Determination of Biomarker Response in a Phase II Window of Opportunity Study of Defactinib (VS-6063), a Focal Adhesion Kinase (FAK) Inhibitor, in Patients with Resectable Malignant Pleural Mesothelioma

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Window of Opportunity Study in Surgically Resectable Mesothelioma

- Mesothelioma is highly lethal and without effective therapies for most patients
- Time to relapse after most standard therapies is measured in months
- We need to change strategies to be effective
- The neo-adjuvant or “window” setting prior to surgery offers a unique opportunity to rapidly examine the biological activity of novel drugs.
  - Similar approaches used successfully in Neoadjuvant breast studies (I-SPY)
Focal Adhesion Kinase (FAK) is Critical for Cancer Stem Cells

- Targeted deletion of FAK reduces tumor initiating capability
  
  *Luo et al, Cancer Res (2009) 69:466*

  ![Graph showing tumor size over days with and without FAK deletion.](image)

- FAK is a critical pathway for cancer stem cells and disease progression

  *Shibue et al, Cancer Discovery (2012) 2:706*

  ![Imaging and text showing cell mobility, proliferation, and tumor initiation](image)

FAK \[\rightarrow\] VS-6063 \[\rightarrow\] VS-4718

Integrins

\[\downarrow\]

FAK

p130Cas

Elimination of CSCs
Defactinib (VS-6063): Potent, Selective FAK Inhibitor

- Oral compound with good safety profile & initial signs of activity in Phase 1
- Reduces pFAK & CSCs in tumors from treated patients
- Currently under clinical investigation. Indications of interest:
  - Mesothelioma
    - Maintenance (COMMAND – ongoing)
    - Adjuvant (planned)
    - Window (ongoing)
  - NSCLC – Kras mutant (ongoing)
  - SCLC (proposed)
  - Ovarian (ongoing)
  - TNBC (proposed)
VS-6063-203 Study Objectives

• **Primary Objectives**
  – To assess biomarker responses in patient derived tumor and other surrogate tissues including but not limited to:
    • inhibition of phospho-FAK
    • changes in cancer stem cells and markers
    • alterations in markers of cell cycle and apoptosis

• **Secondary Objectives**
  – To evaluate the safety of defactinib in patients with malignant mesothelioma.
  – To evaluate the pharmacokinetics of defactinib in plasma of subjects with malignant mesothelioma.
  – To evaluate tumor response by PET/CT by RECIST modified for mesothelioma
VS-6063-203: “WINDOW” Study Design

- Preoperative patients receive defactinib (400 mg BID orally) for 12 days
- Pre- and post-treatment biopsies and PET/CT
- Surgical resection of tumor 30 days post last dose of defactinib
- Biopsies analyzed by immunohistochemistry, Next Gen Sequencing, and RNA seq.

Study Initiated in December, 2013
- 10 subjects enrolled to date. Plan to enroll up to 20-25 subjects
Eligibility Criteria

• Histologically confirmed malignant pleural mesothelioma that is not metastatic or unresectable.

• Participants are eligible to undergo excisional surgery such as extrapleural pneumonectomy (EPP) or pleurectomy/decortication (P/DC) or any other mesothelioma surgery.

• Localized disease. The malignancy is confined to one affected hemithorax. Mediastinal N2 lymph nodes via cervical mediastinoscopy or EBUS must be negative in order to be eligible.

• Normal pulmonary, cardiac function, renal, hepatic hematologic and performance functions.

• ECOG 0-1 or Karnofsky >80%

• Age ≥ 18 years of age
Exclusion Criteria

• Prior chemotherapy or radiotherapy for mesothelioma.

• History of upper gastrointestinal bleeding, ulceration, or perforation within 12 months prior to the first dose of study drug.

• Known history of stroke or cerebrovascular accident within 6 months prior to first dose of study drug.

• Known infection with HIV or AIDS

• Confirmed Hepatitis A, B or C.

• Active treatment for a secondary malignancy or any malignancy within the last 5 years (excluding superficial bladder cancer or non-melanoma skin cancer).

• Pregnant or breastfeeding.
Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>400 mg defactinib BID</th>
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<tbody>
<tr>
<td>Patients, n</td>
<td>10</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>8 (80.0%)</td>
</tr>
<tr>
<td>Female</td>
<td>2 (20.0%)</td>
</tr>
<tr>
<td>Median age, years (range)</td>
<td>71 (55-83)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
</tr>
<tr>
<td>Epithelial</td>
<td>4 (40.0%)</td>
</tr>
<tr>
<td>Biphasic</td>
<td>2 (20.0%)</td>
</tr>
<tr>
<td>Sarcomatoid</td>
<td>4 (40.0%)</td>
</tr>
<tr>
<td>ECOG PFS</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>7 (70.0%)</td>
</tr>
<tr>
<td>1</td>
<td>3 (30.0%)</td>
</tr>
</tbody>
</table>

VS-6063-203
## Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>400 mg defactinib BID (n=10)</th>
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</thead>
<tbody>
<tr>
<td>Bilirubin Increased</td>
<td>4 (40.0%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (20.0%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (20.0%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>2 (20.0%)</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>2 (20.0%)</td>
</tr>
<tr>
<td>Back Pain</td>
<td>2 (20.0%)</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (20.0%)</td>
</tr>
<tr>
<td>Abdominal Pain Upper</td>
<td>2 (20.0%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2 (20.0%)</td>
</tr>
</tbody>
</table>
VS-6063 (defactinib) inhibits FAK activity in mesothelioma biopsies

- VS-6063 treatment at Day12 [Core Needle Biopsy] was compared with Control [Surgical Biopsy at >30 days after VS-6063]
- Mean pFAK (Y397) reduced by 70% in the patients evaluated to date

VS-6063-203
VS-6063-203: Tumor CSC RNA Changes in Malignant Mesothelioma

- CD133 is reduced during VS-6063 treatment (post = Day 12) in 5 of 7 patient tumors
- Other CSC markers (CXCR2, SOX2, and POSTN) are also reduced during VS-6063 treatment
- These CSC markers, including CD133, are increased following pemetrexed-cisplatin chemotherapy (Paul Baas, iMIG presentation)
VS-6063-203: Encouraging Early Signal After 12 Days of Treatment

*Note PET/CT performed to guide biopsy and tumor response assessed using RECIST modified for mesothelioma

*Unlocked, in-progress data as of Aug 2014
Radiographic image of patient response

Patient: 01-005 (Epithelial MPM)

VS-6063-203
Pretreatment PETCT

Epithelial MPM

Post treatment PETCT

01-005

5.90mm

19.50mm

10.60mm

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2.20mm

11.70mm

8.30mm
Pre-treatment PETCT

Sarcomatoid MPM

Post treatment PETCT

01-001

Pretreatment PETCT

Post treatment PETCT

VS-6063-203
Pretreatment PETCT

Post treatment PETCT

Sarcomatoid MPM

01-004
Summary of Preliminary VS-6063-203 Study Data

- Defactinib was well tolerated with no apparent negative impact on surgical outcome
- Defactinib inhibits FAK activity
- Defactinib inhibits multiple CSC markers
- Intriguing signs of tumor reduction observed after 12 days of dosing following defactinib treatment
- Next steps
  - Increase of treatment period from 12 days to 35 days with surgery 7 days post-last dose.
  - Enrollment of an additional 10-15 subjects
  - Further analysis of additional stem cell markers and genomic profiling (DNA/RNA)

- Window studies prior to surgery are a viable opportunity to explore the biological activity of novel drugs in mesothelioma.