FAK INHIBITOR VS-6063

NON-CONFIDENTIAL SUMMARY

NOVEMBER 2014
Verastem: Company Summary

• Verastem (VSTM) is a small publically traded Biotech company based in Boston, MA
  — ~40 employees

• Founded in 2010 by Bob Weinberg (MIT) & Eric Lander (Broad Institute)

• Focused on development of small molecule anticancer drugs that target Cancer Stem Cells (CSCs)

• Clinical programs:
  — Lead program: VS-6063 is a selective inhibitor of FAK & PYK2 protein kinases
    • Multiple phase 1 & 2 clinical trials in various solid tumor indications
  — VS-4718 is a structurally distinct backup FAK inhibitor (Phase 1)
  — VS-5584 is a selective dual PI3K/mTOR kinase inhibitor (Phase 1)
# Clinical Development of VS-6063

<table>
<thead>
<tr>
<th></th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Registration-Directed</th>
</tr>
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<tr>
<td><strong>VS-6063</strong></td>
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<tr>
<td>Mesothelioma</td>
<td><strong>COMMAND</strong> – Switch maintenance following front-line therapy</td>
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<tr>
<td>Mesothelioma</td>
<td>Window of opportunity</td>
<td></td>
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<tr>
<td>Mesothelioma</td>
<td>With VS-5584 in relapsed</td>
<td></td>
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<tr>
<td>Lung</td>
<td>KRASmt NSCLC</td>
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<td>Ovarian</td>
<td>In combo with paclitaxel</td>
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<tr>
<td>Ovarian</td>
<td>Window of opportunity</td>
<td></td>
<td></td>
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<tr>
<td>Breast</td>
<td>Neo-adjuvant in combination with paclitaxel</td>
<td></td>
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</tr>
</tbody>
</table>

**Ongoing**

**Planned**
Verastem Team

Executive Management

Robert Forrester
President/CEO, BOD
CEO/CFO, CombinatoRx/COLY
MeesPierson, Barclays, UBS

Christoph Westphal, M.D., Ph.D.
Executive Chairman of BOD, Cofounder
Cofounder/CEO: MNTA, ALNY, XLRN, SIRT, VSTM
Cofounder: Alnara (now Lilly), OvaScience (OVAS)

Jack Green
Chief Financial Officer
CFO, Genzyme Transgenics Corporation (GTC)

Joanna Horobin, M.B., Ch.B.
Chief Medical Officer
President/CEO, Syndax
10 marketed drugs (Taxotere®, Camptosar®)
Breakthrough designation for Entinostat

Jonathan Pachter, Ph.D.
VP, Head of Research
Head of Cancer Biology, OSI (now Astellas)
Schering-Plough (now Merck)

Daniel Paterson
Chief Business Officer
CEO: The DNA Repair Co. (now On-Q-ity)
PharMetrics (now IMS), Axion

Board of Directors

Timothy Barberich
Former CEO/Chair Sepracor (SEPR)

Henri Termeer
Lead Director
Former CEO/Chair Genzyme

Alison Lawton
Former Genzyme (now Sanofi)

Paul Friedman, M.D.
Former President/CEO Incyte (INCY)

Louise Phanstiel
BOD: Cedars Sinai, MYGN

Michael Kauffman, M.D., Ph.D.
CEO Karyopharm (KPTI), former CMO Onyx

Stephen Sherwin, M.D.
BOD: BIIB; NBIX, RIGL
Scientific Advisory Board

Robert Weinberg, Ph.D.
Whitehead Institute/MIT
Co-founder & Chairman of SAB

Peter Elliott, Ph.D.
Former SVP/Head – R & D, SIRT (now GSK)
Millennium (co-developed Velcade®)

Eric Lander, Ph.D.
Broad Institute/MIT/HMS
Pioneer of Human Genome Project

Richard Sackler, M.D.
Chairman – Purdue Pharma

Phil Sharp, Ph.D.
MIT – 1993 Nobel Prize in Medicine
Cofounder: Biogen, Alnylam; Sirtris SAB

