Verastem Oncology Announces New Data Published in The Lancet Oncology Supports Potential of VS-6766 as Treatment for RAS Mutant Tumors

October 28, 2020

Investigator-Initiated Phase 1 Study is First to Evaluate a Dual RAF/MEK Inhibitor Using Innovative Intermittent Dosing Schedules in Patients Harboring RAS/RAF Pathway Mutations

Study Finds VS-6766 Regimen is Tolerable and Shows Antitumor Activity in Recommended Phase 2 Single Agent Dose

Phase 2 Registration-Directed Trials with VS-6766 Alone and in Combination with Defactinib in Low-Grade Serous Ovarian Cancer and KRAS Mutant Non-Small Cell Lung Cancer Expected to Commence by Year-End 2020

BOSTON--(BUSINESS WIRE)--Oct. 28, 2020-- Verastem, Inc. (Nasdaq:VSTM) (also known as Verastem Oncology), a biopharmaceutical company committed to advancing new medicines for patients battling cancer, today announced new data have been published today in *The Lancet Oncology*. The study evaluated the intermittent dosing schedule of VS-6766 (formerly known as CH5126766) to inform further testing of VS-6766 as both a single agent in RAS/RAF-mutant cancers such as KRAS mutant non-small cell lung cancer (NSCLC) or in combination with small molecules including the FAK inhibitor defactinib in KRAS mutant solid tumors (NCT03875820). In this dose-escalation study, tolerability and antitumor activity were observed across various cancers with RAS/RAF/MEK pathway mutations.

"The positive results observed with this innovative intermittent dosing regimen of VS-6766 demonstrate its significant potential across various cancers with RAS/RAF/MEK pathway mutations," stated 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 were encouraged by the data, demonstrating both antitumor activity and tolerability of VS-6766, and this intermittent schedule can be used alone or for combination therapy schedules with other anticancer agents for a variety of difficult-to-treat cancers."

The full manuscript, titled "Intermittent schedules of the oral RAF–MEK inhibitor CH5126766/VS-6766 in patients with *RAS/RAF*-mutant solid tumours and multiple myeloma: a single-centre, open-label, phase 1 dose-escalation and basket dose-expansion study," can be accessed here.

"These results support the potential of VS-6766 as a treatment for a variety of cancers where conventional approaches have been sub-optimal and there is significant unmet need. We believe VS-6766 has the potential to be the backbone of RAS therapy by addressing the multiple points of resistance and toxicity issues that have made advancing new options difficult," said Brian Stuglik, Chief Executive Officer of Verastem Oncology. "Our Phase 2 registration-directed trials with VS-6766 in low grade serous ovarian cancer and KRAS mutant NSCLC are scheduled to begin by the end of this year. These adaptive design trials are a capital efficient approach to rapidly evaluate VS-6766 alone or in combination with defactinib to determine which regimen to take forward into the expansion phase of the trial."

Results from the Phase 1 Study Investigating Intermittent Dosing of VS-6766 in Patients with RAS/RAF-mutated Solid Tumors and Multiple Myeloma

Between June 2013 to January 2019, 58 patients, including 51 patients with solid tumors and seven patients with multiple myeloma, were enrolled in a study conducted at The Institute of Cancer Research (ICR) and The Royal Marsden Hospital in the U.K. The study consisted of two parts; 1) dose escalation part to determine the recommended dosage (29 patients) and 2) basket expansion part to investigate efficacy and safety of the recommended dosage determined in the dose escalation part (29 patients).

Four mg twice weekly was established as the recommended Phase 2 dose for VS-6766 monotherapy and was deemed tolerable based on clinician's assessment with several patients remaining on study for more than six months.

In the subsequent basket expansion part, seven (26.9%) of 26 response-evaluable patients with RAS mutations in the basket expansion achieved objective responses, with response rates in patients with NSCLC, gynecological malignancies, colorectal cancer (CRC), melanoma, and multiple myeloma being 3/10 (30%), 3/5 (60%), 0/4 (0%), 0/1 (0%), and 1/6 (16.7%), respectively. In all six responders with solid tumors, tumor shrinkage was observed at the time of the first restaging scan after two cycles of treatment, with partial responses confirmed after two to four cycles. Five of the six responses lasted more than six months.

Among the 57 safety-evaluable patients, the most common Grade 3/4 treatment related adverse events (TRAEs) were rash (19%), CPK elevation (11%), hypoalbuminemia (11%), and fatigue (7%). Five (9%) patients experienced treatment-related serious adverse events. In the study, TRAEs were manageable, resolved spontaneously or reversed with dose modification. There were no treatment-related deaths. The study also confirmed a long half-life of 55 hours and target engagement in the form of reduction of both p-ERK and p-MEK in three patients who underwent paired biopsies, supporting intermittent dosing schedules.

This study was supported by Chugai Pharmaceutical Co., Ltd. Verastem in-licensed VS-6766 from Chugai in January 2020.

About VS-6766

VS-6766 (formerly known as CH5126766 and CKI27) 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.

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.[1,2]

About the VS-6766/Defactinib Combination

RAS mutant tumors are present in 30% of all human cancers and have historically presented a difficult treatment challenge and are often associated with significantly worse prognosis. Challenges associated with identifying new treatment options for these types of cancers include resistance to single agents, identifying tolerable combination regimens with MEK inhibitors and new RAS inhibitors in development addressing only a minority of all RAS mutated cancers.

The combination of VS-6766 and defactinib has been found to be clinically active in patients with KRAS mutant tumors. In an ongoing investigator-initiated Phase 1/2 FRAME study, the combination of VS-6766 and defactinib is being evaluated in patients with LGSOC, KRAS mutant NSCLC and colorectal cancer (CRC). Updated interim data from this study presented at the 2nd Annual RAS-Targeted Drug Development Summit in September 2020 demonstrated a 56% overall response rate and long duration of therapy among patients with KRAS-G12 mutant LGSOC. Based on an observation of higher response rates seen in NSCLC patients with KRAS-G12V mutations in the study, Verastem will also be further exploring the role of VS-6766 and defactinib in KRAS-G12V NSCLC. The FRAME study was expanded in August 2020 to include new cohorts in pancreatic cancer, KRAS mutant endometrial cancer and KRAS-G12V NSCLC.

About Verastem Oncology

Verastem Oncology (Nasdaq: VSTM) is a development-stage 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 RAF/MEK inhibition and focal adhesion kinase (FAK) inhibition. 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 anticipated timeline for Phase 2 registration-directed trials with VS-6766 in low grade serous ovarian cancer and KRAS mutant NSCLC. 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.

[1] 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.

[2] 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.

View source version on businesswire.com: https://www.businesswire.com/news/home/20201028006278/en/

Investors:
John Doyle
Vice President, Investor Relations & Finance
+1 781-469-1546

jdoyle@verastem.com

Media:
Lisa Buffington
Corporate Communications
+1 781-292-4205

Source: Verastem, Inc.