PROTOCOL TITLE: A Phase 2 Study of Defactinib and Avutometinib, in Combination with Nivolumab for patients with anti-PD1 refractory LKB1-Mutant Advanced Lung Adenocarcinoma

WINSHIP PROTOCOL #: WINSHIP5947-23

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OTHER AGENT(S): Nivolumab

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REVISION HISTORY

Revision #	Version Date	Summary of Changes
1	5-13-24	Page 11: Reference to how Nivolumab will be supplied. Page 14: Sentences removed related to Avutometinib Page 17: Risks add to does modifications and management guidance for specific toxicities Page 18: Management addition regarding hyperbilirubinemia Page 19: Removal of maximum number of dose reductions related to creatine phosphokinase elevation

		Page 20: Removal of dose modification instruction for Grade2 other toxicities; Grade 1, 2, 3, 4 footnotes added. Page 22: Grades 1-4 added to Ocular findings in Retinal Toxicities table Page 25: BCRP Inhibitors/Inducers row added to Concomitant Therapies Restrictions table Page 6: stk11 is equal to 1kb 1 Page 36: Participants must receive prior authorization from their insurance companies to cover nivolumab prior to enrollment on study.
2	5-20-25	Opened enrollment to any line of therapy after platinum chemotherapy and immunotherapy.
3	9-9-25	Decrease CRCL inclusion to 50, and increase qtc to 470

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1. Study Summary

1.1 Synopsys

Title:	A Phase 2 Study of Defactinib and Avutometinib, in Combination with Nivolumab for patients with anti-PD1 refractory LKB1-Mutant Advanced Lung Adenocarcinoma
Study Description:	Two cohorts of patients will be enrolled: Cohort A: patients with LKB1 and KRAS mutation; Cohort B: LKB1 mutation without concomitant KRAS mutation. The efficacy of the combination regimen will be evaluated in both cohorts individually.
Objectives:	**Primary Objective**: The primary objective of the phase II study is to determine the efficacy (6-months PFS rate) of Defactinib and Avutometinib when combined with the, Nivolumab in patients with LKB1 mutated lung adenocarcinoma. **Secondary Objectives:** 1. To determine the toxicity profile of defactinib and avutometinib in combination with nivolumab 2. To assess the response rate (RECIST) and overall survival 3. To identify biomarkers in tumor tissue that predict for a favorable or unfavorable outcome **Exploratory Objective:** To evaluate the effect of treatment on selected biomarkers (Pyk2/FAK and MEK/ERK) in the tumor microenvironment and systemic circulation.
Endpoints:	**Primary Endpoint:** Efficacy as measured by 6-month PFS rate **Secondary Endpoints:** Safety, PFS, OS, duration of overall response (DOR)
Study Population:	25 patients will be enrolled in each of the two cohorts; The initial 10 patients will be used for a safety-run if deemed to be safe. For each cohort separately, a time-to-Event Bayesian optimal phase 2 (TOP) design will be carried out with two planned interim analyses for futility assessment. The design holds a maximum statistical power of 85% under 0.1 type I error to reject null hypothesis of 25% 6-mo PFS rate if the underlying rate is over 50%. Histological confirmation of non-squamous NSCLC, LKB1 mutation, disease progression on prior immune checkpoint inhibition, ECOG Performance status of 0/1, adequate hepatic, renal and bone marrow function, ability to take oral medications on a regular basis, and willingness to sign informed consent. Patients with treated and stable brain metastasis

	will be eligible. Patients that suffered a clinically significant immune AE with prior immunotherapy will be excluded. This study is hypothesis generation, not a registrational study.
Phase:	Phase II
Description of Sites/Facilities Enrolling Participants:	Winship Cancer Institute of Emory University (Atlanta, GA).
Description of Study Intervention:	Eligible patients will be initiated on therapy with defactinib (oral administration) 200mg orally twice daily for 21 days of each 28-day cycle, Avutometinib 3.2 mg orally twice weekly for 21 days of each 28-day cycle, in combination with nivolumab 480 mg iv on day 1 of each cycle. Treatment cycles will be repeated every 4 weeks. Treatment will be continued until disease progression or unacceptable toxicity. During treatment, scans will be every 8 weeks (2 cycles) for cycles 1-4, then every 3 cycles afterwards. The RECIST criteria will be utilized (version 1.1) for response assessment. Toxicity will be graded by NCI CTC version 5.0. Archived tumor samples will be obtained from all the study participants, but is not a requirement for study entry; on study repeat biopsy will be optional in each cohort during the second stage of accrual (statistical design). Biomarker studies will be conducted on the tumor samples and peripheral blood collections.
Study Duration:	How long subjects remain on study treatment depends on how well the cancer responds and how well subjects are able to tolerate any side effects. Subjects will continue to receive study drug as long as there is a benefit from it. Subjects will be contacted every 3 months for up to 5 years upon leaving the study.

****STK11 =’s LBK1**

1.2 Schema

Study Population

- LKB1-Mutant Lung Adenocarcinoma
- Advanced
- Measurable disease
- Refractory to prior PD1 therapy

Defactinib
200mg orally twice daily for 21 days of each 28-day cycle
Avutometinib
3.2 mg orally twice weekly for 21 days of each 28-day cycle
Nivolumab
480mg intravenously once on Day 1 of each 28-day cycle

1.3 Schedule of Assessments

	Pre-Study	Cycle 1[f]			All Subsequent cycles			EOT
	28 days	Wk 1	Wk 2	Wk 3	Wk 1	Wk 2	Wk 3	
Defactinib (twice daily)		X	X	X	X	X	X	
Nivolumab (day 1)		X			X			
Avutometinib (twice weekly)		X	X	X	X	X	X	
Informed consent	X							
Demographics	X							
Medical history	X							
Concurrent meds	----------X----------							
Physical exam	X	X		X	X			X
Vital signs	X	X		X	X			X
Height	X							
Weight	X	X			X			X
Performance status	X	X			X			X
CBC w/diff, plts	X	X		X	X			X
Serum chemistry, TSH, CPK	X	X		X	X			X
PT, PTT and INR	X							
EKG	X							
Adverse event evaluation	----------X----------							X
Tumor measurements	X	X[e]						
Radiological evaluation	X	X[e]						
Pregnancy test	X[a]				X[a]			X[a]
Ophthalmologic examination	X[g]	*C2D1, C5D1, and every 3 cycles (+/- 5 days)*[g]						
Tumor biopsy	X[b]			X				
Tumor Genomic testing	X[d]							
Peripheral blood	X	X			X[c]			

a: In women of reproductive age and have not undergone hysterectomy. Urine or blood test is acceptable
b; Baseline tumor samples will be provided from archived tissue or optional biopsy. This is not a requirement to enter study. Optional biopsy can be performed at c2d1 +/- 1 week
c: will be collected during screening on day 1 of cycle 1, 2, 3, 4 and at progression for correlative studies
d. This will be done as per clinical standard of care, and previous results acceptable demonstrating LKB1 and/or KRAS as per cohort. This will be done on validated next generation sequencing platforms. **Any FDA approved NGS will be acceptable. These will typically be commercially available platforms, most common at our institution will be Caris testing**
e. Scans include PET scans or ct chest and abdomen. During treatment, scans will be every 8 weeks (2 cycles) for cycles 1-4, then every 3 cycles afterwards.
f. All on treatment assessments have a +/- 2 day window
g. Ophthalmological examination by an ophthalmologist must be conducted. If an ophthalmologist is not available, a qualified optometrist may conduct the examination, but the results must be reviewed by an ophthalmologist within 72 hours. This must be performed at Baseline (within 28 days prior to first dose, at C2D1, C5D1, and every 3 cycles thereafter), and urgently

at any time on-treatment as clinically indicated. The results of the baseline examination must be available prior to dosing. Ophthalmologic examination must include visual acuity testing, slit lamp examination of the anterior eye segment, intraocular pressure, dilated fundoscopy, and retinal optical coherence tomography (OCT).

2. Objectives (and Endpoints)

OBJECTIVES	ENDPOINTS
Primary	
- The primary objective of the phase II study is to determine the efficacy (6-months PFS rate) of defactinib and avutometinib when combined with nivolumab in patients with LKB1 mutated lung adenocarcinoma.	The primary endpoint is the 6m PFS rate. The rate will be calculated with an 95% confidence interval using Kaplan-Meier method based on the efficacy evaluable population. Patients who fail to have a response assessment for other reasons (e.g., refusal due to travel constraints) will be considered unevaluable and will not be included in the denominator when calculating the rate.
Secondary	
- To evaluate response rate, overall survival and toxicity assessment.	For progression-free survival (PFS) and overall survival (OS), the Kaplan-Meier method will be used to estimate the median event-free time with 95% confidence interval. For the duration of overall response, summary statistics will be used to describe the mean and median duration of response.
Tertiary/Exploratory	
Biomarker evaluation will be conducted on archived tumor samples and on-study biopsies obtained in a subset of patients.	Analysis of Biomarker Correlative

3. Background

Lung cancer is the leading cause of cancer related deaths in the United States with more than 225,000 cases diagnosed annually. More than 85% of the patients have non-small cell lung cancer that includes adenocarcinoma, squamous cell carcinoma, large cell carcinoma and bronchioloalveolar carcinoma. Nearly 50% of the patients with advanced NSCLC present with advanced stage disease.

Systemic therapy remains the mainstay of treatment of advanced stage NSCLC. Combination chemotherapy with a platinum-based regimen had remained as the standard therapy for patients with advanced stage disease until recently [1]. Improvements in overall survival and quality of life have been demonstrated with platinum-based regimens over supportive care alone in randomized clinical trials [2]. Among the platinum compounds, both cisplatin and carboplatin have been extensively studied for the treatment of NSCLC. In general, carboplatin-based regimens have a favorable tolerability profile over cisplatin-based regimens [3, 4]. Despite the marginally higher response rate with cisplatin-based regimens, considering the palliative intent of therapy, carboplatin-based regimens have found wide applicability in routine care.

The optimal duration of treatment for patients with advanced NSCLC has been the subject of study ever since the role of chemotherapy was established [5, 6]. Randomized studies that compared the use of combination chemotherapy for a defined number of cycles versus continuation until progression or higher number of courses failed to demonstrate an advantage for the latter approach. Therefore, administration of 4 to 6 cycles of combination chemotherapy followed by observation became the standard of care for first-line therapy of advanced NSCLC. With the advent of well-tolerated novel chemotherapeutic and molecularly targeted agents, recent studies have shown benefit of single agent maintenance therapy after achievement of maximal disease control with combination regimens.

3.1 Study Rationale

Personalized therapy for advanced NSCLC

In recent years, the emergence of immune checkpoint inhibitors and novel targeted therapies have resulted in substantial improvements in outcome for advanced NSCLC. For patients with lung adenocarcinoma, molecular testing for treatable genetic alterations in EGFR, ALK, ROS1, B-RAF, RET, HER2, MET, KRAS and NTRK is considered the standard of care; for patients with these 'treatable' genetic alterations, molecularly targeted therapies provide high response rates and robust progression-free survival. We recently demonstrated that Osimertinib, an EGFR tyrosine kinase inhibitor, improves overall survival when used for the treatment of patients with EGFR exon 19 or 21 mutation [7].

For patients without a 'treatable' genetic alteration, assessment of PD-L1 expression is routinely done by immune histochemistry; for tumors with PD-L1 expression > 50%, pembrolizumab used as monotherapy is a standard of care; for tumors with PD-L1 expression < 50%, pembrolizumab or atezolizumab are used in combination with platinum-based chemotherapy. These approaches have been shown to improve overall survival when compared to platinum-based chemotherapy alone [8, 9]. Despite these improvements, robust and durable benefit is limited to approximately 20% of these patients.

For patients that develop disease progression after immune checkpoint inhibition, the current standard approach is docetaxel in combination with ramucirumab, a VEGF-R2 targeted monoclonal antibody. This regimen provides

modest improvements in PFS and OS. Development of more effective salvage therapy options for patients who develop disease progression on first line immunotherapy (+/- chemotherapy) remains a major research priority. Nivolumab currently is approved in the both the first and second line NSCLC space.

Resistance to immune checkpoint inhibition

A number of investigators are conducting research to determine the reasons behind why only a subset of patients respond to immune checkpoint inhibitors. For instance, patients with EGFR mutation do not achieve clinical benefit with immune checkpoint inhibition as monotherapy [10]. Skoulidis et al [11] have demonstrated an intrinsic resistance to immune checkpoint inhibition in LKB1 and KRAS co-mutated NSCLC; LKB1 mutated tumors promoted resistance to PD-1 inhibition, while tumors with KRAS mutation alone responded well to immune checkpoint inhibition.

