P1269 VIP152 IS A NOVEL CDK9 INHIBITOR WITH IMPROVED SELECTIVITY, TARGET MODULATION, AND CARDIAC SAFETY IN PATIENTS WITH LYMPHOMA

Topic: 20. Lymphoma Biology & Translational Research

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Background: Cyclin dependent kinase 9 (CDK9) controls transcriptional elongation, its inhibition may be effective in controlling cancer. To date, no drugs specifically targeting CDK9 have been approved due to challenges with therapeutic window. VIP152 was designed to be a highly potent and selective CDK9 inhibitor with favorable pharmacokinetic (PK) and pharmacodynamic (PD) effects to improve efficacy in patients with lymphoma.

Aims:

- To demonstrate the pharmacodynamic effects and safety profile associated with a selective CDK9 inhibitor with a favorable pharmacokinetic profile.
- To demonstrate the utility of a selective CDK9 inhibitor for treatment of hematologic patients with an unmet medical need such as high-grade B cell lymphoma (HGBL) and chronic lymphocytic leukemia who relapse or are refractory to ibrutinib and venetoclax (R/R CLL).

Methods: VIP152, fadraciclib, alvocidib (flavopiridol), KB-0742, and AZD4573 are evaluated in a CDK9/Cyclin T assay in the presence of low and high ATP and in a kinome scan at 1 µM. Differential expression (DE) analysis from VIP152, atuveciclib and KB-0742 treatment of 2 lymphoma cell lines by RNA seq is compared to DE of samples from 7 VIP152 treated HGBL patients. VIP152 cytotoxicity is evaluated in CRISPR/Cas9 edited HG-3 CLL cell line with homozygous TP53 edits R175H or R248Q, and in samples from 8 R/R CLL patients who relapsed or were refractory to ibrutinib and venetoclax.

Results: In the presence of low ATP, the IC50 for VIP152 is 4.5 nM where others have IC50s from 3.2-29.4 nM. With high ATP, VIP152, AZD4573 and alvocidib maintain potency in low nM range, while fadraciclib and KB-0742 have 760 nM-1.7 µM IC50s. The kinome scan shows VIP152, KB-0742 and fadraciclib have the least number of hits. Kd values show VIP152 is the most selective CDK9 inhibitor versus all other CDKs. In patients at the current clinical dose of 30 mg administered once weekly, the average VIP152 unbound plasma concentration over a 24h period is 18 nM. The VIP152 IC50 of 4.5 nM unbound is maintained for 15h indicating target coverage. VIP152 PK exposure is dose-linear and proportional with low intra/inter-subject variability. Analysis of triplicate ECG data from 58 solid and heme cancer patients demonstrates that VIP152 does not prolong QTc interval after single or multiple doses (5-30 mg). DE analysis of MYC+ DLBLC cell lines with VIP152, atuveciclib or KB-0742 1µM treatment indicate that 85%, 76% or 68% of DE genes are downregulated, respectively and only VIP152 and atuveciclib achieve significant DE of MYC. DE is reproducible in HGBL patients' whole blood at Cycle 1 Day 1 and Day 15 (r=0.9627) and findings will be validated in the ongoing clinical trial. VIP152 treatment demonstrates significant cytotoxicity in both WT and TP53 mutant CLL lines. R/R CLL samples treated with VIP152 showed a significant reduction in viability in a concentration-dependent manner.

Summary/Conclusion: VIP152 is a potent and selective CDK9 inhibitor currently in development with a favorable cardiac safety profile. PK/PD demonstrates unbound plasma concentrations exceed in vitro IC50. Selective transcriptional downregulation is observed with 30mg IV weekly. Samples from patients with DLBCL or CLL are sensitive to VIP152 and updated PK, PD and ctDNA dynamics from the ongoing phase 1 trials (NCT02635672).

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Abstract Book Citations: Authors, Title, HemaSphere, 2022;6:(S3):pages. The individual abstract DOIs can be found at https://journals.lww.com/hemasphere/pages/default.aspx.

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