Chris Walsh, Ph.D.
Harvard Medical School
Cofounder: Genzyme, Vicuron; Sirtris SAB

Joseph (Yossi) Schlessinger, Ph.D.
Yale Medical School
Cofounder: Sugen (Pfizer), Plexxikon (Daiichi-Sankyo)

Translational Research

José Baselga, M.D., Ph.D.
Physician in Chief; MSKCC
Senior Medical Advisor

George Daley, M.D., Ph.D.
Director – Stem Cell Program
Harvard Medical School/HHMI

Max Wicha, M.D.
Director – University of Michigan
Comprehensive Cancer Center

Eric Winer, M.D.
Director – Breast Oncology Center
Dana Farber Cancer Institute/HMS
Verastem Objectives for CRUK Combinations Alliance

• Combine VS-6063 with novel agents

• Some current combination interests with VS-6063
  – Immune Checkpoint Antibodies
    • Proprietary preclinical rationale can be supplied under confidentiality
  – Cdk4/6 inhibitors
    • NF2/Merlin is often lost along with INK4a (p16/ARF)
    • Rationale to target NF2 loss with VS-6063 & p16 loss with cdk4/6 inhibitor

• Open to additional novel combos with scientific rationale
FAK as a Cancer Target
FAK as an Anti-Cancer Target

- FAK (Focal Adhesion Kinase) is activated in response to Integrin and Growth Factor receptor stimulation
- FAK activation triggers signaling pathways essential for tumor cell proliferation, survival, migration, invasion, angiogenesis and resistance to chemo- & radiation therapy
- FAK inhibition blocks both primary tumor growth & metastasis

Brunton VG & Frame MC. *Curr Opin Pharmacol.* 2008;8:427
Schlaepfer DD et al. *Biochim Biophys Acta.* 2004;1692:77
# FAK is Highly Expressed in Advanced Stages of Cancer

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Normal</th>
<th>Benign</th>
<th>Pre-Invasive</th>
<th>Invasive</th>
<th>Metastatic</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid</td>
<td>+</td>
<td>+</td>
<td>+/++++</td>
<td>+++</td>
<td>+++</td>
<td>Ann Surg Oncol 3: 100, 1996.</td>
</tr>
<tr>
<td>Liver</td>
<td>-</td>
<td>+</td>
<td>+++</td>
<td></td>
<td>+/++++</td>
<td>Clin Cancer Res 10: 2812, 2004</td>
</tr>
</tbody>
</table>
High pFAK Correlates with Poor Prognosis in Ovarian Cancer

- High tumor FAK and pFAK expression correlate with poor survival (Sood et al., J Clin Invest 2010)
VS-6063 Selective FAK/PYK2 Inhibitor

VS-6063

- Lead FAK/PYK2 Inhibitor
- Oral compound with good safety profile & initial signs of activity in Phase 1
- USAN name: defactinib
- Orphan designation in US and EU for mesothelioma

FAK EC<sub>50</sub> = 15 nM
PYK2 EC<sub>50</sub> = 95 nM
**VS-6063 (Defactinib) Highlights**

- Good safety profile across several clinical trials
- Early signs of clinical activity
- Multi-national registration-directed Mesothelioma study in progress
  - Mesothelioma study targets maintenance setting where there are no existing options for patients
  - Orphan drug designation for Mesothelioma in US and EU
- VS-6063 can be combined with SoC chemotherapy (weekly paclitaxel)
- Most advanced FAK inhibitor in the clinic
**VS-6063 Development Rationale**

1. **Verastem research identified one potential patient selection/enrichment marker**
   - Tumors lacking Merlin (product of NF2 tumor suppressor gene) especially sensitive to FAK inhibitors (Shapiro Sci Trans Med 2014)
     - Merlin loss especially prevalent (~50%) in mesothelioma

