

STUDY DESIGN

- This trial in progress is an open-label, multicenter Phase 1 study to characterize safety, tolerability, preliminary antitumor activity, PK, and PD of VIP943 monotherapy in subjects with advanced CD123+ hematologic malignancies specifically acute myeloid leukemia (AML), myelodysplastic syndromes (MDS) and B-cell acute lymphoblastic leukemia (B-ALL).
- Subjects are eligible if the cancer has progressed or was nonresponsive to all available curative therapies or if available therapy was declined due to medical inappropriateness or subject choice.
- Frequency, severity, and relationship to study drug of any treatment-emergent adverse events or abnormalities of laboratory tests will be studied.
- VIP943 is given as 1-hour intravenous infusions weekly. Each cycle is 28 days.

DOSING SCHEMA



*At least 2 dose levels will be expanded. Expansion beyond 2 dose levels depends on the pharmacokinetics/ pharmacodynamics and safety and efficacy observed in escalation cohorts.

STUDY SITES

Country	Site	Patients Dosed
USA	Sarah Cannon Research Institute, Nashville, TN	4
	University of Cincinnati, OH	3
	MD Anderson, Houston, TX	2
	University of Alabama at Birmingham, AL	1
	Fred Hutchinson Cancer Center, Seattle, WA	1

REFERENCES

1. Kirchhoff et al, Cancers 2020
2. Stelte-Ludwig et al, AACR Annual Meeting, 2024
3. Stelte-Ludwig et al, ASH Annual Meeting, 2023
4. Dohner et al, Blood, 2022
5. Zeidan et al, Blood, 2023

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