



## **Verastem Oncology Announces Presentation of Preclinical Data Supporting the Combination of VS-6766 and Defactinib in Metastatic Uveal Melanoma**

June 22, 2020

*Data Presented at the American Association for Cancer Research 2020 Virtual Annual Meeting II Show Synergism between FAK and RAF/MEK Inhibition Supporting Clinical Evaluation of Defactinib with VS-6766 in Metastatic Uveal Melanoma*

*Verastem's RAF/MEK Inhibitor (VS-6766) and FAK Inhibitor (Defactinib) Currently Being Investigated Clinically in Low-Grade Serous Ovarian and KRAS Mutant Non-Small Cell Lung Cancers*

BOSTON--(BUSINESS WIRE)--Jun. 22, 2020-- Verastem, Inc. (Nasdaq:VSTM) (also known as Verastem Oncology), a biopharmaceutical company committed to developing and commercializing new medicines for patients battling cancer, today announced results from a study that provides preclinical proof-of-concept for combining VS-6766, its RAF/MEK inhibitor, with defactinib, its focal adhesion kinase (FAK) inhibitor, for the treatment of metastatic uveal melanoma (UM), the most prevalent eye cancer among adults. The data comprise one of four virtual posters with Verastem authors being presented today at the American Association for Cancer Research (AACR) 2020 Virtual Annual Meeting II, which is taking place June 22-24, 2020.

Uveal melanoma arises from the melanin-producing cells in the eye, similar to how it arises in cutaneous melanoma. While it's considered rare, primary UM metastasizes in 50% of patients with only 8% of patients surviving 2 years after development of metastatic disease.<sup>1</sup> Previously, MEK inhibitors, including selumetinib and trametinib, have failed to show substantial clinical benefit for patients with metastatic uveal melanoma.<sup>2,3</sup> Indeed, no current therapies improve overall survival for metastatic UM and there is a high unmet need for novel therapies.<sup>4</sup>

In the current preclinical study, FAK inhibition (FAKi; e.g., defactinib) demonstrated synergistic growth-inhibitory effects in UM cells when combined with a MEK inhibitor (MEKi) or the investigational RAF/MEK inhibitor VS-6766. Additionally, MEKi increased phosphorylation of FAK, suggesting the need for FAK blockade in combination with MEKi for more complete antitumor effect. Accordingly, FAKi combination with MEKi induced apoptotic cell death leading to rapid tumor regression in UM xenografts, whereas the MEKi or FAKi as single agents showed tumor growth inhibition but failed to showed tumor shrinkage. Furthermore, the FAKi/MEKi combination was successful at reducing tumor burden in liver metastasis UM models.

"The study identified and reinforced FAK as a viable pathway to inhibit downstream from the GNAQ pathway, which is constitutively active in UM," said J. Silvio Gutkind, PhD, Distinguished Professor of Pharmacology and Associate Director for Basic Science at UC San Diego Moores Cancer Center, and senior investigator of the study. "We observed that co-targeting of FAK and RAF/MEK signaling led to tumor collapse in UM xenograft and liver metastasis models in vivo. Based on the encouraging results of this study, we are excited to work toward clinical testing of defactinib with VS-6766 for patients with metastatic uveal melanoma."

"These data build on a growing body of evidence that underscore the potential of the VS-6766/defactinib combination for treatment of a variety of solid tumors with significant medical need," said Brian Stuglik, Chief Executive Officer of Verastem Oncology. "We will continue to evaluate the combination in metastatic uveal melanoma along with rapidly advancing our broader clinical development program in solid tumors."

The combination of VS-6766 and defactinib is being evaluated in patients with Low Grade Serous Ovarian Cancer (LGSOC), and KRAS mutant non-small cell lung cancer (NSCLC) and colorectal cancer (CRC) in the ongoing investigator-initiated Phase I trial. The company also plans to support a Phase II investigator-initiated study of the combination of VS-6766 and defactinib in uveal melanoma anticipated to begin in late 2020.