2. **FAK inhibitors found to effectively target cancer stem cells (CSCs) across broad range of cancer types**
   - Standard of care (SoC) anticancer agents typically target bulk tumor, but fail to target cancer stem cells which drive tumor recurrence and metastasis
   - VS-6063 can potentially be used to target CSCs in combination with SoC agents for more durable clinical response

3. **VS-6063 can be combined with chemotherapy**
   - Phase 1 paclitaxel combo in ovarian cancer
     - No impact on paclitaxel pharmacokinetics in patients
     - Generally well tolerated with no dose limiting toxicities or exacerbation of paclitaxel related toxicities
Mesothelioma Rationale:

Loss of Merlin tumor suppressor may predict greater sensitivity to FAK inhibitor VS-6063
Low Merlin Expression Increases Sensitivity to VS-6063 in Mesothelioma Models In Vitro and In Vivo

Mesothelioma Cell Line Panel

VS-6063 inhibits Merlin-negative mesothelioma tumor growth in the lungs of treated mice

Approximately 50% of mesothelioma tumors have low Merlin

Merlin

Actin

Vehicle

VS-6063 50 mg/kg
FAK Inhibitor VS-6063 Preferentially Targets Cancer Stem Cells (CSCs)
What is a Cancer Stem Cell (CSC)?

• Tumors are heterogeneous in composition
  – Bulk tumor (may be effectively targeted by chemotherapy)
  – Cancer stem cells
    • Resistant to chemotherapy
    • Enriched by chemotherapy (clinically and preclinically)

• Cancer Stem Cells
  – Resistant to standard of care therapy
  – Functionally defined by their tumor-initiating capability
  – Mediate cancer recurrence & metastasis
  – May be identified by specific markers (e.g. ALDH; CD133; SOX2)

• Combinations are important to target both cancer stem cells (VS-6063) & bulk tumor for a more durable clinical response
**Targeting Cancer Stem Cells for a Durable Clinical Response**

**Problem:**
- Initial tumor
- Tumor reduction but CSCs survive
- Recurring tumor

**Current cancer treatments**

**Solution:**
- Initial tumor
- Tumor reduction and elimination of CSCs
- Durable clinical response

**CSC drugs + current cancer treatments**
Clinical Evidence: Cancer Stem Cells & Poor Prognosis in Breast Cancer

• Presence of ALDH1-positive CSCs in residual disease in axillary nodes after neoadjuvant chemo & surgery associated with poor prognosis

Sakakibara et al, Cancer 2012

N = 115 patients with confirmed lymph node metastases at diagnosis

Standard neoadjuvant chemotherapy: AC x 4 followed by weekly PTX x 12

ALDH1 assessed by IHC

** p<0.001
FAK is Critical for Cancer Stem Cells

- Targeted deletion of FAK reduces tumor initiating capability

  *Luo et al, Cancer Res (2009) 69:466*

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

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

Integrins → FAK → VS-6063 → VS-4718 → p130Cas → Elimination of CSCs

Tumor initiation

Cell mobility

Proliferation

Tumor initiation
VS-6063 Preferentially Targets CSCs in TNBC Cell Lines: Multiple *in vitro* CSC assays

**Aldefluor-Positive CSCs**

![Graph showing Aldefluor-Positive CSCs](image)

**2° Tumorsphere Formation**

![Graph showing 2° Tumorsphere Formation](image)

**CSCs: Hoechst Dye Exclusion**

![CSCs: Hoechst Dye Exclusion](image)
VS-6063 Reduces CSCs & Tumor-Initiating Capability In TNBC Xenograft Tumor Model in Contrast to Paclitaxel

Mice bearing MDA-MB-231 tumors were treated with 50 mg/kg VS-6063 po BID or vehicle control for 25 days and CSC endpoints were assessed. Tumor initiating capability in 2° mice was decreased by VS-6063, but increased by paclitaxel treatment.
VS-6063 maintains stable disease in a Breast Cancer xenograft model after neoadjuvant chemotherapy

![Graph showing relative tumor growth over days with treatments control, cisplatin, and cisplatin + VS-6063, with a p-value of 0.03 for the difference between cisplatin + VS-6063 and control.]

