VS-6063-104: A Phase 1 Dose Escalation Study of VS-5584, a Dual PI3K/mTOR Inhibitor, Administered with a Fixed Dose of VS-6063, a Focal Adhesion Kinase Inhibitor, in Subjects with Relapsed Malignant Mesothelioma

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BACKGROUND

Cancer Stem Cells (CSCs)

- CSCs are tumor cells resistant to standard therapies and capable of seeding new tumors
- CSC survival may result in tumor recurrence and metastasis
- SOC agents used for the treatment of malignant pleural mesothelioma (MPM) have been shown in pre-clinical models and clinical samples to increase the proportion of CSCs

VS-6063 (defactinib)

- Preferentially targets CSCs through the inhibition of focal adhesion kinase (FAK)
- PK and toxicity profile previously characterized in Phase 1 studies in advanced solid tumors

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VS-5584

- Preferentially targets CSCs through dual inhibition of PI3K & mTOR kinases
- Phase 1 evaluation in advanced solid tumors is ongoing

VS-6063 + VS-5584

- FAK & PI3K/mTOR inhibition may combine for more robust shut down of AKT survival signaling and reduction of CSCs **(see Fig 1)**
- Both FAK & PI3K/mTOR inhibitors have shown early signs of clinical activity in mesothelioma
- Pre-clinical studies show elimination of tumor initiating capability in mesothelioma cell lines using the VS-6063 + VS-5584 combination **(see Fig 2A)**, and enhanced efficacy of the combination over either single agent in reducing tumor burden in an orthotopic mesothelioma mouse model **(see Fig 2B)**
- Both agents are currently being evaluated in 3 clinical trials in mesothelioma, including VS-6063 as monotherapy for neo-adjuvant and maintenance Rx, and VS-6063 + VS-5584 combination for relapsed mesothelioma as described herein

FIGURE 1:
Signal Cross Talk Between FAK and PI3K/mTOR Pathways

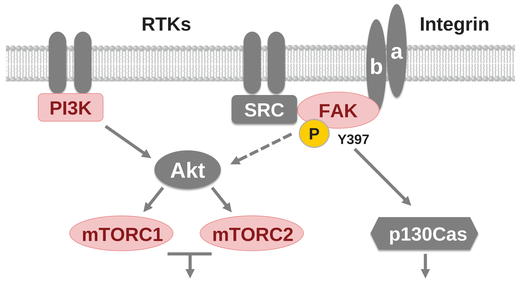
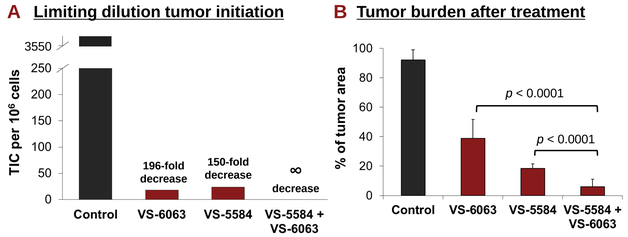


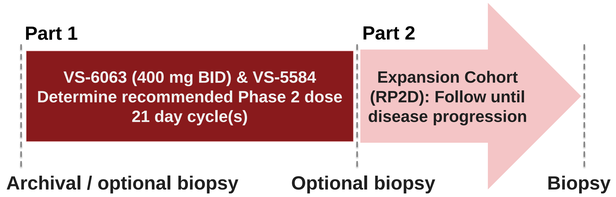
FIGURE 2:
VS-6063/VS-5584 Combination Shows Enhanced Preclinical Anti-CSC and Anti-Tumor Efficacy Compared with Single Agents



[A] H28 mesothelioma cells were treated with DMSO, VS-6063, VS-5584, or combination VS-6063 + VS-5584. Cells recovered after treatment were implanted into mice in limiting dilutions. Resulting tumor initiating frequency was measured. No tumors were initiated by cells treated with combination VS-6063 + VS-5584.

[B] Mice with orthotopic MM87 mesothelioma tumors were treated with DMSO, VS-6063, VS-5584, or combination VS-6063 + VS-5584. Two of 10 mice were tumor free in the VS-6063 + VS-5584 combination group. No tumor free mice were seen in the other groups.

STUDY DESIGN



- VS-5584 administered orally on an intermittent (3x weekly) dosing schedule
- VS-6063 administered orally 400 mg BID
- Escalating dose levels of VS-5584 will be studied in Part 1
- Up to an additional 20 evaluable patients will be enrolled in Part 2

OBJECTIVES

Primary Efficacy Objectives

- Determine MTD of VS-5584 when given with fixed dose of VS-6063
- Determine Recommended Phase 2 Dose (RP2D) and schedule of combination
- Assess safety and tolerability of the combination in relapsed mesothelioma

Secondary Efficacy Objectives

- Assess pharmacokinetics of VS-5584 and VS-6063 when co-administered

Exploratory Efficacy Objectives

- Response rate
- Duration of response
- Biomarker correlation with response
- Pharmacodynamics

ELIGIBILITY CRITERIA

Key Inclusion Criteria

- Histological proof of malignant mesothelioma (pleural or peritoneal)
- Relapsed disease following at least one prior line (≥3 cycles) of chemotherapy
- Evaluable or measurable disease as assessed by RECIST v1.1
- Archival tumor tissue or study-specific sample available for biomarker analysis
- KPS ≥70%

Key Exclusion Criteria

- Previous extra pleural pneumonectomy (EPP)
- History of upper GI bleed, ulceration or perforation
- Uncontrolled or severe concurrent medical condition (including uncontrolled brain metastases)
- Known history of stroke or cerebrovascular accident in prior 6 months
- Major surgery within 28 days
- Serious active infection

STUDY STATUS

- Currently enrolling across 4 sites in the United Kingdom and United States

SUMMARY

- VS-6063 (defactinib) is a potent, selective FAK kinase inhibitor
- VS-5584 is a potent, selective inhibitor of PI3K & mTORC1/2
- Both agents preferentially target CSCs and reduce bulk tumor growth in preclinical mesothelioma models
- Synergistic activity of VS-6063 & VS-5584 on CSCs & bulk tumor has been observed in preclinical models
- A Phase 1 combination study of VS-6063 & VS-5584 in patients with relapsed mesothelioma is ongoing

Clinical Trial Registry Number NCT02372227; Presented at the 2015 IASLC World Conference on Lung Cancer in Denver, Colorado USA

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