A Phase 1/2 Trial of Trametinib and Ponatinib in Patients with KRAS Mutant Advanced Non-Small Cell Lung Cancer

PROTOCOL FACE PAGE FOR
MSK THERAPEUTIC/DIAGNOSTIC PROTOCOL

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

One MSK Sites	
Manhattan	All Protocol Activities
Commack	Limited Protocol Activities
Basking Ridge	Limited Protocol Activities
Westchester	Limited Protocol Activities

Nassau	Limited Protocol Activities
Monmouth	Limited Protocol Activities
Bergen	Limited Protocol Activities

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Study Title:	A Phase 1/2 Trial of Trametinib and Ponatinib in Patients with KRAS-Mutant Lung Adenocarcinomas
Study Objectives:	**Phase 1: Dose escalation** Primary Objective: Determine the maximum tolerated dose of Trametinib and Ponatinib in patients with KRAS mutant NSCLC **Phase 2:** Primary Objective: Assess overall response rate (CR+PR) of Trametinib and Ponatinib for patients with KRAS-mutant NSCLC. Secondary Objectives: 1) Measure progression-free survival and overall survival among patients treated with Trametinib and Ponatinib 2) describe the toxicity profile of the combination **Correlative Objectives (to be performed in Phase 2 portion):** 1) Assess for sustained MAPK inhibition by assessment of pERK on pre-treatment and on treatment biopsies 2) Assess for sustained PI3K inhibition by assessment of pAKT on pre-treatment and on treatment biopsies 3) Assess for sustained FGFR by assessment of pFRS2 on pre-treatment and on treatment biopsies 4) Explore role of concurrent genetic alterations identified on routine molecular profiling 5) Evaluate for changes in circulating tumor DNA (ctDNA) during treatment
Patient Population	Patients with locally advanced or metastatic lung adenocarcinomas with a confirmed KRAS mutation who have developed progressive disease during or following treatment with at least one prior line of platinum containing chemotherapy and at least one prior line of PD-1/L1 inhibitor.
Number of Patients	Phase 1: up to 12 patients if only dose levels 1-3 are used Phase 2: a maximum of 25 patients (including 6 patients from Phase I)
Inclusion Criteria	All patients must have: • Histologically or cytologically proven of advanced lung adenocarcinoma • KRAS mutation • Radiographic progression following prior treatment with platinum doublet chemotherapy and prior treatment with a PD-1/L1 inhibitor. Patients who are deemed not eligible for therapy with a PD-1/L1 inhibitor will also be eligible. • Able to take oral medications • Measurable disease as per RECIST 1.1. Previously irradiated sites of tumor may be considered measurable if there is radiographic progression at the site subsequent to the time of completing radiation. • Karnofsky performance status (KPS) ≥ 70% • Age >18 years old

	• Adequate organ function: - AST, ALT ≤ 2.5 x ULN - Total bilirubin ≤ 1.5 x ULN -Albumin≥2.5g/dL - Creatinine < 1.5 x ULN OR calculated creatinine clearance ≥50mL/min - Absolute neutrophil count (ANC) ≥ 1,200 cells/mm^3 - Hemoglobin≥9.0 g/dL - Platelets ≥100,000/mm^3. • A negative serum pregnancy test obtained within two weeks prior to the administration of the experimental agents in all women of child bearing potential
Exclusion Criteria	Patients are to be excluded from the study if they meet any of the following criteria: • Patients with symptomatic brain metastasis requiring escalating doses of steroids • Patients with grade 2 or greater diarrhea prior to study initiation despite maximal medical management • History of acute pancreatitis within 1 year of study entry or history of chronic pancreatitis. • History of or ongoing alcohol abuse that, in the opinion of the Investigator, would compromise compliance or impart excess risks associated with study participation. • Pregnant or lactating women • Any type of systemic therapy (chemotherapy or experimental drugs) within 2 weeks of starting treatment on protocol • Patients who have received prior treatment with MEK inhibitor • A history of clinically significant interstitial lung disease or pneumonitis • Significant uncontrolled or active cardiovascular disease, specifically including, but not restricted to: History of clinically significant (as determined by the treating physician) atrial arrhythmia; or any ventricular arrhythmia, History of congenital long QT syndrome., Abnormal QTc (≥ 450 msec in males and ≥ 470 msec in females), Ejection fraction ≤ 50% as assessed by echocardiogram. • History of arterial thrombotic disease, specifically including, but not restricted to: Myocardial infarction or unstable angina, cerebrovascular event (CVA) or transient ischemic attack (TIA), Peripheral vascular disease or claudication. • Uncontrolled hypertension (Diastolic blood pressure > 100 mmHg; Systolic blood pressure > 150 mmHg). • History of venous thromboembolism (e.g. deep venous thrombosis or pulmonary embolism) within 6 months of study entry. Note: Participants enrolled after this window must be on appropriate therapeutic anticoagulation.

