Verastem Oncology Announces Publication of the Primary Results from the Phase 2 RAMP 201 Trial of Avutometinib in Combination with Defactinib in Patients with Recurrent Low-Grade Serous Ovarian Cancer in the Journal of Clinical Oncology

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Robust objective response rates were observed (31% overall, 44% in KRAS-mutant, and 17% in KRAS wild-type) in patients whose cancer had progressed after multiple prior lines of therapy

The majority of patients (82%) had some reduction in target lesions, regardless of KRAS mutation status

Median progression-free survival was 12.9 months overall, 31.0 months in KRAS-mutant, and 12.8 months in KRAS wild-type

BOSTON--(BUSINESS WIRE)--Jul. 11, 2025-- Verastem Oncology (Nasdaq: VSTM), a biopharmaceutical company committed to advancing new medicines for patients with RAS/MAPK pathway-driven cancers, today announced that the primary analysis of the Phase 2 RAMP 201 clinical trial was published online in the *Journal of Clinical Oncology (JCO).* The data reported in the publication showed that avutometinib plus defactinib demonstrated a confirmed overall response rate (ORR) of 31% in all patients with recurrent low-grade serous ovarian cancer (LGSOC). The full manuscript, titled "Efficacy and Safety of Avutometinib ± Defactinib in Recurrent Low-Grade Serous Ovarian Cancer: Primary Analysis of ENGOT-OV60/GOG-3052/RAMP 201," will also appear in the print publication of *JCO*.

"The publication of the primary analysis of the RAMP 201 study in recurrent low-grade serous ovarian cancer in the *Journal of Clinical Oncology* reflects the meaningful clinical advancement demonstrated by the combination of avutometinib plus defactinib for patients with recurrent low-grade serous ovarian cancer," said John Hayslip, M.D., chief medical officer at Verastem Oncology. "The findings supported the recent FDA approval of the combination in KRAS-mutated recurrent low-grade serous ovarian cancer and our ongoing global Phase 3 RAMP 301 trial of the combination in recurrent low-grade serous ovarian cancer with and without a KRAS mutation."

The Company will submit the RAMP 201 publication and the recent publication of the FRAME study to the National Comprehensive Cancer Network® (NCCN®) in support of its consideration of inclusion of the KRAS wild-type population evaluated in these trials in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Currently, the combination is listed as an NCCN Category 2A recommendation for the treatment of KRAS-mutated recurrent LGSOC, which is aligned with the FDA-approved indication.

JCO Publication of RAMP 201

The Phase 2 RAMP 201 trial evaluated the safety, tolerability, and efficacy of avutometinib with and without defactinib in patients with recurrent LGSOC who had received a median of three (range one to nine) prior lines of therapy, including chemotherapy, hormonal therapy, bevacizumab, and MEK inhibitors. The publication included the primary analysis of the Phase 2 RAMP 201 trial that showed a confirmed ORR of 31% (34/109) in all 109 evaluable patients, 44% (25/57) in patients with a KRAS mutation, and 17% (9/52) in patients with KRAS wild-type. The median duration of response (DOR) was 31.1 months for all patients, 31.1 months in the KRAS mutant population, and 9.2 months in the KRAS wild-type population. Median progression-free survival (PFS) was 12.9 months for all patients, 22.0 months in the KRAS mutant population, and 12.8 months in the KRAS wild-type population. The majority of patients (82%) had some reduction in target lesions, regardless of KRAS mutation status. The disease control rate (DCR) at 6 or more months was 61% in the total population, 70% in the KRAS-mutated population, and 50% in the KRAS wild-type population.

