Verastem Oncology Announces Multiple Presentations Focused on RAS/MAPK Pathway Inhibition at AACR Annual Meeting 2025

March 25, 2025 at 4:35 PM EDT

VS-7375, a potential best-in-class oral KRAS G12D (ON/OFF) inhibitor more potent than other KRAS G12D inhibitors in preclinical models

VS-7375, when combined with cetuximab, demonstrated strong tumor regressions in preclinical KRAS G12D models, including complete responses in a colorectal cancer model

In a patient-derived LGSOC xenograft model, an FAK inhibitor addition to avutometinib augmented tumor regression with stronger inhibition of MAPK, PI3K and YAP/TEAD signaling than either agent alone

The combination of avutometinib, a RAF/MEK clamp, with a pan-RAF inhibitor led to strong tumor regressions in multiple NRAS- and BRAF-driven tumor models corresponding with nearly complete shutdown of RAS/MAPK pathway signaling

BOSTON--(BUSINESS WIRE)--Mar. 25, 2025-- Verastem Oncology (Nasdaq: VSTM), a biopharmaceutical company committed to advancing new medicines for patients with RAS/MAPK pathway-driven cancers, announced today multiple oral and poster presentations at the American Association for Cancer Research (AACR) Annual Meeting 2025 to be held on April 25-30 in Chicago, Illinois. These presentations will highlight clinical and preclinical data from the Company's development programs, including VS-7375 (GFH375), an oral KRAS G12D (ON/OFF) inhibitor and avutometinib, an oral RAF/MEK clamp, and defactinib, an oral FAK inhibitor.

"At this year's AACR annual meeting, we show that VS-7375, our oral KRAS G12D (ON/OFF) inhibitor, was found to be more potent than other KRAS G12D inhibitors in preclinical models. In addition, using a patient-derived LGSOC xenograft model, we and our collaborators further explored the mechanism by which our FAK inhibitor increases the anti-tumor efficacy of avutometinib. The results demonstrate that compared to avutometinib alone, the FAK inhibitor/avutometinib combination inhibits RAS/MAPK pathway signaling more deeply while also blocking key adaptive resistance mechanisms including PI3K and YAP/TEAD signaling," said Jonathan Pachter, Ph.D., Chief Scientific Officer of Verastem Oncology.

Key Data Presentations:

Oral Presentation: Minisymposium

- **Title:** Correlative preclinical studies to elucidate mechanisms of synergy of the combination of the RAF/MEK clamp avutometinib and the FAK inhibitor defactinib in low-grade serous ovarian cancer
- **Abstract #:** 6368
- **Presenter**: Udai Banerji, M.D.
- **Session:** Targeted Therapies and Combinations, Clinical Research
- **Session Date/Time:** April 29, 2025 from 2:30 to 4:30 pm CST

In a patient-derived LGSOC xenograft model, addition of a FAK inhibitor with avutometinib augmented tumor regression, more strongly inhibited RAS/MAPK pathway signaling compared to avutometinib alone and suppressed multiple putative mechanisms of resistance to avutometinib monotherapy including PI3K and YAP/TEAD signaling.

Poster Presentations:

- **Title:** GFH375 (VS-7375): An oral, selective KRAS G12D (ON/OFF) inhibitor with potent anti-tumor efficacy as single agent and in combination with other anticancer therapies in preclinical models
- **Abstract #:** 4394
- **Session:** RAS Inhibitors, Experimental and Molecular Therapeutics
- **Location/Poster Board #: Poster Section 21, Board # 29**
- **Date and Time:** April 29, 2025 from 9:00 am to 12:00 pm CST

VS-7375 (GFH375), a selective oral KRAS G12D (ON/OFF) inhibitor, was found to be more potent than other KRAS G12D inhibitors in preclinical models. In addition, the combination of VS-7375 with the anti-EGFR antibody, cetuximab, induced strong tumor regressions in preclinical models, including complete responses in all mice in a colorectal cancer model.

