Forward-Looking Statements

This presentation and other matters discussed today, or answers that may be given to questions asked, include forward-looking statements about the Company’s strategy, future plans and prospects, including statements regarding the development of the Company’s compounds, including VS-6063, VS-4718, VS-5584 and VS-507, and the Company’s FAK, PI3K/mTOR, Wnt and diagnostics programs generally, the timeline for clinical development and regulatory approval of the Company’s compounds, the structure of the Company’s planned clinical trials, the Company’s rights to develop or commercialize its compounds, the Company’s obligations to make milestone payments and royalties and the ability of the Company to finance contemplated development activities. The words “anticipate,” “believe,” “estimate,” “expect,” “intend,” “may,” “plan,” “predict,” “project,” “target,” “potential,” “will,” “would,” “could,” “should,” “continue,” “proposed,” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Each forward-looking statement is subject to risks and uncertainties that could cause actual results to differ materially from those expressed or implied in such statement. Applicable risks and uncertainties include the risks that the preclinical testing of the Company’s compounds may not be predictive of the success of later clinical trials, that the Company will be unable to successfully complete the clinical development of its compounds, including VS-6063, VS-4718, and VS-5584, that the development of the Company’s compounds will take longer or cost more than planned, and that the Company’s compounds will not receive regulatory approval or become commercially successful products. Other risks and uncertainties include those identified under the heading “Risk Factors” in the Company’s Annual Report on Form 10-K for the year ended December 31, 2012 and in any subsequent SEC filings. The forward-looking statements contained in this presentation reflect the Company’s current views with respect to future events, and the Company does not undertake and specifically disclaims any obligation to update any forward-looking statements.
Agenda

• 12:45 Introduction

• 1:00 Focal Adhesion Kinase (FAK) and Cancer Stem Cells

• 1:20 FAK Program Status: VS-6063 + Paclitaxel in Ovarian Cancer

• 1:40 Mesothelioma and the VS-6063 Registration-Directed Trial

• 2:30 FAK Portfolio Expansion: VS-6063 into Lung Cancer and VS-4718 into Phase 1

• 2:45 The Potential of Dual mTORC1/2 and PI3K Inhibition and VS-5584

• 3:15 Q&A

• 3:30 Close
## Today’s Speakers

<table>
<thead>
<tr>
<th>Name</th>
<th>Role and Affiliations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>José Baselga, M.D., Ph.D.</strong></td>
<td>Physician in Chief, Memorial Sloan-Kettering Cancer Center, Verastem scientific advisory board member</td>
</tr>
<tr>
<td><strong>Robert Weinberg, Ph.D.</strong></td>
<td>Founding Member, Whitehead Institute, Verastem scientific co-founder and chair of the scientific advisory board</td>
</tr>
<tr>
<td><strong>Richard Gralla, M.D.</strong></td>
<td>Albert Einstein College of Medicine, President, NY Lung Cancer Alliance, Verastem mesothelioma steering committee</td>
</tr>
<tr>
<td><strong>Robert Forrester</strong></td>
<td>President/CEO, Former CEO/CFO, CombinatoRx (now ZLCS), SVP, COLY (now Pfizer)</td>
</tr>
<tr>
<td><strong>Joanna Horobin, M.B., Ch.B.</strong></td>
<td>Chief Medical Officer, Former CEO/President, Syndax Pharmaceuticals, VP, Oncology, Rhone-Poulenc Rorer (now Sanofi)</td>
</tr>
<tr>
<td><strong>Christoph Westphal, M.D., Ph.D.</strong></td>
<td>Executive Chairman, Cofounder, Former Cofounder/CEO: MNTA, ALNY, SIRT (now GSK), Cofounder: Alnara (now Lilly), OvaScience</td>
</tr>
<tr>
<td><strong>Jonathan Pachter, Ph.D.</strong></td>
<td>VP, Head of Research, Former Head of Cancer Biology, OSI (now Astellas), Schering-Plough (now Merck)</td>
</tr>
</tbody>
</table>
Cancer Stem Cells are a Reason for Failure of Current Therapies

- Current cancer treatments often fail to cure
- Cancer stem cells resist chemotherapy
- Cancer stem cells drive disease progression

Graph showing 5-year relative survival rate for breast cancer:

- Early Disease: 99%
- Advanced Disease: 23%

Bar chart indicating disease status at diagnosis.
Verastem is at the Forefront of Cancer Stem Cell Biology

Identification of Selective Inhibitors of Cancer Stem Cells by High-Throughput Screening

The Epithelial-Mesenchymal Transition Generates Cells With Properties of Stem Cells
Mani, Weinberg, et al. 2008

Hallmarks of Cancer: The Next Generation
Hanahan, Weinberg. 2011

Other companies involved in cancer stem cell drug development

Eisai
GlaxoSmithKline
DAINIPPON SUMITOMO PHARMA
OncoMed Pharmaceuticals
Bayer
Astellas
Boehringer Ingelheim
Stemline

The New York Times
THE WALL STREET JOURNAL
Targeting Cancer Stem Cells For a Durable Clinical Response

Problem:

Current cancer treatments

Initial Tumor → Tumor reduction but CSCs survive → Recurring Tumor

Solution:

CSC drugs + current cancer treatments

Initial Tumor → Tumor reduction and elimination of CSCs → Durable clinical response
Platform to Discover Drugs Targeting Cancer Stem Cells

High-Throughput Screening

- EMT
- Cancer non-stem cells
- Cancer stem cells

- High-throughput screening
- Selectivity filters
- Drug candidates

In vitro characterization

- CD44
- CSCs: 4.90%
- Non-CSCs
- Placebo Control
- CD44
- 70.12%
- Paclitaxel
- CD44
- 0.20%
- CSC Inhibitor

Candidate Drug Selection

- Number of compounds
- >10X
- 5-10X
- 4X
- 3X
- 2X
- 1X
- 2X
- 3X
- 4X
- 5-10X
- >10X

- Non-CSC selective
- CSC selective

In vivo tumor models

- xenograft
- Control
- Compound
- Liberase
- Viable cells
- ALDH assay
- Tumorsphere assays
- Re-implantation in limiting dilutions
# Portfolio of Product Candidates Targeting Cancer Stem Cells

