

Safety and efficacy of VIP152, a PTEFb / CDK9 inhibitor, in patients with double-hit lymphoma

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BACKGROUND

- Positive transcription elongation factor b (PTEFb) is composed of cyclin-dependent kinase 9 (CDK9) and cyclin T complex. It mediates transcription of short-lived anti-apoptotic survival proteins and oncogenes like myeloid leukemia cell differentiation protein-1 (MCL-1) and MYC, respectively, playing a critical role in a variety of cancers.
- VIP152 (formerly BAY 1251152), a potent and highly selective CDK9 inhibitor (Figure 1), has been evaluated in a Phase 1 dose-escalation study in patients with advanced cancer (NCT02635672).¹

Figure 1. Selectivity of VIP152

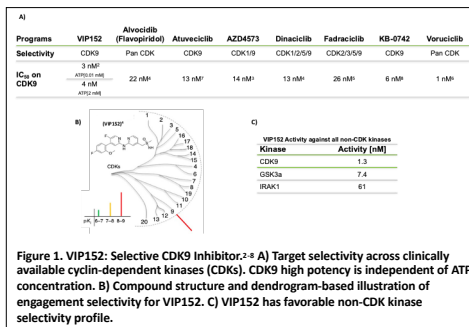


Figure 1. VIP152: Selective CDK9 Inhibitor.¹⁻³ A) Target selectivity across clinically available cyclin-dependent kinases (CDKs). CDK9 high potency is independent of CDK concentration. B) Compound structure and dendrogram-based illustration of engagement selectivity for VIP152. C) VIP152 has favorable non-CDK kinase selectivity profile.

- A maximum tolerated dose of 30 mg administered once weekly in consecutive 21-day cycles was established in a dose escalation first-in-human study in solid tumor and non-Hodgkin lymphoma subjects. Neutropenia was the dose-limiting toxicity.
- Early signs of clinical activity at higher dose levels were observed with durable disease control in individual patients with pancreatic cancer and salivary gland cancer (~10 and ~17 months of treatment, respectively).
- Of the 31 subjects dosed, a patient with double-hit lymphoma (DHL) from the 30-mg cohort achieved a complete metabolic response (CMR).
- DHL is defined as dual rearrangement of the MYC gene and either the B-cell lymphoma 2 (BCL2) or BCL6 genes.
- Resulting MYC and BCL2/BCL6 overexpression make DHL particularly difficult to treat, with no standard of care and poor prognosis.
- Considering the impact of CDK9 inhibition on MYC, an exploratory cohort of six patients with DHL was added to the Phase 1 study of VIP152.

METHODS

- VIP152 was administered once weekly as a 30-minute IV infusion on Days 1, 8 and 15 of a 21-day cycle.
- Tumor response was assessed according to the revised Cheson criteria.⁸

RESULTS

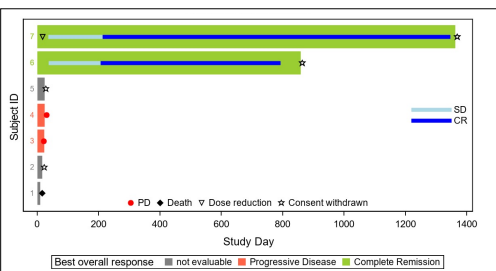
Patients and Treatment

- To date, 7 patients have been enrolled (including the first DHL patient from the dose escalation portion) and were evaluable at the time of data cutoff (24NOV2020) and are reported here.
- Baseline characteristics are presented in Table 1.
- All subjects received front-line R-CHOP or R-EPOCH. Two subjects had prior stem cell transplant. Additional therapies included: R-DHAP, R-GemOx, R-ICE and durvalumab.

Table 1. Baseline Characteristics

Characteristic	Total (n=7)
Female / Male n (%)	1 (14) / 6 (86)
Median age (range), years	70 (58-84)
ECOG PS 1 / 2, n (%)	5 (71) / 2 (29)
2 / ≥3 prior systemic chemotherapies, n (%)	4 (57) / 3 (43)
Refractory to last treatment, n (%)	3 (43)
Refractory to last CD20-containing therapy, n (%)	3 (43)
Bulky disease >5 cm	4 (57)
Ann Arbor stage III/IV at study entry, n (%)	6 (86)

Figure 2. Duration of Treatment



Subject 1: Cause of death was clinical disease progression; however, scans were not performed for response criteria determination.
 Subjects 2 and 5: Clinical progression and withdrawal by subject.
 Subjects 6 and 7: Withdrawal by subject to eliminate hospital visits during COVID conditions.

