VS-5584

PI3K/mTOR Kinase Inhibitor Completing Phase 1 Dose Escalation
Summary: Verastem is actively seeking proposals through the CRUK Combinations Alliance with PI3K/mTOR inhibitor VS-5584

• Combinations of interest to Verastem
  —BTK inhibitor combination in lymphoma/leukemia (e.g. DLBCL)
  —Combination with cisplatin + XRT in cervical cancer
  —Combination with androgen receptor blockade in prostate cancer
  —Combination with platinum in BRCA mutant cancers (ovarian ca post PARPi, TNBC etc.)
  —Combination with weekly paclitaxel in endometrial ca

• Additional concepts with strong scientific rationale
VS-5584 overview/positioning

**VS-5584**

- PI3K/mTOR dual kinase inhibitor
  - Equipotent against mTORC1, mTORC2 and all four PI3K class I isoforms
  - High selectivity 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

<table>
<thead>
<tr>
<th>mTOR IC₅₀ (nM)</th>
<th>PI3K isoform IC₅₀ (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alpha     Beta  Delta  Gamma</td>
</tr>
<tr>
<td>3.4</td>
<td>2.6        21      3.0     2.7</td>
</tr>
</tbody>
</table>
## Pan-PI3K & mTOR dual inhibitors

<table>
<thead>
<tr>
<th>Pan-PI3K/mTOR dual inhibitors</th>
<th>mTOR</th>
<th>PI3K</th>
<th>α</th>
<th>β</th>
<th>δ</th>
<th>γ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gedatolisib (PF-05212384)</td>
<td></td>
<td></td>
<td>1</td>
<td>0.4</td>
<td>0.6</td>
<td>0.8</td>
</tr>
<tr>
<td>Pfizer I.V., weekly</td>
<td>Active, Ph 2 CRC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VS-5584 Verastem Oral, 3x / week</td>
<td>Active, Ph 1</td>
<td>3.4</td>
<td>2.6</td>
<td>21</td>
<td>3.0</td>
<td>2.7</td>
</tr>
<tr>
<td>PQR-309 Piqur Oral, once daily</td>
<td>Active, Ph 1</td>
<td>mTORC1 and 2</td>
<td>Pan-PI3K, data unreleased</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
PI3K/mTOR inhibitors as Cancer Stem Cell targeting agents
VS-5584 preferentially target CSCs \textit{in vitro} in a panel of orthogonal cancer stem cell assays

VS-5584 treatment, breast cancer cell lines:

<table>
<thead>
<tr>
<th>Aldefluor assay</th>
<th>CD44/CD24 assay</th>
<th>Hoechst Dye Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Graph" /></td>
<td><img src="image2.png" alt="Graph" /></td>
<td><img src="image3.png" alt="Graph" /></td>
</tr>
</tbody>
</table>

### Aldefluor assay
- **X-axis:** VS-5584, µM
- **Y-axis:** % Cell Viability
- **Legend:**
  - Aldefluor -
  - Aldefluor +

### CD44/CD24 assay
- **X-axis:** VS-5584, µM
- **Y-axis:** % Cell Viability
- **Legend:**
  - CSCs
  - non-CSCs

### Hoechst Dye Exclusion
- **X-axis:** µM VS-5584
- **Y-axis:** % Side Population CSCs

*Verastem, Inc. Confidential*
Dual PI3K/mTOR inhibitor VS-5584 preferentially targets CSCs in vivo, in contrast to mTORC1 inhibitor everolimus

VS-5584 treatment, MCF7 breast cancer xenograft model:

Treatment (control vs. VS-5584 vs. Everolimus – mTORC1 inhibitor) → Harvest tumors → Dissociation → Viable cells → Aldefluor assay → Tumorsphere assay → Re-implantation in limiting dilutions

