Verastem Oncology Announces Nature Medicine Publication of the Results from the First-in-Human Phase 1 FRAME Study of Avutometinib in Combination with Defactinib in Solid Tumors, including Low-Grade Serous Ovarian Cancer

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FRAME study demonstrated a 42.3% ORR and 20.1 months median PFS for all patients with low-grade serous ovarian cancer (LGSOC), regardless of KRAS mutation; for patients with KRAS-mutated LGSOC, ORR and mPFS were 58.3% and 30.8 months, respectively

Study conducted by the Institute of Cancer Research and The Royal Marsden NHS Foundation Trust demonstrated the importance of the intermittent dosing schedule of the combination of avutometinib and defactinib to improve tolerability and anti-tumor activity

BOSTON--(BUSINESS WIRE)--Jun. 30, 2025-- Verastem Oncology (Nasdaq: VSTM), a biopharmaceutical company committed to advancing new medicines for patients with RAS/MAPK pathway-driven cancers, today announced that updated results from the Phase 1/2 FRAME study conducted by The Institute of Cancer Research, London, and The Royal Marsden NHS Foundation Trust were published online in *Nature Medicine*. The full manuscript, titled "Defactinib with avutometinib in patients with solid tumors: the phase 1 FRAME trial," was the first-in-human study to evaluate the safety, tolerability, and efficacy of avutometinib in combination with defactinib in patients with low-grade serous ovarian cancer (LGSOC), non-small cell lung cancer (NSCLC), and other solid tumor types.

"The FRAME study was the early foundation for the recent FDA approval of avutometinib plus defactinib in KRAS-mutated recurrent low-grade serous ovarian cancer and we are pleased to see that the mature data set continues to show the safety and tolerability of this combination therapy," said Dan Paterson, president and chief executive officer of Verastem Oncology. "This supports our ongoing commitment to advancing our research into the combination for use in other solid tumors, including RAMP 205 in first-line metastatic pancreatic cancer."

The FRAME study enrolled patients, across dose escalation and dose expansion cohorts, with RAS-MAPK-driven solid tumors including LGSOC, NSCLC, colorectal, pancreatic and endometrial cancers. The updated data include an extended follow-up period and more detailed analyses from the FRAME study, featuring efficacy and safety data that demonstrated the novel combination of avutometinib and defactinib continues to be well-tolerated and shows encouraging responses in patients with LGSOC, consistent with previous findings.

"This was the first clinical study to show significant clinical activity of the combination of avutometinib, a RAF/MEK clamp, with defactinib, a FAK inhibitor. The FRAME study demonstrated an important potential advancement in the treatment of solid tumor diseases like low-grade serous ovarian cancer where seventy percent of these tumors are driven by the RAS/MAPK pathway and with thirty percent of these patients carrying a KRAS mutation," said Professor Udai Banerji, co-Director of the Drug Development Unit, The Institute of Cancer Research and The Royal Marsden Hospital NHS Foundation Trust, London. "We are pleased to have contributed to the development of avutometinib and defactinib. With FRAME's encouraging efficacy signal, the recommended Phase 2 dose was selected and the intermittent dosing schedule evaluated, which is the dose and schedule recently FDA approved in the U.S. and being used in the global confirmatory Phase 3 RAMP 301 trial."

In 26 patients with LGSOC who were evaluable for efficacy, the overall response rate (ORR) was 42.3% (11/26) and median progression-free survival (mPFS) was 20.1 months. In the 24 patients whose samples could be sequenced for KRAS mutations, ORR and mPFS were 58.3% (7/12) and 30.8 months in the 12 patients with KRAS mutations, and 33.3% (4/12) and 8.9 months in the 12 patients without KRAS mutations. In 11 patients who had previously received a MEK inhibitor, the ORR was 27.3% (3/11). Additionally, in two patients with LGSOC who had brain metastases prior to enrolling, MRI imaging at 30 months post-treatment with the combination showed the metastases had shrunk in both patients.