Days: 0, 10, 20, 30, 40

Relative Tumor Growth: 0, 2, 4, 6, 8, 10

Treatments: Control, Cisplatin, Cisplatin + VS-6063

Arrows indicate times of cisplatin and VS-6063 treatments.
Summary of Key VS-6063 Clinical Experience and Ongoing Trials
Phase 1 Single Agent Dose Escalation
Completed Phase 1 Study in Subjects with Advanced Solid Tumors (n=46)

• Patient Population:
  – Subjects with histologically or cytologically confirmed diagnosis of a non-hematologic malignancy that is unresponsive to currently available therapies

• Primary Objectives:
  • Determine the maximum tolerated dose and assess overall safety and tolerability

• Study Design:
  – Standard 3+3 design, dose escalation

• Dose Range:
  – 12.5 mg to 750 mg p.o. BID in continuous 3 week cycles
  – Recommended phase 2 dose (RP2D) is 400mg PO BID

• Demographics:
  – Sex: 17M, 29F
  – Race: 43 white, 2 black, 1 other
  – Mean Age: 57.1 years
### VS-6063 Phase I: Generally Well Tolerated with Few Grade 3 Events

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Grade 1 n (%)</th>
<th>Grade 2 n (%)</th>
<th>Grade 3 n (%)</th>
<th>Grade 4 n (%)</th>
<th>Grade 5 n (%)</th>
<th>Any Grade n (%)</th>
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</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>16 (34.8)</td>
<td>3 (6.5)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>19 (41.3)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11 (23.9)</td>
<td>5 (10.9)</td>
<td>2 (4.3)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>18 (39.1)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12 (26.1)</td>
<td>3 (6.5)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>15 (32.6)</td>
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<tr>
<td>Hyperbilirubinaemia</td>
<td>5 (10.9)</td>
<td>9 (19.6)</td>
<td>1 (2.2)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>15 (32.6)</td>
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<tr>
<td>Decreased appetite</td>
<td>9 (19.6)</td>
<td>4 (8.7)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>13 (28.3)</td>
</tr>
<tr>
<td>Headache</td>
<td>11 (23.9)</td>
<td>1 (2.2)</td>
<td>1 (2.2)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>13 (28.3)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>10 (21.7)</td>
<td>2 (4.3)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>12 (26.1)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>9 (19.6)</td>
<td>1 (2.2)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>10 (21.7)</td>
</tr>
<tr>
<td>Constipation</td>
<td>5 (10.9)</td>
<td>3 (6.5)</td>
<td>1 (2.2)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>9 (19.6)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>9 (19.6)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>9 (19.6)</td>
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<tr>
<td>Dehydration</td>
<td>1 (2.2)</td>
<td>6 (13.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>7 (15.2)</td>
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<tr>
<td>Cough</td>
<td>6 (13.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>6 (13.0)</td>
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<tr>
<td>Chest pain</td>
<td>3 (6.5)</td>
<td>3 (6.5)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>6 (13.0)</td>
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<tr>
<td>Arthralgia</td>
<td>4 (8.7)</td>
<td>2 (4.3)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>6 (13.0)</td>
</tr>
<tr>
<td>Back pain</td>
<td>1 (2.2)</td>
<td>5 (10.9)</td>
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<td>6 (13.0)</td>
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<td>Oropharyngeal pain</td>
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<td>1 (2.2)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>6 (13.0)</td>
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<tr>
<td>Dyspnoea</td>
<td>3 (6.5)</td>
<td>3 (6.5)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>6 (13.0)</td>
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<tr>
<td>Hypertension</td>
<td>3 (6.5)</td>
<td>2 (4.3)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>5 (10.9)</td>
</tr>
</tbody>
</table>