"Our paper showed that the combination of avutometinib plus defactinib demonstrated clinically meaningful and durable responses in patients with recurrent low-grade serous ovarian cancer. The recent FDA accelerated approval of the combination in KRAS-mutated recurrent low-grade serous ovarian cancer, which is based on these results, is fantastic news. The fact that a majority of patients had some reduction in target lesions, regardless of KRAS mutation status, underscores the advancement the combination represents in this rare ovarian cancer and its potential to be the new standard of care in recurrent low-grade serous ovarian cancer," said Professor Susana Banerjee, M.B.B.S., M.A., Ph.D., F.R.C.P, Consultant Medical Oncologist at The Royal Marsden NHS Foundation Trust and Team Leader in Women's Cancers at The Institute of Cancer Research, London and Global Lead Principal Investigator of ENGOTov60/GOG3052/NCRI/RAMP201.

The results also demonstrated that the combination is well-tolerated, with a 10% discontinuation rate due to adverse events (AEs). The most common AEs (all grades, grade ≥3) were nausea (67.0%, 2.6%), diarrhea (58.3%, 7.8%), and increased creatine phosphokinase levels (60.0%, 24.3%).

"The publication of the Phase 2 RAMP 201 trial supports our understanding of the role that the combination of avutometinib plus defactinib plays in treating patients with recurrent low-grade serous ovarian cancer. We are excited to continue to build on the findings from the trial and advance the research in this disease with the ongoing international Phase 3 RAMP 301 trial, which is evaluating the combination in patients with and without a KRAS mutation," said Rachel Grisham, M.D., Section Head, Ovarian Cancer at Memorial Sloan Kettering Cancer Center in New York, NY and Global Lead Principal Investigator of GOG-3097/ENGOT-ov81/GTG-UK/RAMP 301.

The RAMP 201 study results were initially presented in an oral plenary session at the International Gynecologic Cancer Society (IGCS) Annual Meeting in October 2024.

About RAMP 201

RAMP 201 (ENGOTov60/GOG3052/NCRI) (NCT04625270) was 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 trial (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) evaluated 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 evaluated a low dose of the combination to inform individualized dose reduction.

About Low-Grade Serous Ovarian Cancer (LGSOC)

LGSOC is a rare ovarian cancer that is insidious and persistent. 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. Approximately 70 percent of LGSOC shows RAS pathway-associated mutations, and 30 percent of people with LGSOC have a KRAS mutation. The majority of patients report a negative impact of LGSOC on their mental and physical health, fertility, and long-term quality of life.

About AVMAPKI and FAKZYNJA Combination Therapy

AVMAPKI (avutometinib) inhibits MEK kinase activity while also blocking the compensatory reactivation of MEK by upstream RAF. RAF and MEK proteins are regulators of the RAS/RAF/MEK/ERK (MAPK) pathway. Blocking RAF and/or MEK activates FAK, a key mediator of drug resistance. FAKZYNJA (defactinib) is a FAK inhibitor and together, the avutometinib and defactinib combination was designed to provide a more complete blockade of the signaling that drives the growth and drug resistance of RAS/MAPK pathway-dependent tumors.

The U.S. Food and Drug Administration (FDA) approved AVMAPKI™ FAKZYNJA™ CO-PACK (avutometinib capsules; defactinib tablets) for the treatment of adult patients with KRAS-mutated recurrent LGSOC who have received prior systemic therapy on May 8, 2025. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial. Verastem is conducting RAMP 301 (GOG-3097/ENGOT-ov81/GTG-UK) (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) with and without a KRAS mutation. Verastem is also evaluating avutometinib in combination with defactinib and other agents as a potential treatment for patients with advanced pancreatic cancer (RAMP 205; NCT05669482) and advanced KRAS G12C mutant non-small cell lung cancer (RAMP 203; NCT05074810). Avutometinib and defactinib are not approved by the FDA or any other regulatory authority, either in combination or with other therapies, for any of these investigative uses. Neither avutometinib nor defactinib are approved by the FDA or any other regulatory authority on a stand-alone basis for any use.

AVMAPKI FAKZYNJA CO-PACK U.S. Indication

Indication

AVMAPKI FAKZYNJA CO-PACK is indicated for the treatment of adult patients with *KRAS*-mutated recurrent low-grade serous ovarian cancer (LGSOC) who have received prior systemic therapy.