Role of LKB1 and FAK in lung cancer

The tumor suppressor LKB1 is a serine/threonine kinase that regulates lung cancer motility and metastasis. LKB1 is mutated in 30% of NSCLC tumors and cell lines. LKB1 ranks as the 3rd most frequently mutated gene in lung adenocarcinoma after p53 and Ras[12-14]. LKB1 activity is regulated by the pseudokinase **STRADα** and the scaffolding protein MO25 through a phosphorylation-independent mechanism. Our data show that LKB1 regulates NSCLC cell polarity[15] and phosphorylated focal adhesion kinase (FAK) during cell motility to oversee cell adhesion. FAK regulates cell migration and invasion through adhesion signaling[16]. FAK signals through integrins and growth factor receptors to relay cues from the extracellular matrix through the plasma membrane, and into the cytoplasm. FAK acts as a signaling node at cell adhesion sites called focal contacts to promote cytoskeletal reorganization, adhesion, migration, and survival[16]. A series of tyrosine phosphorylations controls FAK activation whereby ligand binding to a FAK-associated integrin autophosphorylates Y^{397}-FAK[17]. This reveals a binding motif for SH2-domain-containing proteins such as Src, which further phosphorylates FAK at Y^{861}, Y^{925}, Y^{576}, and Y^{577} [18-20]. Thus, FAK phosphorylation at Y^{861} and Y^{397} are markers for FAK activation[21]. FAK mRNA and protein expression are increased in most cancers including colon, breast, and ovarian, and are most often associated with a more invasive phenotype[22-26]. In lung cancer, a retrospective analysis on 172 patients with lung adenocarcinoma showed that FAK positive patients (total FAK and not pY-FAK) had worse survival than FAK negative patients, where 88% of the cases were FAK positive[27]. Currently, there are several small molecule FAK inhibitors in development and Phase I clinical trials for the treatment of non-hematologic malignancies[28-31]

3.2 Clinical Experience

The combination of the 3.2 mg BIW avutometinib and 200 mg BID defactinib, administered 3 weeks of every 4-week cycle, was selected based on the results of an IST (VS-6063-003, FRAME) that compared the safety of 3.2 mg BIW avutometinib + 200 mg BID defactinib, 3.2 mg avutometinib + 400 mg BID defactinib and 4.0 mg avutometinib + 200 mg BID defactinib. There was a DLT of Grade 2 rash in 2 of 3 patients in receiving 3.2 mg avutometinib + 400 mg defactinib, while there were no DLTs with the other two regimens. Due to chronic Grade 2 toxicities in patients on treatment >6 months, the dose of 3.2 mg BIW avutometinib + 200 mg BID defactinib for 3 of 4 weeks was selected as the RP2D. The response rate in patients with KRAS mt low-grade serous ovarian cancer (LGSOC) was 64% (7 of 11 subjects with PR) and it was 46% (11 of 24 patients with PR) for all patients with recurrent LGSOC. Estimated median PFS across all LGSOC was 23 months (Banerjee et al.,

2021). Of the 18 evaluable patients with KRAS mt NSCLC, 3 patients (2 with KRAS G12V and 1 with KRAS G12C) achieved PR. Median PFS was 16 weeks and 7 patients received treatment for ≥24 weeks (Krebs et al., 2021).

4. Study Intervention/Investigational Agent

4.1 Description

DEFACTINIB and AVUTOMETINIB are non-covalent Pyk2/FAK and RAF/MEK kinase inhibitors respectively, with nanomolar potency. Avutometinib and Defactinib are to be taken orally as capsules and as tablets, respectively. Nivolumab- will be given by infusion. All drugs will be given in a 28-day cycle. A study diary must be kept by patients when taking avutometinib and defactinib to determine their compliance in taking the investigational agents.

The intracellular RAS-regulated RAF/MEK/ERK (MAPK) signaling cascade is the most mutated oncogenic pathway in human malignancies. Aberrant signaling through the RAS/RAF/MEK/ERK pathway drives tumor cell proliferation, differentiation, survival, and migration.

Avutometinib is a dual inhibitor of RAF and MEK in the MAPK pathway and blocks both MEK kinase activity and the ability of RAF to phosphorylate MEK, in contrast to other MEK inhibitors in development and/or registered. This mechanism of sequential blockade enables avutometinib to block MEK signaling more consistently without the compensatory and paradoxical activation of MEK that precludes the efficacy of other small molecule inhibitors of MEK and RAF.

Avutometinib was active in nonclinical in vitro and in vivo models against the validated anticancer targets RAF and MEK and combines these anticancer inhibitory activities in a single orally available compound. Avutometinib as a monotherapy has also demonstrated anticancer activity in two single-agent Phase 1 studies and two Investigator-sponsored studies (see the Avutometinib Investigator's Brochure [IB] for details).

Defactinib and other FAK inhibitor compounds (VS-6062 and VS-4718), as surrogates, have shown synergistic activity with BRAF and MEK inhibitors in both in vitro and in vivo preclinical solid tumor models (see the defactinib IB for details). In mouse models of BRAF-mutant (mut) melanoma, KRAS mut ovarian cancer, or uveal melanoma, FAK inhibition has been shown to induce tumor regression when combined with RAF, MEK or RAF/MEK inhibitors, respectively, while the single agents have only induced tumor stasis.

The combination of avutometinib and defactinib has demonstrated nonclinical and clinical anticancer activity (see avutometinib IB for details). In vitro it was shown to produce additive or synergistic activity against solid tumors in several cell lines screening for synergy. The addition of defactinib to avutometinib therapy may also reduce the FAK -mediated adaptive resistance to MAPK inhibitors (Diaz Osterman 2019, Kang 2013, Tong 2019).

Proof-of-concept safety and activity data in patients with advanced cancer are being gathered in Investigator-sponsored trials (ISTs). In a Phase 1 clinical study (IST-VS-6766-002; CCR3808), avutometinib as a monotherapy has shown preliminary efficacy in patients with RAS/RAF-mut solid tumors, including gynecological cancers. In 5 patients with RAS/RAF-mut gynecological cancers treated at a dose of 4 mg twice-weekly, 3 patients achieved a partial response (PR), including patients with KRAS mut LGSOC, BRAF mut LGSOC, and KRAS-mut endometrial cancer. The responses were greater than 6 months in duration.

The combination of avutometinib and defactinib is currently being evaluated in patients with advanced solid tumors, including LGSOC, in the Investigator Sponsored FRAME study (IST-VS-6063-003; CCR4642, FRAME; EudraCT: 2017-001035-39). In the FRAME proof-of-concept study, there have been durable objective responses in patients with LGSOC with and without KRAS mutations following treatment with avutometinib 3.2 mg twice

weekly for 3 weeks out of every 4 weeks and defactinib 200 mg twice daily for 3 weeks out of every 4 weeks (Banerjee 2021, Banerji 2020, Shinde 2020).

Preliminary efficacy results from the FRAME study, as of an April 2021 data cut-off date, are available for a total of 24 LGSOC patients (Banerjee 2021). Specific observations included the following:

- Overall response rate (ORR):
  - ORR in all patients with LGSOC = 46% (11 of 24 patients with confirmed partial response [PR] [2 additional patients with unconfirmed PR]).
  - ORR in patients with KRAS-mut LGSOC = 64% (7 of 11 patients with confirmed PR [1 additional patient with unconfirmed PR]).
  - ORR in patients with KRAS-wt LGSOC = 44% (4 of 9 patients with confirmed PR).
  - ORR in patients with KRAS-undetermined LGSOC = 0 of 4 patients with confirmed PR and 1 of 4 patients with unconfirmed PR.
- Median progression-free survival (PFS) of 23 months.
- Eight of the 11 patients with PR remained on study interventions as of the April 2021 data cut-off date.
- Among the 13 patients with best response of stable disease (SD), 5 remained on study interventions as of the April 2021 data cut-off date.
- Ten of 24 patients with LGSOC had previously received MEK inhibitors, including 4 patients with PRs (3 confirmed, 1 unconfirmed).

The developing results from the FRAME study support the potential of the avutometinib -defactinib combination for the treatment of patients with both KRAS-mut and -wt LGSOC. Overall, the demonstrated nonclinical and clinical anticancer activity of avutometinib monotherapy and in combination with defactinib in LGSOC justifies their comparison in the current study.

Nivolumab, a monoclonal anti-PD-1 immunotherapeutic checkpoint inhibitor, is FDA approved for the treatment of squamous and non-squamous NSCLC. Of the second line treatment options currently available, immunotherapies more often result in prolonged benefit for a population of patients, with about 20% of patients having >12 month PFS. Despite this efficacy, there is an unmet need to find drugs which synergize immunologically to allow a larger proportion of patients to benefit long term from therapy.

Nivolumab is active in the second line treatment of non-squamous NSCLC, as demonstrated in the trial CheckMate 057, Nivolumab versus Docetaxel in advanced non-squamous NSCLC. In this trial, nivolumab had an overall survival benefit compared with docetaxel.

4.2 Drug/Device Handling

The control of AVUTOMETINIB, DEFACTINIB will be accomplished by following an established approved Standard Operation Procedure (SOP) at Emory University Investigational Pharmacy (IDS). IDS will be used according to the pharmacist supplier to control handling, storage, ordering, receiving, and control of drugs and assure compliance with the standards of the U.S. Food and Drug Administration (FDA) and of the study sponsor. An Emory Investigator holds the IND and is considered to be a Sponsor-Investigator.

NIVOLUMAB will be provided commercially. We have received IDS exemption for Nivolumab to be sourced via commercial pharmacy.

4.3 Accountability

Drug accountability may be noted by the internal monitor during site visits and at the completion of the study. The study drug supply will be disposed of per Winship's Investigational Drug Service (IDS) SOP.
Compliance will be assessed by the investigator and/or study personnel at each patient visit. This information must be captured in the source document at each patient visit.

Dose changes and interruptions of study drug must be specifically documented in the patient source documents and eCRF.

The designated site personnel will be responsible for maintaining accurate records of the quantity and dates of all study drug supplies received, dispensed, and returned, in accordance with applicable regulations and the site's SOPs. The quantity of study drug lost, destroyed, or otherwise unaccounted for must also be accounted for and documented. The patient will be required to maintain a medication diary of each dose of medication. The medication diary (Appendix B) will be returned to clinic staff at the end of each cycle.
Dose changes and interruptions of study drug must be specifically documented in the patient source documents and eCRF.

5. Procedures Involved

5.1 Study Design

This is a phase II study to determine the efficacy of avutometinib and defactinib with nivolumab in patients with LKB1 mutated lung adenocarcinoma. Two cohorts of patients will be enrolled.

Cohort A: Patients with LKB1 and KRAS co-mutation
Cohort B: Patients with LKB1 mutation without KRAS mutation
Enrollment to each cohort will proceed concurrently.

25 patients will be enrolled in each of the two cohorts; The initial 10 patients will be used for a safety-run-in (5 pts/cohort); if deemed to be safe. For each cohort separately, a time-to-Event Bayesian optimal phase 2 (TOP) design will be carried out with two planned interim analyses for futility assessment. The two planned interim analyses will be implemented after 10 and 20 patients have been treated.

5.2 Dosing and Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 21. Appropriate dose modifications are described below. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Avutometinib

- Avutometinib will be administered BIW PO (e.g., Monday/Thursday, Tuesday/Friday, or Wednesday/Saturday) for 3 weeks, followed by a 1-week rest period, in each 4-week (28-day) cycle.
- Avutometinib should be swallowed whole with a glass of water (approximately 8 ounces or 240 mL). Patients should be advised not to open, break, or chew the capsules.

- Avutometinib should be administered with or without a meal.
- In the event of emesis occurring after Avutometinib ingestion, the patient should simply adhere to the dosing schedule and resume dosing at the next scheduled time with the prescribed dosage. Patients should record the date and time of the emesis in their dosing diary.
- If a scheduled dose of Avutometinib is missed and less than 24 hours has passed the dose can be made up. If more than 24 hours have passed the patient should not attempt to make up the dose and should proceed to the next scheduled dose. Patients should enter any missed or made-up doses including the reason the dose was missed in the dosing diary, as applicable.
- Patients must avoid grapefruit, grapefruit juice, St. John's Wort and other medications (with or without prescriptions), supplements, herbal products or foods that are strong inhibitors or inducers of CYP3A4 while on Avutometinib. Please see table 7 for additional information on restrictions on the use of CYP 3A4 inhibitors, inducers, and substrates, and Appendix D for a list CYP3A4 inhibitors, inducers, and substrates.
- Refer to the Pharmacy Manual for additional instructions regarding Avutometinib administration.

Defactinib

- Defactinib will be administered BID PO for 3 weeks, followed by a 1-week rest period, in each 4-week (28-day) cycle.
- Defactinib should be swallowed whole with a glass of water (approximately 8 ounces or 240 mL). Advise patients not to break or chew the tablets
- Defactinib should be administered within 30 minutes following a meal.
- In the event of emesis occurring after defactinib ingestion, the patient should simply adhere to the dosing schedule and resume dosing at the next scheduled time with the prescribed dosage. Patients should record the date and time of the emesis in their dosing diary.
- If a scheduled dose of defactinib is missed and less than 6 hours have passed since the scheduled dosing time, patient should immediately take the missed dose. If more than 6 hours have passed since the scheduled dosing time, patient should not take the missed dose. Patient should wait and take the next regularly scheduled dose.
- Patients must avoid grapefruit, grapefruit juice, St. John's Wort and other medications (with or without prescriptions), supplements, herbal products or foods and that are strong inhibitors or inducers of CYP2C9, CYP3A4, or P-gp while on defactinib. Please see Table 7 for additional information on restrictions on the use of CYP2C9, CYP 3A4, and P-gp inducers, and substrates, and Appendix D for lists of CYPC9, CYP3A4, and P-gp inhibitors, inducers, and/or substrates.
- Refer to the Pharmacy Manual for additional instructions regarding defactinib administration.

Defactinib will be given on a twice-daily oral schedule at a dose of 200 mg. The drug is to be taken with food. Each treatment cycle will include four weeks of therapy. Defactinib will be administered on a continuous daily schedule for 3 of 4 week cycle. Avutometinib, as a dose of 3.2mg, must be taken by mouth twice weekly for 3 weeks of every 4 week cycle. Avutometinib is to be taken with or without food. Patients will be asked to complete a pill diary to document compliance. The medication diary will be returned to clinic staff at the end of each course. Patients will be evaluated before initiation of each new cycle of therapy. Nivolumab will be administered at a dose of 480mg IV once every four weeks. Treatment cycles will be repeated every 4 weeks.

Table 1: Study Interventions

Study Interventions Intervention Name	**Avutometinib**	**Defactinib**
Dosage Level(s) and Frequency	• 3.2 mg BIW (combined with defactinib), 3 weeks of every 4--week cycle	200 mg BID (combined with avutometinib), 3 weeks of every 4-week cycle
Route of Administration	Oral	Oral
Dose Formulation	Capsule	Tablet
Unit Dose Strength(s)	0.8 mg	200 mg
Number of Capsules/Tablets per Dose	• 3.2 mg: 4 capsules	200 mg: 1 tablet
Formulation Excipients	Excipients (mannitol and magnesium stearate) that are listed in the US FDA Inactive Ingredients Database for approved drug products and/or GRAS	Excipients (microcrystalline cellulose, lactose monohydrate, sodium starch glycolate, and magnesium stearate) that are listed in the US FDA Inactive Ingredients Database for approved drug products and/or GRAS

Abbreviations: BID: twice daily; FDA: Food and Drug Administration; GRAS: Generally Regarded as Safe

Nivolumab Treatment
Nivolumab 480mg IV will be administered once on Day 1 of each 28-day cycle.