	• History of central serous retinopathy or retinal vein occlusion • Patients with baseline risk factors for central serous retinopathy or retinal vein occlusion such as evidence of new optic disc cupping, evidence of new visual field defects, and intraocular pressure >21 mmHg are excluded from the trial • History of prior malignancy within 2 years that requires treatment. Patients who are considered NED from a malignancy may be considered on a case by case basis. • Any other condition that, in the opinion of the investigator, may compromise the safety, compliance of the patient, or would preclude the patient from successful completion of the study
Study Drug	Trametinib and Ponatinib

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<tr>
<td>Study Design</td>
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Phase 1: Dose Escalation
This study will determine the maximum tolerated dose of Trametinib and Ponatinib.

<table>
<tr><th>Dose levels</th><th>Trametinib Dose</th><th>Ponatinib Dose</th></tr>
<tr><td>Dose level -3</td><td>0.5mg PO q daily</td><td>15mg PO q daily</td></tr>
<tr><td>Dose Level -2</td><td>1.0 mg PO q daily</td><td>15mg PO q daily</td></tr>
<tr><td>Dose Level -1</td><td>1.5mg PO q daily</td><td>15mg PO q daily</td></tr>
<tr><td>Dose Level 1</td><td>2 mg PO q daily</td><td>15mg PO q daily</td></tr>
<tr><td>Dose Level 2</td><td>2 mg PO q daily</td><td>30mg PO q daily</td></tr>
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Phase 2:
Once the phase 1 portion of the study has been completed, patients will be enrolled in the phase 2 portion of the single-arm, two-stage, open-label study of Trametinib and Ponatinib in the treatment of patients with KRAS-mutant lung cancers. After screening and registration, patients will be treated with the combination of Trametinib and Ponatinib. Response to therapy will be assessed by interval imaging every 8 weeks (every 2 cycles) with CT scan of the chest and imaging of any other target lesion with response evaluated by RECIST 1.1. Patients with known brain metastases at the time of screening will also undergo CT/MRI Brain every 8 weeks. A maximum of 25 patients will be enrolled during this portion of the study.

Correlative studies:
Biopsies will be required before beginning treatment, 28 +/- 7 days after initiation of study drug and at the time of progression in patients enrolled in the phase 2 portion. At prespecified time points, patients will have image-guided core needle biopsies with 3-4 cores obtained. At least 2 cores will be immediately frozen in liquid nitrogen with the remaining cores fixed in formalin. IHC will be performed to evaluate expression of specific proteins of interest including: pERK, pFRS2, pAKT. IMPACT, our next-generation sequencing based mutation platform that assesses for genetic alterations in 410 cancer-related genes, will be used for molecular analysis.
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2.1 OBJECTIVES AND SCIENTIFIC AIMS

Phase 1 Trial:

A. Primary Objective: Determine the maximum tolerated dose of the combination of Trametinib and Ponatinib

Phase 2 Trial:

A. Primary Objectives: Assess overall response rate (CR+PR) of Trametinib and Ponatinib patients with KRAS mutant NSCLC.
B. Secondary Objectives: Measure progression free survival and overall survival among patients treated with Trametinib and Ponatinib and define the safety and tolerability of the combination.