<table>
<thead>
<tr>
<th></th>
<th>PreClin</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Focal Adhesion Kinase (FAK)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>VS-6063</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mesothelioma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Japanese</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Development</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung (KRASm NSCLC)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovarian</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>VS-4718</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solid Tumors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PI3K and mTORC1/2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>VS-5584</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solid Tumors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>and Lymphomas</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Wnt/β-Catenin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Eisai</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Research</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Collaboration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Upcoming Milestones

H1 2013
- FDA Meeting
- EU Meeting
- VS-4718 IND
- VS-6063 EU Orphan
- VS-4718 Phase 1 in solid tumors
- VS-6063 Phase 1 combo
- AACR
- ASCO

H2 2013
- VS-5584 IND
- VS-6063 US Orphan
- VS-6063 Meso trial
- VS-5584 Phase 1
- VS-6063 Phase 1b combo expansion
- VS-6063 Japanese Phase 1
- VS-6063 NSCLC
- VS-6063 Phase 1 combo safety
- EORTC

2014
- VS-4718 Phase 1
- VS-6063 Phase 1b combo biomarkers and activity
- VS-4718 Phase 1b biomarkers
- VS-5584 Phase 1
- VS-6063 NSCLC
- VS-6063 Japanese Phase 1
- AACR, ASCO & EORTC

Estimates based on currently proposed clinical plans and are subject to change
Agenda

- 12:45 Introduction
- 1:00 Focal Adhesion Kinase (FAK) and Cancer Stem Cells
- 1:20 FAK Program Status: VS-6063 + Paclitaxel in Ovarian Cancer
- 1:40 Mesothelioma and the VS-6063 Registration-Directed Trial
- 2:30 FAK Portfolio Expansion: VS-6063 into Lung Cancer and VS-4718 into Phase 1
- 2:45 The Potential of Dual mTORC1/2 and PI3K Inhibition and VS-5584
- 3:15 Q&A
- 3:30 Close
Robert Weinberg, Ph.D.
The complexity of the invasion-metastasis cascade rivals that of the earlier steps of primary tumor formation.

The invasion-metastasis cascade
Induction of EMT by Snail and Twist EMT-inducing TFs also generates CD44\(^{hi}\) CD24\(^{lo}\) cells.

CD44\(^{lo}\)/CD24\(^{hi}\) (position of non-stem cells)

CD44\(^{hi}\)/CD24\(^{lo}\) (position of stem cells)

S.A. Mani & W. Guo
Filopodium-like structures contribute to cell-matrix adhesions in 3D

<table>
<thead>
<tr>
<th></th>
<th>D2A1 cells/Matrigel on-top</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 min</td>
<td></td>
</tr>
<tr>
<td>30 min</td>
<td></td>
</tr>
<tr>
<td>60 min</td>
<td></td>
</tr>
<tr>
<td>80 min</td>
<td></td>
</tr>
<tr>
<td>100 min</td>
<td></td>
</tr>
<tr>
<td>140 min</td>
<td></td>
</tr>
<tr>
<td>160 min</td>
<td></td>
</tr>
</tbody>
</table>

Integrin α5-YPet

How does the EMT create cancer stem cells?

**FLPs = filopodium-like structures**

Tsukasa Shibue

<table>
<thead>
<tr>
<th>nonmetastatic cells</th>
<th>metastatic cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>few/no FLP</td>
<td>abundant FLPs</td>
</tr>
<tr>
<td>few/no mature adhesion plaque</td>
<td>abundant mature adhesion plaques</td>
</tr>
<tr>
<td>minimal FAK activation</td>
<td>potent FAK activation</td>
</tr>
<tr>
<td>slow/no proliferation</td>
<td>rapid proliferation</td>
</tr>
</tbody>
</table>
Abundant FLP formation is a common attribute of metastatic cells

<table>
<thead>
<tr>
<th>nontumorigenic</th>
<th>nonmetastatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matrigel on-top, 12h</td>
<td></td>
</tr>
<tr>
<td>MCF10A</td>
<td>MCF7</td>
</tr>
<tr>
<td>SK-BR-3</td>
<td>ZR-75-1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>metastatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDA-MB-436</td>
</tr>
<tr>
<td>Sum159</td>
</tr>
<tr>
<td>MDA-MB-157</td>
</tr>
<tr>
<td>Sum1315</td>
</tr>
</tbody>
</table>

in the lungs, 48h

nonmetastatic
SK-BR-3

metastatic
Sum1315

F-actin
DAPI

lifeact-TagRFP-T
integrin α5-YPet
PECAM-1 (white)
Hoechst 33342

Tsukasa Shibue
EMT induction elevates FLP-forming ability

EMT induction in HMLER cells stimulates their FLP-forming and tumor-initiating abilities, which is attributable in part to the elevated β-parvin expression.

Tsukasa Shibue
EMT promotes metastasis via FLP-dependent FAK activation.

FAK signaling serves as a key intermediary in EMT-dependent induction of metastatic aggressiveness.
FLP formation empowers initial proliferation of cancer cells

The formation of FLPs predicts, and contributes functionally to, the subsequent proliferation of cancer cells both after metastatic dissemination and orthotopic implantation.
FAK Inhibition Preferentially Reduces CSCs in Multiple Assays

**HMLE: Selective for CSCs**

![Graph showing % Cell Viability vs. VS-4718 concentration. Red dots represent non-CSCs, green dots represent CSCs.]

**Tumorsphere Formation**

![Bar graph showing Secondary Spheres (% of Control) for different VS-4718 concentrations (Control, 1 μM, 3 μM).]

**Aldefluor-Positive CSCs**

![Graph showing Aldefluor-Positive CSCs (% of Control) vs. VS-4718 concentration for MDA-MB-231 cells.]

**CSCs: Hoechst Dye Exclusion**

![Images comparing control and 1 μM VS-4718 treated samples, highlighting reduced CSCs.]