5.3 Toxicities and Definition of Dose-Limiting Toxicity

Avutometinib

- The most commonly reported treatment-emergent adverse events (TEAEs) (≥25%) regardless of causality for avutometinib monotherapy in Phase 1 study NO21895 included dermatitis acneiform and rash (67%), diarrhea (65%), blood CPK increased (58%), asthenia (46%), peripheral oedema (40%), nausea (38%), vision blurred (37%), constipation (33%), hypoalbuminemia (33%), vomiting (29%), AST increased (27%), stomatitis (27%) and pyrexia (25%). While not a frequent AE in the Phase 1 study NO21895, mucositis/mouth ulcer was seen in 38% of patients in IST-CCR3808.
- The most common treatment-related TEAEs reported in IST-CCR3808 were rash (91%), CPK elevation (66%), visual abnormalities (45%), mucositis/mouth ulcer (39%), diarrhea (34%), fatigue (34%), limb oedema (30%), hypoalbuminemia (27%), nausea (25%), dry skin (23%), and fissures (20%).
- The identified risks for avutometinib treatment are skin toxicity, eye toxicity, CPK elevation, gastrointestinal tract toxicities, and edema.
- The potential risks are effects on the bone and cartilage, hematological toxicity, drug-drug interactions, liver function abnormalities, and tissue mineralization.

Defactinib

- Frequent TEAEs (≥20%) regardless of causality with defactinib monotherapy in solid tumor patients as reported in the current IB include nausea (29%), fatigue (26%), diarrhea (25%), hyperbilirubinaemia combined with blood bilirubin increased (23%), and dyspnea (20%).
- GI disorders were the most common type of treatment-related TEAEs as reported in IB ed 12, with nausea being the most common individual treatment-related TEAE (23%) and diarrhea (21%), and vomiting (14%) being among the most common. Other common treatment-related TEAEs included hyperbilirubinemia (25%), fatigue (21%), and decreased appetite (10%).
- The only identified risk for defactinib treatment is hyperbilirubinemia/increased bilirubin.
- The important potential risks for defactinib treatment are GI effects, drug-drug interactions, most specifically with strong inhibitors or inducers of CYP3A4 or CYP2C9, and interaction with warfarin.

Nivolumab

- Please see Nivolumab Package Insert.

Overlapping Toxicities

In Phase 1 FRAME study, no toxicities unique to the combination of avutometinib + defactinib were observed in the preliminary data from 52 patients treated with the combination as of 18 Mar 2020. GI disorders, especially nausea and diarrhea, are frequent TEAEs common to both avutometinib and defactinib.

The most common treatment-related AEs observed in patients receiving the combination were rash (90%), CPK elevation (56%), hyperbilirubinaemia (42%), AST elevation (38%), fatigue (31%), glossitis/oral mucositis/mouth ulcers (31%), ALT elevation (29%), diarrhoea (29%), visual disturbance (29%), nausea (25%) and peripheral oedema (21%), most of which were Grades 1 or 2 and reversible.

GI toxicities and drug-drug interactions with inhibitors or inducers of CYP3A4 are overlapping risks for avutometinib and defactinib.

The combination of avutometinib, defactinib, and nivolumab has not been studied previously. Overlapping toxicities for the three agents may not be known.

DLT DEFINITIONS

All adverse events will be graded according to NCI CTCAE v. 5.0 with attribution. To be evaluable for DLT, patient must receive at least 66% of the planned doses of defactinib, avutometinib, and nivolumab i.e. 14 of 28 days in cycle 1. A DLT is defined as a clinically significant AE or laboratory abnormality that meets any of the following criteria within the first cycle:

▪ Grade 4 hematologic toxicity (excluding anemia) lasting more than 7 days
▪ Grade 3 anemia lasting more than 7 days or requiring blood transfusion
▪ Grade 4 anemia regardless of duration
Grade ≥3 thrombocytopenia if associated with clinically significant bleeding
▪ Grade ≥3 fever with neutropenia of any duration
▪ Grade ≥3 nausea and or vomiting lasting more than 72 hours in spite of standard supportive therapy
▪ Grade ≥3 non-hematologic toxicity (exclude alopecia and skin rash that resolves to grade 2 or less with a treatment break not to exceed 10 days; also excluding fatigue or anorexia lasting < 7 days); Lab abnormalities will not be considered DLT if it is not of any significant clinical consequence requiring intervention and not directly attributed to the receipt of the investigational agents. Also, grade ≥3

amylase or lipase elevation NOT associated with symptoms or clinical manifestations of pancreatitis does not count as a DLT
▪ Grade ≥3 electrolyte abnormality that lasts >72 hours, in the absence of clinical symptoms, or of any duration if associated with clinical symptoms.
▪ Inability to re-treat patient within 14 days of scheduled treatment due to treatment-related toxicity (non-treatment related events that result in treatment delay will not be considered a DLT)
▪ Inability to deliver 66% of the planned dose i.e. ≥14 days of treatment with defactinib and avutometinib within the first 28 days due to treatment discontinuation as a result of intolerable treatment-related toxicity

5.4 Dose Modification

In general, no dose modification will be needed for Grade 1 or 2 toxicities.. Any dose modification must be based on the maximum toxicity experienced during a cycle. No dose re-escalation is permitted. A maximum of one dose reduction is allowed prior to discontinuation of treatment.

Study interventions may be held up to 28 days due to toxicity. Doses held for > 28 days due to treatment-related toxicity will result in permanent discontinuation, unless approved by the DSMC. . If there is a dose interruption due to toxicity, the missed doses will be skipped rather than delayed, with no extension of cycle length. Dosing resumes at the next scheduled administration.

There are no dose reductions for nivolumab.

Table 2: Dose Reductions for Toxicity: Avutometinib when Combined with Defactinib

Dose Level	Avutometinib
Starting Dose	3.2 mg BIW for 3 of 4 weeks
Dose -1	2.4 mg BIW for 3 of 4 weeks
Dose -2	Discontinue

Abbreviations: BIW: twice a week

Table 3: Dose Reductions for Toxicity: Defactinib when Combined with Avutometinib

Dose Level	Defactinib
Starting Dose	200 mg BID for 3 of 4 weeks
Dose -1	200 mg QD for 3 of 4 weeks
Dose -2	Discontinue

Abbreviations: BID: twice a day; QD: once a day

Table 4: Dose Modifications and Management Guidance for Specific Toxicities

Dose Modifications and Management of Toxicities except Ocular
Dose modification and clinical management guidance for specific toxicities (except Ocular) is provided below.

Dose Modifications and Management Guidance for Specific Toxicities

Toxicity	Adverse Reaction Grade(CTCAE v5.0)	Dose Modification	Management Guidelines and Dosing Notes
Rash[a]	Grade 1 (papules and/or pustules covering < 10% ofbody surface area [BSA], which may or may not be associated with symptomsof pruritis or tenderness)	No change	Treat with any of the following: minocycline (recommended dose: 200 mg BID [loading dose] followed by 100 mg PO BID x 7 to 10days), topical tetracycline, topical clindamycin, topical silver sulfadiazine, oral diphenhydramine, or oral prednisone (short course) at discretion of the Investigator Provide supportive care per institutional guidelines Patients who develop rash/skin toxicities should be seen by a qualified dermatologist and should receive evaluation for symptomatic/supportive care management, as clinically needed. General recommendations for symptomatic care include: • Pruritic lesions: cool compresses and oral antihistamine therapies • Fissuring lesions: Monsel's solution, silver nitrate, or zinc oxide cream • Desquamation: thick emollients and mild soap • Paronychia: antiseptic bath, local potent corticosteroids in addition to antibiotics; if no improvement, consult dermatologist or surgeon • Infected lesions: appropriate bacterial/fungal culture-driven systematic or topical antibiotics
	Grade 2 (papules and/or pustules covering 10-30% of BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL[b];papules and/or pustules covering > 30% BSA with or without mild symptoms)	No change. If rash does not respond to supportive care or reoccurs after resolution to Grade ≤1, consult the DSMC regarding possible dose modification.	
	Grade 3 (papules and/or pustules covering > 30% ofBSA, with moderate or severe symptoms; limiting self-care ADL[c]; associated with local superinfection with oral antibioticsindicated)	Interrupt dosing. Resume one dose level lower if resolution to Grade 2. Resume at current dose if resolution to Grade ≤ 1.	
	Grade 4 (life-threatening consequences; papules and/or pustules covering any % of BSA, which mayor may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated)	Discontinue	NA
	Grade 1 (> ULN to 1.5 xULN if baseline was normal; > 1.0 to 1.5 x baseline if baseline was abnormal)	No change	Hold defactinib and monitor at least weekly until return to baseline.

Toxicity	Adverse Reaction Grade(CTCAE v5.0)	Dose Modification	Management Guidelines and Dosing Notes
Hyperbilirubinemia (Blood bilirubin increased)[d]	Grade 2 (> 1.5 x ULN to 3x ULN if baseline was normal; > 1.5 x to 3 x baseline if baseline was abnormal)	If patient has Gilbert's syndrome and isolated Grade 2, no change. For isolated Grade 2 in the absence of Gilbert's syndrome, hold until resolution to Grade 1, then resume at same dose. For Grade 2 hyperbilirubinemia (with or without Gilbert's syndrome) with Grade 2 AST or ALT elevation, hold dose, then resume at same dose upon Grade 1 resolution. For Grade > 2 hyperbilirubinemia (with or without Gilbert's syndrome) with Grade ≥ 2 AST or ALT elevation, (meeting the definition of Hy's Law), permanently discontinue.	Exclude other causes of hyperbilirubinemia. Exclude Hy's law.
	Grade 3 (> 3 to 10 x ULN ifbaseline was normal; >3 to 10 x baseline if baseline was abnormal)	Regardless of presence or absence of Gilbert's syndrome, if increased bilirubin is not associated with increased ALT or AST, interrupt dosing untilbilirubin returns to Grade ≤ 2. If on retreatment bilirubin returns to Grade ≥ 3, withhold treatment until toxicity is Grade ≤ 2 or bilirubin returns to baseline levels then decrease the dose by one dose level. If at any time bilirubin increases to Grade ≥ 2 and is associated with a Grade ≥ 2 increase in AST and/or ALT, permanently discontinue.	
	Grade 4 (> 10 x ULN if baseline was normal; > 10 xbaseline if baseline was abnormal)	Discontinue unless duration ≤ 1 week.	If the event resolves to at least baseline in < 1 week, resume prior dose.
	Grade 1 (> ULN to 2.5ULN)	No change	Monitor at least bimonthly until return to baseline or normal.
	Grade 2 (> 2.5 to 5 x ULN)	No change	Monitor at least weekly until return to baseline or normal.

Toxicity	Adverse Reaction Grade(CTCAE v5.0)	Dose Modification	Management Guidelines and Dosing Notes
Creatine Phosphokinase Elevation[e]	Grade 3 (> 5 to 10 x ULN)	Interrupt dosing until CPK returns to Grade 0-1 within 3 weeks.	Investigators should assess for myoglobinuria using dipstickor accurate urine analysis and consider additional diagnostic evaluation (e.g., CPK-MB, CPK electrophoresis, troponin) to help determine the etiology of the CPK abnormality and to guide treatment. Investigators should check for any cardiac symptoms and conduct a muscle examination. Information regarding muscle symptoms,exercise, concomitant medications, and alcohol consumption should be recorded. CPK should be monitored at least weekly until levels return to baseline or normal.
	Grade 4 (> 10 x ULN)	1st occurrence: interrupt dosing until CPK returns to Grade 0-1 within 3 weeks. 2nd occurrence (or 3rd occurrence if applicable): Interrupt dosing until CPK returns to Grade 0-1 within 3 weeks, then decrease dose by 1 dose level number. If with any occurrence the CPK level does not return to Grade 0-1 within 3 weeks, discontinue. Regardless of the grade, if at anytime a diagnosis of rhabdomyolysis or another medically significant event related to CPK elevation is made, discontinue study treatment.	Investigators should assess for myoglobinuria using dipstick or accurate urine analysis and consider additional diagnostic evaluation (e.g., CPK-MB, CPK electrophoresis, troponin) to help determine the etiology of the CPK abnormality and to guide treatment. Investigators should check for any cardiac symptoms and conduct a muscle examination. Information regarding muscle symptoms, exercise, concomitant medications, and alcohol consumption should be recorded. CPK should be monitored at least weekly until levels return to baseline or normal. Any Grade 4 CPK elevation must be discussed with the Principal Investigatorr and study treatment continuation will be allowed only upon written agreement from the DSMC.
	Grade 1	No change	Supportive care per institutional guidelines[g]
	Grade 2	No change.	

Toxicity	Adverse Reaction Grade(CTCAE v5.0)	Dose Modification	Management Guidelines and Dosing Notes
Other Toxicities EXCEPT Ocular Toxicities [f, g]	Grade 3	First occurrence: interrupt dosing until toxicity Grade ≤2 Subsequent occurrences: interrupt dosing until toxicity Grade ≤2. Consult the DSMC regarding dose level for resumed dosing.	
	Grade 4	Discontinue	NA

Abbreviations: ADL: Activities of Daily Living; ALP = alkaline phosphatase, ALT: alanine aminotransferase; AST: aspartate aminotransferase; BID: twice daily; BSA: body surface area; CPK: creatine phosphokinase; CTCAE: CommonTerminology Criteria for Adverse Events; GI = gastrointestinal; NA = not applicable; ULN: upper limit of normal.

[a] Rash includes events such as acneiform rash (CTCAE grade definitions shown), which is a disorder characterized by an eruption of papules and pustules, typically appearing in face, scalp, upper chest and back, and macular papular rash, which is a disorder characterized by the presence of macules (flat) and papules (elevated). Macular papular rash, also known as morbilliform rash, frequently affects the upper trunk, spreading centripetally and associated with pruritis. Macular papular rash symptoms may include burning and tightness. Only up to Grade 3 is applicable for macular papular rash.

[b] Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[c] Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

[d] A finding based on laboratory test results that indicate an abnormally high level of bilirubin in the blood. Excess bilirubin is associated with jaundice.