Correlative Studies: Only Phase II patients will be included in correlative analysis

1) Assess for sustained MAPK inhibition by assessment of pERK on pre-treatment and on treatment biopsies
2) Assess for sustained PI3K inhibition by assessment of pAKT on pre-treatment and on treatment biopsies
3) Assess for sustained FGFR by assessment of pFRS2 on pre-treatment and on treatment biopsies
4) Explore role of concurrent genetic alterations identified on routine molecular profiling
5) Evaluate for changes in circulating tumor DNA (ctDNA) during treatment

3.0 BACKGROUND AND RATIONALE

Background:

3.1 Oncogene identification in NSCLC

NSCLC is the leading cause of cancer death, causing an estimated 158,000 deaths in the US[1]. Recent major advances include the development of PD-1 checkpoint inhibitors (Nivolumab[2], Pembrolizumab[3], and Atezolizumab[4]) has demonstrated benefit in this patient population, however response rates remain low and despite these advances, median survival for metastatic lung cancer measured in recent trials is only 12 months.

In the past decade, there has been a shift from classifying lung cancer by histology to molecular classification based on presence or absence of oncogenic mutations[5]. The efforts to molecularly classify lung cancer began with the discovery of EGFR (epidermal growth factor receptor) mutations and its therapeutic implications. EGFR tyrosine kinase inhibitors (TKIs) were developed and studied extensively in clinical trials and in EGFR mutant NSCLC induce disease responses superior to cytotoxic chemotherapy. Similarly, other oncogenic drivers have been identified (ALK, ROS1) in small subsets of patients and treatment with targeted therapy has been successful.

3.2 KRAS mutation in NSCLC

Somatic KRAS mutations occur in 20% of patients with metastatic lung adenocarcinomas, the vast majority of mutations occurring at codon 12 or 13. While numerous different point mutations have been described, among individuals with KRAS mutant metastatic lung cancers treated, there are no apparent differences in outcome based on KRAS mutation subtype. Identification of effective therapies for these patients has been elusive. Direct RAS inhibitors are in development, but thus far have limited selectivity for individual genotypes and have not yet entered clinical trials.[6] KRAS encodes a GTPase that couples growth factor signaling to the MAPK cascade. Oncogenic *KRAS* mutations compromise its GTPase activity, leading to accumulation of KRAS in

the active GTP-bound state and thereby to hyperactive signaling that initiates and maintains cancer growth. The MAPK pathway converges at the MEK1/MEK kinases, for which the only known substrates are the ERK1/ERK2 kinases.

3.3 Trametinib

3.3.1 Trametinib in Pre-clinical studies

Trametinib is a reversible, highly selective allosteric inhibitor of MEK1/MEK2 activation and kinase activity, with a half-maximum inhibitory concentration (IC_{50}) of 0·7–0·9 nmol/L. It is currently FDA approved as both a single agent and in combination with dabrafenib for the treatment of BRAF mutant melanoma. In enzymatic and cellular studies, Trametinib inhibited kinase activity of MEK1 and MEK2, prevented RAF-dependent MEK phosphorylation, and prolonged inhibition of phosphorylated ERK (a substrate of MEK). Cell lines and mouse xenograft models with activating mutations in RAS were also sensitive to Trametinib[7]. Pharmacokinetic profiling in mice indicated a mean effective half-life ($t_{1/2}$) of 33 h, with a low peak: trough ratio (around 1·6–2·8) after single or repeat dosing of Trametinib.[8]

3.3.2 Clinically described adverse events with Trametinib

Data reported from the initial phase I[9] and phase II[10] studies of Trametinib indicate skin toxicity was the most common treatment-related adverse event observed 11% had grade 3 events. Diarrhea, the next most common non-hematological adverse event, was predominantly grade 1 (all doses combined and 2 mg a day) and was manageable with standard treatments. Peripheral edema was reported in one third of all patients, with no occurrences higher than grade 2. Treatment-related ocular toxic effects were recorded in 31 (15%) patients, including three events of central serous retinopathy and one of retinal vein occlusion. Cardiovascular toxicity has been reported, most commonly in the form of hypertension (including 8% of patients with grade 3 hypertension), as well as decrease in left-ventricular ejection fraction and left-ventricular dysfunction. Further details regarding clinically described adverse events can be found in the Trametinib package insert[11].