---

**Novel Drugs Targeting Cancer Stem Cells**

Secondary Spheres (% of Control) for Control (1 μM) and 3 μM VS-4718.
Targeting Cancer Stem Cells For a Durable Clinical Response

Problem:
Current cancer treatments

Initial Tumor ➔ Tumor reduction but CSCs survive ➔ Recurring Tumor

Solution:
CSC drugs + current cancer treatments

Initial Tumor ➔ Tumor reduction and elimination of CSCs ➔ Durable clinical response
Combination of Cancer Stem Cell Drug & Chemotherapy Reduces Tumor-Initiating Capability

- Ovarian cancer cells treated in *vitro* & allowed to recover for 4 days
- 1,000 cells from each treatment arm were implanted into immunodeficient mice

**No tumors initiated in combination-treatment arm**

**Graph:**
- % Tumor Free Mice over Days 0 to 72
- Treatments: Control, Paclitaxel, VS-4718, VS-4718 + Paclitaxel

**Image:**
- TOV21G human ovarian cancer cells

**Legend:**
- Control
- Paclitaxel
- VS-4718
- VS-4718 + Paclitaxel
Agenda

• 12:45 Introduction
• 1:00 Focal Adhesion Kinase (FAK) and Cancer Stem Cells
• 1:20 FAK Program Status: VS-6063 + Paclitaxel in Ovarian Cancer
• 1:40 Mesothelioma and the VS-6063 Registration-Directed Trial
• 2:30 FAK Portfolio Expansion: VS-6063 into Lung Cancer and VS-4718 into Phase 1
• 2:45 The Potential of Dual mTORC1/2 and PI3K Inhibition and VS-5584
• 3:15 Q&A
• 3:30 Close
# Portfolio of Product Candidates Targeting Cancer Stem Cells

<table>
<thead>
<tr>
<th></th>
<th>PreClin</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Focal Adhesion Kinase (FAK)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VS-6063</td>
<td></td>
<td></td>
<td>Registration-directed trial</td>
<td></td>
</tr>
<tr>
<td>Mesothelioma</td>
<td></td>
<td>Phase 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Japanese Development</td>
<td></td>
<td>Phase 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung (KRASm NSCLC)</td>
<td></td>
<td>Phase 1/1b in combo with paclitaxel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovarian</td>
<td></td>
<td>Phase 1/1b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VS-4718</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solid Tumors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PI3K and mTORC1/2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VS-5584</td>
<td></td>
<td>IND Phase 1/1b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solid Tumors and Lymphomas</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Wnt/β-Catenin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eisai</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Research Collaboration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
FAK Program Summary

• FAK is a critical regulator of cancer stem cells and disease progression

• Strong pre-clinical evidence and initial clinical proof-of-concept for targeting FAK in mesothelioma, ovarian and lung cancer

• Two candidates in clinical development with 5 clinical trials ongoing/planned in near term
  – VS-6063 Phase 1/1b study in combination with paclitaxel in ovarian cancer ongoing
  – VS-6063 registration-directed study in mesothelioma on track for Q3 initiation
  – VS-6063 Japan bridging trial on track to start in Q3
  – VS-6063 NSCLC trial on track to start in Q3
  – VS-4718 first-in-human Phase 1 ongoing
**VS-6063 – First in Class FAK Inhibitor**

- Oral compound with good safety profile and initial signs of activity in Phase 1
- USAN name: defactinib
- Orphan designation in European Union for mesothelioma
- Two clinical FAK competitors
  - Boehringer Ingelheim: Phase 1
  - GlaxoSmithKline: Phase 1

---

**Composition of matter through 2029**

FAK Enzymatic IC$_{50}$ = 24 nM  
FAK Cellular EC$_{50}$ = 24 nM

---

**pFAK EC$_{50}$**

<table>
<thead>
<tr>
<th>Compound</th>
<th>EC$_{50}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>VS-6063</td>
<td>24 nM</td>
</tr>
<tr>
<td>GSK2256098</td>
<td>77 nM</td>
</tr>
</tbody>
</table>

Verastem data
**VS-6063 Phase 1 Study in 46 Patients with Advanced Solid Tumors: Good Safety Profile and Stable Disease in 43% of Patients >100mg BID**

**Primary Endpoint: Safety and Tolerability**

<table>
<thead>
<tr>
<th>Adverse Events*</th>
<th>Grade</th>
<th>N (%)</th>
<th>N (%)</th>
<th>N (%)</th>
<th>N (%)</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>14</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>17</td>
<td>(37)</td>
</tr>
<tr>
<td>Unconjugated hyperbilirubinemia</td>
<td>6</td>
<td>9</td>
<td>2</td>
<td>0</td>
<td>17</td>
<td>(37)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8</td>
<td>6</td>
<td>1</td>
<td>0</td>
<td>15</td>
<td>(33)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>13</td>
<td>(28)</td>
</tr>
<tr>
<td>Headache</td>
<td>9</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>10</td>
<td>(22)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>10</td>
<td>(22)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>8</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>9</td>
<td>(20)</td>
</tr>
</tbody>
</table>

*Treatment-Related Adverse Events (≥20%)

婕明 SF J Clin Oncol 2011 29:1 (suppl; abstr 3002)

**Initial Signs of Clinical Activity**

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Duration (weeks)</th>
<th>Stable disease of circa 6 months +</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC</td>
<td>(425 mg BID; 2 priors)</td>
<td></td>
</tr>
<tr>
<td>Ovarian</td>
<td>(425 mg BID; 4 priors)</td>
<td></td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>(200 mg BID; 2 priors)</td>
<td></td>
</tr>
<tr>
<td>Ovarian</td>
<td>(425 mg BID; 5 priors)</td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>(300 mg BID; 6 priors)</td>
<td></td>
</tr>
<tr>
<td>Pancreatic</td>
<td>(100 mg BID; 5 priors)</td>
<td></td>
</tr>
<tr>
<td>Ovarian</td>
<td>(500 mg BID; 6 priors)</td>
<td></td>
</tr>
</tbody>
</table>
Clinical Trial Designs for Drugs Targeting Cancer Stem Cells

Concurrent:

**CSC Drugs + Chemo**

- Initial Tumor
- Tumor Reduction & Elimination of CSCs

Theoretical Result

More Durable Clinical Response

Maintenance:

- **Chemo**
  - Initial Tumor
  - Tumor Reduction but CSCs are Enriched

- **CSC Drugs**
  - More Durable Clinical Response
VS-6063 Concurrently with Weekly Paclitaxel (Phase 1/1b)

- Targeting cancer stem cells concurrently with chemotherapy, to reduce both cancer stem cells and tumor bulk