This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Important Safety Information

Warnings and Precautions

- **Ocular Toxicities:** Ocular toxicities, including visual impairment and vitreoretinal disorders, occurred. Perform comprehensive ophthalmic evaluation at baseline, prior to cycle 2, every three cycles thereafter, and as clinically indicated. Withhold AVMAPKI FAKZYNJA CO-PACK for ocular toxicities until improvement at the same or reduced dose. Permanently discontinue AVMAPKI FAKZYNJA CO-PACK for any grade 4 toxicity.
- **Serious Skin Toxicities:** Skin toxicities, including photosensitivity and severe cutaneous adverse reactions (SCARSs) occurred. Adhere to concomitant medications. Monitor for skin toxicities and interrupt, reduce or permanently discontinue AVMAPKI FAKZYNJA CO-PACK based on severity, tolerability and duration.
- **Hepatotoxicity:** Monitor liver function tests prior to each cycle, on day 15 of the first 4 cycles, and as clinically indicated. Withhold, reduce or discontinue AVMAPKI FAKZYNJA CO-PACK based on severity and persistence of abnormality.
- **Rhabdomyolysis:** Monitor creatine phosphokinase prior to the start of each cycle, on day 15 of the first four cycles, and as clinically indicated. If increased CPK occurs, evaluate patients for rhabdomyolysis or other causes. Withhold, reduce or permanently discontinue AVMAPKI FAKZYNJA CO-PACK based on severity and duration of the adverse reaction.
- **Embryo-Fetal Toxicity:** AVMAPKI FAKZYNJA CO-PACK can cause fetal harm. Advise patients of the potential risk to a fetus and to use effective contraception.

Adverse Reactions

The most common (≥ 25%) adverse reactions, including laboratory abnormalities, were increased creatine phosphokinase, nausea, fatigue, increased aspartate aminotransferase, rash, diarrhea, musculoskeletal pain, edema, decreased hemoglobin, increased alanine aminotransferase, vomiting, increased blood bilirubin, increased triglycerides, decreased lymphocyte count, abdominal pain, dyspepsia, dermatitis acneiform, vitreoretinal disorders, increased alkaline phosphatase, stomatitis, pruritus, visual impairment, decreased platelet count, constipation, dry skin, dyspnea, cough, urinary tract infection, and decreased neutrophil count.

Drug Interactions

- **Strong and moderate CYP3A4 inhibitors**: Avoid concomitant use with AVMAPKI FAKZYNJA CO-PACK.
- **Strong and moderate CYP3A4 inducers**: Avoid concomitant use with AVMAPKI FAKZYNJA CO-PACK.
- **Warfarin:** Avoid concomitant use of AVMAPKI FAKZYNJA CO-PACK with warfarin and use an alternative to warfarin.
- **Gastric acid reducing agents**: Avoid concomitant use of AVMAPKI FAKZYNJA CO-PACK with proton pump inhibitors (PPIs) or H2 receptor antagonists. If use of an acid-reducing agent cannot be avoided, administer FAKZYNJA 2 hours before or 2 hours after the administration of a locally acting antacid.

Use in Specific Populations

- **Lactation**: Advise not to breastfeed.
- **Fertility:** May impair fertility in males and females.

Click here for full Prescribing Information.

About Verastem Oncology

Verastem Oncology (Nasdaq: VSTM) is a biopharmaceutical company committed to developing and commercializing new medicines to improve the lives of patients diagnosed with RAS/MAPK pathway-driven cancers. Verastem markets AVMAPKI™ FAKZYNJA™ CO-PACK in the U.S. 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, FAK inhibition, and KRAS G12D inhibition. For more information, please visit www.verastem.com and follow us on LinkedIn.