### **Details for all abstracts selected for presentation at the AACR 2020 Virtual Meeting II are as follows:**

**Title:** FAK and MEK co-targeting: A new multimodal precision therapy for GNAQ-driven uveal melanoma

**Lead author:** Justine S. Paradis

**Poster #:** 6406/30

**Session:** PO.ET06.05

**Date and Time:** Monday, June 22, 2020; 9:00 a.m. to 6:00 p.m. EDT

**URL:** <https://www.abstractsonline.com/pp8/#!/9045/presentation/5323>

**Title:** The dual PI3K- $\delta$ /PI3K- $\gamma$  inhibitor duvelisib inhibits signaling and proliferation of solid tumor cells expressing PI3K- $\delta$  and/or PI3K- $\gamma$

**Lead author:** Silvia Coma

**Poster #:** 663/10

**Session:** PO.ET06.06

**Date and Time:** Monday, June 22, 2020; 9:00 a.m. to 6:00 p.m. EDT

**URL:** <https://www.abstractsonline.com/pp8/#!/9045/presentation/1880>

**Title:** Single cell expression analysis of PIK3 genes to direct solid tumor treatment with the dual PI3K- $\delta$ , $\gamma$  inhibitor duvelisib

**Lead author:** Samantha Hidy

**Poster #:** 1552/3

**Session:** PO.TB06.02

**Date and Time:** Monday, June 22, 2020; 9:00 a.m. to 6:00 p.m. EDT

**URL:** <https://www.abstractsonline.com/pp8/#!/9045/presentation/7806>

**Title:** PEGylated recombinant human hyaluronidase, PEGPH20, significantly enhances the anti-tumor activity of the combination of focal adhesion

kinase inhibitor and anti-PD-1 antibody by targeting CXCR4-expressing myeloid cells in a murine model of PDAC

**Lead author:** Arsen Osipov

**Poster #:** 1588/9

**Session:** PO.TB06.04

**Date and Time:** Monday, June 22, 2020; 9:00 a.m. to 6:00 p.m. EDT

**URL:** <https://www.abstracksonline.com/pp8/#/9045/presentation/7864>

#### About VS-6766

VS-6766 (formerly known as CH5126766, CKI27 and RO5126766) is a unique inhibitor of the RAF/MEK signaling pathway. In contrast to other MEK inhibitors in development, VS-6766 blocks both MEK kinase activity and the ability of RAF to phosphorylate MEK. This unique mechanism allows VS-6766 to block MEK signaling without the compensatory activation of MEK that appears to limit the efficacy of other inhibitors. The combination of VS-6766 and the focal adhesion kinase (FAK) inhibitor defactinib is currently being investigated in an investigator-initiated Phase 1 dose escalation and expansion study. The expansion cohorts are currently ongoing in patients with KRAS mutant advanced solid tumors, including low grade serous ovarian cancer (LGSOC), non-small cell lung cancer (NSCLC) and colorectal cancer (CRC).<sup>6</sup> The ongoing clinical study of the VS-6766/defactinib combination is supported by single-agent Phase 2 studies which investigated defactinib in KRAS mutant NSCLC<sup>7</sup> and VS-6766 in KRAS mutant NSCLC and LGSOC.<sup>5</sup>

#### About Defactinib

Defactinib (VS-6063) is an oral small molecule inhibitor of FAK and PYK2 that is currently being evaluated as a potential combination therapy for various solid tumors. The Company has received Orphan Drug designation for defactinib in ovarian cancer and mesothelioma in the US, EU and Australia. Preclinical research by Verastem Oncology scientists and collaborators at world-renowned research institutions has described the effect of FAK inhibition to enhance immune response by decreasing immuno-suppressive cells, increasing cytotoxic T cells, and reducing stromal density, which allows tumor-killing immune cells to enter the tumor.<sup>8,9</sup> Additionally, in both preclinical and clinical studies, FAK activation has been shown to occur as a potential resistance mechanism in response to MEK inhibitor treatment, and synergy of a FAK inhibitor with a RAF/MEK inhibitor has been shown in several preclinical models. The combination of defactinib and VS-6766 is currently being investigated in an investigator-initiated Phase 1 dose escalation and expansion study. The expansion cohorts are currently ongoing in patients with KRAS mutant advanced solid tumors, including low grade serous ovarian cancer (LGSOC), non-small cell lung cancer (NSCLC) and colorectal cancer (CRC).<sup>6</sup> The ongoing clinical study of the VS-6766/defactinib combination is supported by single-agent Phase 2 studies which investigated defactinib in KRAS mutant NSCLC<sup>7</sup> and VS-6766 in KRAS mutant NSCLC and LGSOC.<sup>8</sup> Defactinib is also in clinical testing in combination with pembrolizumab for treatment of patients with pancreatic cancer, NSCLC and mesothelioma.<sup>10</sup>