- Initial target population – recurrent ovarian cancer
  - Signs of clinical activity in the single-agent Phase 1 study
  - Recurrent tumors are enriched in cancer stem cells
  - Tumor FAK expression correlates to poor survival (Anil Sood, MDACC)
  - Access to biopsiable tissue
VS-6063 and Weekly Paclitaxel can be Combined

- Expansion into other indications where paclitaxel is standard of care
- Dose escalation portion of study enrollment complete Q2 2013
- Subjects with advanced ovarian cancer and ≤4 prior therapies
- No DLTs observed
- No exacerbation of paclitaxel AE profile in combination with VS-6063
- Two dose levels
  - 200mg BID x 3 patients
  - 400mg BID x 3 patients
Ongoing Trial Narrative: Encouraging in-progress Data

- 59 year old white female, diagnosed Jan 2012 with stage 4 serous ovarian cancer

<table>
<thead>
<tr>
<th>Prior Treatment</th>
<th>Setting</th>
<th>Duration (months)</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin, paclitaxel</td>
<td>Adjuvant following surgery</td>
<td>~ 7.4</td>
<td>Completed course, relapsed ~3 months later</td>
</tr>
<tr>
<td>Doxorubicin (Doxil and Adriamycin)</td>
<td>First line</td>
<td>~ 1.6</td>
<td>Toxicity</td>
</tr>
</tbody>
</table>

- Started weekly paclitaxel and VS-6063 in Mar 2013
- Stage 4 at study entry - baseline lesions included an abdominal lesion and a lymph node within the liver
- Remains on study – now in Cycle 4. Paclitaxel interrupted due to neuropathy, VS-6063 is well tolerated and dosing continues
- Complete Response observed at end of cycle 2. To be reconfirmed at end of cycle 4
VS-6063: Phase 1b Stage of Combination with Weekly Paclitaxel in Ovarian Cancer

- VS-6063 400mg BID + weekly paclitaxel
- 10-day single agent VS-6063 run-in to measure CSC biomarkers and pFAK
- Continue on combination until progression
  - May continue on VS-6063 alone if experiencing paclitaxel toxicity
- Up to 15 additional patients to be enrolled
Agenda

• 12:45 Introduction

• 1:00 Focal Adhesion Kinase (FAK) and Cancer Stem Cells

• 1:20 FAK Program Status: VS-6063 + Paclitaxel in Ovarian Cancer

• 1:40 Mesothelioma and the VS-6063 Registration-Directed Trial

• 2:30 FAK Portfolio Expansion: VS-6063 into Lung Cancer and VS-4718 into Phase 1

• 2:45 The Potential of Dual mTORC1/2 and PI3K Inhibition and VS-5584

• 3:15 Q&A

• 3:30 Close
Cancer Stem Cells in Mesothelioma

- CSCs identified in 90% of human mesothelioma patient samples
- Standard of care agents increase proportion of mesothelioma CSCs
- FAK inhibitors reduce proportion of mesothelioma CSCs
Low Merlin Expression Increases Sensitivity to VS-6063 in Mesothelioma Models

Mesothelioma Cell Line Panel

Approximately 50% of mesothelioma tumors have low merlin
Initial Proof of Concept for FAK Inhibitors in Mesothelioma: GSK2256098 Phase 1 Study – Recurrent Mesothelioma

2nd Line Treatment in Recurrent Mesothelioma

<table>
<thead>
<tr>
<th>Group</th>
<th>Median Progression Free Survival (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Historical control</td>
<td>6 weeks</td>
</tr>
<tr>
<td>(n=660)</td>
<td></td>
</tr>
<tr>
<td>All Patients</td>
<td>18 weeks</td>
</tr>
<tr>
<td>(n=29)</td>
<td></td>
</tr>
<tr>
<td>Merlin high</td>
<td>11 weeks</td>
</tr>
<tr>
<td>(n=9)</td>
<td></td>
</tr>
<tr>
<td>Merlin low</td>
<td>24 weeks</td>
</tr>
<tr>
<td>(n=14)</td>
<td></td>
</tr>
</tbody>
</table>

Biomarker for patient stratification

1 Historical data from Vorinostat Phase 3 (Krug et al; ESMO 2011)

2 Phase 1 trial of GSK2256098 presented at EORTC-NCI-AACR Molecular Therapeutics mtg (Nov. 6-9, 2012)
Jocelyn Farrar, DNP, CCRN, ACNP-BC

Video Presentation
Richard Gralla, M.D.
Principle Malignancies Treated by Thoracic Oncologists

Non-Small Cell Lung Cancer

Small Cell Lung Cancer

Mesothelioma

Thymoma / Thymic Carcinoma
## SELECTED MOLECULARLY TARGETED AGENTS IN THORACIC ONCOLOGY

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Agent</th>
<th>Number of Patients Potentially Eligible for Agent / Year in the USA</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC</td>
<td>Erlotinib</td>
<td>10,000 – 12,000</td>
</tr>
<tr>
<td>NSCLC</td>
<td>Crizotinib</td>
<td>3000 - 4000</td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>VS-6063</td>
<td>2500 - 3000</td>
</tr>
</tbody>
</table>
Worldwide Incidence of Mesothelioma Continues to Increase

Asbestos Mining, Use & Danger Persists
Worldwide Incidence of Mesothelioma Continues to Increase

- WHO estimates total worldwide fatalities of 59,000/year
  - Britain:
    - Most rapidly increasing cancer in women and 3rd most rapid in men
  - Japan
    - New diagnoses almost tripled from 2006 – 2012 (500 – 1278 patients/per year)

- Asbestos exposure is primary risk factor with latency period typically 20 - 40 years
  - Approximately 2 million tons of asbestos are used per year
  - Top consuming countries: ("BRIC") Brazil, Russia, India, China
  - Japan only banned asbestos in 2006
  - Many countries have yet to ban asbestos
Mesothelioma is a Devastating Cancer

- Highly aggressive and lethal cancer
  - Typically diagnosed late-stage (Stages III and IV)
  - There is no known effective screening method for early detection
  - 9 to 12 month survival from time of diagnosis in most studies

