2. SYNOPSIS

Name of Sponsor/Company: Verastem Oncology, Inc. **Name of Finished Product:** Avutometinib (VS-6766) Defactinib (VS-6063) **Name of Active Ingredient:**	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*

Title of Study:

A Phase 2 Study of VS-6766 (Dual RAF/MEK Inhibitor) as a Single Agent and In Combination with Defactinib (FAK Inhibitor) in Recurrent KRAS-Mutant (KRAS-MT) and BRAF-Mutant (BRAF-MT) Non-Small Cell Lung Cancer (NSCLC) (RAMP 202)

Lead Principal Investigator:

Principal Investigators:

The list of investigators and study sites are available upon request.

Study Center(s):

The list of investigators and study sites are available upon request.

Publications (Reference):

Capelletto E, Bironzo P, Denis L, Koustenis A, Bungaro M, Novello S. Single agent VS-6766 or VS-6766 plus defactinib in KRAS-mutant non-small-cell lung cancer: the RAMP-202 phase II trial (Capelletto 2022)

Dates of Study:	**Phase of Development:**
Study initiation: 02 Mar 2021 Study completion: 12 Dec 2023	Phase 2

Objectives:

Primary objectives: In Part A, to determine the optimal regimen, avutometinib monotherapy or avutometinib in combination with defactinib, in the treatment of NSCLC characterized by mutation G12V in the human KRAS protooncogene (KRAS-mt) and to assess the initial efficacy of avutometinib in combination with defactinib in treatment of NSCLC characterized by mutations in the human RAF protein B protooncogene (BRAF-mt). In Part B, to determine the efficacy of the optimal regimen identified in Part A in the treatment of KRAS-G12V NSCLC and the efficacy of avutometinib in combination with defactinib in the treatment of V600E and non-V600E mutations in BRAF-mt NSCLC.

Secondary objectives: In Part A and Part B, to characterize the safety and toxicity profile of avutometinib as monotherapy and in combination with defactinib in KRAS-mt and in BRAF-mt NSCLC. In Part A, to evaluate additional efficacy parameters for avutometinib monotherapy and avutometinib combination therapy with defactinib. In Part B, To evaluate additional efficacy parameters for the optimal regimen identified in Part A for treatment of KRAS-G12V NSCLC and to evaluate additional efficacy parameters of avutometinib in combination with defactinib in the treatment of V600E and non-V600E BRAF-mt NSCLC. To characterize the pharmacokinetics (PK) of avutometinib, defactinib, and relevant metabolites.

Exploratory objectives: To evaluate pharmacodynamics (PD) and predictive biomarkers and assess efficacy in the treatment of NSCLC patients with KRAS-Other (ie, non-G12V) mutations.

Methodology:

Part A - Go Forward Regimen Selection: A Go Forward (GF) strategy was used to choose between avutometinib monotherapy and the avutometinib-defactinib combination regimens in patients with KRAS-G12V randomized 1:1

between treatment Arms 1 and 2; treatment Arm 3 comprised patients with KRAS-Other mutations treated with the combination regimen in Part A as an exploratory cohort.

- Arm 1: Avutometinib Monotherapy in KRAS-G12V NSCLC
- Arm 2: Avutometinib + Defactinib Combination in KRAS-G12V NSCLC
- Arm 3: Avutometinib + Defactinib Combination in KRAS-Other NSCLC

Accrual in Arms 1 and 2 was to be conducted in patients with KRAS-G12V NSCLC until GF regimen selection was made using data on overall response rate (ORR: partial response [PR] + complete response [CR]) defined according to Response Evaluation Criteria in Solid Tumors version 1.1 [RECIST 1.1]). A GF regimen selected between Arm 1 and Arm 2 was required to meet two criteria: an observed ORR greater than the observed ORR in the alternative regimen and an observed ORR of ≥ 15%. If the ORRs of Arm 1 and Arm 2 were equal, monotherapy was to be declared the GF regimen if it met the 15% ORR criterion.

In Part A, activity of avutometinib in combination with defactinib was also assessed in BRAF-mt patients.

- Arm 4: Avutometinib + Defactinib Combination in BRAF-V600E NSCLC
- Arm 5: Avutometinib + Defactinib Combination in BRAF-non-V600E NSCLC

An assessment of ORR in each arm was conducted after Part A. For each arm, the number of patients enrolled could be increased in the Part B Expansion Phase if there were ≥ 2 responders in the cohort treated.

In Part B - Expansion Phase if GF Regimen Selected in Part A: The GF regimen determined in Part A was to be evaluated in NSCLC patients with KRAS-G12V mutations with a second cohort comprising KRAS-Other mutations to be treated. The primary ORR endpoint was to be evaluated in a two-step manner by an Independent Review Committee (IRC). The first evaluation was to be in patients with KRAS-G12V NSCLC treated with the GF regimen. If successful, ORR was to be assessed in KRAS-G12V NSCLC in combination with the other types of KRAS mutations selected for evaluation in Part B.