#### About COPIKTRA® (duvelisib)

COPIKTRA is an oral inhibitor of phosphoinositide 3-kinase (PI3K), and the first approved dual inhibitor of PI3K-delta and PI3K-gamma, two enzymes known to help support the growth and survival of malignant B-cells. PI3K signaling may lead to the proliferation of malignant B-cells and is thought to play a role in the formation and maintenance of the supportive tumor microenvironment.<sup>11,12,13</sup> COPIKTRA is indicated for the treatment of adult patients with relapsed or refractory chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) after at least two prior therapies and relapsed or refractory follicular lymphoma (FL) after at least two prior systemic therapies. COPIKTRA is also being developed by Verastem Oncology for the treatment of peripheral T-cell lymphoma (PTCL), for which it has received Fast Track status and Orphan Drug Designation, and is being investigated in combination with other agents through investigator-sponsored studies.<sup>14</sup> For more information on COPIKTRA, please visit [www.COPIKTRA.com](http://www.COPIKTRA.com). Information about duvelisib clinical trials can be found on [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

#### About Verastem Oncology

Verastem Oncology (Nasdaq: VSTM) is a commercial biopharmaceutical company committed to the development and commercialization of new medicines to improve the lives of patients diagnosed with cancer. Our pipeline is focused on novel small molecule drugs that inhibit critical signaling pathways in cancer that promote cancer cell survival and tumor growth, including phosphoinositide 3-kinase (PI3K), focal adhesion kinase (FAK) and RAF/MEK inhibition.

Our first FDA approved product is available for the treatment of patients with certain types of indolent non-Hodgkin's lymphoma (iNHL).

For more information, please visit [www.verastem.com](http://www.verastem.com).

#### Forward-Looking Statements Notice

This press release includes forward-looking statements about Verastem Oncology's strategy, future plans and prospects, including statements related to the potential clinical value of the RAF/MEK/FAK combination. The words "anticipate," "believe," "estimate," "expect," "intend," "may," "plan," "predict," "project," "target," "potential," "will," "would," "could," "should," "continue," "can," "promising" 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 and uncertainties, among other things, regarding: the success in the development and potential commercialization of our product candidates, including defactinib in combination with VS-6766; the occurrence of adverse safety events and/or unexpected concerns that may arise from additional data or analysis or result in unmanageable safety profiles as compared to their levels of efficacy; our ability to obtain, maintain and enforce patent and other intellectual property protection for our product candidates; the scope, timing, and outcome of any legal proceedings; decisions by regulatory authorities regarding labeling and other matters that could affect the availability or commercial potential of our product candidates; whether preclinical testing of our product candidates and preliminary or interim data from clinical trials will be predictive of the results or success of ongoing or later clinical trials; that the timing, scope and rate of reimbursement for our product candidates is uncertain; that third-party payors (including government agencies) may not reimburse; that there may be competitive developments affecting our product candidates; that data may not be available when expected; that enrollment of clinical trials may take longer than expected; that our product candidates will experience manufacturing or supply interruptions or failures; that we will be unable to successfully initiate or complete the clinical

development and eventual commercialization of our product candidates; that the development and commercialization of our product candidates will take longer or cost more than planned; that we or Chugai Pharmaceutical Co., Ltd. will fail to fully perform under the VS-6766 (CH5126766) license agreement; that we may not have sufficient cash to fund our contemplated operations; that we may be unable to make additional draws under our debt facility or obtain adequate financing in the future through product licensing, co-promotional arrangements, public or private equity, debt financing or otherwise; that we will be unable to execute on our partnering strategies for defactinib in combination with VS-6766; that we will not pursue or submit regulatory filings for our product candidates, and that our product candidates will not receive regulatory approval, become commercially successful products, or result in new treatment options being offered to patients.

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, 2019 as filed with the Securities and Exchange Commission (SEC) on March 11, 2020 and in any subsequent filings with the SEC. The forward-looking statements contained in this press release reflect Verastem Oncology's views as of the date hereof, and the Company does not assume and specifically disclaims any obligation to update any forward-looking statements whether as a result of new information, future events or otherwise, except as required by law.

## References

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- <sup>14</sup> [www.clinicaltrials.gov](http://www.clinicaltrials.gov), NCT03372057.

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