CSC Population (Aldefluor +)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>% ALDH+ CSCs</th>
<th>Placebo</th>
<th>Everolimus</th>
<th>VS-5584</th>
</tr>
</thead>
<tbody>
<tr>
<td>placebo</td>
<td>0.5</td>
<td><img src="image1.png" alt="Graph" /></td>
<td><img src="image2.png" alt="Graph" /></td>
<td><img src="image3.png" alt="Graph" /></td>
</tr>
<tr>
<td>everolimus</td>
<td>1.5</td>
<td><img src="image4.png" alt="Graph" /></td>
<td><img src="image5.png" alt="Graph" /></td>
<td><img src="image6.png" alt="Graph" /></td>
</tr>
<tr>
<td>vs-5584</td>
<td>1.0</td>
<td><img src="image7.png" alt="Graph" /></td>
<td><img src="image8.png" alt="Graph" /></td>
<td><img src="image9.png" alt="Graph" /></td>
</tr>
</tbody>
</table>

2° Tumorspheres

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Spheres / 2000 Cells</th>
<th>Placebo</th>
<th>Everolimus</th>
<th>VS-5584</th>
</tr>
</thead>
<tbody>
<tr>
<td>placebo</td>
<td>200</td>
<td><img src="image10.png" alt="Graph" /></td>
<td><img src="image11.png" alt="Graph" /></td>
<td><img src="image12.png" alt="Graph" /></td>
</tr>
<tr>
<td>everolimus</td>
<td>400</td>
<td><img src="image13.png" alt="Graph" /></td>
<td><img src="image14.png" alt="Graph" /></td>
<td><img src="image15.png" alt="Graph" /></td>
</tr>
<tr>
<td>vs-5584</td>
<td>600</td>
<td><img src="image16.png" alt="Graph" /></td>
<td><img src="image17.png" alt="Graph" /></td>
<td><img src="image18.png" alt="Graph" /></td>
</tr>
</tbody>
</table>

Tumor Initiating Frequency

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Tumor Initiating Frequency (% of Control)</th>
<th>Placebo</th>
<th>Everolimus</th>
<th>VS-5584</th>
</tr>
</thead>
<tbody>
<tr>
<td>placebo</td>
<td>0</td>
<td><img src="image19.png" alt="Graph" /></td>
<td><img src="image20.png" alt="Graph" /></td>
<td><img src="image21.png" alt="Graph" /></td>
</tr>
<tr>
<td>everolimus</td>
<td>100</td>
<td><img src="image22.png" alt="Graph" /></td>
<td><img src="image23.png" alt="Graph" /></td>
<td><img src="image24.png" alt="Graph" /></td>
</tr>
<tr>
<td>vs-5584</td>
<td>150</td>
<td><img src="image25.png" alt="Graph" /></td>
<td><img src="image26.png" alt="Graph" /></td>
<td><img src="image27.png" alt="Graph" /></td>
</tr>
</tbody>
</table>

Treatment with VS-5584 reduces the population of CSCs and tumor initiating cells, and reduces the ability of remaining cells to generate new tumors

Kolev et al. Cancer Res. 2015
Combined inhibition of PI3K and mTOR is critical for CSC targeting

siRNA transfection VS-5584 phenocopy, SUM159 cells:

Kolev et al., Cancer Res 2015
VS-5584 preferentially targets CSCs in a SCLC model in vivo: ~70-fold reduction in tumor initiating frequency

VS-5584 treatment, NCI-H841 SCLC model:

Antitumor Efficacy

SP CSC Assay

Limiting Dilution Assay

*VS-5584 25mg/kg, oral gavage, qd MWF, 3 cycles
Kolev et al. Cancer Res. 2015
VS-5584 in combination with cisplatin/etoposide targets CSCs in a SCLC model in vivo

NCI-H841 SCLC model:

NCI-H841 → Control → Recover y of viable cells → Re-implantation in limiting dilutions

Cisplatin/Etoposide

VS-5584

Cis/Eto + VS-5584 -> VS-5584 maintenance

Tumor Initiation

Kolev et al. AACR 2015 Meeting, Abstract 1525
VS-5584 extends efficacy in combination with chemotherapy in SCLC xenograft models

