Verastem Oncology Announces Positive Data and Regulatory Update from Planned Interim Analysis of Registration-Directed Phase 2 RAMP-201 Trial of Avutometinib and Defactinib in Recurrent Low-Grade Serous Ovarian Cancer

January 24, 2023

Combination of Avutometinib with Defactinib Declared as Go Forward Treatment Regimen in Low-Grade Serous Ovarian Cancer (LGSOC) Program

Blinded Independently Confirmed Response Rates in Both KRAS Mutant and KRAS Wild-Type Tumors and Favorable Safety and Tolerability Profile Supports Continued Development in All Recurrent LGSOC

Company Intends to File for Accelerated Approval; Timing Based on Mature Data from RAMP 201 Study and Finalization of Confirmatory Study Plans

Management to Host Conference Call Today at 6:00 PM ET

BOSTON--(BUSINESS WIRE)--Jan. 24, 2023-- Verastem Oncology (Nasdaq: VSTM), a biopharmaceutical company committed to advancing new medicines for patients with cancer, today announces positive interim data from Part A of the ongoing RAMP 201 (ENGOTov60/GOG3052) international registration-directed Phase 2 study evaluating the safety and efficacy of avutometinib (VS-6766) alone and in combination with defactinib among patients with recurrent low-grade serous ovarian cancer (LGSOC). The Company is also providing a regulatory update following a productive meeting with the U.S. Food and Drug Administration (FDA).

“The interim data from the ongoing phase 2 RAMP 201 trial show that the combination of avutometinib with defactinib yields encouraging response rates with a well-tolerated safety profile in women with heavily pre-treated recurrent low-grade serous ovarian cancer,” said Dr. Susana Banerjee, MBBS, MA, PhD, FRCP, global lead investigator of the study, Consultant Medical Oncologist at The Royal Marsden NHS Foundation Trust and Team Leader in Women’s Cancers at The Institute of Cancer Research, London. “The contribution of defactinib, rates of tumor shrinkage in both KRAS mutant and KRAS wild-type LGSOC and a high disease control rate seen so far are important initial findings leading to the decision to move forward with the combination regimen. We look forward to the final analysis.”

Results of RAMP 201 Part A Interim Analysis

The objective of Part A (selection phase) of the RAMP 201 LGSOC study was to select the go forward regimen between avutometinib monotherapy or the combination of avutometinib and defactinib to be studied in Part B (expansion phase) of the study. In addition, the efficacy was assessed in both KRAS mutant and KRAS wild type LGSOC. Part A randomized eligible patients to avutometinib monotherapy (n=33) or the combination of avutometinib and defactinib (n=31). The combination of avutometinib and defactinib has been declared the go forward treatment regimen based on a higher rate of confirmed objective responses in a planned interim analysis with prespecified criteria.

Overall, patients on the combination arm were heavily pretreated with an average of 4 prior systemic regimens (up to 11), including prior platinum-based chemotherapy, endocrine therapy and bevacizumab in most patients and prior MEK inhibitor therapy in about 20% of patients.

Of the 29 patients evaluable for response by blinded independent central review (BICR) in the combination arm, the initial results showed a confirmed objective response rate (ORR) of 28% in all patients and 27% vs 29% in KRAS mutant (n=15) and KRAS wild-type (n=14) LGSOC, respectively. Three additional patients with KRAS mutant LGSOC showed an unconfirmed partial response. In addition, the vast majority of patients showed tumor regression, as the overall disease control rate (stable disease plus partial response) was 93%. Most evaluable patients (62%) were still on study treatment on the combination arm at the time of the data cut with a minimum follow-up of 5 months.

The confirmed ORR for the monotherapy arm by BICR was 7% in evaluable patients (n=30). The overall disease control rate for the monotherapy arm by BICR was 90%.

Across both the combination and monotherapy arms, there have been no additional safety signals reported with a continued favorable safety and tolerability profile. The most common treatment-related adverse events for the combination in all treated patients were diarrhea, nausea, blood creatine phosphokinase (CPK) increased, vision blurred, dermatitis acneiform and rash, fatigue and peripheral edema, most of which were mild to moderate, with 9% discontinuation due to adverse events.

“LGSOC is a difficult disease to treat and one in urgent need of more effective and tolerable therapies. The majority of patients with LGSOC present with advanced stage disease and experience chronic symptoms from their cancer. Prior studies have shown disappointing response rates with conventional chemotherapy or hormonal therapy and there are currently no agents that are FDA approved specifically for the treatment of this cancer,” said Rachel N. Grisham, M.D., Section Head, Ovarian Cancer and Director, Westchester Gynecologic Medical Oncology at Memorial Sloan Kettering Cancer Center NY, and the study’s principal US investigator. “The interim positive data from RAMP 201 are encouraging and indicate the combination of avutometinib and defactinib remains a promising approach for treating patients with recurrent LGSOC.”

Target enrollment for the combination arm in RAMP 201 has been achieved. The Company is planning a RAMP 201 presentation at a scientific conference in mid-2023.

Regulatory Update Following Type B FDA Meeting on LGSOC Program

A recent FDA meeting was held to discuss the encouraging results to date of the ongoing RAMP 201 trial evaluating avutometinib ± defactinib among patients with recurrent LGSOC, confirm the go forward treatment regimen selection and discuss the regulatory path forward. The combination of

avutometinib with defactinib has been selected vs monotherapy as the go forward treatment in all recurrent LGSOC regardless of KRAS status, acknowledging the demonstrated contribution of defactinib.

