



Verastem Oncology Announces Preliminary Data from Investigator-initiated Study Highlighting Clinical Activity of RAF/MEK and FAK Combination in KRAS Mutant Tumors Presented at the American Association for Cancer Research 2020 Virtual Annual Meeting I

April 27, 2020 at 12:11 AM EDT

Combination of VS-6766 and Defactinib Demonstrates 67% (4/6 Patients) Overall Response Rate in KRAS Mutant Low-Grade Serous Ovarian Cancer in Phase 1 Trial

Subsequent Combined Analysis (VS-6766 Monotherapy and Defactinib Combination) Demonstrates 57% (4/7 Patients) Overall Response Rate in KRAS^{G12V} Non-Small Cell Lung Cancer

Management to Host Investor Conference Call Today at 8:00 AM ET

BOSTON--(BUSINESS WIRE)--Apr. 27, 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 the ongoing investigator-initiated Phase 1 clinical study investigating VS-6766, its RAF/MEK inhibitor, in combination with defactinib, its FAK inhibitor, in patients with KRAS mutant advanced solid tumors. The data will be presented as a virtual poster today at the American Association for Cancer Research (AACR) 2020 Virtual Annual Meeting I.

This ongoing study is an open label, dose escalation and expansion study. The expansion cohorts are currently ongoing in patients with advanced solid tumors, including low-grade serous ovarian cancer (LGSOC), KRAS mutant non-small cell lung cancer (NSCLC) and KRAS mutant colorectal cancer (CRC). In the LGSOC cohort, among the patients with KRAS mutant tumors (n=6), 4 patients responded, for an overall response rate (ORR) of 67%. Median time on treatment was 20.5 months. In the KRAS mutant NSCLC cohort (n=10), 1 patient achieved a partial response and 8 patients achieved disease control. In this cohort, 70% of patients continued on treatment at least 12 weeks and 30% of patients continued on treatment at least 24 weeks.

Based on an observation of higher response rates seen in patients with KRAS^{G12V} mutations in the investigator-initiated Phase 1 combination study, we conducted a combined analysis with data from the combination study and the prior single-agent study that utilized a twice-weekly dosing schedule of VS-6766¹ to get a more complete picture of activity in KRAS^{G12V} mutations. The subsequent, combined analysis (VS-6766 monotherapy and defactinib combination) showed a 57% ORR (4/7 patients); as a single agent (2/5 patients) and in combination with defactinib (2/2 patients) in KRAS^{G12V} mutant NSCLC. Similarly, the combined analysis showed a 60% ORR (3/5 patients); as a single agent (1/2 patients) and in combination with defactinib (2/3 patients) in KRAS^{G12V} mutant gynecologic cancers. These additional analyses were conducted by Verastem Oncology to understand the impact that various KRAS variants may have had on response to identify potential signals to pursue in future prospective studies. This additional analysis was not part of the AACR 2020 poster presentation.

"Earlier research has demonstrated MEK inhibitors can cause upregulation of FAK in KRAS mutant tumors, which are notoriously difficult to treat and quite common across solid tumors. The combination of a RAF/MEK and FAK inhibitor can potentially overcome this challenge and opens up an exciting new pathway for treatment," stated Professor Udai Banerji, Professor of Molecular Cancer Pharmacology at The Institute of Cancer Research, London, and Honorary Consultant in Medical Oncology, MBBS, MD, DNB, PhD, FRCP at The Royal Marsden NHS Foundation Trust, London, and lead investigator of the clinical study. "We found that the combination of VS-6766 and defactinib in low-grade serous ovarian cancer (LGSOC) was well tolerated by the patients in the trial and shows promising clinical activity, including durable response that is associated with clinically meaningful benefit. The study continues to enroll additional patients into the ovarian, lung and colorectal expansion cohorts with additional responses seen in all cohorts."

"We are encouraged by these early response rates in KRAS mutant LGSOC and in KRAS^{G12V} mutant tumors as they underscore the significant potential of this novel approach in areas of high unmet medical need," said Brian Stuglik, Chief Executive Officer of Verastem Oncology. "The potential of the combination of VS-6766 and defactinib is rapidly evolving as we continue to gain more insights and analyze the data. We plan to initiate discussions with regulatory authorities as soon as possible to define a path forward, with the goal of commencing a registration-directed clinical trial during 2020."

Initial Results from the Phase 1 Study Investigating the Combination of VS-6766 and Defactinib in Patients with KRAS Mutant Cancers and Subsequent Analyses

The poster presentation describes safety and dose response data from the dose-escalation portion and expansion cohorts from an open-label, investigator-initiated Phase 1 study conducted in the United Kingdom assessing the combination of RAF/MEK and FAK inhibitor therapy in patients with LGSOC and KRAS mutant NSCLC. The study evaluated the combination of VS-6766 and defactinib. VS-6766 was administered using a twice-weekly dose escalation schedule and was administered 3 out of every 4 weeks. Defactinib was administered using a twice-daily dose escalation schedule, also 3 out of every 4 weeks. Dose levels were assessed in 3 cohorts: cohort 1 (VS-6766 3.2mg, defactinib 200mg); cohort 2a (VS-6766 4mg, defactinib 200mg); and cohort 2b (VS-6766 3.2mg, defactinib 400mg).