- Tumor encases the lungs leading to pain and suffocation
  - Highly symptomatic with 93% of patients having 3+ symptoms (pain, shortness of breath most commonly)
Pleural Nodules of Mesothelioma

Images reprinted with permission. © 2004 NJ Vogelzang, MD.
Current Therapy for Mesothelioma is Limited

- Surgery for resectable disease, but few patients are cured
- First-line standard therapy for mesothelioma is combination pemetrexed + cisplatin – demonstrated 2-3 month overall survival benefit and symptom benefits versus single agent cisplatin
- No standard second-line therapy
- Management of symptoms: shortness of breath and pain
- Hospice care

**Typical Treatment of Advanced Mesothelioma**

1. **1st line**
   - 4-6 cycles Pemetrexed + cisplatin
   - Median PFS: 5.7 mos\(^1\)
   - Partial Response Rate: 41%

2. **Treatment holiday**
   - PFS: 4mos

3. **2nd line**
   - No Standard
   - PFS: 6wks\(^2\)

---

\(^1\) Pemetrexed + Cisplatin Phase 3 (Vogelzang et al; JCO 2003)  
\(^2\) Vorinostat Phase 3 (Krug et al; ESMO 2011)
PEMETREXED + CISPLATIN versus CISPLATIN
Phase III Study Design: Target of 6 Cycles

Pemetrexed + Cisplatin

- 500 mg/m²
- 75 mg/m²

Versus

Cisplatin

- 75 mg/m²

All agents given on Day 1 every 3 weeks
- KPS ≥ 70%
- Unresectable MPM; no prior chemotherapy

PEMETREXED + CISPLATIN versus CISPLATIN
Survival and Response

- **Method:** Kaplan-Meier

Graph showing survival rates for Pemetrexed + Cisplatin (n=226) versus Cisplatin (n=222). The survival rates are compared over months, with the cumulative percentage alive on the y-axis and months on the x-axis.

**Key Statistics:**

- **Survival Rates:**
  - Pemetrexed + Cisplatin: 100, 75, 50, 25%
  - Cisplatin: 100, 75, 50, 25%

- **Response Rate:**
  - Pemetrexed + Cisplatin: 41.3%
  - Cisplatin: 16.7%

- **Fisher’s Exact P-value:** <0.001

- **Median Survival (months):**
  - Pemetrexed + Cisplatin: 12.1
  - Cisplatin: 9.3

- **Hazard Ratio:** 0.77

- **Log-Rank P-value:** 0.020

PEMETREXED + CISPLATIN *versus* CISPLATIN

Thoracic Symptoms: 18-week Results

Reference: Vogelzang et al *JCO 2003*
Lung Function by Treatment

Lung Cancer Symptom Scale: Dyspnea

Lung Cancer Symptom Scale: Pain

Change From Baseline (mm)

Cycle

P/C
C

P = .064
P = .017
P = .017

NS

PEMETREXED + CISPLATIN versus CISPLATIN

General Symptoms: 18-week Results

- Fatigue
- Anorexia
- Activity level

**Graph:**
- Pem + cis
- Cisplatin

- **Fatigue:**
  - Pem + cis: p=0.010
  - Cisplatin: p=0.058

- **Anorexia:**
  - Pem + cis: p=0.017
  - Cisplatin: p=0.058

**Reference:** Vogelzang et al, *JCO* 2003

100% = best score
PEMETREXED + CISPLATIN versus CISPLATIN
Global Assessment: 18-week Results

% Target AUC

Global QoL  Symptom distress

Reference: Vogelzang et al JCO 2003

100% = best score
Patient-Determined Pain and Global Quality-of-Life (QoL) Scores by Response (model-based means—All Patients)

### Pain

<table>
<thead>
<tr>
<th>Response</th>
<th>Baseline (mm)</th>
<th>Change From Baseline (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR/PR</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>SD</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>PD</td>
<td>0</td>
<td>-5</td>
</tr>
</tbody>
</table>

Analysis of variance by response group (*P* values)

<table>
<thead>
<tr>
<th>Comparison</th>
<th><em>P</em> Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR/PR vs SD</td>
<td>.254</td>
</tr>
<tr>
<td>CR/PR vs PD</td>
<td>.003</td>
</tr>
<tr>
<td>SD vs PD</td>
<td>.034</td>
</tr>
</tbody>
</table>

### Global QoL

<table>
<thead>
<tr>
<th>Response</th>
<th>Baseline (mm)</th>
<th>Change From Baseline (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR/PR</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>SD</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>PD</td>
<td>0</td>
<td>-8</td>
</tr>
</tbody>
</table>

Analysis of variance by response group (*P* values)

<table>
<thead>
<tr>
<th>Comparison</th>
<th><em>P</em> Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR/PR vs SD</td>
<td>.413</td>
</tr>
<tr>
<td>CR/PR vs PD</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>SD vs PD</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Endpoints and treatment: Relationships and role of patient reported outcomes ("PROs")
Clinical Trial Designs for Drugs Targeting Cancer Stem Cells

Concurrent:

CSC Drugs + Chemo

Initial Tumor

Tumor Reduction & Elimination of CSCs

Theoretical Result

More Durable Clinical Response

Maintenance:

Chemo

CSC Drugs

Initial Tumor

Tumor Reduction but CSCs are Enriched

More Durable Clinical Response
## Registration-Directed Study in Malignant Pleural Mesothelioma

<table>
<thead>
<tr>
<th>Sample Size for PFS</th>
<th>• 350 – 400</th>
</tr>
</thead>
</table>
| **Design**          | • Randomized, double blind, placebo controlled, no cross-over allowed  
|                     | • Central review of CT scans |
| **Population**      | • Patients with good performance status, evaluable lesions and disease control immediately after ≥4 cycles of Alimta + platinum |
| **Study Sites**     | • North America, Europe, AUS/NZ, South Africa, (Japan) |
| **Endpoints**       | • Primary: Progression Free Survival, Overall Survival  
|                     | • Secondary: Quality of Life using LCSS-meso, ORR |
Key Eligibility Criteria

- Performance status ≥70%
- Karnofsky Performance Criteria
- Measurable or Evaluable Disease
- RECIST v1.1
- Tumor material for Merlin Status
- Adequate Liver, Kidney and Cardiac Function