- **Title:** RAF/MEK clamp avutometinib combined with a pan-RAF inhibitor induces nearly complete MAPK pathway inhibition with deep tumor regressions in NRAS or BRAF class III mutant models
- **Abstract #:** 4393
- **Session:** RAS Inhibitors, Experimental and Molecular Therapeutics
- **Location/Poster Board #: Poster Section 21, Board # 28**
- **Date and Time:** April 29, 2025 from 9:00 am to 12:00 pm CST

Combining avutometinib with a pan-RAF inhibitor (exarafenib or belvarafenib) led to strong tumor regressions in multiple NRAS- and BRAF-driven tumor models corresponding with nearly complete inhibition of RAS/MAPK pathway signaling.

Late-Breaking and Clinical Abstracts:

- **Title:** A Single-Arm Phase 1 Trial of Avutometinib (RAF/MEK inhibitor), Abemaciclib (Abema), and Fulvestrant in CDK4/6 inhibitor (CDK4/6i)-pretreated patients (pts) with HR+ Metastatic Breast Cancer (MBC) - *Investigator-Sponsored Trial*
- Abstract #: CT028
- Session: Phase 0 and Phase I Clinical Trials
- **Location/Poster Board #: Poster Section 49, Board #7**
- **Date and Time:** April 28, 2025 from 9:00 am to 12:00 pm CST

- **Title:** Mechanistic rationale for combination of RAF/MEK glue avutometinib with a pan-RAF inhibitor for RAS-mutant tumor-selective therapy
- **Abstract #:** LB424
- **Session:** Late-Breaking Research: Experimental and Molecular Therapeutics 4
- **Location/Poster Board #: Poster Section 51, Board #6**
- **Date and Time:** April 30, 2025 from 9:00 am to 12:00 pm CST

The accepted abstracts are available on the AACR conference website: AACR Annual Meeting 2025 | Meetings | AACR. Late-breaking and clinical abstracts will be available on April 25, 2025.

nAbout the Avutometinib and Defactinib Combinatio

Avutometinib is an oral RAF/MEK clamp that potently 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 Raf And Mek Program 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 VS-7375, an Oral KRAS G12D (ON/OFF) Inhibitor

VS-7375 is a potential best-in-class, potent, and selective oral KRAS G12D dual ON/OFF inhibitor. VS-7375 is the lead program from the Verastem Oncology discovery and development collaboration with GenFleet Therapeutics. Verastem filed an investigational new drug (IND) application in the U.S. for VS-7375 in the first quarter of 2025. GenFleet's IND for VS-7375 (known as GFH375 in China) was approved in China in June 2024, and the first patient was dosed in a Phase 1/2 study in July 2024.

About the GenFleet Therapeutics Collaboration

The collaboration with GenFleet Therapeutics aims to advance three oncology discovery programs related to RAS/MAPK pathway-driven cancers. The collaboration provides Verastem with an exclusive option to obtain a license for each of the three compounds in the collaboration after the successful completion of pre-determined milestones in a Phase 1 trial. Verastem selected VS-7375 (also known as GFH375), an oral KRAS G12D (ON/OFF) inhibitor, as its lead program in December 2023 and the license for VS-7375 that was exercised in January 2025 is the first one from this collaboration. The licenses would give Verastem development and commercialization rights outside the GenFleet markets of mainland China, Hong Kong, Macau, and Taiwan.

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 RAS/MAPK pathway-driven cancers. 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 includes 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 anticipated timing for the IND application for VS-7375/GFH375, the expected outcome and benefits of the Company's collaboration with GenFleet Therapeutics (Shanghai), Inc., 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 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, or that GenFleet may fail to fully perform under the agreement; 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; risks associated with preliminary and interim data, which may not be representative of more mature data; that our product candidates may not receive regulatory approval, become commercially successful products, or result in new treatment options being offered to patients; and the risks identified under the heading "Risk Factors" 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. 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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