[e] A finding based on laboratory test results that indicate an increase in levels of creatine phosphokinase in a blood specimen.

[f] Includes GI Toxicities (e.g., diarrhea).

[g] Includes clinical laboratory changes in the liver-related enzymes ALT, AST, and ALP.

h For GI Toxicities, interruption and/or reduction of dosing as well as supportive treatment will improve gastrointestinal toxicity. If gastrointestinal bleeding is suspected, interruption of dosing and a standard work-up of the gastrointestinal tract is required.
Recommended diarrhoea management:
Grade 1 (Increase of < 4 stools per day over baseline; mild increase in ostomy output compared to baseline): No change in study drug. Consider treatment with loperamide (4 mg at first onset, followed by 2 mg every 2-4 hours until diarrhoea free for 12 hours).
Grade 2 (Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL): no change in study drug. Manage as described for Grade 1.
Grade 3 (Increase of ≥ 7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL): decrease dose or interrupt dosing. Manage as described for Grade 1. Dose can be re-escalated when diarrhea is Grade ≤ 1.
Grade 4 (Life-threatening consequences; urgent intervention indicated): discontinue patient from study or treat with a reduced dose (previous dose level or intermediate dose after approval of Verastem) according to clinical judgment. Manage as described for Grade 1.

Table 5: Dose Modification Guidelines for Ocular Toxicities

A special grading system rather than the CTCAE grading system should be used for the assessment of ocular toxicities. Where appropriate, abnormalities observed during the ophthalmologic examination as well as symptoms should be carefully monitored until improved.

Corneal keratitis, Blurred vision, Conjunctivitis or Iritis

Ocular abnormality[a]	Grading	Description	Management
Corneal keratitis[b]	Grade 1	Nonconfluent superficial keratitis	No dose interruption

Ocular abnormality[a]	Grading	Description	Management
	Grade 2	Confluent superficial keratitis, cornea epithelial defect, or 3 line or more vision loss in best corrected distance visual acuity [Corneal examination finding(s): Moderate superficial keratopathy]	Delay dose until resolved to ≤ Grade 1, then maintain dose
	Grade 3	Sterile corneal ulcer or stromal opacity, or best corrected distance visual acuity 20/200 or worse [Corneal examination finding(s): Severe superficial keratopathy]	Delay dose until resolved to ≤ Grade 1, then reduce dose by 1 level. If more than the allowed dose reductions are needed, discontinue study drug
	Grade 4	Corneal perforation or Infectious keratitis	Discontinue study drug
Blurred vision[c]	Grade 1	BCVA worse than baseline but no worse than 20/40	Dosing not interrupted
	Grade 2	BCVA worse than baseline but no worse than 20/200	Delay dose until BCVA same as baseline or 20/40 whichever is worse, then maintain dose
	Grade 3	BCVA 20/200 or worse	Delay dose until BCVA same as baseline or 20/40 whichever is better, then reduce dose by 1 level
Conjunctivitis[d]	Grade 1	Nonconfluent superficial punctate defects, mild vasodilation	No dose interruption
	Grade 2	Confluent superficial punctate staining moderate to severe vasodilation	Delay dose until resolved to ≤ Grade 1, then maintain dose
	Grade 3	Conjunctival ulcer or very severe injection	Delay dose until resolved to ≤ Grade 1, then reduce dose by 1 level. If more than the allowed dose reductions are needed, discontinue study drug
Iritis[e]	Grade 1	Rare cell in anterior chamber	No dose interruption
	Garde 2	1-2 + Cell or Flare in anterior chamber	Delay dose until resolved to ≤ Grade 1, then maintain dose
	Grade 3	3+ Cell or Flare in anterior chamber	Delay dose until resolved to ≤ Grade 1, then reduce dose by 1 level. If more than the allowed dose reductions are needed, discontinue study drug
	Grade 4	Hypopyon	Discontinue study drug

[a] (1) Please assure that other causes are excluded particularly for common conditions (e.g. allergic conjunctivitis) prior to considering dose modification guidelines. (2) Dose modifications for corneal adverse reactions should be based on both corneal examination findings and changes in best-corrected visual acuity (BCVA). (3) Advise patients to use preservative-

free lubricant eye drops and avoid contact lenses unless directed by an ophthalmologist. Consideration should be given to the use of ophthalmic topical steroids.

[b] A normal corneal exam is considered a clear cornea and no epithelial defect

[c] A normal vision exam is when the best corrected distance visual acuity (BCVA) same as baseline BCVA

[d] A normal examination implies that the transparent membrane of the eye should not have any vasodilation or epithelial defects. Also, other common causes of conjunctivitis should be excluded (e.g. allergic conjunctivitis)

[e] A normal eye exam implies that the iris should have a clear anterior chamber

Uveitis

Ocular abnormality	**Grading**	**Description**	**Management**
Uveitis[a]	Grade 1	Rare cell in anterior chamber	Dosing not interrupted and monitor.
	Grade 2	1-2 + Cell or Flare in anterior chamber	Hold dose until resolved to Grade 1 or less and then Resume at the dose
	Grade 3	3+ Cell or Flare in anterior chamber	Delay dose until resolved to Grade 1 or less, then resume at reduce dose (1 level)
	Grade 4	Hypopyon	Discontinue study drug

[a] Please assure that other causes are excluded particularly for common conditions prior to considering dose modification guidelines.

Retinal Toxicities

Ocular finding	**Grading [a]**	**OCT Exam**	**Management**
RPE detachment	Grade 1-4	First occurrence: No change in drug	No dose modification A-Follow-up OCT examination in 2 weeks
	Grade 1-4	Follow-up 1 OCT: RPE is still present in two weeks	Reduce dose by one dose level OCT examination obtained again in 2 weeks
	Grade 1-4	Follow-up 2 OCT: RPE is still present in two weeks and loss of 1 line in BCVA	Hold until the RPE detachment is shown to be resolving If no resolution in two weeks, discontinue study drug

Abbreviations: BCVA = Best-corrected visual acuity OCT: optical coherence tomography; RPE: Retinal pigment epithelium

[a] For RPE detachment (defined as disorder characterized by the separation of the inner retina layers from the underlying pigment epithelium) CTCAE v5.0 should be applied. Definition of Grade 3 is: Macular sparing rhegmatogenous detachment, and Grade4 is: Macula-off rhegmatogenous retinal detachment.

*Table 6***:** *Recommended Nivolumab Dosage Modifications for Adverse Reactions*

No dose reduction for nivolumab is recommended. In general, withhold nivolumab for severe (Grade 3) immune-mediated adverse reactions. Permanently discontinue nivolumab for life threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immunemediated reactions that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating steroids.

Adverse Reaction	**Severity**	**Dosage Modification**

Immune-Mediated Adverse Reactions		
Pneumonitis	Grade 2	Withhold[a]
	Grades 3 or 4	Permanently discontinue
Colitis	Grade 2 or 3	Withhold[a]
	Grade 4	Permanently discontinue
Hepatitis with no tumor involvement of the liver	AST/ALT increases to >3 and ≤8 times ULN or Total bilirubin increases to >1.5 and ≤3 times ULN.	Withhold[a]
	AST or ALT increases to >8 times ULN Or Total bilirubin increases to >3 times ULN.	Permanently discontinue
Hepatitis with tumor involvement of the liver[b]	Baseline AST/ALT is >1 and ≤3 times ULN and increases to >5 and ≤10 times ULN or Baseline AST/ALT is >3 and ≤5 times ULN and increases to >8 and ≤10 times ULN.	Withhold[a]
	AST/ALT increases to >10 times ULN or Total bilirubin increases to >3 times ULN.	Permanently discontinue
Endocrinopathies[c]	Grade 3 or 4	Withhold until clinically stable or Permanently discontinue depending on severity
Nephritis with Renal Dysfunction	Grade 2 or 3 increased blood creatinine	Withhold[a]
	Grade 4 increased blood creatinine	Permanently discontinue
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold
	Confirmed SJS, TEN, or DRESS	Permanently discontinue
Myocarditis	Grades 2, 3, or 4	Permanently discontinue
Neurological Toxicities	Grade 2	Withhold[a]
	Grade 3 or 4	Permanently discontinue
Other Adverse Reactions		
Infusion-Related Reactions	Grade 1 or 2	Interrupt or slow the rate of infusion
	Grade 3 or 4	Permanently discontinue

[a] Consider resuming in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper as per standard of care. Permanently discontinue if no complete or partial resolution within 12 weeks of last dose or inability to reduce prednisone to 10 mg per day (or equivalent) or less within 12 weeks of initiating steroids.

[b] If AST and ALT are less than or equal to ULN at baseline, withhold or permanently discontinue nivolumab based on recommendations for hepatitis with no liver involvement.

[c] Depending on clinical severity, consider withholding for Grade 2 endocrinopathy until symptom improvement with hormone replacement. Resume once acute symptoms have resolved.

ALT = alanine aminotransferase, AST = aspartate aminotransferase, DRESS = Drug Rash with Eosinophilia and Systemic Symptoms, SJS = Stevens Johnson Syndrome, TEN = toxic epidermal necrolysis, ULN = upper limit normal

Concomitant Therapies Restrictions

Table 7: Prohibited Concomitant Therapies

Prohibited Concomitant Therapy	**Guidance**
Other Anticancer Therapy or Investigational Agents	During the study intervention period, patients are not to receive any additional anticancer therapy or other investigational agents not outlined in the protocol. Radiotherapy is not permitted.
Colony-stimulating factors (CSFs)	Primary CSF prophylaxis is not permitted. Otherwise adhere to ASCO guidelines(1).
Warfarin	Due to the potential for drug-drug interaction with defactinib, the use of warfarin is prohibited. If patients require anticoagulation an alternative to warfarin should be used. Patients who require anticoagulation but cannot discontinue warfarin are excluded from this study.
Strong CYP3A4 Inhibitors	Use of a strong CYP3A4 inhibitor during treatment with avutometinib ± defactinib is prohibited. Co-administration with a strong CYP3A4 inhibitor could increase study intervention exposure, which may increase the risk of treatment-related toxicities.
Strong CYP2C9 Inhibitors	Use of a strong CYP2C9 inhibitor during treatment with defactinib is prohibited. Co-administration with a strong CYP2C9 inhibitor could increase study intervention exposure, which may increase the risk of treatment-related toxicities.
Strong CYP3A4 Inducers	Use of a strong CYP3A4 inducer during treatment with avutometinib ± defactinib is prohibited. Co-administration with a strong CYP3A4 inducer could decrease study intervention(s) exposure, which may reduce study intervention(s) efficacy.
Strong CYP2C9 Inducers	Use of a strong CYP2C9 inducer during treatment with defactinib is prohibited. Co-administration with a strong CYP2C9 inducer could decrease study intervention exposure, which may reduce study intervention efficacy.

Prohibited Concomitant Therapy	Guidance
CYP3A4 and CYP2C9 substrates with narrow therapeutic index	Use of CYP3A4 and CYP2C9 substrates with narrow therapeutic index during treatment with defactinib is prohibited, as defactinib could increase the risk of treatment-related toxicities of these drugs.
Strong P-gp Inhibitors or Inducers	Use of a strong P-gp inhibitor or inducer during treatment with defactinib is prohibited, as P-gp inhibitor or inducer co-administration could change study intervention exposure.
Strong BCRP Inhibitors or Inducers	Use of a strong BCRP inhibitor or inducer during treatment with avutometinib (VS-6766) is prohibited, as a strong BCRP inhibitor or inducer may change avutometinib (VS-6766) exposure, which may impact avutometinib (VS-6766) efficacy or treatment-related toxicities.

Abbreviations: ASCO: American Society for Clinical Oncology; CSF: colony-stimulating factor ; regCYP: cytochrome P450; QD: once daily; P-gp: P-glycoprotein; PK: pharmacokinetic.

Table 8: Concomitant Therapies: Use with Caution During Treatment with Avutometinib and Defactinib

The study investigator should be contacted with any questions regarding concomitant use of these medications.

Concomitant Therapy: Use with Caution	Guidance
Weak or Moderate CYP2C9 or CYP3A4 Inhibitors	Weak or moderate CYP3A4 inhibitors should be used with caution during treatment with avutometinib ± defactinib, as they could increase study intervention exposure, which may increase the risk of treatment-related toxicities Weak or moderate CYP2C9 inhibitors should be used with caution during treatment with defactinib, as they could increase study intervention exposure, which may increase the risk of treatment-related toxicities.
Weak or Moderate CYP2C9 or CYP3A4 Inducers	Weak or moderate CYP3A4 inducers should be used with caution during treatment with avutometinib ± defactinib, as they could decrease study intervention(s) exposure, which may reduce study intervention(s) efficacy. Weak or moderate CYP2C9 inducers should be used with caution during treatment with defactinib, as they could decrease study intervention exposure, which may reduce study intervention efficacy.
CYP2C9 or CYP3A4 Substrates	Substrates of CYP3A4 or CYP2C9 should be used with caution. Co-administration of a CYP3A4 substrate with defactinib may increase the toxicity of these drugs. Co-administration of a CYP2C9 substrate with defactinib may increase the exposure of these drugs.

Concomitant Therapy: Use with Caution	**Guidance**
	An alternative drug that is not a substrate of CYP2C9 or CYP3A4 should be considered.
Weak or Moderate P-gp Inhibitors or Inducers	Weak or moderate P-gp inhibitors or inducers should be used with caution during treatment with avutometinib ± defactinib, as they could change study intervention(s) exposure.
UGT1A1 substrates	Substrates of UGT1A1 substrates should be used with caution. Co-administration of a UGT1A1 substrates substrate with defactinib may increase the toxicity of these drugs. (See Appendix D). An alternative drug that is not a substrate of UGT1A1 substrates should be considered.
P-gp substrates	Substrates of P-gp (See Appendix D) should be used with caution. Co-administration of a P-gp substrate with defactinib may increase the toxicity of these drugs. An alternative drug that is not a substrate of P-gp should be considered.
OATP1B1 or OATP1B3 substrates	Substrates of OATP1B1 or OATP1B3 should be used with caution.(SeeAppendix D). Co-administration of a OATP1B1 or OATP1B3 substrates with defactinib may increase the toxicity of these drugs. An alternative drug that is not a substrate of OATP1B1 or OATP1B3 should be considered.
Medications that modify gastric pH	The effect of medications that modify gastric pH on study intervention activity and exposure has not been clinically evaluated. Therefore, avoid concomitant use of gastric acid reducing agents (proton-pump inhibitors, H2-receptor antagonists, antacids).