3.3.3 Trametinib in Phase 1 and Phase II trials in NSCLC

A multicenter phase I study conducted in patients with advanced solid tumor malignancies, including lung cancer, explored multiple dosing strategies. Pharmacokinetic data showed that steady state could be achieved without loading doses. The dose of 2mg once daily was chosen as the recommended phase 2 dose based on combined safety, pharmacokinetic, pharmacodynamics, and efficacy data. The objective response rate in an unselected NSCLC patient population in this study was 7%, both in patients with and without KRAS mutations.[9]

In a subsequent randomized open label phase II study, Trametinib was compared to docetaxel as second-line treatment in patients with advanced or metastatic NSCLC harboring a *KRAS* mutation who failed one prior platinum-containing chemotherapy regimen. 129 patients were randomized in the 2:1 fashion. Median PFS was 12 weeks in the Trametinib arm and 11 weeks in the docetaxel arm (hazard ratio [HR] 1.14; 95% CI 0.75–1.75;*P* = 0.5197). There were 10 (12%) partial responses (PRs) in the Trametinib arm and 5 (12%) PRs in the docetaxel arm (*P* = 1.0000).[10]

3.4.1 Ponatinib

Ponatinib (AP24534) is a tyrosine kinase inhibitor recently approved by the FDA for the treatment of chronic myeloid leukemia (CML) and Philadelphia chromosome positive acute lymphoblastic leukemia (ALL). Ponatinib was initially developed as an inhibitor of the BCR-ABL fusion protein, which is formed by a reciprocal translocation involving chromosomes 9 and 22 in hematopoietic stem cells and characterizes approximately 95% of cases of chronic myeloid leukemia. In addition to its inhibitory activity against the BCR-ABL fusion oncoprotein, Ponatinib is a potent inhibitor of a number of tyrosine kinases relevant to the treatment of human malignancies, including FLT3, KIT, VEGFR2, FGFR1, PDGFR and RET (Table 3.4.1). Ponatinib's activity as an FGFR inhibitor has also been validated in multiple FGFR amplified and mutated cancer cell models (endometrial, bladder, gastric, breast, lung and colon).[12]

Table 3.4.1 Ponatinib Kinase Screening Data

Kinase	IC_{50} (nM)
ABL	0.37
ABL^{T315I}	2.00
FLT3	12.6
KIT	12.5
RET	0.16
SRC	5.4
VEGFR2	1.5
FGFR1	2.2
PDGRFα	1.1

3.4.2 Ponatinib in clinical trials

AP24534-07-101 was a phase 1 dose escalation trial to determine the safety, tolerability and maximum tolerated dose (MTD) of Ponatinib in patients with refractory chronic myeloid leukemia (CML) or Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL). Enrollment in the United States was completed at 81 patients as of October 2010. The primary objective of the trial was to determine the MTD of daily oral Ponatinib. Following oral administration, maximum plasma levels of Ponatinib occurred between 4 and 6 hours after dosing. The steady-state terminal elimination half-life ($t_{1/2}$) was 20-28 hours for doses exceeding 15mg. Initial Ponatinib dosing was 2 mg orally once daily, escalating up to 60 mg once daily. At the 45 mg dose level, 1 dose limiting toxicity (DLT) of grade 3 rash was observed. At the 60 mg dose level, 4 patients experienced DLTs of clinical pancreatitis or elevation of pancreatic enzymes. At this dose level, 1 patient also experienced grade 3 fatigue and an additional patient experienced grade 3 elevated AST and ALT. Based upon these findings, the recommended Ponatinib dose for future phase 2 clinical trials was 45 mg once daily.[13]

AP24534-10-201 was conducted as a phase 2 registration trial of Ponatinib in patients with refractory CML and Philadelphia chromosome-positive ALL. 449 heavily pretreated patients who had CML or Ph-positive ALL were enrolled. Ponatinib was administered at an initial dose of 45 mg once daily. The median follow-up was 15 months. Among 267 patients with chronic-phase CML, 56% had a major cytogenetic response, 46% had a complete cytogenetic response, and 34% had a major molecular response.[14]

3.4.3 Clinically described adverse events with Ponatinib

The adverse reactions described in this section were identified in AP24534-10-20, a phase 2 registration trial of Ponatinib with CML or Ph+ ALL whose disease was considered to be resistant or intolerant to prior tyrosine kinase inhibitor (TKI) therapy including those with the BCR-ABL T315I mutation. All patients received a starting dose of 45 mg Ponatinib once daily. Overall, the most common non-hematologic adverse reactions (≥ 20%) were hypertension, rash, abdominal pain, fatigue, headache, dry skin, constipation, arthralgia, nausea, and pyrexia. The rates of treatment-emergent adverse events resulting in discontinuation were 13% in CP-CML, 11% in AP-CML, 15% in BP-CML, and 9% in Ph+ ALL. The most common adverse events that led to treatment discontinuation were thrombocytopenia (4%) and infections (1%). Dose modifications (dose delays or dose reductions) due to adverse reactions occurred in 74% of the patients. The most common adverse reactions (≥5%) that led to dose modifications include thrombocytopenia (30%), neutropenia (13%), lipase increased (12%), rash (11%), abdominal pain (11%), pancreatitis (6%), and ALT, AST, or GGT increased (6%). Complete description of toxicity information can be found in the must updated version of Ponatinib package insert.[15]

