Verastem Oncology Announces FDA Acceptance and Priority Review of New Drug Application for Avutometinib in Combination with Defactinib for the Treatment of Recurrent KRAS Mutant Low-Grade Serous Ovarian Cancer

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PDUFA target action date is June 30, 2025

If approved, avutometinib in combination with defactinib would be the first-ever FDA-approved treatment specifically for adults with recurrent KRAS mutant LGSOC

BOSTON--(BUSINESS WIRE)--Dec. 30, 2024-- Verastem Oncology (Nasdaq: VSTM), a biopharmaceutical company committed to advancing new medicines for patients with cancer, today announced that the U.S. Food and Drug Administration (FDA) has accepted for review the New Drug Application (NDA) under the accelerated approval pathway for avutometinib, an oral RAF/MEK clamp, in combination with defactinib, an oral FAK inhibitor, for the treatment of adult patients with recurrent low-grade serous ovarian cancer (LGSOC), who received at least one prior systemic therapy and have a KRAS mutation. The NDA, which was completed in October 2024, has been granted Priority Review with a Prescription Drug User Fee Act (PDUFA) action date of June 30, 2025. In addition, the FDA has stated that it is not currently planning to hold an advisory committee meeting to discuss the application.

“The FDA filing acceptance and Priority Review for the combination of avutometinib and defactinib underscores the critical unmet need among patients diagnosed with this rare and insidious disease. We are excited by today’s news and to potentially bring the first ever FDA-approved treatment specifically for recurrent KRAS mutant LGSOC to patients in the U.S.,” said Dan Paterson, president and chief executive officer of Verastem Oncology. “With the acceptance of this NDA, we’re taking an important step forward in addressing a condition that has long been overlooked, and we look forward to working with the FDA during its review process and preparing for a commercial launch in mid-2025.”

There are currently no FDA-approved treatments specifically for LGSOC, a rare and distinct ovarian cancer that differs from high-grade serous ovarian cancer in both its biology and how it responds to treatment. Priority Review is granted by the FDA for treatments that offer, if approved, significant improvements over available options or that provide a treatment option where no adequate or approved therapy currently exists.

The filing was based on a primary analysis of the Phase 2 RAMP 201 clinical trial that evaluated the combination of avutometinib and defactinib in patients with recurrent LGSOC. The results were presented in an oral presentation at the International Gynecologic Cancer Society (IGCS) Annual Global Meeting in October 2024 and demonstrated that the combination of avutometinib plus defactinib resulted in a substantial overall response rate confirmed by blinded independent central review, with responses that were typically durable, and that the combination was generally well-tolerated in patients with recurrent KRAS mutant LGSOC. The NDA also includes supportive data from the FRAME Phase 1 trial, the first study conducted with the combination therapy in recurrent LGSOC.

The Company is currently enrolling patients with recurrent LGSOC regardless of KRAS mutation status for RAMP 301, an international Phase 3 trial, which will serve as a confirmatory study for the initial indication and has the potential to support an expanded indication regardless of KRAS mutation status.

About RAMP 201

RAMP 201 (ENGOTov60/GOG3052) (NCT04625270) is an adaptive, two-part multicenter, parallel cohort, randomized, open-label Phase 2 registration-directed trial evaluating the efficacy and safety of avutometinib alone and in combination with defactinib in patients with recurrent low-grade serous ovarian cancer (LGSOC). 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 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 a 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.

nAbout the Avutometinib and Defactinib Combinatio

Avutometinib is an oral RAF/MEK clamp that potentially inhibits MEK1/2 kinase activities and induces 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. In contrast to currently available MEK-only 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 the MEK-only inhibitors.

Defactinib is an oral, selective inhibitor of focal adhesion kinase (FAK) and proline-rich tyrosine kinase-2 (Pyk2), the two members of the focal

adhesion kinase family of non-receptor protein tyrosine kinases. FAK and Pyk2 integrate signals from integrin and growth factor receptors to regulate cell proliferation, survival, migration, and invasion. FAK activation has been shown to mediate resistance to multiple anti-cancer agents, including RAF and MEK inhibitors.