Abbreviations: AUC: area under the curve; CYP: cytochrome P450; QD: once daily.

Additional information can be found at: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers and https://www.drugbank.ca/categories/DBCAT002635 (CYP2C9 inhibitors).

5.6 Study Procedures

Baseline evaluations are to be conducted within 4 weeks prior to start of protocol therapy. Scans must be done ≤4 weeks prior to the start of therapy. See schedule of events

General Concomitant Medication and Supportive Care Guidelines

All appropriate supportive care measures for adverse events related to therapy will be utilized according to standard of care guidelines. No prophylactic therapy will be given unless clinically indicated.

Rash Prophylaxis and Symptomatic Care

Prophylactic medications must be used during the first 2 cycles of avutometinib and defactinib dosing and will be optional starting with Cycle 3 to mitigate against dermatologic toxicities. Hydrocortisone 1% cream, moisturizer and sunscreen (sun protection factor [SPF]≥30) should be applied topically twice daily, along with a systemic antibiotic (minocycline 100 mg daily or doxycycline 100 mg BID). Application of topical agents should include the most commonly affected skin areas such as face, scalp, neck, upper chest, and upper back.

In addition, patients should be advised to avoid unnecessary exposure to sunlight. For patients who cannot tolerate a component of the prophylaxis, that component may be eliminated; the reason for the change will be documented in the eCRF.

Patients who develop rash/skin toxicities should be seen by a qualified dermatologist at the investigator's clinical discretion and should receive evaluation for symptomatic/supportive care management.

General recommendations for symptomatic care include:

- Pruritic lesions: cool compresses and oral antihistamine therapies
- Fissuring lesions: Monsel's solution, silver nitrate or zinc oxide cream
- Desquamation: thick emollients and mild soap
- Paronychia: antiseptic bath, local potent corticosteroids in addition to antibiotics; if no improvement, consult dermatologist or surgeon
- Infected lesions: appropriate bacterial/fungal culture-driven systematic or topical antibiotics

Dose modification and management guidance by rash adverse reaction grade is found in Table-5.

Antitumor Effect – Solid Tumors

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009] (**Appendix 1**). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

Progression-Free Survival

PFS is defined as the time from the date of first protocol therapy to the date of first documentation of disease progression or death due to any cause, whichever occurs first. For those subjects who are still alive and have not yet progressed, the subject's data will be censored at the last disease assessment

Overall Survival

OS is measured from the date of first protocol treatment to the date of the subject's death. If the subject is alive or the vital status is unknown, then the subject's data will be censored at the date the subject was last known to be alive.

5.7 Description of Study Procedures

Medical history

Findings from medical history (obtained at screening) and physical examination shall be given a baseline grade according to the procedure for AEs. Increases in severity of pre-existing conditions during the study will be considered AEs, with resolution occurring when the grade returns to the pre-study grade or below.

Physical examination

Physical examinations should be conducted according to the Schedule of Events. Full physical examinations should be conducted at screening/baseline, Day 1 of cycle 2 and beyond, and EOT (evaluate all major organ systems, including the following categories: general, head, eyes, ears, mouth/throat, neck, heart, lungs, abdomen, lymph nodes, joints, extremities, integumentary, neurologic, and psychiatric). Other examinations may be focused, at the discretion of the Investigator, to identify changes from baseline or evaluate changes based on the patient's clinical symptoms. Weight is to be recorded at each visit, height at screening/baseline visit only.

Vital signs

Vital signs (blood pressure [BP], pulse, temperature, and respiration rate) will be evaluated according to the assessment schedules. Body weight is also recorded along with vital signs.

On infusion days, patients receiving treatment will be monitored during and after infusion of Nivolumab as presented in the bulleted list below.

- Supine BP will be measured using a semi-automatic BP recording device with an appropriate cuff size, after the patient has rested for at least 5 minutes. BP and pulse will be collected from patients receiving treatment before, during, and after each infusion at the following times (based on a 60-minute infusion):
- Prior to the beginning of the infusion (measured once from approximately 30 minutes before up to 0 minutes [i.e., the beginning of the infusion]).
- Approximately 30 minutes during the infusion (**halfway** through infusion).
- At the end of the infusion (approximately 60 minutes ±5 minutes).
- A 1-hour observation period is required after the first infusion. If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be at the Investigator's discretion (suggested 30 minutes after each infusion).

If the infusion takes longer than 60 minutes, then BP and pulse measurements should follow the principles as described above or be taken more frequently if clinically indicated. The date and time of collection and measurement will be recorded on the appropriate eCRF. Additional monitoring with assessment of vital signs is at the discretion of the Investigator per standard clinical practice or as clinically indicated.

Electrocardiograms

Resting 12-lead ECGs will be recorded at screening and as clinically indicated throughout the study. ECGs should be obtained after the patient has been in a supine position for 5 minutes and recorded while the patient remains in that position.

At Screening, a single ECG will be obtained on which QTcF must be <470 ms.

In case of clinically significant ECG abnormalities, including a QTcF value >470 ms, 2 additional 12-lead ECGs should be obtained over a brief period (e.g., 30 minutes) to confirm the finding. If 3 are taken, can use the average of the three for the qtc

The Investigator or qualified Sub-Investigator will review all ECG interpretations and interval duration measurements for clinical significance. Any ECG interpretation deemed to be clinically significant will be reported as an AE.

Clinical laboratory tests

The following clinical laboratory tests will be performed (see the Schedule of Assessments)

- Hematology and Clinical Chemistry
- CPK
- Urinalysis
- Tumor Biopsy
- Coagulation parameters: Activated partial thromboplastin time and International normalized ratio to be assessed at baseline and as clinically indicated
- Pregnancy test (female subjects of childbearing potential only)
- Thyroid Stimulating Hormone
    - free T3 and free T4 only if TSH is abnormal
- Other laboratory tests
    - Hepatitis A antibody, hepatitis B surface antigen, hepatitis C antibody
    - HIV antibody

6. Statistical Considerations

6.1 Study Design/Endpoints

The first 5 patients/cohort (total N=10) will be served as a safety run-in. If deemed to be safe, the trial will continue. Basically, it is a phase II clinical trial including two concurrent cohorts with the time-to-event (6-months PFS) Bayesian optimal phase 2 (TOP) design for each. The TOP design is novel and allows for real-time go/no-go decision making when some patients' 6-month PFS status, the primary endpoint, are pending, thereby shortening the trial duration, and it also is efficient, allows any arbitrary number of interim looks, and maximizes statistical power with a well-controlled type I error rate. Based on the existing knowledge about salvage therapy in stage IV NSCLC (49) and a clinical meaningful expectation, we consider a 6-month PFS rate < 25% as not interesting (null hypothesis H0) and > 50% as promising (alternative hypothesis H1). We will enroll a maximum of 25 patients with three futility interim looks after 10 and 20 patients were treated with Go/No-Go rules illustrated in Table 6.

Table 9: Go/No-go Rules.

Interim	# treated	# 6-mon progression free	# pending	Action
1	10	<= 2	>= 4	Suspend
	10	<= 2	<= 3	No go
	10	>= 3	<= 7	Go
2	20	3	<= 15	Go if ESS < 7.33
	20	4	<= 15	Go if ESS < 10.56
	20	5	<= 15	Go if ESS < 13.89
	20	6	<= 15	Go if ESS < 17.28
	20	>= 7	<= 13	Go
Final	25	<= 25	>= 1	Suspend
	25	<= 9	0	No Go
	25	>= 10	0	Go

Based on Table9, we perform the interim looks when the number of enrolled patients reaches 10 and 20. When the total number of patients reaches the maximum sample size of 25, we reject the null hypothesis and conclude that the treatment is promising if the number of responses >= 10; otherwise we conclude that the treatment is not promising. Here, ESS is the effective sample size, which is defined as

$$\text{ESS} = \text{Num. non} - \text{pending patients} + \frac{\text{sum of the follow} - \text{up time for pending patients}}{\text{length of assessment window}}$$

Specifically, let n denote the interim sample size and N denote the maximum sample size. Let p_{eff} denote the probability of efficacy (response rate) and define the null hypothesis $H_0: p_{eff} \leq 0.25$, representing that the treatment is inefficacious. We will stop enrolling patients and claim that the treatment is not promising if

$$Pr(p_{eff} > 0.25|data) < \lambda(\frac{n}{N})^{\alpha},$$

where λ=0.875 and α=0.45 are design parameters optimized to maximize the power under the alternative hypothesis $H_1: p_{eff} = 0.5$, while controlling the type I error rate at 0.1 (i.e., the chance of incorrectly claiming that an inefficacious treatment is promising is no more than 10%). Assuming a Beta(0.25,0.75) prior distribution for p_{eff}, the above decision rule corresponds to the following go/no-go rules and yields a maximum statistical power of 0.855 under H_1.

Table 10 shows the operating characteristics of the design based on 1000 simulations using the TOP web application. In the simulation, the assessment window is 1.5 months, and the patient arrival is uniformly distributed with an accrual rate of 3 patients per month. The time to response is simulated from a Uniform

distribution by controlling 50% of the responses occurring in the latter half of the response assessment window.

Table 10: Operating characteristics

Response rate	*Early stopping (%)*	*Claim promising (%)*	*Sample size*	**Average trial duration (month)**
0.25	89.1	4.3	14	5.45
0.5	16.7	79.5	23	9

6.2 Analysis datasets

Safety Population: The safety analysis dataset will include all eligible patients who begin treatment and receive at least one dose of protocol therapy. Patients will be analyzed in the cohort to which they were enrolled.

Efficacy Evaluable Population: All evaluable patients will be included in the analysis of efficacy endpoints. The term evaluable is defined as any eligible patient who receives at least one dose of protocol therapy and does not withdraw consent until the patient's first response assessment. Patients who fail to have a response assessment due to early progression or death will be categorized as non-responders.

6.3 Analysis of primary endpoint

The primary endpoint is the 6m PFS rate. The rate will be calculated with an 95% confidence interval using Kaplan-Meier method based on the efficacy evaluable population. Patients who fail to have a response assessment for other reasons (e.g., refusal due to travel constraints) will be considered unevaluable and will not be included in the denominator when calculating the rate.

6.4 Analysis of secondary endpoints

For progression-free survival (PFS) and overall survival (OS), the Kaplan-Meier method will be used to estimate the median event-free time with 95% confidence interval. For the duration of overall response, summary statistics will be used to describe the mean and median duration of response.

Analysis of Biomarker Correlative Study

A total of 50 patients with LKB1-mutated lung cancer (half of them also with KRAS mutation) will enroll in the clinical trial with archived tissue samples available. We will obtain fresh tissue as possible, as biopsies are not mandatory for the study.

Overall, using available baseline biomarker information from the three projects, we will assess their prognostic effect on OS or PFS by calculating their prediction performance (e.g., Uno's C-index[33]) for each biomarker individually or multiple biomarkers jointly through Cox proportional hazard model. A prognostic risk score may be generated based on the coefficients from the model.[34]

Analysis of Safety Data

All adverse events (including serious adverse events) will be summarized and described within each cohort. They will initially be reviewed regardless of attribution, but also whether they are possibly, probably, or definitely related to treatment. The incidence of severe adverse events or toxicities will be described. We will assess the proportion of patients who experience grade 3 or higher toxicity. To assess tolerability, we will also capture the proportion of patients who go off treatment due to adverse events. Will analyze SAEs as well, as well as laboratory data collected.

Stopping rule for safety

The first 5 patients in each cohort will be used as a safety run-in. The DLT is defined as above within the first cycle of treatment. We anticipate the DLT rate would not exceed 30%. Based on a Bayesian rule, if there are >=2 DLTs out of 5for a cohort, we would stop the enrollment for the cohort due to the safety concern, otherwise the trial will continue with the safety data being monitored by DSMB on a regular base. The potential stopping boundary for safety at the two interim looks would be >= 4 DLTs out of 10 and <= 8 DLTs out of 20. The safety stopping boundary is calculated based on the Bayesian Toxicity Monitoring (BTM) application (https://www.trialdesign.org) to control for the probability of excessive toxicity being less than 70%.

7. Sharing of Results with Participants

In general, study staff will not provide any individual results to subjects (ex. outcome trial results or results from subject's samples studies). If something of urgent medical importance to the participating subjects will be found, the PI (or co-Is) will inform the subject, although we expect that this will be a very rare occurrence. Samples and data will only be used for research.

8. Study Timelines

8.1 Duration of therapy

In the absence of treatment delays due to adverse event(s), treatment may continue for until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

8.2 Duration of follow-up

Subjects will be contacted every 3 months for up to 5 years upon leaving the study.

Patient records may be reviewed until death to assess progression and survival. Survival information may be collected by clinic visit, email, or telephone after ending protocol treatment and until the study is terminated, the patient dies, or the patient is lost to follow-up.

A participant will be considered lost to follow-up if he fails to return for three scheduled visits and is unable to be contacted by the study site staff after three or more attempts at contact by phone.
The following actions must be taken if a participant fails to return to the clinic for a required study visit:
The site will attempt to contact the participant and reschedule the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.

Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

9. Inclusion and Exclusion Criteria

Inclusion Criteria

- Patients must have been histologically or cytologically diagnosed with non-small cell lung cancer, specifically lung adenocarcinoma
- Patients must have advanced stage disease that is not amenable to combined modality therapy or surgical resection
- Patients must have known LKB1 mutation
- Patients must have known KRAS mutation (Cohort A only)
- Patients must have progressed on immune checkpoint inhibitor alone and first line chemotherapy, either combined or sequentially, for advanced stage disease. There is no limit on prior lines of therapy.
- Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥20 mm with conventional techniques or as ≥10 mm with spiral CT scan.
- Age ≥18 years.
- ECOG performance status 0 or 1

- Adequate recovery from toxicities related to prior treatments to at least Grade 1 by CTCAE v 5.0. Exceptions include alopecia and peripheral neuropathy grade ≤ 2.