Front line + maintenance model
VS-5584 in NCI-H841 SCLC xenograft model:

[Graph showing tumor weight over study days for Cisplatin, Cisplatin + VS-5584, and Vehicle groups.]
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>
</tr>
</thead>
<tbody>
<tr>
<td>VS-5584</td>
<td>3.4</td>
<td>2.6</td>
<td>21</td>
<td>2.7</td>
<td>3.0</td>
</tr>
<tr>
<td>CAL-101</td>
<td>&gt;10,000</td>
<td>8500</td>
<td>840</td>
<td>550</td>
<td>11</td>
</tr>
<tr>
<td>IPI-145</td>
<td>1600</td>
<td>85</td>
<td>27</td>
<td>2.5</td>
<td></td>
</tr>
</tbody>
</table>
VS-5584:
Phase 1 dose escalation, solid tumors
VS-5584 Phase 1 solid tumors
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
• 5 – 75 mg doses evaluated; MTD reached

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 observed
VS-5584 Phase 1 Trial Update (VS-5584-101)

- 75 patients dosed
- Currently in confirmatory expansion cohort at 55mg M/W/F
- Overall, well tolerated; toxicities include HTN (DLT), mucositis, rash
- Mucositis: all grade 1-2
- Hyperglycemia has been minimal
- Initial single agent clinical activity (PRs and prolonged SD) observed in some tumors
- Additional data from Phase I available under CDA
VS-5584, a pan-PI3K/mTOR inhibitor, will be moving into single agent cohorts and phase 1b combination cohorts with chemotherapy

- VS-5584 is equipotent against mTORC1, mTORC2 and all four PI3K class I isoforms
- Combined inhibition of PI3K and mTOR is critical to CSC targeting

<table>
<thead>
<tr>
<th>mTOR IC50 (nM)</th>
<th>PI3K isoform IC50 (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alpha</td>
</tr>
<tr>
<td></td>
<td>3.4</td>
</tr>
</tbody>
</table>

Phase 1: Dose escalation of oral, intermittent dosing in advanced non-hematologic malignancies or lymphoma

- Continues to be safe and well tolerated
- 5-75mg dose range evaluated, MTD reached
- Ongoing RP2D confirmation cohort at 55 mg dose

Planned single-agent expansion cohorts at RP2D in NHL/CLL and ovarian/endometrial cancer

1Kolev VN et al. PI3K/mTOR dual inhibitor VS-5584 preferentially targets cancer stem cells. Cancer Res. 2015
VS-5584 Clinical Development Strategies – Current Concepts

- Targeting CSC (combination strategies)

- Targeting TORC2 mediated genome stability (in combination with DNA damaging agents (i.e. platinum, etc.)

- Targeting reciprocal pathway activation in setting of ER/AR inhibition

- Supported by preclinical activity (in vitro and in vivo models)

- Confirmation/follow up of clinical signals from phase 1 trial

- Learnings from clinical activity and development of competitive drugs (Dual PI3K/mtor inhibitors, PI3K inhibitors, TORC1/TORC2 inhibitors, AKT inhibitors, rapalogs, etc)
VS-5584: Rationale for Combining with Chemotherapy

• VS-5584 targets CSC in preclinical models:
  - In SCLC models, VS-5584 inhibits CSC, inhibits tumor growth, and maintains response to platinum.
  - In TNBC models, VS-5584 inhibits CSC, inhibits tumor growth, and maintains response to paclitaxel

• In GBM, TORC2 mediates cisplatin resistance through NF-kB in an Akt-independent manner (Tanaka, et al).

