FAK INHIBITOR DEFACTINIB (VS-6063) TARGETS MESOTHELIOMA CANCER STEM CELLS

Rationale for maintenance therapy after conventional therapy

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Disclosure

- I am an employee and stockholder of Verastem Inc.
- I will be discussing investigational drugs
Focal Adhesion Kinase: Key roles in cancer stem cell biology & tumor microenvironment

**Focal Adhesion Kinase (FAK)**
- Non-receptor tyrosine kinase
- Mediates proliferation & survival signaling downstream of integrin & growth factor receptors
- Key roles in Cancer Stem Cell biology & stromal interactions

**Defactinib (VS-6063) – FAK inhibitor**
- Registration-directed trial in mesothelioma
- Phase 2 trial in mt Kras NSCLC
- Phase 1/2 combination trial with paclitaxel in ovarian cancer
Importance of targeting cancer stem cells for a durable response

Initial tumor

Pemetrexed + Platinum

Disease control but CSCs are enriched

VS-6063

More durable clinical response

Tumor recurrence

Theoretical result

Bulk tumor  Cancer stem cell (CSC)
Standard-of-care chemotherapy enriches cancer stem cells in both mesothelioma cell lines and patient tumors

**Mesothelioma CSCs in vitro**

*H2052 cell line*

- MPM cells treated with SOC chemotherapies are enriched for cancer stem cells

**Mesothelioma CSCs in vivo**

*Paired patient biopsies*

- Brown = ALDH+ (cancer stem cells)
  - Treatment of MPM tumors with SOC chemotherapy enriches cancer stem cells
12 day VS-6063 treatment reduces pFAK & CSC markers in tumors of mesothelioma patients

Phase 2 “Window of Opportunity”:

**Tumor pFAK**

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<thead>
<tr>
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<th>Control</th>
<th>VS-6063 Treatment</th>
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<tbody>
<tr>
<td>pFAK ELISA</td>
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<td>1</td>
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**Cancer Stem Cells (CXCR2+/CD133+)**

<table>
<thead>
<tr>
<th>Marker</th>
<th>RNA fold change</th>
<th>Decrease in CSC marker</th>
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<tbody>
<tr>
<td>CXCR2</td>
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</tr>
<tr>
<td>CD133</td>
<td>1.5</td>
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Change from baseline (normalized to 1) using matched samples from individual patients
Low merlin expression increases sensitivity to VS-6063 in mesothelioma models

Approximately 40-50% of mesothelioma tumors have low merlin

VS-6063 reduces CSCs & tumor-initiating potential in both merlin-low & merlin-high mesothelioma tumor models

**Merlin-high mesothelioma (H28)**

Treatment with VS-6063 reduces tumor initiating capability

**Merlin-low mesothelioma (MM87)**

Treatment with VS-6063 reduces tumor initiating capability and ALDH+ CSCs
FAK inhibitor extends duration of antitumor efficacy following standard of care chemotherapy in mesothelioma

**Modeling maintenance, mesothelioma PDX model**

Summary & conclusions

- FAK inhibitor defactinib (VS-6063) reduces bulk tumor growth, especially when expression of the tumor suppressor Merlin is low.
- Defactinib reduces tumor-initiating cells (CSCs) in both Merlin-low & Merlin-high mesothelioma preclinical models.
- In mesothelioma patients treated with defactinib (12 days), reduction of pFAK & CSC RNA markers was observed in tumors.
- FAK inhibitor treatment delayed tumor growth following cisplatin/pemetrexed treatment in a mesothelioma PDX model.

These data provide rationale for the current clinical testing of defactinib in a maintenance setting to potentially prolong response following front line chemotherapy in mesothelioma patients.

Pemetrexed & platinum enrich the proportion of CSCs in preclinical models & mesothelioma patient biopsies.

Initial tumor → Pemetrexed + Platinum → Disease control but CSCs are enriched → CSC-targeting agents (VS-6063) → More durable clinical response