Forward-Looking Statements Notice

This press release includes forward-looking statements within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934. All statements other than historical statements of fact regarding Verastem's expectations, beliefs, goals, plans or prospects including, without limitation, statements about AVMAPKI FAKZYNJA CO-PACK's potential to benefit adult patients living with KRAS-mutated recurrent low-grade serous ovarian cancer in the United States, AVMAPKI FAKZYNJA CO-PACK's potential to be a transformational medicine, and AVMAPKI FAKZYNJA CO-PACK's potential to be an important treatment option for patients with KRAS-mutated recurrent low-grade serous ovarian cancer should be considered forward-looking statements. These forward-looking statements generally can be identified by the use of words such as "anticipate," "expect," "plan," "could," "may," "believe," "estimate," "forecast," "goal," "project," and other words of similar meaning. Such forward-looking statements address various matters about, among other things, Verastem Oncology's programs and product candidates, strategy, future plans and prospects, including statements related to the potential for and timing of commercialization of product candidates, the timing of commencing and completing trials and compiling data, the expected timing of the presentation of data by the Company and the potential clinical value of various of the Company's clinical trials. Each forward-looking statement contained in this press release is subject to risks and uncertainties that could cause actual results to differ materially from those expressed or implied by such statement. Applicable risks and uncertainties include, among others: the uncertainties inherent in research and development, such as the possibility of negative or unexpected results of clinical trials; that 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; that data may not be available when expected; the risk that our preliminary and interim data may not be representative of more mature data; uncertainties related to the recent change in the U.S. presidential administration, including regulatory and policy changes that may adversely affect our business; that our product candidates may not receive regulatory approval, become commercially successful products, or result in new treatment options being offered to patients; that the launch of AVMAPKI FAKZYNJA CO-PACK in the United States may not be successful; that the product may not be adopted by health care professionals; that pricing for the product may not be viewed favorably and we may not be successful in securing reimbursement coverage from third-party payors, including government agencies, for the product; that we may not be able to establish the product as the standard of care for KRAS-mutant recurrent LGSOC; that the actions or advice of regulatory agencies may impact our ability to obtain and maintain regulatory approval for our product; that the market opportunities for the product, that are based on internal and third-party estimates, may prove to be incorrect; that there may be competitive developments affecting our product candidates; that our product may cause adverse safety events or unexpected concerns may arise from additional data or analysis, or result in unmanageable safety profiles as compared to its level of efficacy; that we may be unable to successfully validate, develop and obtain regulatory approval for companion diagnostic tests for our product that require or would commercially benefit from such tests, or experience significant delays in doing so; that our product may experience manufacturing or supply interruptions or failures; that we may 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 may not have sufficient cash to fund our contemplated operations, including certain of our product commercialization and development programs; that we may not attract and retain high quality personnel; that we may not be able to expand the approved indication for AVMAPKI FAKZYNJA CO-PACK; that we may not be able to successfully obtain, maintain and protect intellectual property on our development and marketed products; that we may not be able to manage growth and operating expenses through disciplined investments in operations and achieve a self-sustainable financial profile in the future and avoid or successfully manage unexpected expenditures; that we may be unable to maintain strategic business collaborations; that our dependence on third parties for the development and commercialization of certain products may prove to be unsuccessful; that we may face government investigations and substantial changes in governmental policies, regulations, funding and enforcement; and the risks identified under the heading "Risk Factors" as detailed in the Company's Annual Report on Form 10-K for the year ended December 31, 2024, as filed with the Securities and Exchange Commission (SEC) on March 20, 2025, as well as the other information we file with the SEC, are possibly realized. We caution investors not to place considerable reliance on the forward-looking statements contained in this press release. You are encouraged to read our filings with the SEC, available at www.sec.gov, for a discussion of these and other risks and uncertainties. The forward-looking statements in this press release speak only as of the date of this press release, and we undertake no obligation to update or revise any of these statements. Our business is subject to substantial risks and uncertainties, including those referenced above. Investors, potential investors, and others should give careful consideration to these risks and uncertainties.

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Dr. Grisham has financial interests related to Verastem Oncology.

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For Investor and Media Inquiries:

Julissa Viana
Vice President, Corporate Communications,
Investor Relations & Patient Advocacy
investors@verastem.com or
media@verastem.com

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