Phase 1 Study of VIP236, a Small Molecule Drug Conjugate, in Patients with Advanced Cancer: Trial in Progress

#TPS3168

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BACKGROUND AND RATIONALE

VIP236, a first-in-class small molecule drug conjugate (SMDC), consists of an $\alpha_v\beta_3$ integrin small molecule binder, a peptide linker cleaved by neutrophil elastase (NE) in the tumor microenvironment (TME), and an optimized camptothecin (optCPT) payload VIP126, which was optimized for high permeability and low active efflux[1,2]. The overall drug design strategy for VIP236 is targeted delivery to the TME and tumors expressing $\alpha_v\beta_3$ integrin on their cell surface with release of the optCPT by NE also present in the TME. VIP126, when delivered as a component of VIP236, is anticipated to kill tumor cells while reducing detrimental effects to surrounding, normal tissue.

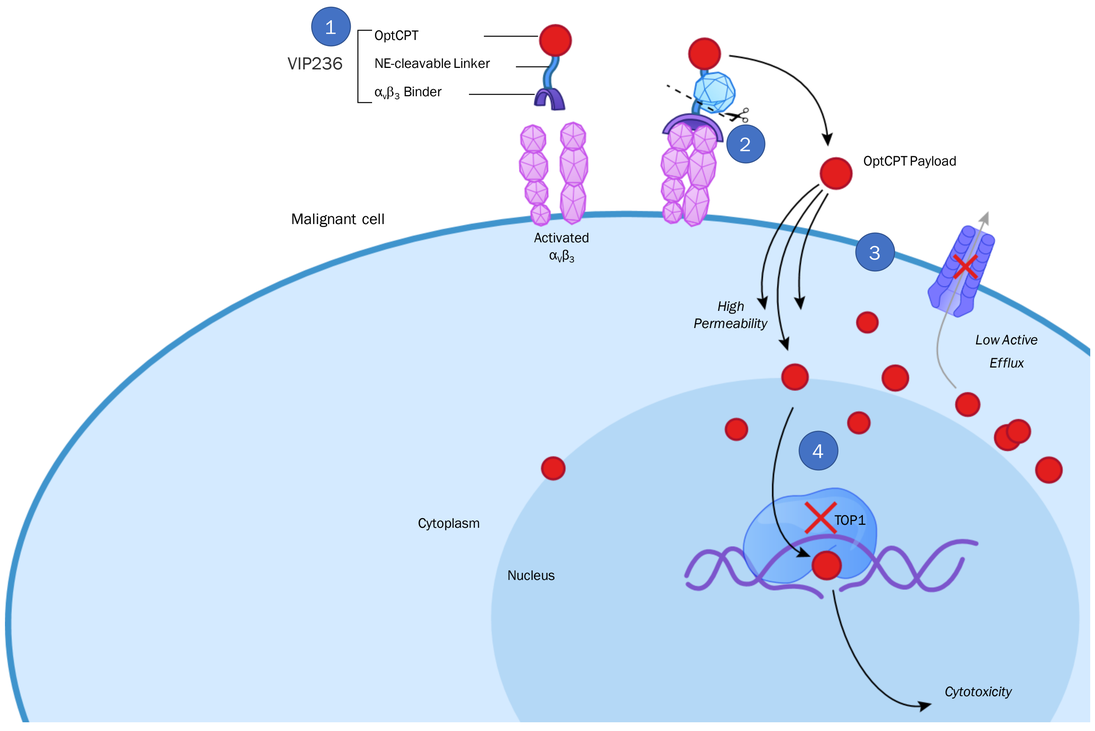

Figure 1. Mode of Action of VIP236.

1) VIP236 is an $\alpha_v\beta_3$ integrin binder linked to an optCPT payload.
2) NE in the tumor microenvironment specifically cleaves the linker releasing the payload.
3) OptCPT efficiently penetrates the cell membrane and accumulates in the tumor cell due to low active efflux (ie, resistance to drug transporters).
4) The payload then inhibits topoisomerase 1 causing DNA damage and leading to cytotoxicity.

STUDY OBJECTIVES

PRIMARY

- To determine the maximum tolerated dose (MTD), safety and tolerability of VIP236 in subjects with advanced cancer.

SECONDARY

- To evaluate tumor activity by standard response criteria for solid tumors using RECIST 1.1 criteria, including disease control rate (DCR), overall response rate (ORR), duration of response (DOR), and progression-free survival (PFS).
- To assess the pharmacokinetics (PK) of VIP236 and VIP126 (payload).

EXPLORATORY

- Evaluate the effect of VIP236 on circulating tumor DNA (ctDNA).
- Identify activated oncogenic pathways in tumor biopsies, ctDNA and/or blood samples.
- Effect of germline pharmacogenetics on the safety of VIP236.

STUDY DESIGN

- This trial in progress is an open-label, global, multicenter Phase 1 study to characterize safety, tolerability, preliminary antitumor activity and pharmacokinetics of VIP236 monotherapy in subjects with advanced cancer.
- Enrollment includes “all-comer” patients with histologically confirmed advanced or metastatic solid tumors that are relapsed or refractory to standard of care. Subjects must have exhausted all available standard therapies or be deemed ineligible for potential available therapies.
- Frequency, severity, and relationship to study drug of any treatment-emergent adverse events or abnormalities of laboratory tests will be studied.
- Tumor response will be assessed using RECIST 1.1 criteria.
- VIP236 is given as 1-hour intravenous infusions. Each cycle is 21 days.

DOSING SCHEMA

ORIGINAL DOSING SCHEDULE

- Dosing 2 days on/5 days off
- 5 total patients

Cohort 3a 0.40 mg/kg n=2
Cohort 2a 0.20 mg/kg n=2
Cohort 1 0.10 mg/kg n=1

CURRENT DOSING SCHEDULE

- Dosing once every 3 weeks
- 15 total patients

Cohort 8b TBD
Cohort 7b TBD
Cohort 6b 1.0mg/kg — In Progress
Cohort 5b 0.80mg/kg n=3
Cohort 4b 0.60 mg/kg n=3; Backfill Cohort 4b 0.60 mg/kg n=2
Cohort 3b 0.40 mg/kg n=3; Backfill Cohort 3b 0.40 mg/kg n=2
Cohort 2b 0.20 mg/kg n=2

STUDY SITES

Country	Site	Patients Dosed
USA	Honor Health, Scottsdale, AZ	5
	NEXT Austin, TX	6
	NEXT San Antonio, TX	5
Australia	Macquarie University, Macquarie Park, New South Wales	0
	ICON Brisbane, Queensland	2
	ICON Adelaide, Southern Australia	2

REFERENCES

1. Lerchen et al, Cancers **2022**, 14, 391.
2. Lerchen et al, Cancers **2023**, 15, 4381.

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