Included data up to 28 days after last dose of study drug. Highest grade reported for each subject

* Reported by >10% of Subjects in any dose group (n=46)
### VS-6063 Phase 1 Study: Summary of Dose Escalation and DLTs (n=46)

<table>
<thead>
<tr>
<th>Dose Level (mg BID)</th>
<th>DLTs/ Number of Patients</th>
<th>DLTs</th>
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<tbody>
<tr>
<td>12.5</td>
<td>0/3</td>
<td>None</td>
</tr>
<tr>
<td>25</td>
<td>0/3</td>
<td>None</td>
</tr>
<tr>
<td>50</td>
<td>0/3</td>
<td>None</td>
</tr>
<tr>
<td>100</td>
<td>0/3</td>
<td>None</td>
</tr>
<tr>
<td>200</td>
<td>1/6</td>
<td>Headache</td>
</tr>
<tr>
<td>300</td>
<td>1/6</td>
<td>Unconjugated hyperbilirubinemia</td>
</tr>
<tr>
<td>425</td>
<td>1/6</td>
<td>Unconjugated hyperbilirubinemia</td>
</tr>
<tr>
<td>500</td>
<td>0/3</td>
<td>None</td>
</tr>
<tr>
<td>750</td>
<td>0/3</td>
<td>None</td>
</tr>
<tr>
<td>300 fed</td>
<td>0/4</td>
<td>None</td>
</tr>
<tr>
<td>425 fed</td>
<td>2/6</td>
<td>Fatigue Unconjugated hyperbilirubinemia</td>
</tr>
</tbody>
</table>

* 400 mg po BID selected as RP2D
Ovarian Phase 1b in Combination with Paclitaxel
Combining VS-6063 with Paclitaxel for Patients with Ovarian Cancer

Goals
- Target cancer stem cells concurrently with chemotherapy
- Evaluate feasibility of combination of VS-6063 with weekly paclitaxel - paves the way to several other indications where paclitaxel is standard of care

Objectives
- Evaluate safety and tolerability of combination of VS-6063 with weekly paclitaxel
- Measure pharmacokinetics of paclitaxel in combination with VS-6063
- Confirm pharmacodynamic effect of VS-6063 on pFAK target

Protocol permits single agent VS-6063 “maintenance” following paclitaxel

Phase 1
- Completed: 200mg, 400mg BID
- $N=6$

Phase 1b
- Completed Recruitment
- $N=16$

VS-6063 (dose escalation BID) + paclitaxel (80mg/m²/week)

VS-6063 (400mg BID) + paclitaxel (80mg/m²/week)
The 24 hr serum concentration of paclitaxel (80 mg/m2) was determined on Day 1 in the absence of VS-6063.

Following 14 days of continuous VS-6063 administration (200 or 400 mg BID) the 24hr serum concentration of paclitaxel was re-evaluated. (n=6)
Combination of VS-6063 and Weekly Paclitaxel Does not Worsen the Well-Known Side Effect Profile of Paclitaxel Alone