In the patients with LGSOC (n=8), the ORR was 50% (n=4). Among the patients with KRAS mutant LGSOC (n=6), the ORR was 67% (n=4). Of the 4

patients who have responded, 3 had a prior MEK inhibitor and as of November 2019 had been on study for a median of 20.5 months (range 7-23 months). In the patients with NSCLC (n=10), all of which had KRAS mutations, 1 patient achieved a partial response and 1 patient with a 22% tumor reduction still on treatment as of November 2019. Median time on treatment for this cohort was approximately 18 weeks.

Based on an observation of higher response rates seen in patients with KRAS^{G12V} mutations in the investigator-initiated Phase 1 combination study, we conducted a combined analysis with data from the combination study and the prior single-agent study that utilized a twice-weekly dosing schedule of VS-6766¹ to get a more complete picture of activity in KRAS^{G12V} mutations. The subsequent, combined analysis (VS-6766 monotherapy and defactinib combination) showed a 57% ORR (4/7 patients); as a single agent (2/5 patients) and in combination with defactinib (2/2 patients) in KRAS^{G12V} mutant NSCLC. Similarly, the combined analysis showed a 60% ORR (3/5 patients); as a single agent (1/2 patients) and in combination with defactinib (2/3 patients) in KRAS^{G12V} mutant gynecologic cancers. These additional analyses were conducted by Verastem Oncology to understand the impact that various KRAS variants may have had on response to identify potential signals to pursue in future prospective studies. This additional analysis was not part of the AACR 2020 poster presentation.

The most common side effects seen in the Phase 1 study were rash, creatine kinase elevation, nausea, hyperbilirubinemia and diarrhea, most being NCI CTC Grade 1/2 and all were reversible. The recommended Phase 2 dose was determined to be cohort 1 (VS-6766 3.2mg, defactinib 200mg).

The preliminary data reported in the study suggest that a novel intermittent dosing schedule of RAF/MEK and FAK inhibitor combination therapy has promising clinical activity in patients with KRAS mutant LGSOC and KRAS^{G12V} mutant NSCLC, including patients previously treated with a MEK inhibitor. Expansion cohorts remain ongoing.

Details for the AACR 2020 Virtual Meeting I presentation are as follows:

Title: Phase 1 study of the combination of a RAF-MEK inhibitor CH5126766 (VS-6766) and FAK inhibitor defactinib in an intermittent dosing schedule with expansions in KRAS mutant cancers

Lead author: Udai Banerji, The Institute of Cancer Research and The Royal Marsden

Poster #: CT143

Session: VPO.CT01 - Phase I Clinical Trials

Date and Time: Monday, April 27, 2020; 9:00 a.m. to 6:00 p.m. ET

URL: <https://www.abstractsonline.com/pp8/#!/9045/presentation/10642>

Conference Call and Webcast Information

The Verastem Oncology management team will host a conference call and webcast on Monday, April 27, 2020, at 8:00 AM ET to discuss the Phase 1 RAF/MEK/FAK combination data. The call can be accessed by dialing (877) 341-5660 (U.S. and Canada) or (315) 625-3226 (international), five minutes prior to the start of the call and providing the passcode 8390795.

The live, listen-only webcast of the conference call can be accessed by visiting the investors section of the Company's website at www.verastem.com. A replay of the webcast will be archived on the Company's website for 90 days following the call.

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).² The ongoing clinical study of the VS-6766/defactinib combination is supported by single-agent Phase 2 studies which investigated defactinib in KRAS mutant NSCLC³ and VS-6766 in KRAS mutant NSCLC and LGSOC.¹

About Defactinib

Defactinib 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.^{4,5} 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).² The ongoing clinical study of the VS-6766/defactinib combination is supported by single-agent Phase 2 studies which investigated defactinib in KRAS mutant NSCLC³ and VS-6766 in KRAS mutant NSCLC and LGSOC.⁴ Defactinib is also in clinical testing in combination with pembrolizumab for treatment of patients with pancreatic cancer, NSCLC and mesothelioma.⁶

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.

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 and the timing of commencing a registration-directed trial for 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

¹ Chénard-Poirier, M. et al. Results from the biomarker-driven basket trial of RO5126766 (CH5127566), a potent RAF/MEK inhibitor, in RAS- or RAF-mutated malignancies including multiple myeloma. *Journal of Clinical Oncology* 2017; 35. 10.1200/JCO.2017.35.15_suppl.2506.

² <https://clinicaltrials.gov>, NCT03875820

³ Gerber D. et al. Phase 2 study of the focal adhesion kinase inhibitor defactinib (VS-6063) in previously treated advanced KRAS mutant non-small cell lung cancer. *Lung Cancer* 2020; 139:60-67.

⁴ Jiang H et al. Targeting focal adhesion kinase renders pancreatic cancers responsive to checkpoint immunotherapy. *Nat Med* 2016; Aug 22(8) 851-60.

⁵ Sulzmaier F.J. et al. FAK in cancer: mechanistic findings and clinical applications. *Nature Rev Cancer*. 2014 14: 598-610.

⁶ www.clinicaltrials.gov, NCT02758587

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Investors:

John Doyle
Vice President, Investor Relations & Finance
+1 781-469-1546
jdoyle@verastem.com

Media:

Lisa Buffington
Corporate Communications
+1 781-292-4205
lbuffington@verastem.com

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