Adverse Events of Special Concern

Vascular Occlusion

Arterial and venous thrombosis and occlusions, including fatal myocardial infarction, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease, and the need for urgent revascularization procedures have occurred in at least 27% of Ponatinib-treated patients from the phase 1 and phase 2 trials. Ponatinib can cause fatal and life-threatening vascular occlusion within 2 weeks of starting treatment. Ponatinib can also cause recurrent or multi-site vascular occlusion. In the dose-escalation (phase 1) clinical trial, 49% (32/65) of patients with CML or Ph+ ALL developed vascular occlusive events. The median time to onset of the first vascular occlusion event was 5 months. Ponatinib can cause fatal and life-threatening vascular occlusion in patients treated at dose levels as low as 15 mg per day. Patients with and without cardiovascular risk factors, including patients age 50 years or younger, experienced these events. Vascular occlusion adverse events were more frequent with increasing age and in patients with prior history of ischemia, hypertension, diabetes, or hyperlipidemia.

Arterial Occlusion and Thrombosis

Arterial occlusion and thrombosis occurred in at least 20% (92/449) of Ponatinib-treated patients with some patients experiencing events of more than one type. Patients have required revascularization procedures (cerebrovascular, coronary, and peripheral arterial) due to vascular occlusion from Ponatinib.

Cardiac vascular occlusion, including fatal and life-threatening myocardial infarction and coronary artery occlusion has occurred in 12% (55/449) of Ponatinib-treated patients. Patients have developed heart failure concurrent or subsequent to the myocardial ischemic event. Cerebrovascular occlusion, including fatal stroke, has occurred in 6% (27/449) of Ponatinib-

treated patients. Ponatinib can cause stenosis over multiple segments in major arterial vessels that supply the brain (e.g., carotid, vertebral, middle cerebral artery).

Peripheral arterial occlusive events, including fatal mesenteric artery occlusion and life-threatening peripheral arterial disease, have occurred in 8% (38/449) of Ponatinib-treated patients. Patients have developed digital or distal extremity necrosis and have required amputations. Renal artery stenosis, associated with worsening, labile or treatment-resistant hypertension, has occurred in some Ponatinib-treated patients.

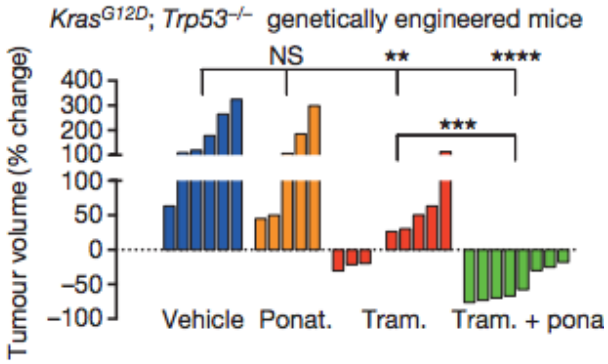
Venous Thromboembolism

Venous thromboembolic events occurred in 5% (23/449) of Ponatinib-treated patients, including deep venous thrombosis (8 patients), pulmonary embolism (6 patients), superficial thrombophlebitis (3 patients), and retinal vein thrombosis (2 patients).