1:1 Randomization
CT scan at treatment start and every 6 weeks

≥ 4 cycles
Platinum/Alimta

≤6 weeks

PR/SD

n~375

Merlin Low

VS-6063 400 mg BID

2 4 6 weeks

Merlin High

Placebo BID

VS-6063 400 mg BID

Placebo BID
### Adaptive Design Enables Two Paths to Registration

| Powering for PFS                  | • 90% power  
|                                  | • Potential for accelerated approval on PFS |
| Powering for OS                  | • Resize at primary PFS analysis to achieve adequate power for OS  
|                                  | • Potential for full approval on OS |
| Interim Analysis & Adaptive Design | • Pre-planned interim evaluation by DSMB at 128 PFS events  
|                                  | • Futility, continue enrolling all patients, or enroll merlin low only  
|                                  | • Can do a sample size re-estimation if merlin-low only |
VS-6063: Adaptive Design Enables Multiple Paths to Registration

- Enroll Merlin Low/High
- Interim Analysis 50% PFS Events
  - Enrich
  - Continue
  - Futile
- Enroll Merlin Low Only
- Sample Size Re-Estimation for PFS
  - PFS Significant
  - PFS not Significant
  - Sample Size Re-Estimation for OS
  - Primary OS Analysis
- Primary PFS Analysis
  - Stop Study
  - Continue
  - Enroll Merlin Low/High

Novel Drugs Targeting Cancer Stem Cells
Clinical Assay for Merlin Expression in Mesothelioma

1. Clinical specimens retrospectively analyzed from 300 mesothelioma patients
2. Tumor Cell Line Sensitivity found for Merlin-Low

Clinical Assay Validation

- Assay validated by Labcorp
- H – Score [0-300] from IHC
- Binary cut-off: High/Low
- Testing in 125 mesotheliomas
- Central Laboratory and Pathology Review
Site Qualification and Regulatory Progress on Schedule

• ~35 sites qualified to date in 11 countries
• Regulatory submissions/allowances on track
• US Investigator meeting held. Others shortly

- Australia
- Belgium
- Canada
- France
- Netherlands
- New Zealand
- South Africa
- Spain
- Sweden
- UK
- USA

• Estimated time to full enrollment for PFS: 24 months
• Will update clinicaltrials.gov with country/site initiations
• First study update announcement expected on year end 2013 conference call (March 2014) with enrollment and target dates
VS-6063: Japanese Development Strategy

• Facilitate Japanese inclusion into global mesothelioma trial
• Create a path to possible Japanese approval
• Phase 1 bridging study
  – Dose escalation as a single agent
  – Patient population: advanced solid tumors
• 3-5 expansion sites for global mesothelioma study selected

Confirm RP2D of 400mg BID in Japanese subjects

VS-6063 dose escalation

RP2D

VS-6063-202
Global Mesothelioma Study
Team to Execute the Global Regulatory Study

- Leadership with extensive late-stage development experience
  - Joanna Horobin, M.B., Ch.B. – Chief Medical Officer
    - Syndax Pharmaceuticals, Rhone-Poulenc Rorer, EntreMed
    - 10 marketed compounds including Taxotere and Camptosar
  - Mitchell Keegan, Ph.D. – Vice President, Development
    - Gloucester, Curis
    - Istodax, Erivedge

- CRO with global pharmacovigilance and orphan drug drug experience

Mesothelioma Steering Committee

- Paul Baas, Amsterdam: Conducted the Phase 3 thalidomide study
- Richard Gralla, NY: Expert on Quality of Life in Mesothelioma
- Lee Krug, NY: Conducted the Phase 3 vorinostat trial
- Larry Schwartz, NY: Imaging expert
- Dean Fennell, UK: President Elect for iMig
- Hedy Kindler, Chicago: Leading US clinical researcher
- Anna Nowak, Australia: Leading clinical researcher in malignant mesothelioma
Agenda

• 12:45 Introduction

• 1:00 Focal Adhesion Kinase (FAK) and Cancer Stem Cells

• 1:20 FAK Program Status: VS-6063 + Paclitaxel in Ovarian Cancer

• 1:40 Mesothelioma and the VS-6063 Registration-Directed Trial

• 2:30 FAK Portfolio Expansion: VS-6063 into Lung Cancer and VS-4718 into Phase 1

• 2:45 The Potential of Dual mTORC1/2 and PI3K Inhibition and VS-5584

• 3:15 Q&A

• 3:30 Close
Targeting cancer stem cells that are implicated in epithelial solid tumors: 80% of all cancers

Mesothelioma
WW Incidence ~59,000

Ovarian
WW Incidence ~225,000

Breast
WW Incidence ~1,400,000

Lung
WW Incidence ~1,600,000
Potential Indication Expansion to Non-Small Cell Lung Cancer

- Lung cancer with KRAS mutation accompanied by 2nd mutation in INK4a/ARF or p53 shown to be especially sensitive to FAK inhibition
- Sensitivity determined by both FAK genetic knockdown and *in vivo* xenograft experiments with small-molecule FAK inhibitor (Konstantinidou, *Cancer Discovery*, 2013)

**KRAS & INK4a/ARF mutated xenografts**

<table>
<thead>
<tr>
<th>Survival (%)</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>A549 NSCLC</td>
<td>Placebo VS-6062</td>
</tr>
<tr>
<td>A427 NSCLC</td>
<td>Placebo VS-6062</td>
</tr>
</tbody>
</table>
VS-6063: Phase 2 Study in KRAS-mutated NSCLC

- Endpoints: PFS at 12 weeks, ORR and OS
- Increase safety database for VS-6063
- Targeted initiation Q3 2013
- 8-10 clinical sites

<table>
<thead>
<tr>
<th>KRAS</th>
<th>INK4a</th>
<th>p53</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort A</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Cohort B</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Cohort C</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Cohort D</td>
<td>✓</td>
<td>✓</td>
</tr>
</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)
VS-4718: Second FAK Inhibitor in Clinical Development

- Orally available, potent and selective inhibitor of FAK kinase
- Targets cancer stem cells in *in vitro* & *in vivo* cancer models
- Phase 1 first-in-human study open and enrolling patients

### Biochemical Properties

![Chemical structure](image)

