PI3K/MTOR KINASE INHIBITOR VS-5584

NON-CONFIDENTIAL SUMMARY

APRIL 2015
**Verastem: Company Summary**

- Verastem (VSTM) is a publically traded Biotech company based in Boston, MA

- Founded in 2010 by Bob Weinberg (Whitehead Institute, MIT) & Eric Lander (Broad Institute)

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

- Clinical programs:
  - VS-5584 is a selective dual PI3K/mTOR kinase inhibitor (Phase 1)
  - VS-6063 (lead program) is a selective inhibitor of FAK & PYK2 protein kinases
    - Multiple phase 1 & 2 clinical trials in various solid tumor indications including the registration directed COMMAND study in Malignant Pleural Mesothelioma
  - VS-4718 is a structurally distinct FAK & PYK2 inhibitor (Phase 1)
Verastem Objectives for CRUK Combinations Alliance

• Combine VS-5584 with novel agents
  – Phase 1 combination study with FAK inhibitor VS-6063 currently enrolling in mesothelioma

• Selected combinations of interest with VS-5584
  – PARP inhibitors
  – Androgen receptor antagonists
  – Aromatase inhibitors

• Selected indications of interest
  – SCLC
  – Ovarian cancer
  – ER positive and Triple Negative Breast Cancer

• Open to additional novel combos and indications with strong scientific rationale
Scientific Rationale
Targeting Cancer Stem Cells for a Durable Clinical Response

Problem:
Initial tumor → Tumor Reduction but CSCs Survive → Recurring Tumor

Solution:
Initial tumor → Tumor Reduction and Elimination of CSCs → Durable Clinical Response

Current cancer treatments

CSC drugs + current cancer treatments

Initial tumor

Durable Clinical Response
VS-5584 Highlights

- PI3K/mTOR dual kinase inhibitor
  - Equipotent against mTORC1, mTORC2 and all four PI3K class I isoforms
  - Highly selective vs. other protein & lipid kinases

- Preferentially targets cancer stem cells *in vitro & in vivo*

- Broad, robust anti-tumor activity in xenograft & PDX models

- Phase I dose escalation in progress in patients with solid tumors
  - 3x/week intermittent dosing schedule
Inhibition of PI3K/mTOR Targets Cancer Stem Cells in Multiple Assays

**HMLE CSC Assay**

![Graph showing cell viability percentage for CSCs and non-CSCs with VS-5584 concentration on the x-axis.]

**Dye Exclusion CSC Assay**

![Image of flow cytometry analysis with arrows indicating 21% CSCs in control and 0.002% CSCs with VS-5584, 300 nM.

**Aldefluor CSC Assay**

![Graphs showing Aldefluor-positive CSCs as a percentage of control with VS-5584 and Paclitaxel concentrations on the x-axis.

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![Graphs showing Aldefluor-positive CSCs as a percentage of control with VS-5584 and Paclitaxel concentrations on the x-axis.]

**Paclitaxel**

![Graphs showing Aldefluor-positive CSCs as a percentage of control with Paclitaxel concentrations on the x-axis.]

**Novel Drugs Targeting Cancer Stem Cells**

- VS-5584
- Paclitaxel

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**Legend:**
- CSCs
- non-CSCs
- Control
- VS-5584, 300 nM
- Paclitaxel

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**Aldefluor-Positive CSCs (% of Control)**

- VS-5584
- Paclitaxel

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**Concentration, nM**

- 0.1
- 1
- 10
- 100
- 1000
- 10000

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**Concentration, µM**

- 0.001
- 0.01
- 0.1
- 1
- 10
- 100
VS-5584 Reduces CSCs in MCF7 Breast Cancer Model: Contrast to mTORC1 Inhibitor Everolimus

ALDH CSC assay

2° Tumorspheres

Tumor Initiation in 2° Mice

Kolev et al. (2015) Cancer Res 75: 446

Novel Drugs Targeting Cancer Stem Cells
Combined Inhibition of PI3K and mTOR is Critical for CSC Targeting Phenocopies VS-5584

Kolev et al. (2015) Cancer Res 75: 446

Novel Drugs Targeting Cancer Stem Cells
VS-5584 Preferentially Targets CSCs & Extends Efficacy of Chemotherapy in SCLC Models

**Blockade of Tumor Initiating Capacity**

Mice bearing SCLC xenograft tumors treated with VS-5584 20 mg/kg, po, 3x/wk
– Viable cells dissociated & CSCs tested

↓ CSCs
↓ Tumor-Initiating Potential in 2° Mice

VS-5584 Extends Cisplatin Efficacy in SCLC Xenograft Model

<table>
<thead>
<tr>
<th>% Side Population</th>
<th>Vehicle</th>
<th>VS-5584</th>
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<tbody>
<tr>
<td>1.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5</td>
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<tr>
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<table>
<thead>
<tr>
<th># Cells</th>
<th>Control</th>
<th>VS-5584</th>
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<tbody>
<tr>
<td>1,000,000</td>
<td>4(4)</td>
<td>2(4)</td>
</tr>
<tr>
<td>100,000</td>
<td>2(3)</td>
<td>0(3)</td>
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<tr>
<td>1,000</td>
<td>1(3)</td>
<td>0(3)</td>
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</table>