3.6 Rationale for combination of Trametinib and Ponatinib: MEK and FGFR1 inhibition

Recent efforts in the laboratories of Dr. Scott Lowe and Dr. Neal Rosen explored potential resistance mechanisms to MEK inhibition.[16] In KRAS mutant lung cancer cell lines, while Trametinib stably inhibited ERK signaling initially, prolonged exposure resulted in increased ERK signaling, as measured by pERK, suggesting pathway reactivation occurs after prolonged drug exposure. Prolonged exposure to Trametinib also resulted in compensatory activation of the PI3K pathway (assessed by AKT phosphorylation). After demonstrating MEK inhibition alone was not sufficient for sustained MAPK inhibition, a pool-based shRNA screen was performed to identify genes whose inhibition sensitizes KRAS-mutant lung cancer cells to Trametinib. FGFR1 was identified as a top candidate and subsequent work demonstrated that exposure to Trametinib resulted in significant upregulation of FGFR1 expression and increase in phosphorylation of the FGFR adaptor protein FRS2. These findings were confirmed clinically as paired tumor biopsies of 2 patients undergoing treatment with single agent Trametinib demonstrated increase in pFRS2 compared to pre-treatment biopsy.

Figure 1: In vivo effects of MEK/FGFR1 inhibition[11]



Waterfall plot depicting tumor growth in genetically engineered mouse model of *Kras*^{G12D}-induced lung adenocarcinoma treated with Trametinib and Ponatinib (as single agents and in combination).

Knockdown of FGFR1 via shRNAs alone did not impact cell proliferation; synergistic effects were seen when combined with Trametinib. These findings led to the hypothesis that the combination of MEK and FGFR1 inhibition could enhance the activity of MEK inhibitors providing an effective therapeutic strategy for KRAS mutant lung cancers. Suppression of FGFR1 synergized with Trametinib to promote tumor cell death *in vitro* and *in vivo.*

While this effect what seen with multiple FGFR inhibitors, the greatest synergy was observed with Ponatinib, an FDA-approved multi-targeted tyrosine kinase inhibitor that blocks signaling from

FGFR as well as ABL.[17] The combination of Trametinib and Ponatinib blocked the rebound in MAPK and PI3K signaling following Trametinib treatment, as measured by pERK and pAKT respectively. Combination therapy resulted in marked tumor regression in multiple *in vivo* models including KRAS-mutant patient derived xenografts and a genetically engineered mouse model of KRAS-mutant lung cancer (Figure 1).[16] Sensitivity to the combination was precisely predicted by FRS2 phosphorylation, confirming its status as a measurable marker of FGFR activation.

3.7 Benefit and Desired Outcome:

While great strides have been made in identifying molecular drivers of NSCLC leading to the development of targeted therapies (EGFR, ROS1, ALK), strategies to combat KRAS driven tumors have been largely ineffective. Overcoming resistance to MEK inhibition with Trametinib through the addition of the FGFR inhibitor Ponatinib is an innovative approach to achieve sustained MAPK pathway inhibition. Tolerability and preliminary evidence of efficacy in this phase 1/2 study would justify further evaluation of the combination, potentially changing our fundamental approach towards treating KRAS mutant NSCLC

4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.2 Design

This phase 1/2 study is a single arm, open label, single institution study of Trametinib and Ponatinib in patients with KRAS mutant NSCLC

Planned accrual:

Phase 1: up to 12 patients (if only dose level 1-2 are used)

Phase 2: up to 25 patients (including up 6 patients from Phase 1 portion)

4.3 Intervention

Phase 1

The phase 1 portion will be open to patients with KRAS mutant advanced stage NSCLC who have progressed following treatment with at least one line of platinum-doublet chemotherapy and at least one line of immunotherapy (PD-1 inhibitor). The study will follow a standard 3+3 dose escalation. All patients within a cohort will be observed for toxicity for 4 weeks, prior to enrollment at the next dose level. We predict three dose levels (33% and 67%of the MTD) of Ponatinib will be required. Given concerns of vascular events with escalating doses of Ponatinib, the MTD of Ponatinib (45mg) will not be explored.

The FDA approved dose of Trametinib that has been evaluated in patients with NSCLC is 2mg daily and will be used in a continuous fashion. The FDA approved dose of Ponatinib is 45mg daily, and the dose will be 15mg or 30mg, depending on the dose level. If dose de-escalation is needed, the dose of Ponatinib will remain at 15mg daily and the dose of Trametinib will be decreased to 1.5mg, 1.0mg, and 0.5mg daily according to the dose level. By trial design, a maximum of 18 patients will be required to complete the phase I portion if only dose levels 1-3 are used. Patients who discontinue treatment before completing 21 of 28 days of therapy for reasons other than development of a DLT (progression of disease or withdrawal of consent) will be

replaced. Toxicity will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0. At the end of the phase 1 portion, a total of 6 patients will have been treated at the MTD and will be counted towards accrual to the phase 2 portion. Patients will continue to receive treatment until intolerable toxicity or progression of disease. All patients who receive at least one dose of treatment with Trametinib and Ponatinib will be evaluable for toxicity. Patients must receive at least 21 days of therapy to be considered evaluable for response.