- FAK Enzymatic IC\(_{50}\) = 22 nM
- FAK Cellular EC\(_{50}\) = 31 nM

*Composition of matter through 2028*

### Cancer Stem Cells

- *Triple negative breast cancer*

![Graph](image)
**VS-4718: Dose Escalation Scheme**

- Phase 1 dose escalation in patients with advanced cancers initiated Q2 2013
- 3+3 modified Fibonacci design
- Pre/post treatment biopsies
- Expansion at recommended Phase 2 dose
- Clinical sites
  - Sarah Cannon, Cedars Sinai and Florida Cancer Specialists
- Up to 30 patients

---

**Determine Recommended Phase 2 Dose**

VS-4718 dose escalation
28-day cycle

---

VS-4718 Expansion Cohort (RP2D) Follow until disease progression
FAK Program Summary

• FAK is a critical regulator of cancer stem cells and disease progression

• Strong pre-clinical evidence and initial clinical proof-of-concept for targeting FAK in mesothelioma, ovarian and lung cancer

• Two candidates in clinical development with 5 clinical trials ongoing/planned in near term
  – VS-6063 Phase 1/1b study in combination with paclitaxel in ovarian cancer ongoing
  – VS-6063 registration-directed study in mesothelioma on track for Q3 initiation
  – VS-6063 Japan bridging trial on track to start in Q3
  – VS-6063 NSCLC trial on track to start in Q3
  – VS-4718 first-in-human Phase 1 ongoing
Agenda

• 12:45 Introduction

• 1:00 Focal Adhesion Kinase (FAK) and Cancer Stem Cells

• 1:20 FAK Program Status: VS-6063 + Paclitaxel in Ovarian Cancer

• 1:40 Mesothelioma and the VS-6063 Registration-Directed Trial

• 2:30 FAK Portfolio Expansion: VS-6063 into Lung Cancer and VS-4718 into Phase 1

• 2:45 The Potential of Dual mTORC1/2 and PI3K Inhibition and VS-5584

• 3:15 Q&A

• 3:30 Close
Jose Baselga, M.D., Ph.D.
Lack of inhibition of mTOR correlates with resistance to PI3K inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Resistant</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>BYL719 1 μM h:</td>
<td>0 1 2 6 10 24</td>
<td>0 1 2 6 10 24</td>
<td>0 1 2 6 10 24</td>
<td>0 1 2 6 10 24</td>
<td>0 1 2 6 10 24</td>
<td>0 1 2 6 10 24</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pAkt (473)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>total Akt</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pS6 (240/4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pS6 (235/6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>total S6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>actin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

![Graph showing levels of pS6 (240/4) for resistant and sensitive cells with p=0.0001](image)

Elkabets et al. Science Transl Med. In press
Lack of inhibition of mTOR in patients resistant to PI3K inhibitors

A

<table>
<thead>
<tr>
<th>Non responding tumors</th>
<th>Responding tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated (pre)</td>
<td>BYL719 (post)</td>
</tr>
<tr>
<td>(1)</td>
<td>(4)</td>
</tr>
<tr>
<td>(2)</td>
<td>(5)</td>
</tr>
<tr>
<td>(3)</td>
<td>(6)</td>
</tr>
</tbody>
</table>

B

- p-value: 0.046
- p62 (240/44 H-score % value before treatment)

C

- Patient #4
  - p62 (240/44 H-Score)
  - tumor volume change (% pre-treated)
  - 5.6 months
- Patient #5
  - p62 (240/44 H-Score)
  - tumor volume change (% pre-treated)
  - 13.9 months
Synergism between mTOR and PI3K inhibitors

Elkabets et al. Science Transl Med. In press
<table>
<thead>
<tr>
<th>Portfolio of Product Candidates Targeting Cancer Stem Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Focal Adhesion Kinase (FAK)</strong></td>
</tr>
<tr>
<td><strong>VS-6063</strong></td>
</tr>
<tr>
<td>Mesothelioma</td>
</tr>
<tr>
<td>Registration-directed trial</td>
</tr>
<tr>
<td>Japanese Development</td>
</tr>
<tr>
<td>Phase 1</td>
</tr>
<tr>
<td>Lung (KRASm NSCLC)</td>
</tr>
<tr>
<td>Phase 2</td>
</tr>
<tr>
<td>Ovarian</td>
</tr>
<tr>
<td>Phase 1/1b in combo with paclitaxel</td>
</tr>
<tr>
<td><strong>VS-4718</strong></td>
</tr>
<tr>
<td>Solid Tumors</td>
</tr>
<tr>
<td>Phase 1/1b</td>
</tr>
<tr>
<td><strong>PI3K and mTORC1/2</strong></td>
</tr>
<tr>
<td><strong>VS-5584</strong></td>
</tr>
<tr>
<td>Solid Tumors and Lymphomas</td>
</tr>
<tr>
<td>IND</td>
</tr>
<tr>
<td>Phase 1/1b</td>
</tr>
<tr>
<td><strong>Wnt/β-Catenin</strong></td>
</tr>
<tr>
<td><strong>Eisai</strong></td>
</tr>
<tr>
<td>Research Collaboration</td>
</tr>
</tbody>
</table>
VS-5584: Dual mTORC1/2 and pan-PI3K Inhibitor

- Potent against mTORC1/2 & all Class 1 PI3K isoforms
- Oral formulation
- IND-enabling toxicity studies ongoing
- Phase 1 dose escalation in patients with advanced cancers planned to initiate Q4 2013
  - Solid tumors and lymphomas

Composition of matter through 2029

### IC_{50} (nM)

<table>
<thead>
<tr>
<th></th>
<th>mTOR</th>
<th>PI3K-Alpha</th>
<th>PI3K-Beta</th>
<th>PI3K-Delta</th>
<th>PI3K-Gamma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3.4</td>
<td>2.6</td>
<td>21</td>
<td>3.0</td>
<td>2.7</td>
</tr>
</tbody>
</table>

Elimination of CSCs
VS-5584 Potently Targets Human B-Cell Lymphoma Cell Lines

- PI3K-delta inhibitors CAL-101 and IPI-145 have shown promising clinical activity in patients with B-cell malignancies

