VIP236: A small molecule drug conjugate with an optimized camptothecin payload has significant activity in patient-derived and metastatic cancer models

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INTRODUCTION

VIP236 is a small molecule drug conjugate comprised of an \( \text{casp} \), targetin motif linked to an optimized camptothecin (optiCPT) payload with a neurotrophin (NE) cleavable linker. \( \text{casp} \) has a history of pre-clinical and clinical trials for anti-angiogenic treatments and is under clinical investigation with a good safety record. With VIP236 the targeting of activated \( \text{casp} \) allows for potent homing to the tumor microenvironment, where the enriched NE cleaves the linker extracellularly and releases the optimized camptothecin payload. The payload is designed for rapid and efficient uptake into the tumor cell while at the same time addressing the transporter liabilities of the camptothecin payload resulting in a low efflux ratio. In the cell, the opCPT payload binds and inhibits DNA topoisomerase 1 (TOP1), leading to DNA damage and apoptosis.

We have previously shown that the high cytotoxicity of VIP236 in vitro depends on NE cleavage, and a high potency of VIP236 in several CDX models was achieved1,2. Here we demonstrate the efficacy of patient-derived titanium PXD models and further evaluate the mode of action.

RESULTS

Verification of \( \text{casp} \) and Neutratosin Elastase Presence in Patient Samples and Confirming Induced DNA Damage

Patient samples (50 each indication) were evaluated to confirm \( \text{casp} \) and neutrophil elastase expression in advance cancers, where clinical data indicates correlation of NE expression and poor prognosis. In some indications additional immunohistochemical staining of \( \text{casp} \) on the tumor cells was observed (e.g., renal). To confirm DNA damage conferred by VIP236-mediated TOP1 inhibition, tumors from the SNU162 CDX mouse model treated with VIP236 were stained for phosphorylated \( \gamma \text{H2AX} \) as a marker for DNA damage. A time-dependent \( \gamma \text{H2AX} \) phosphorylation was observed.

Evaluation of Orthotopic Metastatic TNBC PDx Models

Due to \( \text{casp} \) upregulation during metastasis formation, we specifically investigated the effect of VIP236 in an orthotopic TNBC metastasis model. The metastatic TNBC PDx model MA4296 derived from a relapsed/refractory patient was successfully treated with VIP236 achieving significant regression of the primary tumor (Fig 4A). In lung and brain tissue, a significant reduction of metastases was detected. In liver the effect of metastasis reduction was reduced, however metastasis formation was lower than in brain and lung (Fig 4B). Importantly IPC analysis reveals an increased \( \text{casp} \) and NE staining as consequence of treatment, while TOP1 staining was stable (Fig 4C-D).

CONCLUSIONS

In patient samples NE staining as well as \( \text{casp} \) staining on endothelial cells and in other indications could be confirmed, further confirming the potential of VIP236 as a pan-solid tumor agent in advanced and metastatic cancers.

Treatment dependent phosphorylation of \( \gamma \text{H2AX} \) as marker for DNA damage, verifies the on-target activity of the liberated opCPT payload derived from VIP236.

VIP236 monotherapy exhibits high potency in a broad panel of patient-derived mouse models with excellent tolerability. After treatment termination, a long duration of tumor growth inhibition is observed.

In the orthotopic metastatic breast cancer PDx model IPC analysis reveals an increase of \( \text{casp} \) and NE staining due to VIP236 treatment while TOP1 expression is stable. This could be a possible explanation for the durable anti-tumor efficacy (a positive feedback loop) and helps explain the no to slow regression of the tumor after the end of treatment.

Metastasis formation is successfully reduced in long tissue, but also in hard to target brain metastasis a significant reduction is measured. This observation could indicate blood brain barrier penetration of VIP236.

Superiority to fat-tissueabundant dermatoic and independent of HER2 expression of VIP236 is shown in a gastric PDx model and CDx models.

VIP236 is being evaluated in a first-in-human studies in subjects with advanced or metastatic solid tumors (NCT071288).

REFERENCES


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