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Phase I</th>
<th>Phase Ib</th>
<th>Total (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>200 mg defactinib BID + 80 mg/m² paclitaxel weekly (n=3)</td>
<td>400 mg defactinib BID + 80 mg/m² paclitaxel weekly (n=3)</td>
<td>400 mg defactinib BID + 80 mg/m² paclitaxel weekly (n=16)</td>
</tr>
<tr>
<td>Anemia</td>
<td>3 (100%)</td>
<td>1 (33.3%)</td>
<td>6 (37.5%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2 (66.7%)</td>
<td>3 (100%)</td>
<td>5 (31.3%)</td>
</tr>
<tr>
<td>Bilirubin Increased</td>
<td>2 (66.7%)</td>
<td>0 (00.0%)</td>
<td>6 (37.5%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (66.7%)</td>
<td>1 (33.3%)</td>
<td>4 (25.0%)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>1 (33.3%)</td>
<td>2 (66.7%)</td>
<td>4 (25.0%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (33.3%)</td>
<td>2 (66.7%)</td>
<td>4 (25.0%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1 (33.3%)</td>
<td>2 (66.7%)</td>
<td>3 (18.8%)</td>
</tr>
<tr>
<td>Peripheral Edema</td>
<td>1 (33.3%)</td>
<td>1 (33.3%)</td>
<td>4 (25.0%)</td>
</tr>
<tr>
<td>Peripheral Neuropathy</td>
<td>1 (33.3%)</td>
<td>2 (66.7%)</td>
<td>3 (18.8%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0 (00.0%)</td>
<td>1 (33.3%)</td>
<td>4 (25.0%)</td>
</tr>
<tr>
<td>Urinary Tract Infection</td>
<td>1 (33.3%)</td>
<td>1 (33.3%)</td>
<td>3 (18.8%)</td>
</tr>
</tbody>
</table>

Most Frequently Reported Adverse Events ≥20%

*Unlocked, in progress data, as presented at ASCO 2014
Paired tumor biopsies were obtained in five patients following 10 days of VS-6063 administration (400 mg BID).

Brown = pFAK (y397)
Paired tumor biopsies were obtained in five patients from before and after 10 days of VS-6063 administration (400 mg BID) for measurement of Sox-2 RNA expression.
Initial Data from the Combination Study of VS-6063 and Paclitaxel are Encouraging

Objective Response
- 3 partial responses
- 2 complete responses

Objective Response or SD ≥ 6 months
- Overall 9/22 (41%)

80% of Patients on Study Have Platinum Resistant Tumors

*Unlocked, in-progress data as of 30 Jun 2014
Mesothelioma Window of Opportunity Study
Window of Opportunity Study in Patients with Surgery-Eligible Mesothelioma

- 10 patients received VS-6063 (400 mg BID) for 12 days prior to surgery
- Measure biomarkers in tumor biopsies
- Evaluate tumor response by PET/CT using RECIST modified for mesothelioma
- Provide guidance for future studies

Diagram:

- 80% chance of surgery
- 4-6 cycles of Pem/Cis chemotherapy
- Treatment Holiday
- 2nd Line Chemo or Clinical Trial
- MPM that is resectable
- VS-6063 400 mg BID
- 30 days post-therapy
- ~42 Days

Biopsy/Scan at 0 and 12 Days.
VS-6063 treatment at day 12 (core needle biopsy) was compared with Control (surgical biopsy at >30 days after VS-6063 treatment ceased)

Mean pFAK (Y397) reduced by 70% in the patients evaluated to date
VS-6063 treatment at day 12 (core needle biopsy) was compared with matched controls (day 0 core needle biopsy or archival tissue sample from diagnosis) for CD133 RNA expression.

Reductions following VS-6063 treatment observed across multiple CSC markers in the evaluable patients with matched control biopsies (7 of 10 patients to date).
Encouraging Early Signal After 12 Days of Treatment with VS-6063

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

Unlocked, in-progress data as of Aug 2014
Mesothelioma
COMMAND Study: Switch Maintenance Following Front Line Therapy
COMMAND: A Registration-Directed Study of VS-6063 to Maintain Tumor Control in Mesothelioma

Goal
• To support approval of VS-6063 on a global basis

Patients
• N ~ 350-400

Design
• Multinational, randomized, double blind, placebo controlled
• Stratification based on merlin status with an adaptive enrichment design
• No cross-over allowed
• Conducted and monitored as a pivotal study