- Patients must have normal organ and marrow function as defined below:
  - absolute neutrophil count ≥1,500/mcL
  - Hemoglobin ≥8.0
  - platelets ≥100,000/mcL
  - total bilirubin ≤ 1.5 × upper limit of normal (ULN) for the institution; patients with Gilbert syndrome may enroll if total bilirubin < 3.0 mg/dL (51 µmole/L
  - AST(SGOT)/ALT(SGPT) alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 × ULN (or < 5x ULN in patients with liver metastases)
  - creatinine clearance ≥50 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal.

- Patients must have the ability to ingest oral medications

- The effects of defactinib and avutometinib on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry,for the duration of study participation, for 3 months following the last dose of study therapy for male patients, and 1 month following the last dose of study therapy for female patients. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

- Patients must be able to understand and be willing to sign a written informed consent document.

-Baseline QTc interval < 470 ms using Fredericia's QT correction formula. NOTE: This criterion does not apply to patients with a right or left bundle branch block.

- Participants must receive prior authorization from their insurance companies to cover nivolumab prior to enrollment on study.

Exclusion criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

- Patients who have had systemic therapy within 3 weeks prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier.

- Patients who are receiving any other investigational agents.

- Patients with unstable or symptomatic brain metastasis or known leptomeningeal disease. Asymptomatic brain metastases are allowed if they meet the following criteria: a. Have been treated and have been stable for greater than or equal to 4 weeks as documented by radiologic imaging. b. Have not required increasing doses of corticosteroids within 2 weeks prior to study treatment.

- Patients with history of pre-existing auto-immune conditions that would pose a higher risk for toxicity with nivolumab will be excluded

- Patients who experienced serious auto-immune toxicity with prior immune checkpoint inhibitor therapy

- History of allergic reactions attributed to compounds of similar chemical or biologic composition to avutometinib or defactinib

- Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

- Known hepatitis B, hepatitis C or human immunodeficiency virus (HIV) infection that is active and/or requires therapy.

- Active skin disorder that has required systemic therapy within the past 1 year. Surgically removed early stage skin cancers are allowed. Topical creams are allowed as well.
- History of rhabdomyolysis.
- Concurrent ocular disorders:
    - Patients with history of glaucoma, history of retinal vein occlusion (RVO), predisposing factors for RVO, including uncontrolled hypertension, uncontrolled diabetes.
    - Patients with history of retinal pathology or evidence of visible retinal pathology that is considered a risk factor for RVO, intraocular pressure > 21 mm Hg as measured by tonometry, or other significant ocular pathology, such as anatomical abnormalities that increase the risk for RVO.
    - Patients with active or chronic, visually significant corneal disorders, other active ocular conditions requiring ongoing therapy or clinically significant corneal disease that prevents adequate monitoring of drug-induced keratopathy. Examples of visually significant corneal disorders include corneal degeneration, active or recurrent keratitis, and other forms of serious ocular surface inflammatory conditions. Visually significant corneal disorders do NOT include dry eyes, blepharitis, and uncomplicated corneal erosions.

- Patients with the inability to swallow oral medications or impaired gastrointestinal absorption due to gastrectomy or active inflammatory bowel disease.
- Treatment with warfarin. Patients on warfarin for deep vein thrombosis/pulmonary embolism should be converted to low-molecular-weight heparin (LMWH) or direct oral anticoagulants (DOACs). Exposure to medications (with or without prescriptions), supplements, herbal remedies, or foods with potential for drug-drug interactions with defactinib within 14 days prior tothe first dose of avutometinib or defactinib and during the course of therapy, including:
    - strong CYP3A4 inhibitors or inducers, strong CYP2C9 inhibitors or inducers, strong P-glycoprotein (P-gp) inhibitors or inducers. (See Concomitant therapy restrictions, Table-7 for more detail)
- Patients with a known 'treatable driver mutation' with FDA approved targeted therapy (such as EGFR, ALK, ROS1, NTRK, BRAF, RET, MET exon 14, HER2). The exception is KRAS as listed in the inclusion section.
- History of prior malignancy within past 2 years prior to study entry, with the exception of curatively treated malignancies or malignancies with very low potential for recurrence or progression.
- Female patients who are pregnant or breastfeeding.

10. Vulnerable Populations

This study does not include the following special populations:

- Adults unable to consent
- Individuals who are not yet adults (infants, children, teenagers)
- Pregnant women
- Prisoners
- Cognitively impaired or Individuals with Impaired Decision-Making Capacity

11. Local Number of Participants

This study will enroll a maximum of 50 patients.

12. Recruitment Methods

All subjects will be recruited from the lung cancer clinics at the Winship Cancer Institute. The study will be listed on the NIH clinical trials website and referring physicians will be notified by newsletters sent out by Winship.

13. Withdrawal of Participants

Participants are free to withdraw from participation in the study at any time upon request. An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant study intervention non-compliance or if any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant unable to receive study drug for a continuous duration beyond 4 weeks

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who sign the informed consent form, and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study before the required period as listed in the statistics section, will be replaced.

14. Study Stopping Criteria

In the event that one or more of the following stopping criteria are met, the study will be stopped due to risk of major safety concerns.

I. Any death (other than disease progression) that is at least possibly related to the study agent.
II. Occurrence of two or more Grade 4 events that are at least possibly related to the study agent.

15.Risks to Participants

The identified risks for avutometinib treatment are skin toxicity, eye toxicity, creatine phosphokinase (CPK) elevation, gastrointestinal tract toxicities, and edema. The potential risks are effects on the bone and cartilage, hematological toxicity, drug-drug interactions with strong inducers and inhibitors of CYP3A4, liver function abnormalities, renal toxicity, and tissue mineralization. The identified risk for defactinib treatment is hyperbilirubinemia/increased bilirubin. The important potential risks for defactinib treatment are gastrointestinal effects, interaction with warfarin, and drug-drug interactions; most specifically, drug-drug interactions with strong inhibitors or inducers of CYP3A4 or CYP2C9. Based on the monotherapy safety profiles there are no overlapping identified risks, while drug-drug interactions with inhibitors or inducers of CYP3A4 are overlapping potential risks.

No apparent toxicities unique to the combination were observed in the preliminary data from 52 patients treated with the combination as of 18 Mar 2020. The most common treatment-related adverse events (AEs) were rash (90%), CPK elevation (56%), hyperbilirubinaemia (42%), aspartate aminotransferase (AST) elevation (38%), fatigue (31%), glossitis/oral mucositis/mouth ulcers (31%), alanine aminotransferase (ALT) elevation (29%), diarrhoea (29%), visual disturbance (29%), nausea (25%) and peripheral oedema (21%), most of which were Grades 1 or 2 and reversible.

The monotherapy and combination toxicities are managed using a combination of prophylaxis, supportive care, and dose modifications. Guidance on management of these AEs, including dose interruptions and modifications, is provided in Section 6.7. Detailed information about the known and

expected risks and reasonably expected AEs of avutometinib and defactinib and nivolumab may be found in the IB for each compound.

Nivolumab risks may be reviewed in the Nivolumab Package Insert.

16. Potential Benefits to Participants

There is no guarantee of benefit to subjects who enroll in this protocol. Patients may derive benefit due to improvements in symptoms, tumor shrinkage and delay in disease progression, as suggested by clinical activity seen with both monotherapies and the combination.

17. Data Management and Confidentiality

All information will be collected on study-specific case report forms by the study staff. The data submission schedule is as follows:

At the time of registration:

- Registration Form
- Informed Consent Form (signed by the subject)
- Eligibility Checklist
- Source documents related to eligibility.

Within 2 weeks after registration:

- Baseline study case report forms
- Pertinent source documents

Within 2 weeks after 30-day follow-up:

- On study case report forms
- Pertinent source documents

All study data will be reviewed for completeness and accuracy by the Protocol Chair. The Principal Investigator (or his/her designee) at each respective institution is responsible for review, and ensuring the completeness and accuracy, of the data generated by his/her institution. The study data will also be periodically reviewed by the Emory Winship Cancer Institute Clinical Research Office.

The Data and Safety Monitoring Committee (DSMC) of the Winship Cancer Institute of Emory University will oversee the conduct of this study. This committee will review all pertinent aspects of study conduct including patient safety, compliance with protocol, data collection and efficacy.

Adverse Events (AE's), Serious Adverse Events (SAE's) [including deaths, hospitalizations, and life-threatening events], and Unanticipated Problems (UP's) will be managed and reported, as required to the IRB, the awarding IC, the NIH Office of Biotechnology Activities, and FDA as required. The trial will be monitored on an ongoing/continual basis to mitigate risks.

The DSMC will review selected charts of patients entered to the study. Reviews will occur annually for studies that are low risk or moderate risk. High-risk studies will be reviewed every 6 months. The committee reserves the right to conduct additional audits, if necessary, at any time-point. The Principal Investigator is responsible for notifying the DSMC about the accrual of patients when the first subject has been entered to the study.

The charter for the Winship DSMC is available upon request to the investigator or other study-related personnel. Additionally, the study team [to include the PI] will present all data analyzed to date, record of accrual, and attributable toxicities at the Multidisciplinary Lung Oncology meeting which meets on a regular basis.

As with our ongoing clinical trial, for the current proposal we will adhere strictly to Winship's Data Safety Monitoring Plan which is provided in detail at the following link:

https://winshipcancer.emory.edu/research/clinical-trials-office/data-and-safety-monitoring-committee.html

Any relevant findings or concerns will be shared with the Verastem team.

17.1 Data: Objectives of correlative studies

Correlative studies will be conducted in Projects 2 and 3 of the P01 program using samples from clinical trial participants. Studies will seek to address the following questions:

Project 2: Determine the prognostic significance of STING expression in the response of LKB1-mutated patients underwent RAF/MEKi+FAKi+PD1 blockade clinical trial

In order to evaluate the effect of FAK inhibitor + PD-1 blockade on the STING axis, we will analyze paired pre and post-treatment samples of PBMCs as well as paired tumor biopsies obtained in the context of clinical trial. These specimens will be analyzed for the expression of STING both by immunohistochemistry, as well as by single cell mass cytometry and transcriptomics. These studies will not only identify if this approach leads to changes in STING expression but also the cell type (e.g. tumor cells, or tumor-infiltrating immune cells such as myeloid cells), wherein this change is most evident. These changes will then be correlated with clinical endpoints such as overall or progression-free survival as well as with the changes in other immune cells (such as infiltrating T cells, or NK cells). In particular, as STING expression may be impacted by cytokines such as IFNg, we will particularly evaluate if there are changes in the expression of these cytokines or downstream pathways in immune cells during the course of this clinical trial. These studies obviously represent a collaboration involving not just project 3, but also the P01 Cores 2 and 3.

Project 3: Determine how the combination of RAF/MEK inhibitor, FAK inhibitor and anti-PD-1 antibody treatment alters CD8 T cell recruitment and collective invasion through the microenvironment

We *hypothesize* that hyperactive FAK due to LKB1-inactivation contributes to the resistance to immune response, and that FAK inhibition will enhance the efficacy of ICI. To test this, we will leverage the Phase II clinical trial to determine if patients with mutant LKB1 have better efficacy with the novel combination, increased CD8+ T-cell recruitment, and if pY-FAK activation is associated with LKB1 inactivation and/or KRAS mutation among the different cohorts. Patients will be biopsied according to the clinical protocol. Tissues will be sectioned, paraffin embedded, and processed for IHC [35] for LKB1 (Abcam) and the biomarkers pY^{397}-FAK (Invitrogen), pY^{861}-FAK (Invitrogen), and total FAK (BD Transduction) performed in the lab with QC oversight and scoring by P01 Core 2. We can detect LKB1, pY^{397}- and pY^{861}-FAK by IHC in tissues [36, 37] and LKB1 mutation in the primary tumor [15]. IHC scoring will be based upon percentage of tumor cells stained and intensity of stain, and performed independently in a blinded manner. The number, size, and morphology of CIPs and surrounding vim+, FSP1+ CAFs will be quantified by Core 2 [37]. Immune cell infiltration will be profiled using 8-color immunophenotyping flow cytometry analysis and IHC staining using immune cell surface markers, such as CD8+ T cells and CD56+ NK cells by Core 2. We will also isolate immune cells from the lung to carry

out single-cell RNA (scRNA) sequencing with the 10X platform. This unbiased analysis will reveal changes in immune cells following defactinib treatment plus nivolumab, both at the level of cell types and changes in gene expression in individual cell types. We will use the biopsies to answer several questions: ***(1)*** Does LKB1 loss, *LKB1* mutation, pY-FAK activation, and/or *KRAS* mutation predict for efficacy with the combination regimen?; ***(2)*** Do NSCLC patients with LKB1 loss, *LKB1* mutation, and/or *KRAS* mutation in the primary tumor show enhanced FAK activation? ***(3)*** Does defactinib treatment disrupt CAF:tumor cell interaction within the CIPs and collagen remodeling using IHC and SHG imaging as described in Aim 1-A and published in mice tissues [36, 37]

17.2 Specimens:

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Principal Investigator. The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

All stored samples will be maintained in the laboratory to which it was sent initially for analysis. Study participants who request destruction of samples will be notified of compliance with such request and all supporting details will be maintained for tracking.

Tumor biopsies

Archived tumor samples will be obtained from all the study participants as available. Pre-treatment and on study repeat biopsy will be optional.

Peripheral blood

Peripheral blood samples will be obtained at baseline before initiation of study therapy and during weeks 1 of cycle1 2, 3, 5 and at time of progression. Approximately 20 ml of peripheral blood will be obtained in two vials. The mononuclear cells will be separated based on standard guidelines used in the Phase I Unit of the Winship Cancer Institute from one vial. The cells will be frozen at -80C until analysis.