• TORC2 signaling pathway contributes to genome stability in the face of DNA damaging agents such as platinum (Wick, Shimada, Weisman).
TORC2 Signaling Pathway Guarantees Genome Stability in the Face of DNA Strand Breaks

Kenji Shimada,¹,⁵ Ireos Filipuzzi,²,⁵ Michael Stahl,³ Stephen B. Helliwell,² Christian Studer,² Dominic Hoepfner,² Andrew Seeber,¹,⁴ Robbie Loewith,³ N. Rao Movva,² and Susan M. Gasser¹,⁴,*
¹Friedrich Miescher Institute for Biomedical Research, Maulbeerstrasse 66, 4058 Basel, Switzerland
²Novartis Institutes for Biomedical Research, Novartis Pharma AG, Fabrikstrasse 22, 4056 Basel, Switzerland
³Department of Molecular Biology, University of Geneva, rue Ernest-Ansermet 30, 1211 Geneva, Switzerland
⁴Faculty of Natural Sciences, University of Basel, Klingelbergstrasse 70, 4056 Basel, Switzerland
⁵These authors contributed equally to this work
*Correspondence: susan.gasser@fmi.ch
http://dx.doi.org/10.1016/j.molcel.2013.08.019

TORC2—a new player in genome stability

Ronit Weisman³,*, Adiel Cohen¹ & Susan M Gasser²,*
VS-5584: Rationale for combining with PARP inhibition

Doubling Down on the PI3K-AKT-mTOR Pathway Enhances the Antitumor Efficacy of PARP Inhibitor in Triple Negative Breast Cancer Model beyond BRCA-ness\textsuperscript{1,2}

Pradip De\textsuperscript{*,*}, Yuling Sun\textsuperscript{*}, Jennifer H. Carlson\textsuperscript{*}, Lori S. Friedman\textsuperscript{†}, Brian R. Leyland-Jones\textsuperscript{*,*} and Nandini Dey\textsuperscript{*,*}

*Department of Molecular and Experimental Medicine, Avera Cancer Institute, Sioux Falls, SD; †Department of Internal Medicine, University of South Dakota, Vermillion, SD; Genentech, South San Francisco, CA

Several Clinical Trials Ongoing with combination PARP inhibitors + mTOR/PI3K/AKT inhibitors
- AZD2014 + olaparib
- BKM120/BYL179 + olaparib (TNBC, ovarian ca)
VS-5584: Rationale for NHL / Lymphoproliferative Disorders

• VS-5584 is a potent inhibitor of delta and gamma PI3 kinases.

• Validated target with Idelalisib (approved) and IPI-145 in phase 3 development.

• VS-5584 has potent in vitro activity against B-cell leukemia/lymphoma cell lines

• ABC-type DLBCL driven by PIK3CA and sensitive to pan PI3K inhibitor

• in-vitro and xenograft synergy data with combined mTOR and BTK inhibition in DLBCL
VS-5584: Rationale for Combining with Hormonal Therapy

• In HR+ breast cancer, it is well established (BOLERO-2) that the reciprocal activation of PI3K/mTOR/AKT pathway occurs in setting of blocking ER. Multiple drugs in this class are being evaluated in this setting, following up on success of BOLERO-2 (BKM-120 + fulvestrant. AZD2014 + fulvestrant, etc)

• In prostate cancer, similar reciprocal activation of PI3K/mTOR pathway occurs in setting of androgen receptor inhibition (combinations with abiraterone, enzalutamide, etc) (C Sawyers, et al)
VS-5584: Rationale for Combining with Her2 Targeted Therapies

- Preclinical data in Her2+ breast cancer models with lapatinib + MLN0128 showing synergy (C. Arteaga, Clin Can Res. 2012:18, 2603)
VS-5584: Potential Combination Clinical Trials of Interest

• VS-5584 + BTK inhibitor in ABC subtype of DLBCL

• VS-5584 + Cisplatin + XRT in first-line treatment of locally advanced/metastatic cervical cancer

• Combination VS-5584 + weekly paclitaxel
  - Platinum resistant ovarian ca (2nd-3rd line)
  - 2nd/3rd line endometrial ca
  - TNBC

• Combination VS-5584 + cisplatin in BRCA-mutated cancers
  - BRCA-mutated ovarian ca after PARPi failure
  - other BRCA mutated cancers (CRPC, pancreatic, TNBC)

• Combination with AR inhibitors in castration-resistant prostate cancer