VS-5584 a Dual mTOR and PI3K Inhibitor has Antitumor Activity in Multiple in vivo Xenograft Tumor Models and Enhanced Efficacy in Combination with Cisplatin or Docetaxel

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ABSTRACT

Verastem is developing VS-5584, a potent and selective dual inhibitor of the mammalian target of rapamycin (mTOR) and class I phosphatidylinositol 3-kinase (PI3K), for the treatment of cancer. The PI3K/mTOR signaling pathway is a key regulator of cancer progression and in the survival of cancer stem cells (CSCs). VS-5584 has been shown to be an equipotent inhibitor of all four human Class I PI3K isoforms and the mTOR kinase, and PI3K signaling has been implicated in the maintenance of CSCs in solid tumors. In multiple orthogonal in vitro assays, VS-5584 has shown to preferentially target CSCs and exhibited significant antiproliferative activity across multiple cancer cell lines. Furthermore, oral administration of VS-5584 has been shown to reduce CSCs in xenograft models. The in vivo antitumor efficacy of once daily and intermittent oral administration of VS-5584 was evaluated in multiple xenograft tumor models representing small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), triple negative breast cancer (TNBC) and mesothelioma. Once daily (qd) treatment with VS-5584 demonstrated potent anti-tumor activity, with mean percentage tumor growth inhibition (TGI) ranging from 40% to 97% (P < 0.05). In these models, TGI was dose-dependent with dosages at and above 15 mg/kg showing good antitumor activity (P < 0.05). Interestingly, tumor regression (TR) was observed in 33% (3/9) of mice bearing H226 (SCLC) tumors, 60% (6/10) of mice bearing MDA-MB-468 (TNBC) tumors and 50% (5/10) of mice bearing NCI-H226 mesothelioma tumors. This significant antitumor activity was generally observed at well-tolerated dosages. In studies exploring intermittent dosing schedules, efficacy and tolerability were similar or better with a q5d days on/2 days off or Monday, Wednesday, Friday schedule compared to continuous daily dosing. We also explored the efficacy of VS-5584 in combination with either cisplatin or docetaxel. In these studies, VS-5584 plus either cisplatin or docetaxel showed significant TGI compared to cisplatin alone in H226 SCLC and docetaxel alone in A549 NSCLC xenograft models (P < 0.05). This potent in vivo antitumor activity in xenograft models of NSCLC, SCLC, TNBC and mesothelioma suggests that VS-5584 has the potential for anticancer activity across a variety of cancer types. Intermittent dosing with VS-5584 was sufficient to achieve good efficacy while minimizing side effects, thus allowing a broader therapeutic window compared to qd dosing. VS-5584 in combination with either cisplatin or docetaxel had enhanced antitumor activity compared to either chemotherapy agents in two in vivo models of lung cancer. VS-5584 safety is being evaluated in a Phase 1 clinical trial assessing intermittent dosing in subjects with advanced non-hematologic malignancies or lymphoma.

INTRODUCTION

Figure 1. Structure & Selectivity Profile of VS-5584

Table 1. VS-5584 is a Potent Inhibitor of Recombinant Human PI3Kα, PI3Kβ, PI3Kγ, and PI3Kδ mTOR Kinases, and the H1047R Mutant Form of PI3Kα with Low nM IC50

<table>
<thead>
<tr>
<th>Kinase</th>
<th>VS-5584 (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI3Kα</td>
<td>4</td>
</tr>
<tr>
<td>PI3Kβ</td>
<td>2.4</td>
</tr>
<tr>
<td>PI3Kγ</td>
<td>2</td>
</tr>
<tr>
<td>PI3Kδ</td>
<td>3.7</td>
</tr>
</tbody>
</table>

VS-5584 was selected for these kinase assays among a library of over 400 compounds (Hart et al., Mol Cancer Ther. 2013 12(12) 2541-42).

Figure 2. Intermittent Dosing Schedules (qdx5 or qw) are as Effective as Continuous Daily Dosing (qd) in SUM159 TNBC Xenograft Models

A. VS-5584 Daily Dosing

B. VS-5584 1 Doses/2 Days Off Dosing

C. VS-5584 Three Times a Week Dosing

Figure 3. VS-5584 Induces Apoptosis

Figure 4. VS-5584 has Enhanced Antitumor Activity Compared to Standard Chemotherapeutic Agents in Xenograft Models of NSCLC, TNBC, SCLC and Mesothelioma

Data presented as mean ± SEM.

Figure 5. VS-5584 in Combination with Either Cisplatin or Docetaxel has Enhanced Antitumor Activity

A. A549 NSCLC

B. H996 SCLC

C. H226 TNBC

Data presented as mean ± SEM.

SUMMARY

- Based on the single and combination activity observed across a broad panel of cancer models, VS-5584 has the potential for broad antitumor activity across a variety of different cancer types
- VS-5584 in combination with standard chemotherapeutic agents had enhanced antitumor activity compared to chemotherapeutic agents alone in the models tested
- Intermittent dosing with VS-5584 resulted in significant antitumor activity that was similar to or better than a once daily continuous dosing regimen. This may be due to induction of apoptosis by VS-5584
- These preclinical data provide the rationale for intermittent dosing of VS-5584 being evaluated in an ongoing Phase 1 dose escalation trial (NCT0199138) with the goal of achieving an optimal therapeutic window