Verastem Oncology Announces the Initiation of a Rolling Submission of NDA to FDA Seeking Accelerated Approval of Avutometinib and Defactinib Combination for the Treatment of Adult Patients with Recurrent KRAS Mutant Low-Grade Serous Ovarian Cancer

May 24, 2024 at 7:00 AM EDT

Plan to complete NDA submission with the mature RAMP 201 dataset, anticipated to include 12 months of follow-up, in the second half of 2024

Plan to present the mature dataset from RAMP 201 at a medical conference in the second half of 2024

Avutometinib and defactinib combination have continued to show robust and durable response rates in ongoing RAMP 201 trial in patients with recurrent low-grade serous ovarian cancer

Company to host investor conference call and webcast on Friday, May 24, 2024 at 8:00 am EDT to provide update on RAMP 201 and rolling NDA submission

BOSTON--(BUSINESS WIRE)--May 24, 2024-- Verastem Oncology (Nasdaq: VSTM), a biopharmaceutical company committed to advancing new medicines for patients with cancer, today announced that it has initiated the rolling submission of a New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) seeking accelerated approval of the combination of avutometinib, a RAF/MEK clamp, and defactinib, a selective FAK inhibitor, for adult patients with recurrent KRAS mutant (KRAS mt) low-grade serous ovarian cancer (LGSOC), who received at least one prior systemic therapy. The rolling review process allows the Company to submit completed sections of an application for review by the FDA before all sections become available. The initial sections of the application will include the nonclinical and quality sections. In discussions with the FDA, Verastem reached agreement to submit a primary efficacy analysis based on the RAMP 201 study with 12 months of follow up. Based on discussions with the FDA, we understand that the proposed indication for final submission of the clinical module can be expanded in the event Verastem provides data that demonstrates a substantial improvement over available therapy in the KRAS wild-type (KRAS wt) population. FDA has accepted Verastem's plan to submit the clinical module in the second half of 2024 to complete the NDA application. Previously, the FDA granted Breakthrough Therapy Designation (BTD) for the combination for treatment of patients with recurrent LGSOC, regardless of KRAS status, following one or more previous lines of therapy and Orphan Drug Designation (ODD) for the combination in certain LGSOC indications. The Company plans to request a priority review of the NDA. Currently, there are no FDA-approved treatments specifically for recurrent LGSOC.

"The initiation of our rolling NDA submission of the avutometinib and defactinib combination for accelerated approval, is an important step towards addressing the significant unmet needs that patients face living with KRAS mutant low-grade serous ovarian cancer," said Dan Paterson, president and chief executive officer of Verastem Oncology. "The data from our ongoing RAMP 201 trial continues to support our belief that the avutometinib and defactinib combination has the potential to be a new standard of care in patients with recurrent low-grade serous ovarian cancer, if approved. In the second half of this year, we anticipate completing our NDA submission with the mature data from the RAMP 201 trial and discussing with the FDA a path forward for patients with KRAS wild-type disease. We also expect to present the mature dataset at a medical meeting in the second half of 2024."

RAMP 201 is a Phase 2 registration-directed study evaluating avutometinib and defactinib combination in patients with recurrent LGSOC. The enrollment in RAMP 201 is completed, with 115 patients being treated at the recommended Phase 2 dose (RP2D) of avutometinib 3.2 mg twice weekly and defactinib 200 mg twice daily for 3 out of every 4 weeks, and follow-up continues. Verastem expects to complete the NDA submission after obtaining mature safety and efficacy data from the RAMP 201 trial, including 12 months of follow-up, anticipated in the second half of 2024. Verastem also plans to further discuss the KRAS wt data with FDA to inform the potential path forward for approval for this patient population. The Company plans to present the mature dataset from RAMP 201 at a medical meeting in the second half of 2024. As of February 2024, the interim data continued to show robust overall response rates (ORR) and durable responses with low discontinuation rates due to adverse events (AEs) in patients from RAMP 201 Parts A, B, C, who had a minimum follow-up of five (5) months.