The Company intends to include mature data from RAMP 201, the Verastem sponsored clinical trial, and the FRAME study, led by The Institute of Cancer Research, London, and The Royal Marsden NHS Foundation Trust to potentially support filing for accelerated approval. Both studies are evaluating avutometinib and defactinib in patients with recurrent LGSOC. The Company is in ongoing discussions with the FDA on the confirmatory study and plans to provide an update after agreement with the FDA. Continued enrollment in the combination arm of RAMP 201 is planned to expand the clinical experience in anticipation of initiation of a confirmatory study.

"We appreciate the productive and ongoing discussions with the FDA regarding the progress of our LGSOC program, including the alignment around key next steps as part of our breakthrough therapy designation," said Brian Stuglik, CEO of Verastem Oncology. "With the encouraging results of the RAMP 201 Part A interim analysis and the FRAME study, we will work expeditiously to prepare to file for an accelerated approval that encompasses the totality of the data from both trials as well as progress on the confirmatory study."

Conference Call, Presentation and Webcast Information

The Verastem Oncology management team will host a conference call and webcast today, Tuesday, January 24, 2023, at 6:00 PM ET. The conference call can be accessed by clicking here. The webcast of the conference call and accompanying slides can also 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.

Dr. Banerjee and Dr. Grisham have consulting relationships with Verastem Oncology.

About Avutometinib (VS-6766)

Avutometinib is a RAF/MEK clamp that induces inactive complexes of MEK with ARAF, BRAF and CRAF potentially creating a more complete and durable anti-tumor response through maximal RAS pathway inhibition. Avutometinib is currently in late-stage development.

In contrast to other MEK inhibitors, avutometinib blocks both MEK kinase activity and the ability of RAF to phosphorylate MEK. This unique mechanism allows avutometinib to block MEK signaling without the compensatory activation of MEK that appears to limit the efficacy of other inhibitors. The U.S. Food and Drug Administration granted Breakthrough Therapy designation for the combination of Verastem Oncology's investigational RAF/MEK clamp avutometinib, with defactinib, its FAK inhibitor, for the treatment of all patients with recurrent low-grade serous ovarian cancer (LGSOC) regardless of KRAS status after one or more prior lines of therapy, including platinum-based chemotherapy.

Verastem Oncology is currently conducting clinical trials with its RAF/MEK clamp avutometinib in RAS-driven tumors as part of its (**R**af **A**nd **M**ek **P**rogram). RAMP 201 is a registration-directed trial of avutometinib alone and in combination with defactinib in patients with recurrent LGSOC. Verastem Oncology has established clinical collaborations with Amgen and Mirati to evaluate LUMAKRAS ™ (sotorasib) and KRAZATI ™ (adagrasib) in combination with avutometinib in KRAS G12C mutant NSCLC as part of the RAMP 203 and RAMP 204 trials, respectively. As part of the "Therapeutic Accelerator Award" Verastem Oncology received from PanCAN, the Company is conducting RAMP 205, a Phase 1b/2 clinical trial evaluating avutometinib and defactinib with gemcitabine/nab-paclitaxel in patients with front-line metastatic pancreatic cancer.

About Low-Grade Serous Ovarian Cancer (LGSOC)

LGSOC is a highly recurrent, chemotherapy-resistant cancer, associated with slow tumor growth and high mortality rate. Approximately 6,000 women in the U.S. and 80,000 worldwide are living with this disease. Mutations in the KRAS gene are present in 30% of cases of LGSOC. LGSOC is most often diagnosed in women between the ages of 45-55 years and has a median survival of approximately ten years. The majority of patients experience severe pain and complications as the disease progresses. Chemotherapy is the standard of care for this disease, with limited treatment options currently available.

About RAMP 201

Verastem Oncology has initiated a Phase 2 registration-directed trial evaluating avutometinib alone and in combination with defactinib in patients with recurrent LGSOC as part of RAMP (**R**af **A**nd **M**ek **P**rogram). RAMP 201 (ENGOTov60/GOG3052) is an international collaboration between the European Network of Gynaecological Oncological Trial groups (ENGOT) and the Gynecologic Oncology Group (GOG) and sponsored by Verastem Oncology. It is an adaptive, two-part multicenter, parallel cohort, randomized, open-label trial to evaluate the efficacy and safety of avutometinib alone and in combination with defactinib in patients with recurrent LGSOC. The first part of the study will determine the optimal regimen of either avutometinib monotherapy or in combination with defactinib in patients with recurrent LGSOC randomized 1:1 in each treatment arm. The determination of which regimen to take forward into the expansion phase of the trial will be made based on objective response rate data. The expansion phase of the study will examine efficacy and safety parameters of the regimen selected.

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 various of its clinical trials, the timing of commencing and completing trials, including topline data reports, interactions with regulators and potential for additional development programs involving Verastem Oncology's lead compound. 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 avutometinib in combination with other compounds, including defactinib, LUMAKRAS ™ and others; 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 trial design, labeling and other matters that could affect the timing, 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, including as a result of conducting additional studies; that we or Chugai Pharmaceutical Co., Ltd. will fail to fully perform under the avutometinib license agreement; that we or our other collaboration partners may fail to perform under our collaboration agreements; that we may not have sufficient cash to fund our contemplated operations; that we may be unable to obtain adequate financing in the future through product licensing, co-promotional arrangements, public or private equity, debt financing or otherwise; that Secura Bio, Inc. will achieve the milestones that result in payments to us under our asset purchase agreement with Secura Bio, Inc.; that we will be unable to execute on our partnering strategies for avutometinib in combination with other compounds; 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, 2021 as filed with the Securities and Exchange Commission (SEC) on March 28, 2022 and in the Company’s Quarterly Reports on Form 10-Q for the quarters ended June 30, 2022 and September 30, 2022, as filed with the SEC on August 8, 2022 and November 3, 2022, respectively, 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.

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Source: Verastem Oncology