<table>
<thead>
<tr>
<th>IC_{50} (nM)</th>
<th>mTOR</th>
<th>PI3Kα</th>
<th>PI3Kβ</th>
<th>PI3Kγ</th>
<th>PI3Kδ</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VS-5584</strong></td>
<td>3.4</td>
<td>2.6</td>
<td>21</td>
<td>2.7</td>
<td>3.0</td>
</tr>
<tr>
<td><strong>CAL-101</strong></td>
<td>&gt; 10,000</td>
<td>8500</td>
<td>840</td>
<td>550</td>
<td>11</td>
</tr>
<tr>
<td><strong>IPI-145</strong></td>
<td>9,800</td>
<td>243</td>
<td>97</td>
<td>3.7</td>
<td>0.9</td>
</tr>
</tbody>
</table>

SU-DHL-5 cells (DLBC Lymphoma)  
JeKo cells (Mantle Cell L)  
Mino cells (Mantle Cell L)
VS-5584: Robust Tumor Growth Inhibition in Preclinical Models

Superior to Everolimus in Xenograft Model

Taxane-Resistant Breast Ca Patient-Derived Xenograft

---

Colo205

**Mean Tumor Volume (mm³) ± S.E.M.**

- Placebo Control
- Everolimus (5 mg/kg)
- Everolimus (11 mg/kg)
- Everolimus (35 mg/kg)  
- VS-5584 (11 mg/kg)
- VS-5584 (25 mg/kg)

*** p<0.001

**Tumor Volume (mm³)**

- Vehicle
- VS-5584, 20 mg/kg po
- Docetaxel, 20 mg/kg iv
VS-5584: Dual mTORC1/2 and PI3K Inhibitor with Preferential Effects on Cancer Stem Cells

- VS-5584 is ~30-fold more potent vs CSCs than non-CSCs

**Proliferation**

- CSCs vs Non-CSCs

**Apoptosis**

- Annexin-V Positive Cells

---

*SUM159 Triple Negative Breast Cancer*
**VS-5584 Reduces CSCs in MCF7 Breast Cancer Model:**
Contrast to mTORC1 inhibitor, Everolimus

---

**ALDH CSC assay**

<table>
<thead>
<tr>
<th>% ALDH+ CSCs</th>
<th>p = 0.0074</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
</tr>
<tr>
<td>Compound</td>
<td></td>
</tr>
</tbody>
</table>

---

**2° Tumorspheres**

<table>
<thead>
<tr>
<th>Spheres / 2000 Cells</th>
<th>p = 0.0007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>Everolimus</td>
<td></td>
</tr>
<tr>
<td>VS-5584</td>
<td></td>
</tr>
</tbody>
</table>

---

**Tumor Initiation in 2° Mice**

<table>
<thead>
<tr>
<th>Tumor Initiating Frequency (% of Control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td>Everolimus</td>
</tr>
<tr>
<td>VS-5584</td>
</tr>
</tbody>
</table>

VS-5584 reduced tumor-initiating capability by ~20-fold
VS-5584 Extends Efficacy of Chemotherapy in SCLC Model

SCLC Cell Line Panel

VS-5584 Extends Cisplatin Efficacy in SCLC Xenograft Model

PI3Kα mt or PTEN loss

Cisplatin

VS-5584
Clinical Trial Designs for Drugs Targeting Cancer Stem Cells

Concurrent: **CSC Drugs + Chemo**
- Initial Tumor
- Tumor Reduction & Elimination of CSCs
- Theoretical Result: More Durable Clinical Response

Maintenance:
- **Chemo**
  - Initial Tumor
  - Tumor Reduction but CSCs are Enriched
- **CSC Drugs**
  - More Durable Clinical Response
VS-5584: Phase 1 Dose Escalation and Schedule Finding Study

- Phase 1 dose escalation in patients with advanced solid tumors including lymphomas
- Pre/post treatment biopsies
- Expansion at recommended Phase 2 dose/schedule into cancer stem cell-driven tumors
- Targeted initiation – YE 2013
- Clinical deployment leveraging competitor experience

**VS-5584 dose escalation**

**Biopsy**

**Determine Recommended Phase 2 Dose**

**VS-5584 Expansion Cohort (RP2D) Follow until disease progression**
Agenda

• 12:45 Introduction

• 1:00 Focal Adhesion Kinase (FAK) and Cancer Stem Cells

• 1:20 FAK Program Status: VS-6063 + Paclitaxel in Ovarian Cancer

• 1:40 Mesothelioma and the VS-6063 Registration-Directed Trial

• 2:30 FAK Portfolio Expansion: VS-6063 into Lung Cancer and VS-4718 into Phase 1

• 2:45 The Potential of Dual mTORC1/2 and PI3K Inhibition and VS-5584

• 3:15 Q&A

• 3:30 Close
Upcoming Milestones

H1 2013
- FDA Meeting
- EU Meeting
- VS-4718 IND
- VS-6063 EU Orphan
- VS-4718 Phase 1 in solid tumors
- VS-6063 Phase 1 combo
- AACR
- ASCO

H2 2013
- VS-5584 IND
- VS-6063 US Orphan
- VS-6063 Meso trial
- VS-5584 Phase 1
- VS-6063 Phase 1b combo expansion
- VS-6063 Japanese Phase 1
- VS-6063 NSCLC
- VS-6063 Phase 1 combo safety
- EORTC

2014
- VS-4718 Phase 1
- VS-6063 Phase 1b combo biomarkers and activity
- VS-4718 Phase 1b biomarkers
- VS-5584 Phase 1
- VS-6063 NSCLC
- VS-6063 Japanese Phase 1
- AACR, ASCO & EORTC

Estimates based on currently proposed clinical plans and are subject to change
## Portfolio of Product Candidates Targeting Cancer Stem Cells

<table>
<thead>
<tr>
<th>Product</th>
<th>PreClin</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Focal Adhesion Kinase (FAK)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VS-6063</td>
<td></td>
<td>Registration-directed trial</td>
<td>Phase 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Phase 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VS-4718</td>
<td></td>
<td>Phase 1/1b in combo with paclitaxel</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PI3K and mTORC1/2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VS-5584</td>
<td>IND</td>
<td>Phase 1/1b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VS-5584</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Wnt/β-Catenin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Eisai</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Japanese Development</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Lung (KRASm NSCLC)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ovarian</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Solid Tumors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Solid Tumors and Lymphomas</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Research Collaboration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>