The FDA granted Breakthrough Therapy Designation of the investigational combination of avutometinib and defactinib for the treatment of all patients with recurrent LGSOC regardless of KRAS status after one or more prior lines of therapy, including platinum-based chemotherapy in May 2021. Avutometinib alone or in combination with defactinib was also granted Orphan Drug Designation by the FDA for the treatment of LGSOC in March 2024. The Company believes that this Orphan Drug Designation signifies that LGSOC is a rare ovarian cancer that is a distinct and different disease from other forms of ovarian cancer such as high-grade serous ovarian cancer (HGSOC). LGSOC is highly recurrent and fatal, with no FDA-approved treatment options, and the current standard of care treatments include hormonal therapy or chemotherapy, which have demonstrated an ORR between 6-13% with discontinuation due to AEs of 17-30%.

The Company is currently enrolling patients and activating sites for RAMP 301, an international confirmatory Phase 3 trial, evaluating the avutometinib and defactinib combination versus standard of care chemotherapy or hormonal therapy for the treatment of patients with KRAS mt and KRAS wt recurrent LGSOC.

Conference Call and Webcast Information

Verastem will hold an investor conference call and webcast on Friday, May 24 at 8:00 am EDT, to review the initiation of the NDA submission and limited, topline data from the RAMP 201 trial, with a minimum follow-up of five (5) months and the RAMP 205 data. The call will feature members of Verastem's management team. To access the conference call, please dial (844) 763-8274 (local) or (412) 717-9224 (international) at least 10 minutes prior to the start time and ask to be joined into the Verastem Oncology conference call. A live audio webcast of the call, along with accompany slides, will be accessible here. The Company expects to file an 8-K pertaining to this update.

About RAMP 201

RAMP 201 (ENGOTov60/GOG3052) 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 low-grade serous ovarian cancer. The first part of the study (Part A) determined the selection of the go forward regimen, which was the combination of avutometinib and defactinib versus avutometinib alone, based on overall response rates. The expansion phases of the trial (Parts B and C) are evaluating the safety and efficacy of the go forward regimen of avutometinib 3.2 mg twice weekly and defactinib 200 mg twice daily. The Part D portion of the trial is evaluating a low dose of avutometinib in combination with defactinib to inform individualized dose reduction.

About RAMP 301

RAMP 301 (GOG-3097; ENGOT-ov81/NCRI) is an international collaboration between The GOG Foundation, Inc. (GOG) and the European Network of Gynaecological Oncological Trial groups (ENGOT) sponsored by Verastem Oncology. The trial is expected to enroll a total of 270 patients in the U.S., Canada, the United Kingdom, Europe, Australia and South Korea, who will be randomized to either the combination of avutometinib and defactinib or investigator's choice chemotherapy (pegylated liposomal doxorubicin, paclitaxel, topotecan) or hormone therapy (letrozole, anastrozole). The primary endpoint is progression free survival (PFS) by Blinded Independent Central Review. Secondary endpoints include ORR, duration of response, disease control rate, safety and tolerability, patient reported outcomes, and overall survival.

About Low-Grade Serous Ovarian Cancer (LGSOC)

LGSOC is a rare ovarian cancer that is insidious, persistent and ultimately fatal. LGSOC is distinct and different from high-grade serous ovarian cancer (HGSOC) and requires different treatment. LGSOC is highly recurrent and less sensitive to chemotherapy compared to HGSOC. Approximately 6,000-8,000 women in the U.S. and 80,000 worldwide are living with this disease. LGSOC affects younger women with bimodal peaks of diagnosis at ages between 20-30 and 50-60 and has a median survival of approximately ten years. The majority of patients report negative impact of LGSOC on their mental and physical health, fertility, and long-term quality of life. The current standard of care for this disease includes hormone therapy and chemotherapy, but there are no treatments specifically approved by the U.S. Food and Drug Administration to treat LGSOC.

About the Avutometinib and Defactinib Combination

Avutometinib is a n investigational RAF/MEK clamp that is designed to induce inactive complexes of MEK with ARAF, BRAF and CRAF potentially creating a more complete and durable anti-tumor response through maximal RAS/MAPK pathway inhibition. Avutometinib is designed to block both MEK kinase activity and the ability of RAF to phosphorylate MEK. This differentiated proposed mechanism potentially allows avutometinib to block MEK signaling without the compensatory activation of MEK that appears to limit the efficacy of other MEK-only inhibitors. The U.S. Food and Drug Administration (FDA) granted Breakthrough Therapy Designation of the investigational combination of avutometinib and defactinib, a selective 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. Avutometinib alone or in combination with defactinib was also granted Orphan Drug Designation by the FDA for the treatment of LGSOC.