18. Provisions to Monitor the Data to Ensure the Safety of Participants

Plans to Monitor the Data to Ensure Safety of Participants and Data Integrity

Check the box for the study's risk level:

☐ **No more than minimal risk** - Study not required to follow DSMP guidance, may delete the rest of this section. (Non-invasive sampling or imaging, blood draws, etc. are likely minimal risk if all procedures fall clearly within these categories. If all study procedures do not fall into these categories, and you still believe your study is minimal risk, consult with IRB staff.)

☒ **More than minimal risk** – Continue below.
Review the Data and Safety Monitoring Questionnaire below and select the relevant monitoring table at the end of this section. You must complete only ONE of the tables.
Mark the risk categorization, as determined by the Data and Safety Monitoring Questionnaire, that applies to your study below:

Select one of the following (do not delete this table; review the guidance document for definitions):
☐ Medium Complexity
☒ High Complexity Category A
☐ High Complexity Category B *If choosing this category for a study under an IND or IDE because you believe the study intervention does not significantly impact morbidity or mortality, please provide your rationale:*

Monitoring Table

Please address the specific details below. Please do not alter the table and leave all template text to assist in a quick review. If deemed not applicable, please provide rationale.

DSMP Requirement	How this Requirement is Met	Frequency	Responsible Party(ies)
Real-time review of participant data during initial data collection.	This requirement will be met per Winship's NCI approved DSMP	This will occur every time new information is obtained.	Study team, DSMC
Site Monitoring at pre-determined intervals: The Principal Investigator has a responsibility to ensure that the study is following all aspects of the protocol.	This requirement will be met per Winship's NCI approved DSMP	Annually	DSMC
100% review of regulatory files	DSMC monitors will review the protocol, amendments, informed consent documents, IRB submissions and meet with the principal investigator for clarification of study objectives	Reviewed at first and close-out visits	DSMC
100% review of consent forms	QA check of 5-10 randomly selected consents to validate Central Subject Registration (CSR) and PRMS to conduct QA consent checks in real time as subjects are registered in OnCore vis CSR process	Biannually	PRMS, QM

Review of credentials, training records, the delegation of responsibility logs (if applicable)	Clinical trials monitor will review the electronic regulatory binder and compare them against the staff listed on the DOA log. The monitor also reviews the site's source documents to ensure that all study staff have been properly listed on the DOA and have corresponding documentation (CV, ML, GCP certs, training log) filed in the electronic regulatory study binder	Biannually	Study team, DSMC
Comparison of case report forms (CRF) to source documentation for accuracy and completion	The PI is responsible for ensuring that instances of egregious data insufficiencies that may impact the scientific integrity of the trial	Biannually	Study team, DSMC
Review of documentation of all adverse events	During the monitoring process, the DSMB reviews trial safety data for stopping rules, deviations, study amendments, accrual rates and monitoring reports for therapeutic investigator-initiated clinical trials and any other trial as deemed necessary	Biannually	Study team, DSMC
Monitoring of critical data points (eligibility, study endpoints, etc.)	The assigned monitor will randomly select subject(s) for review. Although the principal investigator and applicable study team members will receive notification of trial monitoring in advance, the subject selection will not be revealed in advance of the monitoring visit.	Biannually	Study team, DSMC
Laboratory review of processing and storage of specimens	The assigned monitor will randomly select subject(s) for review.	Reviewed at first and close-out visits and at least biannually	Study team, DSMC
Assessment of laboratory specimens stored locally	QM will monitor data entered into the study database against the site source documents, including laboratory reports. During visits to the laboratory, QM will ensure study specimens are being properly stored, handled and shipped according to the protocol and lab manual.	Reviewed at first and close-out visits and at least annually	Winship Quality Management Department
Test article accountability review	Protocol-designated pharmacy for clinical research	Reviewed at first and close-out visits and at least biannually	Research Pharmacist

Accountability logs, dispensing records, and other participant records	QM will review accountability and dispensing log, including IP administration forms.	Biannually	Winship Quality Management Department
For FDA regulated studies, the following requirements apply:	Monitoring activities will meet the FDA's requirements as delineated in 21 CFR 50, 21 CFR 56, 21 CFR 812 for studies conducted under an IDE and 21 CFR 312 for studies conducted under an IND.	Annually	DSMC
Monitoring methods (may include centralized, on-site, and self-monitoring)	On-site monitoring of protocol adherence and subject eligibility, comparison of source documents with CRFS for data integrity, review of adverse events, ensure IIP is stored properly and secure; remote monitoring of patient eligibility and consent as well as data quality and adverse events	Annually	DSMC
*For international studies, you are required to engage a CRO that is working in the site country and/or to consult with Emory's legal counsel regarding compliance with the country's clinical research regulations.			

The Data and Safety Monitoring Committee (DSMC) of the Winship Cancer Institute will provide oversight for the conduct of this study. The DSMC functions independently within Winship Cancer Institute to conduct internal monitoring functions to ensure that research being conducted by Winship Cancer Institute Investigators produces high-quality scientific data in a manner consistent with good clinical practice (GCP) and appropriate regulations that govern clinical research. Depending on the risk level of the protocol, the DSMC review may occur every 6 months or annually. For studies deemed Moderate Risk, initial study monitoring will occur within 1 year from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. Subsequent monitoring will occur in routine intervals per the Winship Data and Safety Monitoring Plan (DSMP).

The DSMC will render a recommendation and rating based on the overall trial conduct. The PI is responsible for ensuring that instances of egregious data insufficiencies are reported to the IRB. Continuing Review submissions will include the DSMC recommendation letter. Should any revisions be made to the protocol-specific monitoring plan after initial DSMC approval, the PI will be responsible for notifying the DSMC of such changes. The Committee reserves the right to conduct additional audits if necessary.

Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site.

- **'Expectedness'**: AEs can be 'Unexpected' or 'Expected' (see Section 7.1 above) for expedited reporting purposes only. 'Expected' AEs (the ASAEL) are ***bold and italicized*** in the CAEPR.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

SAE definition: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Expedited Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions.

The AE reporting period begins from the time that the patient signs the informed consent through and including 30 calendar days after the last dose of study drug. All AEs/SAEs should be followed until resolution or stabilization. Any SAE occurring after the reporting period must be promptly reported if a causal relationship to the investigational drug is suspected. If the patient begins a new anticancer therapy, the safety reporting period ends at the time the new treatment is started, however, death must always be reported if it occurs during the AE reporting period irrespective of intervening treatment.

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided.

Routine Adverse Event Reporting

Overdose

Overdoses will not be considered SAEs unless the outcome of the overdose meets seriousness criteria as defined in the protocol. In the event of an overdose that causes an SAE, Verastem Safety and Pharmacovigilance should be notified within 24 hours. The patient should be carefully monitored for potential adverse reactions and symptomatic treatment instituted as per institutional standard of care (SOC). The Investigator will determine if and when dosing should resume.

Pregnancy and Contraception:

The effects of defactinib on conception, pregnancy, and lactation are unknown.

At Screening, all male and female patients of reproductive potential (i.e., not surgically sterile or female patients who are not postmenopausal) must agree to use highly effective methods of contraception for the duration of defactinib and for at least 3 months after the last dose of study drug(s) for male patients, and at least 1 month after the last dose of study drug(s) for female patients. Pregnancy testing should be conducted monthly during the trial. A positive urine test must be confirmed by a serum test. Male patients must also refrain from donating

sperm during their participation in the study and for at least 3 months after the last dose of study drug(s). Female patients should not breastfeed during the study and for at least 3 weeks after the last dose of study drug(s).

A patient must immediately inform the Investigator if the patient or patient's partner becomes pregnant from the time of consent to 30 days after the last dose of study drug(s). Any female patients receiving study drug(s) who become pregnant must immediately and permanently discontinue study drug(s). The pregnant woman should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

Pregnancy per se is not considered as an AE unless there is cause to believe that the study drug(s) may have interfered with the effectiveness of contraceptive medication or if the outcome of pregnancy meets SAE criteria (miscarriage or congenital anomaly/birth defect, etc.), in which case it should be reported in the same manner and timelines as an SAE.

Any SAEs associated with pregnancy (e.g. congenital abnormalities/birth defects/spontaneous miscarriage or any other serious events) must additionally be reported. In addition, any infant death or congenital anomaly occurring more than 30 days after the patient's last dose of study drug(s) that the Investigator suspects is related to the in-utero exposure to the defactinib should also be reported as an SAE. Hospitalization for normal delivery of a healthy newborn is not an SAE.

Consent to provide follow-up information regarding the outcome of the pregnancy and the health of the infant until 30 days old will be requested. Any pregnancy must be reported to Verastem, Inc. within 24 hours of the Investigator's knowledge of the pregnancy using a site-specific SAE/Pregnancy or MedWatch/CIOMS-I Report Forms. The Investigator will observe the pregnant woman until completion of the pregnancy and must notify Verastem, Inc. of the outcome within 24 hours of the Investigator's knowledge of the pregnancy outcome. This notification includes pregnancies resulting in live, normal births.
Highly Effective Methods of Contraception:

Methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. Such methods include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[1]:
    - oral
    - intravaginal
    - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation[1]:
    - oral
    - injectable
    - implantable[2]
- intrauterine device (IUD)[2]
- intrauterine hormone-releasing system (IUS)[2]
- bilateral tubal occlusion[2]
- vasectomized partner[2,3]
- sexual abstinence[4]

[1]Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method.
[2]Contraception methods that are considered to have low user dependency
[3]Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the WCBP study participant and that the vasectomized partner has received medical assessment of the surgical success.
[4]Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient.

Verastem, Inc. Safety and Pharmacovigilance Contact Information:
Investigator to send SAE and Pregnancy Information to:
Verastem, Inc. Safety and Pharmacovigilance
Email: drugsafety@verastem.com
Facsimile: + 1-781-465-7936

19. Provisions to Protect the Privacy Interests of Participants

Data Collection and Management
Data will be collected using an institutional electronic data recording system, Oncore. Electronic case report forms and study calendar will be generated prior to study activation. Investigator responsibilities are set out in the ICH guideline for Good Clinical Practice (GCP) and in the US Code of Federal Regulations. The Investigator will permit study-related audits by Verastem or its representatives, IRB/EC review, and regulatory inspection(s) (e.g., FDA, EMEA), providing direct access to the facilities where the study took place, to source documents, to CRFs, and to all other study documents. The Investigator, or a designated member of the Investigator's staff, must be available at some time during audits to review data and resolve any queries and to allow direct access to the subject's records (e.g., medical records, office charts, hospital charts, and study related charts) for source data verification. The data collection must be completed prior to each visit and be made available so that the accuracy and completeness may be checked.

Disclosure and confidentiality
The investigator will keep all information provided by Verastem in strict confidence and will request similar confidentiality from his/her staff and the IRB/IEC/REB. Study documents provided by Verastem (investigators' brochures and other material) will be stored appropriately to ensure their confidentiality. The information provided to the investigator may not be disclosed to others without direct written authorization from Verastem, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial.

Study records requirements
The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the protocol therapy, that is copies of CRFs and source documents (original documents, data, and records [e.g., hospital records; clinical and office charts; laboratory notes; memoranda; subject's

diaries or evaluation checklists; SAE reports, pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches; photographic negatives, microfilm, or magnetic media; x-rays; subject files; and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study; documents regarding subject treatment and drug accountability; original signed informed consents, etc.]) be retained by the Investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval).

Source data and documents

In accord with ICH-GCP as adopted by the FDA, all information in original records and certified copies of original records or clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the trial is considered source data. Source data are contained in source documents, which can be original records or certified copies of hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries of evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. Case Report Forms (CRFs): Source data may be collected in the source documents or entered directly onto the case report forms.

Training of study site personnel

The study PI (sponsor-investigator) will provide training as appropriate to the delegated responsibility to all staffs involved in the conduct of the study. Before the first patient is enrolled in the study, study staff and co-investigators will review and discuss the requirements of the clinical study protocol and related documents including getting trained in any study-specific procedures and electronic data capture systems to be utilized. The Sponsor-Investigator will ensure that appropriate training relevant to the study is given to all of these staff and any new information relevant to the performance of this study is forwarded to the staff involved. The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing, and other staff).

20. Economic Burden to Participants

The study-supporter will pay for certain items and services the subject may receive in this study. Subjects will have to pay for the items or services for which the study sponsor does not pay. The sponsor will not pay for regular medical care.

21. Consent Process

The initial informed consent discussion will occur in Winship Cancer Institute or the Emory Clinic. At Winship Cancer Institute, the informed consent is an ongoing, interactive process rather than a one-time information session. The consent form document is designed to begin the informed consent process, which provides the patient with ongoing explanations that will help them make educational decisions about

whether to begin or continue participating in the trial. The research team knows that a written document alone may not ensure that the patient fully understands what participation means. Therefore, the research team will discuss with the patient the trial's purpose, procedures, risks and potential benefits, and their rights as a participant. The team will continue to update the patient on any new information that may affect their situation. Consent will be obtained prior to any research-driven procedures. The investigator will assess the patient's capacity during his/her encounters with him or her. The investigator will give the person providing consent adequate opportunity to read the consent document before it is signed and dated. It will be explained to prospective participants that the study involves research, the purpose of the research, the expected duration of participation, as well as the approximate number of participants to be enrolled. The study procedures, and identification of research procedures v. non-research will also be thoroughly discussed. It will be explained to participants that participation is voluntary and that the subject may discontinue at any time. Refusal to participate or withdraw will not involve a penalty or loss of benefits to which the participant is otherwise entitled. Refusal will in no way affect the participant's future are. The participant will also be told of the possible consequences of the decision to withdraw from the research, and procedures for orderly termination of participation. Any significant new findings developed during the course of the research that may affect the participant's willingness to continue to participate will be provided. Also explained will be anticipated circumstances under which the subject's participation may be terminated by the investigator without the participant's consent. Prospective participants will be provided with a description of any reasonably foreseeable risks or discomforts as well as a description of any benefits to the participant or to others that might be reasons expected from the research. Alternative procedures or courses of treatment will also be thoroughly discussed. Prospective participants will also be given detailed information describing the extent to which confidentiality of records identifying the participant will be maintained and what records may be examined by the research staff, IRBs, sponsor, their representatives, and possibly the FDA or OHRP. Also communicated to the participant will be an explanation that emergency medical care will be arranged for a study-related illness or injury, and an explanation of whether funds are set aside to pay for this care and/or compensation, and if so by whom (e.g., sponsor, subject, insurer). The participant is told the source of the study's funding. All participants will be told of any additional costs that may result from participation in the research.