Verastem Oncology is currently conducting clinical trials with avutometinib with and without defactinib in RAS/MAPK-driven tumors as part of its **R**af **A**nd **M**ek **P**rogram or RAMP. Verastem is currently enrolling patients and activating sites for RAMP 301 (GOG-3097/ENGOT-ov81/NCRI) (NCT06072781), an international Phase 3 confirmatory trial evaluating the combination of avutometinib and defactinib versus standard chemotherapy or hormonal therapy for the treatment of recurrent low-grade serous ovarian cancer (LGSOC).

Verastem was granted Priority Review and a Prescription Drug User Fee Act (PDUFA) date of June 30, 2025, for its New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA), for the investigational combination of avutometinib and defactinib in adults with recurrent KRAS mutant LGSOC who received at least one prior systemic therapy. Verastem initiated a rolling NDA in May 2024 to the FDA and completed its NDA submission in October 2024. The FDA granted Breakthrough Therapy Designation for the treatment of patients with recurrent LGSOC 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.

Verastem Oncology has established a clinical collaboration with Amgen to evaluate LUMAKRAS™ (sotorasib) in combination with avutometinib and defactinib in both treatment-naïve patients and in patients whose KRAS G12C mutant non-small cell lung cancer progressed on a G12C inhibitor as part of the RAMP 203 trial (NCT05074810). Verastem has received Fast Track Designation from the FDA for the triplet combination in April 2024. 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 the PanCAN Therapeutic Accelerator Award. FDA granted Orphan Drug Designation to the avutometinib and defactinib combination for the treatment of pancreatic cancer.

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 FDA action on the New Drug Application (NDA) for the avutometinib and defactinib combination product in KRAS-mutant and recurrent low-grade serous ovarian cancer, the potential clinical value of various of the Company's clinical trials, including the RAMP 201, RAMP 203, RAMP 205 and RAMP 301 trials, the timing of commencing and completing trials and compiling data, including topline data and 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 our actual results to differ materially from those expressed or implied in the forward-looking statements we make. 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 or reject 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 is predictive of the results or success of ongoing or later clinical trials; the uncertainty around the timing, scope and rate of reimbursement for our product candidates; internal and third-party estimates about the market opportunities of our drug candidates may prove to be incorrect; third-party payors (including government agencies) may not reimburse; there may be competitive developments affecting our product candidates; 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 review by the FDA of our NDA submission in recurrent 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 the FDA taking action on our NDA seeking accelerated approval; risks associated with preliminary and interim data, which may not be representative of more mature data, including with respect to interim duration of therapy data; our product candidates may 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; 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; the mature RAMP 201 data and associated discussions with the FDA may not support the scope of our NDA submission for the avutometinib and defactinib combination in LGSOC, including with respect to both recurrent KRAS mutant and recurrent KRAS wild type LGSOC; our product candidates may experience manufacturing or supply interruptions or failures; any of our third party contract research organizations, contract manufacturing organizations, clinical sites, or contractors, among others, who we rely on may fail to fully perform; 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; we may be unable to successfully initiate or complete the clinical development and eventual commercialization of our product candidates; the development and commercialization of our product candidates may take longer or cost more than planned, including as a result of conducting additional studies or our decisions regarding execution of such commercialization; we may not have sufficient cash to fund our contemplated operations, including certain of our product development programs; we may not attract and retain high quality personnel; we or Chugai Pharmaceutical Co., Ltd. may fail to fully perform under the avutometinib license agreement; the total addressable and target markets for our product candidates might be smaller than we are presently estimating; we or Secura Bio, Inc. (Secura) may fail to fully perform under the asset purchase agreement with Secura, including in relation to milestone payments; we may 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 may fail to fully perform under the agreement; we may not be able to establish new or expand on existing collaborations or partnerships, including with respect to in-licensing of our product candidates, on favorable terms, or at all; 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; we may not pursue or submit regulatory filings for our product candidates; and our product candidates may 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, 2023, as filed with the Securities and Exchange Commission (SEC) on March 14, 2024, and in any subsequent filings with the SEC, which are available at www.sec.gov. 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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