In 27 patients with LGSOC who were evaluable for safety, only one (4%) discontinued treatment due to Grade 3 skin toxicity. The five most common adverse events (AEs) (all grades, grade ≥3) were: rash (90%, 8%), elevated blood levels of creatine phosphokinase (56%, 9%), AST elevation (43%, 1%), hyperbilirubinemia (38%, 2%), and diarrhea (38%, 1%). The tolerability profile of avutometinib plus defactinib was comparable to the tolerability of each agent as monotherapy.

About the Phase 1/2 FRAME Study

The FRAME study is an open-label, investigator-initiated study that is designed to assess safety, dose response, and preliminary efficacy of the VS-6766/defactinib combination in patients with KRAS mutant solid tumors, including low-grade serous ovarian cancer (LGSOC), non-small cell lung cancer (NSCLC) and colorectal cancer (CRC). The FRAME study is being led by Professor Udai Banerji, MBBS, MD, DNB, PhD, FRCP, Deputy Director of the Drug Development Unit at The Institute of Cancer Research, London, and The Royal Marsden NHS Foundation Trust, and is being conducted in the United Kingdom. In this study, VS-6766 was administered using a twice-weekly dose escalation schedule and was administered three out of every four weeks. Defactinib was administered using a twice-daily dose escalation schedule, also three out of every four weeks. Dose levels were assessed in three cohorts: cohort 1 (avutometinib 3.2mg, defactinib 200mg); cohort 2a (avutometinib 4mg, defactinib 200mg); and cohort 2b (avutometinib 3.2mg, defactinib 400mg). The recommended Phase 2 dose was determined to be cohort 1 (avutometinib 3.2mg, defactinib 200mg).

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

This press release contains 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. The words "anticipate," "believe," "estimate," "expect," "intend," "may," "plan," "predict," "project," "target," "potential," "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. Actual results and future plans may differ materially from those indicated by these forward-looking statements as a result of various important risks, uncertainties and other factors, including, without limitation, risks and uncertainties relating to: the launch AVMAPKI FAKZYNJA CO-PACK in the United States including having the product available in the market following launch and thereafter; the adoption of the product by health care professionals; establishing favorable pricing for the product and securing reimbursement coverage from third-party payors, including government agencies, for the product; establishing the product as the standard of care for KRAS-mutant recurrent LGSOC; actions or advice of regulatory agencies and our ability to obtain and maintain regulatory approval for our product; the market opportunities for AVMAPKI FAKZYNJA CO-PACK are based on internal and third-party estimates that may prove to be incorrect; that there may be competitive developments affecting our product candidates; that data may not be available when expected; 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 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; the discovery and development of novel drug candidates and delivery approaches and successful demonstration of the efficacy and safety of our product candidates; the pre-clinical and clinical results 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 launch, market and sell AVMAPKI FAKZYNJA CO-PACK in the United States and realize all or a substantial portion of the potential market opportunity; that we may not be able to successfully launch, market and sell approved products globally; that there may be delays, interruptions or failures in the manufacture and supply of our product candidates or marketed products; that we successfully obtain, maintain and protect intellectual property on our development and marketed products; that we are able to manage growth and operating expenses through disciplined investment in operations and able to achieve a self-sustainable financial profile in the future and avoid or successfully manage unexpected expenditures; that we are able to maintain strategic business collaborations; the dependence on third parties for the development and commercialization of certain products; the risks and uncertainties related to the recent change in the U.S. presidential administration, including regulatory and policy changes that may adversely affect our business; the risk of future government investigations and substantial changes in governmental polices, regulations, funding and enforcement; as well as those risks and uncertainties more fully discussed in the "Risk Factors" filed with Verastem's 2024 Annual Report on Form 10-K filed with the Securities and Exchange Commission (SEC) on March 20th, 2025, as may be updated from time to time in Verastem's subsequent Quarterly Reports on Form 10-Q, and in other filings that Verastem makes with the SEC.

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