If a GF regimen was selected in patients with KRAS-G12V mutations in Part A, the number of patients initiating that therapy was to be expanded to achieve the requisite statistical power for further assessment of ORR. In addition, a cohort of NSCLC patients with select KRAS-Other mutations was to be accrued. The entry criteria for enrollment were permitted to be modified based on the data derived from Part A.

In Part B - Expansion Phase if GF Regimen Not Selected in Part A: If the GF regimen was not selected following evaluation of the first 32 patients with KRAS-G12V NSCLC, then randomization and treatment of additional patients with KRAS-G12V mutations was permitted to allow for review of additional data. Enrollment of patients with KRAS-Other mutations was permitted at the same time, with patients randomized 1:1 to the two arms; in the alternative, enrollment of patients with KRAS-Other NSCLC was to be started when a GF regimen was determined following subsequent evaluation.

For each BRAF-mt arm, if the threshold of ≥ 2 responders in Part A was met, expansion was to be considered. The number of patients to be added during Part B was based on the results of the initial determination of ORR. The criteria for evaluation of the ORR endpoint were to be determined by the final number of patients enrolled and treated.

Number of Patients (Planned and Analyzed):

Planned: Patients were to be enrolled at approximately 50 sites globally in Parts A and B with an enrollment of approximately 102 patients in Part A (32 patients with KRAS-G12V, 40 patients with KRAS-other, 15 patients with BRAF-V600E, and 15 patients with BRAF-non-V600E). The number of patients in Part B and the total number of patients enrolled was to be determined by the results from Part A.

Analyzed: A total of 139 patients were screened at 37 centers globally: 49 (35.3%) patients failed screening, and 90 (64.7%) patients were enrolled and randomized. Of the 90 patients enrolled, 89 (98.9%) patients were treated and included in the safety analysis (ie, the mITT population); 50 (55.6%) patients entered the survival follow-up. The study was terminated early by the Sponsor due to an ORR that was <15%.

Diagnosis and Main Criteria for Inclusion:

Inclusion: Male or female patients ≥ 18 years of age with NSCLC without histologic evidence of a small cell component that is metastatic (Stage 4) or locally advanced (Stage 3B-C) and unresectable with a confirmed KRAS or BRAF mutation. The patient must have received platinum-based therapy for a non-activating mutation and appropriate treatment with a monoclonal antibody to PD-1 or PD-L1 unless contraindicated and have an Eastern Cooperative Oncology Group performance status of ≤1.

Exclusion: Any history of treatment with a direct and specific inhibitor of KRAS or BRAF (except BRAF-V600E NSCLC) or prior malignancy except those curatively treated or with low potential for recurrence or progression. Systemic anticancer therapy or major surgery within 4 weeks of the first dose of study treatment. Symptomatic brain metastases, congestive heart failure, concurrent ocular or skin disorders, an inability to swallow oral medications, females who are pregnant or breastfeeding, or other medical conditions that would put the patient at unacceptably high risk for the impact of treatment toxicity.

Test Product, Dose and Mode of Administration, Batch Number:

Avutometinib Monotherapy: Avutometinib was administered at 4.0 mg orally twice a week for 3 weeks, followed by a 1-week rest period, in each 4-week (28-day) cycle.

Avutometinib + Defactinib Combination: Avutometinib was administered at 3.2 mg orally twice a week and defactinib was administered at 200 mg orally twice daily for 3 weeks, followed by a 1-week rest period, in each 4-week (28-day) cycle.

Duration of Treatment:

Mean duration of exposure for the 89 patients included in the safety analysis was 3.529 months (range: 0.07 to 23.98 months); median duration of exposure was 1.776 months. Forty-eight (48) of the 89 (53.9%) patients started fewer than 3 treatment cycles; 21 (23.6%) patients started 3 to 5 cycles; 11 (12.4%) patients started 6 to 8 cycles; and 9 patients (10.1%) started 9 or more cycles. The mean number of cycles started was 4.146 (range: 1.00 to 27.00 cycles); the median number of cycles started was 2.000.

Relative dose intensity (RDI) was 90.455 % for the 89 patients who received avutometinib (range: 40.00 to 100.00%); median RDI was 96.296%. The RDI for the 73 patients who received defactinib was 68.608 % (range: 0 to 101.02%); median RDI was 72.414%.

In general, the proportion of dose reductions, dose holds, dose modifications, and drug discontinuations for avutometinib and defactinib were similar during the conduct of the study.

Reference Therapy, Dose and Mode of Administration, Batch Number:

Not applicable.

Criteria for Evaluation:

Primary endpoints: In Part A and Part B, confirmed ORR according to RECIST 1.1 as assessed by the Blinded Independent Radiology Review Committee (BIRC).