Verastem Oncology is currently conducting clinical trials with avutometinib in RAS/MAPK driven tumors as part of its **R**af **A**nd **M**ek **P**rogram or RAMP. RAMP 301 (NCT06072781) is an international Phase 3 confirmatory trial evaluating the combination of avutometinib and defactinib versus standard chemotherapy or hormonal therapy for the treatment of recurrent LGSOC. RAMP 201 (NCT04625270) is a Phase 2 registration-directed trial of avutometinib in combination with defactinib in patients with recurrent LGSOC and enrollment has been completed in each of the dose optimization and expansion phases and the low-dose evaluation.

Verastem Oncology has established clinical collaborations with Amgen and Mirati to evaluate LUMAKRAS™ (sotorasib) in combination with avutometinib and defactinib and KRAZATI™ (adagrasib) in combination with avutometinib in KRAS G12C mutant NSCLC as part of the RAMP 203 (NCT05074810) and RAMP 204 (NCT05375994) trials, respectively. The RAMP 205 (NCT05669482), a Phase 1b/2 clinical trial evaluating avutometinib and defactinib with gemcitabine/Nab-paclitaxel in patients with front-line metastatic pancreatic cancer, is supported by a PanCAN Therapeutic Accelerator Award.

About Verastem Oncology

Verastem Oncology (Nasdaq: VSTM) is a late-stage development 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 RAS/MAPK-driven cancers, specifically novel small molecule drugs that inhibit critical signaling pathways in cancer that promote cancer cell survival and tumor growth, including RAF/MEK inhibition and FAK inhibition. For more information, please visit www.verastem.com and follow us on LinkedIn.

Forward Looking Statements

This press release includes forward-looking statements about, among other things, Verastem Oncology's programs and product candidates, strategy, future plans and prospects, including statements related to the expected timing of the planned rolling New Drug Application (NDA) submission for the avutometinib and defactinib combination in low-grade serous ovarian cancer, the potential clinical value of various of the Company's clinical trials, including the RAMP 201, RAMP 205 and RAMP 301 trials, the timing of commencing and completing trials, including topline data reports, interactions with regulators, the potential for and timing of commercialization of product candidates 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. Forward-looking statements are not guarantees of future performance and are 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 uncertainties inherent in research and development, such as negative or unexpected results of clinical trials, the occurrence or timing of applications for our product candidates that may be filed with regulatory authorities in any jurisdictions; whether and when regulatory authorities in any jurisdictions may approve any such applications that may be filed for our product candidates, and, if approved, whether our product candidates will be commercially successful in such jurisdictions; 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; the market opportunities of our drug candidates are based on internal and third-party estimates which may prove to be incorrect; 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, which may delay our development programs, including delays in submission or review by the FDA of our NDA submission in recurring KRAS mutant LGSOC if enrollment in our confirmatory trial is not well underway at the time of submission, or that the FDA may require the Company to have completed enrollment or to enroll additional patients in the Company's ongoing RAMP-301 confirmatory Phase 3 clinical trial prior to Verastem submitting or the FDA taking action on our NDA seeking accelerated approval; that our product candidates will cause adverse safety events and/or unexpected concerns may arise from additional data or analysis, or result in unmanageable safety profiles as compared to their levels of efficacy; that we may be unable to successfully validate, develop and obtain regulatory approval for companion diagnostic tests for our product candidates that require or would commercially benefit from such tests, or experience significant delays in doing so; that our product candidates may experience manufacturing or supply interruptions or failures; that any of our third party contract research organizations, contract manufacturing organizations, clinical sites, or contractors, among others, who we rely on fail to fully perform; that we face substantial competition, which may result in others developing or commercializing products before or more successfully than we do which could result in reduced market share or market potential for our product candidates; 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 may not have sufficient cash to fund our contemplated operations; that we may not attract and retain high quality personnel; that we or Chugai Pharmaceutical Co., Ltd. will fail to fully perform under the avutometinib license agreement; that our target market for our product candidates might be smaller than we are presently estimating; that Secura Bio, Inc. will fail to fully perform under the asset purchase agreement with Secura Bio, Inc., including in relation to milestone payments; that we will not see a return on investment on the payments we have and may continue to make pursuant to the collaboration and option agreement with GenFleet Therapeutics (Shanghai), Inc. (GenFleet), or that GenFleet will fail to fully perform under the agreement; 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 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.

As a result of these and other factors, we may not achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. 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, 2023 as filed with the Securities and Exchange Commission (SEC) on March 14, 2024 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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