Safety

- Most common adverse events (AEs) were mostly of Grade 1 and Grade 2 severity.
- Two patients had a serious AE (Grade 3 syncope and Grade 3 tumor pain).
- Two patients had dosing held for an AE; however, no patient withdrew from treatment due to any AEs.
- Two subjects received supportive granulocyte colony stimulating factor.
- One death occurred due to clinical disease progression.

Table 2. Most Common Adverse Events

Adverse Events (>20%)	Grade 1	Grade 2	Grade 3	Grade 4	All (n=7)
Constipation	3 (43)	0	0	0	3 (43)
Fatigue	2 (29)	0	1 (14)	0	3 (43)
Nausea	1 (14)	2 (29)	0	0	3 (43)
Abdominal pain	1 (14)	1 (14)	0	0	2 (29)
Diarrhoea	1 (14)	1 (14)	0	0	2 (29)
Lymphocyte count decrease	0	0	1 (14)	1 (14)	2 (29)
Neutropenia	0	1 (14)	1 (14)	0	2 (29)
Skin infection	0	2 (29)	0	0	2 (29)
Tumor pain	0	0	2 (29)	0	2 (29)
Vomiting	1 (14)	1 (14)	0	0	2 (29)

Biomarkers and Efficacy

- Pharmacodynamic biomarker analysis showed significant reduction of MYC, PCNA, and MCL-1 mRNA in all patients across multiple timepoints (Figure 3).
- Antitumor activity consisted of 2 CMR in 7 patients (29%) based on investigator-assessed FDG-PET scans (Figure 4).
- Due to the COVID pandemic, the patients withdrew consent for treatment after 3.7 and 2.3 years, respectively, both in CMR.
- Local analysis of diagnostic tumor show that all 7 DHL patients are of the GCB subtype of DLBCL (Hans, IHC) and all 7 are positive for MYC and BCL2 (FISH).

Figure 3. Pharmacodynamic Biomarker Results

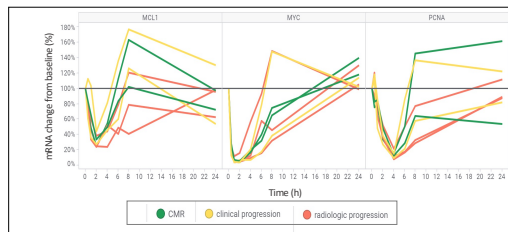
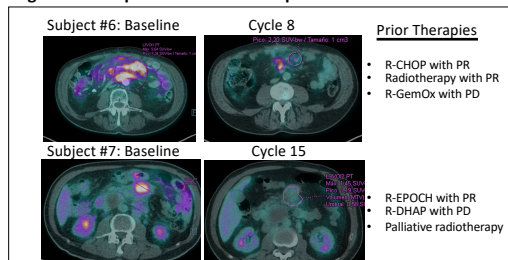
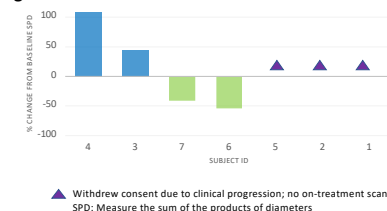


Figure 4. Complete Metabolic Responses



Presented at the 2021 ASCO Annual Meeting, June 4-8, 2021

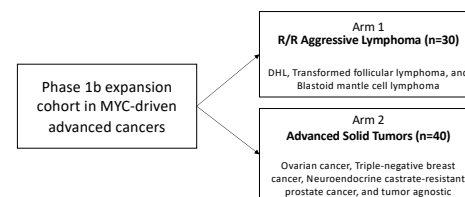
Figure 5. Waterfall Plot of Tumor Size



CONCLUSIONS

- VIP152 has a manageable safety profile, on-target pharmacodynamic activity, and signs of durable (3.7 and 2.3 years) complete metabolic responses (2 of 7) as monotherapy in patients with DHL.
- These encouraging results warrant further evaluation of VIP152 in patients with MYC-driven lymphoma and solid tumors.
- A Phase 1b expansion of the current study is underway (Figure 6).
- MYC-driven aberration can be translocation, overexpression, or genetically defined by Foundation One or similar panel.

Figure 6. Ongoing Phase 1b Expansion (NCT02635672)



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ACKNOWLEDGEMENTS

Vincex Pharma would like to thank the patients for their participation, Melanie Frigault, Hermes Garbán, Karen Green, Joy Greer, Xin Huang, Amy Johnson, and Buyue Yang for their contributions, and InSeption for their medical writing and design support.

Author disclosures were submitted directly to ASCO.

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