Secondary endpoints: In Part A and Part B, assessment of adverse events (AEs), serious AEs (SAEs), physical examinations, clinical laboratory values, and tolerability as well as duration of response (DOR), ORR as assessed by the Investigator, disease control rate (DCR: CR+PR + stable disease [SD]), progression free survival (PFS: time from first dose to first documentation of progressive disease [PD] or death from any cause), and overall survival (OS).

Exploratory endpoints: Mutations, gene expression levels, and protein levels and/or activity related to RAS/RAF/MEK pathway and other markers.

Data Analysis and Statistical Methods per the Statistical Analysis Plan (SAP):

Statistical analysis: Formal hypothesis testing was employed only in Part A and final analysis of ORR. Tabulations were produced for disposition, demography, medical history, concomitant medications, efficacy variables, and safety parameters. For categorical variables, summary tabulation of number and percentage of patients were presented with 2-sided 95% confidence intervals (CIs). For continuous variables, number of patients, mean, median, standard deviation, minimum, and maximum values were reported. Time-to-event data were determined using Kaplan-Meier analysis.

Analysis populations:

The Intent-to-Treat (ITT) population was defined for the randomized component(s) of the study only and comprised all patients randomized to treatment.

Modified Intent-to-Treat (mITT) population was defined as all patients who received at least one dose of either study treatment; for patients receiving combination therapy, at least 1 dose of avutometinib, 1 dose of defactinib, or both was required for inclusion.

The safety population was defined as all patients who received at least one dose of either study treatment, making it the same as the mITT population.

Summary of Results:

Efficacy results:

Not applicable for this abbreviated clinical study report.

Pharmacokinetic results:

Pharmacokinetic results will be presented in a separate report.

Safety results:

For the 89 patients in the Safety Analysis Set, the overall mean and median durations of exposure to treatment were 3.5 and 1.8 months, respectively. The mean and median numbers of treatment cycles started were 4.1 and 2.0, respectively. The mean and median RDIs for the 89 patients who received avutometinib (with or without defactinib) were 90.5% and 96.3%, respectively. The mean and median RDIs for the 73 patients who received defactinib (with avutometinib) were 68.6% and 72.4%, respectively.

One or more TEAEs were reported by all patients (89/89, 100%); in the case of 87 (97.8%) patients, these TEAEs were considered by the investigator as study treatment-related.

TEAEs reported by more than 25% of patients in the study included: nausea, 42 (47.2%) patients; oedema peripheral, 39 (43.8%) patients; diarrhoea, 37 (41.6%) patients; vomiting, 28 (31.5%) patients; and fatigue, 26 (29.2%) patients.

A total of 65/89 (73.0%) patients had one or more dermatological TEAEs. Dermatological TEAEs reported by ≥ 10% of the 89 patients included: rash, 19 (21.3%) patients; dermatitis acneiform, 19 (21.3%) patients; and dry skin, 9 (10.1%) patients.

A total of 34/89 (38.2%) patients had one or more ophthalmological TEAEs. The only ophthalmologic TEAE reported for ≥ 10% of patients was vision blurred in 18 (20.2%) patients.

A total of 57 (64.0%) patients had a TEAE that was assessed as ≥ Grade 3.

A total of 13 (14.6%) patients had a TEAEs resulting in death, none of these deaths were considered related to study drug by the investigator. Treatment emergent SAEs were reported for 37 (41.6%) patients, with 6 (6.7%) patients having SAEs considered by the investigator as study treatment-related.

A total of 22 (24.7%) patients had TEAEs leading to study drug discontinuation. TEAEs leading to dose modification occurred in 55 (61.8%) patients; TEAEs leading to a dose hold occurred in 42 (47.2%) patients; and TEAEs leading to dose reduction occurred in 14 (15.7%) patients.

Worsening in severity grade for a change from baseline in clinical laboratory values was reported for the following test results: decreased albumin in 49 (55.1%) patients; increased AST in 43 (48.3%) patients; decreased hemoglobin in 39 (43.8%) patients; increased CPK in 38 (42.7%) patients; decreased platelets in 27 (30.3%) patients; increased bilirubin in 24 (27.0%) patients; and increased ALT in 19 (21.3%) patients.

Conclusions:

The VS-6766-202 Clinical Study was terminated by the Sponsor because prespecified efficacy requirements (the achievement of a “Go-Forward” regimen) were not met.

Overall, there were no unexpected or new safety signals identified, and dosing with avutometinib monotherapy or avutometinib and defactinib exhibited a generally tolerable and manageable safety profile in participants with metastatic or locally advanced and unresectable NSCLC.

Coronavirus Disease Impact Statement:

Assessments missed for 5 of the 89 (5.6%) patients in the treated population due to the impact of Covid-19.

Date of the Report:

12 September 2024