<table>
<thead>
<tr>
<th>Primary Objectives</th>
<th>Secondary Objectives</th>
<th>Exploratory Objectives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Survival (OS)</td>
<td>Quality of Life (QoL)</td>
<td>Time to new lesion</td>
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<td>(LCSS-Meso)</td>
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<tr>
<td>Progression Free Survival (PFS)</td>
<td>Objective Response Rate (ORR)</td>
<td>Relationship of VS-6063 PK and outcome</td>
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<td></td>
<td>Safety and tolerability</td>
<td>Population PK of VS-6063</td>
</tr>
</tbody>
</table>
COMMAND Schematic

Surgery

80%

20%

4-6cyc Pem/Cis

COMMAND Study

2nd Line Chemo or Clinical Trial

Placebo BID

Merlin Low

VS-6063 400mg BID

CT Scan

≥ 4 cycles Platinum + pemetrexed

PR/SD 350-400

0 2 4 6 8 weeks

Key Endpoints

PFS OS QoL

Placebo BID

Merlin High

VS-6063 400mg BID

Novel Drugs Targeting Cancer Stem Cells
Mesothelioma: VS-6063/VS-5584 Combination Study in Relapsed Mesothelioma
6063/5584 Novel Combo in Relapsed Mesothelioma

- VS-6063 [400 mg BID] + dose escalation of 5584 intermittent dosing (M,W,F of each 21 Day cycle)
- Relapsed/refractory Malignant Pleural Mesothelioma (ie patients NOT eligible for COMMAND)
- Pre/post treatment biopsies where possible (assess target proteins in tumor and genomic analysis)
- Platelet rich plasma for PD
- To be conducted at select existing sites
- Initiate by Q4

**Archival / Optional Biopsy**

**VS-6063 400mg BID + VS-5584 Dose Escalation**

21 Day Cycle(s)

- Modified Fibonacci 3+3 design after starting dose of XXmg 5584 (50%, 40%, 33%) adjusted for available tablet strengths

**Expansion Cohort (RP2D) Follow until disease progression**
KRAS mutant NSCLC
**VS-6063-201: Phase 2 Study in KRAS-mutated NSCLC**

- KRASm NSCLC outcome poor – median PFS 1.5 months (Douillard, JCO 2010)
- Pre-clinical data suggests dysfunction of the tumor suppressors CDKN2A/INK4a/ARF (p16) and/or p53 appears requisite for efficacy of FAK inhibition in KRAS-driven NSCLC
- Endpoints: PFS at 12 weeks, ORR and OS
- Simon’s two-stage design: initial sample size is 11 patients per cohort
  - If 4 or more of 11 patients are progression free at 12 weeks will add 23 patients

<table>
<thead>
<tr>
<th>KRAS</th>
<th>p16</th>
<th>p53</th>
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<tbody>
<tr>
<td>Cohort A</td>
<td>✔️</td>
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<tr>
<td>Cohort B</td>
<td>✔️</td>
<td>✔️</td>
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<tr>
<td>Cohort C</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Cohort D</td>
<td>✔️</td>
<td>✔️</td>
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</tbody>
</table>

**Interim analysis**

- VS-6063 400mg BID
- VS-6063 400mg BID
- VS-6063 400mg BID
- VS-6063 400mg BID

**Go/NoGo**

12-week PFS in ≥4 patients?

**Determine mutation status**

**Initial enrollment (up to 11 patients/arm)**

**Expanded enrollment (up to 23 patients/arm)**
Verastem Combination Alliance Objectives
Verastem Objectives for CRUK Combination Alliance

• Combine VS-6063 with novel agents

• Some current combination interests with VS-6063
  – Immune Checkpoint Antibodies
    • Proprietary preclinical rationale can be supplied under confidentiality
  – Cdk4/6 inhibitors
    • NF2/Merlin is often lost along with INK4a (p16/ARF)
    • Rationale to target NF2 loss with VS-6063 & p16 loss with cdk4/6 inhibitor

• Open to additional novel combos with scientific rationale