Verastem Oncology Provides a Clinical Update for RAMP 203 Trial in Advanced KRAS G12C Mutant Non-Small Cell Lung Cancer

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No dose-limiting toxicities were observed in the RAMP 203 first triplet combination cohort of avutometinib and LUMAKRAS™ (sotorasib) plus defactinib in patients previously treated with a G12C inhibitor

BOSTON--(BUSINESS WIRE)--Dec. 18, 2024-- Verastem Oncology (Nasdaq: VSTM), a biopharmaceutical company committed to advancing new medicines for patients with cancer, today announced preliminary clinical data for the triplet combination of avutometinib and sotorasib plus defactinib in the RAMP 203 Phase 1/2 study in KRAS G12C mutant advanced non-small cell lung cancer (NSCLC). No dose-limiting toxicities (DLTs) have been observed in the triplet combination. RAMP 203 continues to progress, with additional enrollment expected and an interim update is planned to be presented at a medical meeting in the second half of 2025.

“We continue to make progress across our pipeline to develop novel therapies alone or in synergistic combinations that have the potential to improve outcomes in RAS/MAPK pathway-driven cancers. Defactinib, our oral FAK inhibitor, has been an important addition to multiple clinical trials with avutometinib to address key resistance mechanisms in parallel pathway signaling,” said Dan Paterson, chief executive officer at Verastem Oncology. “Recently, we added defactinib to the combination of avutometinib and sotorasib in our RAMP 203 trial. Preliminary data for the triplet combination have shown a generally favorable tolerability profile and encouraging initial anti-tumor activity. We look forward to progressing enrollment and evaluating the safety and efficacy of the triplet combination in treating KRAS G12C mutant non-small cell lung cancer.”

RAMP 203 Clinical Update

As of a November 21, 2024, data cutoff, three patients whose cancer previously progressed on a G12C inhibitor have been treated with the triplet combination of sotorasib 960 mg administered daily on a continuous schedule and avutometinib 3.2 mg twice-weekly (BIW) plus defactinib 200 mg twice-daily (BID). Avutometinib and defactinib are administered on a three out of four weeks schedule. Two of the three patients demonstrated initial tumor reductions of at least 20% at the first scan. As of the data cutoff, all three patients remain on treatment. With no DLTs observed in the first triplet combination cohort, the Company anticipates the enrollment of additional patients to the triplet combination prior to presenting the data at a medical meeting next year.

As previously reported, the doublet combination of avutometinib with sotorasib has completed enrollment (n=28) in the G12C inhibitor treatment-naïve Stage 1 Part B cohort. The KRAS G12C inhibitor prior-treated Stage I Part B cohort is still enrolling patients and is anticipated to complete enrollment in early 2025. Patients in both cohorts continue to be followed for safety and efficacy to determine if observed efficacy supports expanded enrollment. The Company plans to complete enrollment and evaluate the safety and efficacy of the triplet combination, before expanding either of the doublet cohorts.

“We are encouraged by the initial data from the triplet combination of avutometinib and sotorasib plus defactinib in the RAMP 203 trial, which shows early evidence of tumor reductions for patients who have limited treatment options,” said John Hayslip, M.D., chief medical officer at Verastem Oncology. “While the data matures for the doublet combination across cohorts, we are now focused on completing the enrollment in the triplet combination, guided by preclinical data that indicates that the addition of a FAK inhibitor increases the anti-tumor efficacy of avutometinib plus sotorasib in KRAS G12C mutant NSCLC models, and tumors that progress on a G12C-inhibitor treatment can be made to respond again upon treatment with a FAK inhibitor plus avutometinib. As planned, the triplet combination builds on the experience from the RAMP 201 study in recurrent low-grade serous ovarian cancer, where there was a clear advantage to adding defactinib. Based on the RAMP 201 results, we did an assessment of our clinical programs and made the decision to add defactinib to almost all our studies.”

About RAMP 203

RAMP 203 is a Phase 1/2, multicenter, open label, dose evaluation/expansion study evaluating the efficacy and safety of avutometinib and sotorasib with or without defactinib in patients with KRAS G12C mutant non-small cell lung cancer (NSCLC) who have not been previously treated with a KRAS G12C inhibitor as well as in patients who have been previously treated with a KRAS G12C inhibitor (NCT05074810). RAMP 203 is being conducted in collaboration with Amgen.

About the Avutometinib and Defactinib Combination

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 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 completed its rolling New Drug Application (NDA) submission to the 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, 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. 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 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 additional enrollment and expansion of cohorts in the Company's RAMP 203 trial, the expected timing of the presentation of updated RAMP 203 data by the Company, and the potential clinical value of various of the Company's clinical trials, including the RAMP 203 trial. 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 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; that 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 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; 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 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 KRAS wild type LGSOC; 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 or our decisions regarding execution of such commercialization; that we may not have sufficient cash to fund our contemplated operations, including certain of our product development programs; 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 the total addressable and target markets for our product candidates might be smaller than we are presently estimating; that we or Secura Bio, Inc. (Secura) will fail to fully perform under the asset purchase agreement with Secura, 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 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; 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.

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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