CANCER STEM CELL INHIBITORS VS-6063 (DEFACTINIB) & VS-5584 EXHIBIT SYNERGISTIC ANTICANCER ACTIVITY IN PRECLINICAL MODELS OF MESOTHELIOMA

MITCHELL KEEGAN, VP DEVELOPMENT
Developing Potential Treatment Options Throughout the Patient Journey

We want to maximize the potential treatment options for patients with mesothelioma

COMMAND 4-6cyc Pem/Cis → Treatment Holiday → 2nd Line Chemo or Clinical Trial

Window of Opportunity

Surgery

80% 20%

VS-6063+VS-5584 Relapsed or Refractory

Ongoing Planned

November 23, 2014

Novel Drugs Targeting Cancer Stem Cells
Profiles of VS-6063 & VS-5584

**VS-6063 (Defactinib)**

**FAK Kinase Inhibitor**

- Potent, selective inhibitor of FAK & PYK2 tyrosine kinases
- Preferentially targets Cancer Stem Cells (CSCs)
- Various clinical trials in progress

**VS-5584**

**PI3K/mTOR Kinase Inhibitor**

- Potent, selective inhibitor of PI3K & mTOR kinases
- Preferentially targets Cancer Stem Cells (CSCs)
- Phase I

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**PI3K/mTOR**

- RTKs
- PI3K
- T
- AKT
- mTORC1
- mTORC2
- Everolimus

Tumor cell/CSC survival & proliferation
Rationale: Combination of VS-6063 (FAK) with VS-5584 (PI3K/mTOR) for the Treatment of Relapsed/Refractory Mesothelioma

• Both VS-6063 & VS-5584 effectively target CSCs

• Pre-clinical models show synergy between VS-6063 and VS-5584

PI3K/mTOR dual inhibitor GDC-0980 showed 4 PRs among 33 mesothelioma patients in a phase 1 study  ECCO 2013

IC_{50} (nM)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Company</th>
<th>mTOR</th>
<th>PI3Kα</th>
<th>PI3Kβ</th>
<th>PI3Kγ</th>
<th>PI3Kδ</th>
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</thead>
<tbody>
<tr>
<td>VS-5584</td>
<td>Verastem</td>
<td>3.4</td>
<td>2.6</td>
<td>21</td>
<td>2.7</td>
<td>3.0</td>
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<td>GDC-0980</td>
<td>Genentech</td>
<td>5.5</td>
<td>6.6</td>
<td>31</td>
<td>6.5</td>
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</table>
Rationale for Combining VS-5584 with FAK inhibitor: Signal Cross Talk between FAK and PI3K/mTOR Pathways

- FAK & PI3K/mTOR inhibition may combine for more robust shut down of AKT survival signaling
VS-6063 Inhibits Tumor Initiation in Mouse Mesothelioma Models

<table>
<thead>
<tr>
<th>Mesothelioma cells</th>
<th>Drug Treatment</th>
<th>Functional Tests</th>
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</thead>
<tbody>
<tr>
<td>Control</td>
<td>VS-6063</td>
<td>Tumor Initiation in vivo</td>
</tr>
<tr>
<td>Pemetrexed</td>
<td>VS-6063+pemetrexed</td>
<td></td>
</tr>
</tbody>
</table>

**Graph**
- X-axis: Weeks
- Y-axis: Tumor free mice, %
- Legend:
  - Control
  - Pemetrexed
  - VS-6063
  - VS-6063+pemetrexed

**Table**
- Versus Drug Treatment
- Functional Tests

**Text**
- VS-6063 inhibits tumor initiation in mouse mesothelioma models.
- Drug treatment includes control, pemetrexed, VS-6063, and VS-6063+pemetrexed.
- Functional tests include tumor initiation in vivo.

**Diagram**
- Graph shows the percentage of tumor-free mice over weeks for different treatments.
- Control shows no significant change.
- Pemetrexed shows a decrease in tumor-free mice.
- VS-6063 shows a significant decrease in tumor-free mice.
- VS-6063+pemetrexed shows the most significant decrease in tumor-free mice.
Oral Administration of VS-6063 Targets Cancer Stem Cells in Mesothelioma Tumors Grown in Mouse Lungs

Control VS-6063 CSCs (ALDH+)

50 mg/kg, po BID x 2 wks

CSCs (% of total)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>VS-6063</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p&lt;0.05</td>
<td></td>
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</tbody>
</table>

DAPI

Novel Drugs Targeting Cancer Stem Cells

MM87 Xenograft Model
VS-5584 Preferentially Targets CSCs:
~ 70-Fold Reduction in Tumor Initiating Frequency in a SCLC model

Antitumor Efficacy  SP CSC Assay  Tumor Initiation

H841 SCLC model
VS-5584 and VS-6063 exhibit synergistic combination activity in mesothelioma cell lines \textit{in vitro}

**Combination Index Analysis**

VS-6063 + VS-5584
H2052 mesothelioma

VS-6063 + VS-5584
Mero-41 mesothelioma

**Highest Single Agent Analysis**

VS-5584 + VS-6063@1.11 \(\mu\)M

VS-6063 + VS-5584@0.041 \(\mu\)M

Novel Drugs Targeting Cancer Stem Cells
Enhanced Antitumor Efficacy of VS-5584 and VS-6063 Combination Compared to Single Agent in MM87 Mesothelioma *in vivo*

* VS-6063, 50 mg/kg, po bid; VS-5584, 20 mg/kg (MWF) for 2 weeks
* Mesothelioma tumors grown in lungs
* 2 out of 10 mice were tumor free in the VS-6063 and VS-5584 combination group. No tumor free mice in other groups

*J. Testa, Fox Chase*
Summary/Conclusions

• 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 also 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

• These data support a planned Phase I combination study of VS-6063 & VS-5583 in patients with relapsed/refractory mesothelioma
Acknowledgments

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