Non-English-Speaking Participants

A certified translator/interpreter will be present during the consenting process and all questions and concerns will be answered by the treating physician. A Short Form in that specific language will be used. A certified translator/interpreter will be present during the consenting process and this will be documented. We will use what's available on Emory IRB website. For the languages that are not available, we will have the short form translated to that language and submit the IRB for review and approval prior to use. Process to Document Consent in Writing: Winship SOP 2.1:"Obtaining Informed consent for Interventional clinical trial" will be followed.

22. Setting

The research will be conducted at Emory University, and at Emory Saint Joseph's. Potential participants will be identified in medical oncology clinics, multidisciplinary cancer clinic, surgical oncology clinics, and multidisciplinary tumor board at Emory University.

23. Resources Available

Emory University was founded in 1836 and is a national center for teaching, research, and service. Emory University has been named as one of the nation's top 25 universities for more than a decade by the U.S. News and World Report. Emory University research partners include the Georgia Institute of Technology, the University of Georgia, Morehouse School of Medicine, the US Centers for Disease Control and Prevention, Children's Healthcare of Atlanta, and the Georgia Clinical and Translational Science Alliance (GACTSA). Emory University researchers received $734 million from external funding agencies in fiscal year 2018, including approximately $441 million in funding from federal agencies, $359 million of this from the National Institutes of Health (NIH).

Winship Cancer Institute (Winship) is Georgia's first and only National Cancer Institute (NCI)-designated Comprehensive Cancer Center (P30CA138292) and is dedicated to the integration of innovative clinical and basic science research with outstanding patient care for the prevention, treatment and control of cancer. First designated in 2009, Winship's NCI designation was renewed in 2012 and 2016, achieving an "outstanding" rating. Winship earned the prestigious Comprehensive Cancer Center designation from the NCI in 2016, after demonstrating that its outstanding programs are reducing the cancer burden on the state of Georgia through research conducted in its laboratories, its clinical trial program, and its population-based science. The institutional support for Winship was rated as 'exceptional' by the review panel.

The Winship Clinic Building C houses the primary offices and clinical space for cancer services including the medical oncology, hematology, and surgical oncology clinics, the radiation oncology program, and the Winship Ambulatory Infusion Center. In summer 2017, Emory Healthcare completed the expansion of Emory University Hospital Tower on Clifton Road. This nine-floor facility adds 144 inpatient beds to the hospital, of which more than 80% are dedicated to cancer care. The hospital expansion also accommodates cancer patient-specific intensive care units, an expanded BMT Unit with peri-transplant clinics to facilitate continuity of care, and a 24-hour cancer urgent care center, which serves as both a triage facility and short stay treatment center for patients with cancer-related medical concerns.

The Winship Phase I Unit, on the fourth floor of the Emory University Hospital Tower, is the largest unit in Georgia dedicated to the earliest and most critical phase of new cancer therapy evaluation. There is space for 15 private treatment bays, four clinic rooms, its own lab for doing patient blood work, a dedicated secure medication room, computer workspace for research and other support staff, and a "fast track" bay with three chairs for rapid use in patients who, for example, might need only a research lab test done.

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APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

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APPENDIX B Drug Diary

See attached

APPENDIX C Abbreviations and definition of terms

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
APF12	Proportion of patients alive and progression free at 12 months from randomization
AST	Aspartate aminotransferase
BoR	Best objective response
BP	Blood pressure
C	Cycle
CD	Cluster of differentiation
CI	Confidence interval
CL	Clearance
C_{max}	Maximum plasma concentration
$C_{max,ss}$	Maximum plasma concentration at steady state
CR	Complete response
CSA	Clinical study agreement
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
CTLA-4	Cytotoxic T–lymphocyte-associated antigen 4
$C_{trough,ss}$	Trough concentration at steady state
CXCL	Chemokine (C-X-C motif) ligand
DoR	Duration of response

Abbreviation or special term	Explanation
EC	Ethics Committee, synonymous to Institutional Review Board and Independent Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDoR	Expected duration of response
EGFR	Epidermal growth factor receptor
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
GMP	Good Manufacturing Practice
hCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
HR	Hazard ratio
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IFN	Interferon
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IHC	Immunohistochemistry
IL	Interleukin
ILS	Interstitial lung disease
IM	Intramuscular
IMT	Immunomodulatory therapy
IP	Investigational product
irAE	Immune-related adverse event
IRB	Institutional Review Board

Abbreviation or special term	Explanation
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
ITT	Intent-to-Treat
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
mAb	Monoclonal antibody
MDSC	Myeloid-derived suppressor cell
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Minister of Health, Labor, and Welfare
miRNA	Micro-ribonucleic acid
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NE	Not evaluable
NSCLC	Non–small-cell lung cancer
OAE	Other significant adverse event
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PDx	Pharmacodynamic(s)
PFS	Progression-free survival
PFS2	Time to second progression
PGx	Pharmacogenetic research
PK	Pharmacokinetic(s)
PR	Partial response
q2w	Every 2 weeks
q3w	Every 3 weeks
q4w	Every 4 weeks
q6w	Every 6 weeks
q8w	Every 8 weeks
QTcF	QT interval corrected for heart rate using Fridericia's formula

Abbreviation or special term	Explanation
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
RNA	Ribonucleic acid
RR	Response rate
RT-QPCR	Reverse transcription quantitative polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety analysis set
SCLC	Small cell lung cancer
SD	Stable disease
SNP	Single nucleotide polymorphism
SoC	Standard of Care
T_3	Triiodothyronine
T_4	Thyroxine
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
US	United States
WBDC	Web-Based Data Capture
WHO	World Health Organization

APPENDIX D. GUIDANCE ON INHIBITORS, INDUCERS, AND SUBSTRATES

Examples of CYP2C9 and CYP3A4 inhibitors, inducers and substrates are provided below. Examples of P-gp and BCRP inhibitors and inducers are provided below. Examples of P-gp and OATP1B1/1B3 substrates are provided below. Additional information can be found at: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers and https://www.drugbank.ca/categories/DBCAT002635 (CYP2C9 inhibitors).

CYP2C9 or CYP3A4 Inhibitors

Patients receiving avutometinib or defactinib are prohibited from concomitant use of medications (with or without prescriptions), supplements, herbal products or foods that are known to be strong inhibitors of CYP3A4. Patients receiving defactinib are also prohibited from concomitant use of agents that are known to be strong inhibitors of CYP2C9.

The table below provides examples of agents known to inhibit CYP2C9 or CYP3A4 activity. Note that this is not a comprehensive list of all agents which may inhibit CYP2C9 or CYP3A4 activity.

Classification of In Vivo Inhibitors of CYP2C9 and CYP3A4

CYP	Strong Inhibitors[a]	Moderate Inhibitors[b]	Weak Inhibitors[c]
CYP2C9	Nicardipine, Gemfibrozil, Floxuridine, Turmeric, Sulphaphenazole, Clotrimazole	Amiodarone, Fluconazole, Miconazole	Disulfiram, Fluvastatin, Fluvoxamine, Voriconazole
CYP3A4	Boceprevir, Clarithromycin, Conivaptan, Grapefruit Juice[d], Indinavir, Itraconazole, Ketoconazole, Lopinavir/Ritonavir, Mibefradil[e], Nefazodone, Nelfinavir, Posaconazole, Ritonavir, Saquinavir, Telaprevir, Telithromycin, Voriconazole	Amprenavir, Aprepitant, Atazanavir, Ciprofloxacin, Darunavir/Ritonavir, Diltiazem, Erythromycin, Fluconazole, Fluvoxamin, Grapefruit Juice[d], Verapamil	Alprazolam, Amiodarone, Amlodipine, Atorvastatin, Cilostazol, Cimetidine, Cyclosporine, Fluoxetine, Fluvoxamine, Ginkgo[f], Goldenseal[f], Isoniazid, Oral Contraceptives, Ranitidine, Ranolazine, Tipranavir/ Ritonavir, Zileuton

Abbreviations: AUC: area under the curve; CL: clearance; CYP: Cytochrome P450;

[a] A strong inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a substrate for that CYP by ≥ 5-fold or > 80% decrease in CL.

[b] A moderate inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by < 5-fold but ≥ 2-fold or 50 to 80% decrease in CL.

[c] A weak inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by < 2-fold but ≥ 5-fold or 20 to 50% decrease in CL.

[d] The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a "strong CYP3A4 inhibitor" when a certain preparation was used (eg, high dose, double strength) or as a "moderate CYP3A4 inhibitor" when another preparation was used (eg, low dose, single strength).

[e] Withdrawn from the US market because of safety reasons.

[f] Herbal product.

CYP2C9 or CYP3A4 Inducers

Patients receiving avutometinib and defactinib are prohibited from concomitant use of medications (with or without prescriptions), supplements, herbal products, or foods that are known to be strong inducers of CYP3A4. Patients receiving defactinib are also prohibited from concomitant use of agents that are known to be strong inducers of CYP2C9.

The table below provides examples of agents known to induce CYP2C9 or CYP3A4 activity. Note that this is not a comprehensive list of all agents which may induce CYP2C9 or CYP3A4 activity.

CYP2C9 or CYP3A4 Inducers

CYP	Strong Inducers ≥ 80% decrease in AUC	Moderate Inducers 50-80% decrease in AUC	Weak Inducers 20-50% decrease in AUC
CYP2C9	-	Rifampin	Aprepitant, Carbamazepine, Ritonavir
CYP3A4	Carbamazepine, Mitotane, Phenytoin, Rifampin, St. John's Wort [a,b]	Bosentan, Efavirenz, Etravirine, Modafinil, Nafcillin	Amprenavir, Aprepitant, Armodafinil, Echinacea [b], Pioglitazone, Prednisone, Rufinamide

Abbreviations: AUC: area under the curve; CYP: cytochrome P450
[a] The effect of St. John's Wort varies widely and is preparation dependent.
[b] Herbal product

CYP2C9 or CYP3A4 Substrates

Substrates of CYP2C9 or CYP3A4 should be used with caution. Co-administration of a CYP3A4 or CYP2C9 substrate with defactinib may increase treatment-related toxicities of these drugs. Known sensitive substrates and moderate sensitive substrates are listed in the table below Consider finding an alternative drug that is not a substrate of CYP2C9 or CYP3A4.

CYP2C9 and CYP3A4 Substrates

CYP	Sensitive Substrates[a]	Moderate Sensitive Substrates[b]
CYP2C9	Celecoxib	Glimepiride, Phenytoin, Tolbutamide, Warfarin
CYP3A4	Alfentanil, Buspirone, Conivaptan, Darifenacin, Darunavir, Ebastine, Lomitapide, Lovastatin, Midazolam, Naloxegol, Nisoldipine, Saquinavir, Simvastatin, Tacrolimus, Tipranavir, Triazolam	Alprazolam, Aprepitant, Atorvastatin, Colchicine, Eliglustat, Pimozide, Rilpivirine, Rivaroxaban

Abbreviations: AUC: area under the curve; CYP: Cytochrome P450; DDI: drug-drug interaction
[a] Sensitive substrates are drugs that demonstrate an increase in AUC of ≥ 5-fold with strong index inhibitors of a given metabolic pathway in clinical DDI studies.
[b] Moderate sensitive substrates are drugs that demonstrate an increase in AUC of ≥ 2 to <5-fold with strong index inhibitors of a given metabolic pathway in clinical DDI studies.

Medications Known to be P-gp Inhibitors or Inducers

Patients receiving avutometinib or defactinib are prohibited from concomitant use of medications (with or without prescriptions), supplements, herbal products, or foods that are known to be strong inhibitors or inducers of P-gp. Known P-gp inhibitors and inducers are listed in the table below. Consider finding an alternative drug that is not an inhibitor and inducer of P-gp.

P-gp Inhibitors and Inducers

P-gp Inhibitors		P-gp Inducers
Amiodarone, Azithromycin (systemic), Carvedilol, Clarithromycin, Cobicistat and cobicistat-containing coformulations, Cyclosporine (systemic), Daclatasvir, Dronedarone, Elagolix, Eliglustat, Erythromycin (systemic), Flibanserin, Fostamatinib, Glecaprevir-pibrentasvir, Itraconazole, Ivacaftor, Ketoconazole (systemic)	Lopinavir-ritonavir, Propafenone, Quinidine, Quinine, Ranolazine, Ritonavir and ritonavir-containing coformulations, Rolapitant, Tacrolimus (systemic), Telaprevir, Ticagrelor, Verapamil	Carbamazepine, Fosphenytoin, Phenobarbital, Phenytoin, Rifampin (rifampicin), St. John's Wort

Abbreviation: P-gp: P-glycoprotein.
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Medications Known to BCRP inhibitors

Patients receiving avutometinib are prohibited from concomitant use of medications (with or without prescriptions), supplements, herbal products, or foods that are known to be strong inhibitors or inducers of BCRP. Known BCRP inhibitors are listed in the table below. Consider finding an alternative drug that is not an inhibitor and inducer of BCRP.

BCRP inhibitors

BCRP Inhibitors
Curcumin, cyclosporine A, darolutamide, eltrombopag, febuxostat, fostamatinib, rolapitant, teriflunomide

Medications known to be P-gp and OATP1B1/1B3 Substrates

Substrates of P-gp and OATP1B1/1B3 should be used with caution. The table below lists substances that are known to be substrates of P-gp and OATP1B1/1B3 and should be used with caution in patients exposed to defactinib.

Note that this is not a comprehensive list of all agents which may be substrates of P-gp and OATP1B1/1B3.

P-gp and OATP1B1/1B3 Substrates

P-gp Substrates	**OATP1B1 and OATP1B3 Substrates**
Digoxin, Dabigatran etexilate, Fexofenadine, Loperamide, Quinidine, Talinolol,	atorvastatin, bosentan, danoprevir, Telmisartan, fexofenadine, glyburide, pitavastatin, pravastatin, repaglinide, rosuvastatin