TIF

\[
\frac{1}{24,000} \quad \frac{1}{1,615,000}
\]

\( \rho = 5 \times 10^{-6} \)

70-fold decrease in TIF

NCI-H841 SCLC xenograft model

H69 SCLC xenograft model
Potential Clinical Trial Designs for Drugs Targeting Cancer Stem Cells

Concurrent:

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

**SCLC**

Maintenance:

- **Cisplatin + Etoposide**
  - Initial Tumor
  - Tumor Reduction but CSCs are Enriched

**VS-5584**

Theoretical Result

- More Durable Clinical Response
VS-5584 is More Potent than PI3K-delta Inhibitors Against the Proliferation & Survival of B-cell Leukemia/Lymphoma in vitro

<table>
<thead>
<tr>
<th></th>
<th>mTOR</th>
<th>PI3Kα</th>
<th>PI3Kβ</th>
<th>PI3Kγ</th>
<th>PI3Kδ</th>
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<tbody>
<tr>
<td>VS-5584</td>
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<td>2.6</td>
<td>21</td>
<td>2.7</td>
<td>3.0</td>
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<tr>
<td>CAL-101</td>
<td>&gt; 10,000</td>
<td>8500</td>
<td>840</td>
<td>550</td>
<td>11</td>
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<tr>
<td>IPI-145</td>
<td>1600</td>
<td>85</td>
<td>27</td>
<td>2.5</td>
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</table>
Phase 1 Single Agent Dose Escalation
**VS-5584: Phase 1 Dose Finding and Safety Study in Solid Tumors**

**Design**
- Phase 1 dose escalation study in solid tumors

**Status**
- Generally well tolerated to date and the expected on-target effects are clinically manageable
- MTD has not yet been reached
- Expect to report preliminary data in H2 2015

**Sites**
- Royal Marsden Hospital (UK) – Dr. Udai Banerji
- Scottsdale Healthcare (AZ – US) – Dr. Jasgit Sachdev
- Sarah Cannon Research Institute (TN – US) – Dr. Howard Burris
- Memorial Sloan Kettering Cancer Center (NY – US) – Dr. Anna Varghese
- Cedars-Sinai Medical Center (CA – US) – Dr. Monica Mita

**Observations**
- Well within active dose range based on PD biomarker measurements
- Initial clinical activity in multiple tumors including mesothelioma
- Disease control of 6 months or more has been observed

*Unlocked, in-progress data as of 5 Jan 2015*
Mesothelioma: VS-5584/VS-6063 Combination Study in Relapsed Mesothelioma
### VS-5584 and VS-6063 mesothelioma combo, Phase 1

**Phase 1 dose finding and safety study in solid tumors**

1. **Rationale**
   - Strong pre-clinical data demonstrating synergy of VS-5584 and VS-6063 in pre-clinical mesothelioma models
   - 3 FAKi’s have demonstrated SD in meso patients with relapsed disease
   - PI3k/mTOR inhibitor GDC-0980 demonstrated ORR in meso patients with relapsed disease

2. **Goals**
   - Safety of combination
   - Biomarker analysis (assess target proteins in tumor and genomic analysis, PRP for pharmacodynamics)
   - Assess potential activity in mesothelioma

3. **Investigators**
   - Dr. Banerji, Royal Marsden (UK)
   - Dr. Fennell, University of Leicester (UK)
   - Dr. Kindler, University of Chicago (IL)
   - Dr. Zauderer, Memorial Sloan Kettering (NY)

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### 21 day cycle

<table>
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<tr>
<th>VS-6063 (400 mg BID) &amp; VS-5584 Determine recommended Phase 2 dose</th>
</tr>
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<tr>
<td>21 day cycle(s)</td>
</tr>
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</table>

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

- Archival / optional biopsy
- Optional biopsy

**Expansion Cohort (RP2D)** Follow until disease progression

- Biopsy
Enhanced Antitumor Efficacy of VS-5584 and VS-6063 Combination Compared to Single Agent in MM87 Mesothelioma *in vivo*

- Dosing started 11 days post MM87 cell injection with evidence of tumor burden. 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

*Source: J. Testa, Fox Chase*
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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*

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*VP, Head of Research*  
*Head of Cancer Biology, OSI (now Astellas)*  
*Schering-Plough (now Merck)*

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

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*Former CEO/Chair Genzyme*

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*Former President/CEO Incyte (INCY)*

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*CEO Karyopharm (KPTI), former CMO Onyx*

Louise Phanstiel  
*BOD: Cedars Sinai, MYGN*

Stephen Sherwin, M.D.  
*BOD: BIIB; NBIX, RIGL*
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*Millennium (co-developed Velcade®)*

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*Broad Institute/MIT/HMS*
*Pioneer of Human Genome Project*

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*Yale Medical School*
*Cofounder: Sugen (Pfizer), Plexxikon (Daiichi-Sankyo)*

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*Director – Stem Cell Program*
*Harvard Medical School/HHMI*

Eric Winer, M.D.
*Director – Breast Oncology Center*
*Dana Farber Cancer Institute/HMS*