Phase 2

Once the phase 1 portion of the study has been completed, patients will be enrolled in the phase 2 portion of the single-arm, two-stage, open-label study of Trametinib and Ponatinib in the treatment of patients with KRAS-mutant lung cancers**.** After screening and registration, patients will be treated with the combination of Trametinib and Ponatinib. Response to therapy will be assessed by interval imaging every 8 weeks (every 2 cycles) with CT scan of the chest and imaging of any other target lesion with response evaluated by RECIST 1.1. Best overall response rate is the primary endpoint of the study. Patients remaining on trial will be followed for 6 months to determine best overall response rate and patients must receive at least 21 days of therapy to be considered evaluable for response. Following completion of the first stage, investigators will halt accrual until the first stage decision rule has been determined. A maximum of 25 patients will be enrolled in the phase 2 study. Dosing for the phase 2 portion of the study will depend on the results from MTD established in the Phase I portion of the study. Patients will continue to receive treatment until intolerable toxicity or progression of disease.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1 **Trametinib**

Drug: Trametinib (GSK 1120212)

Classification: MEK inhibitor

Chemical Name: Acetamide, *N*-(3-{3-Cyclopropyl-5-[(2-fluoro-4-iodophenyl)amino]-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydropyrido[4,3-d]pyrimidin-1(2*H*)-yl}phenyl)-dimethylsulfoxide

Description: Trametinib dimethyl sulfoxide is a white to almost white powder

Trametinib Tablets: Trametinib will be supplied at 0.5 mg and 1mg (as free base) tablets. 0.5mg tablets are white or yellow, modified oval, biconvex and film-coated.

Schedule, route of administration, and dosing: Subjects will receive Trametinib at the prescribed dose by mouth once daily. In all subjects dose reductions and delays to manage toxicity are allowed under the guidelines in Section 11. Take by mouth on an empty stomach, either one hour before or two hours after a meal.

Compliance: Drug accountability and subject compliance will be assessed with drug dispensing and return records

Study Drug Accountability: The investigator will maintain accurate records of receipt of all Trametinib, including dates of receipt. In addition, accurate records will be kept regarding when and how much study treatment is dispensed and used by each subject in the study. Reasons for deviation from the expected dispensing regimen will be recorded. At completion of the study, all unused Trametinib will be reconciled and destroyed in accordance with applicable state and federal regulations.

Additional information regarding Trametinib can be found in the Trametinib® Package Insert.

5.2**Ponatinib**

Drug: Ponatinib

Classification: kinase inhibitor

Chemical Name: 3-(imidazo[1,2-b]pyridazin-3- ylethynyl)-4-methyl-N-{4-[(4-methylpiperazin-1-yl)methyl]-3-(trifluoromethyl)phenyl}benzamide hydrochloride

Description: Ponatinib hydrochloride off-white to yellow powder

Ponatinib Tablets: Ponatinib will be supplied at 15 mg (as free base) tablets.

Schedule, route of administration, and dosing: Subjects will receive dose of Ponatinib according to dose level as outlined section 4.2. In all subjects dose reductions and delays to manage toxicity are allowed under the guidelines in Section 11. Take by mouth on an empty stomach, either one hour before or two hours after a meal.

Compliance: Drug accountability and subject compliance will be assessed with drug dispensing and return records

Study Drug Accountability: The investigator will maintain accurate records of receipt of all Trametinib, including dates of receipt. In addition, accurate records will be kept regarding when and how much study treatment is dispensed and used by each subject in the study. Reasons for deviation from the expected dispensing regimen will be recorded. At completion of the study, all unused Ponatinib will be reconciled and destroyed in accordance with applicable state and federal regulations.

Additional information regarding Ponatinib can be found in the Ponatinib® Package Insert.

6.1 CRITERIA FOR SUBJECT ELIGIBILITY.

6.2 Subject Inclusion Criteria

- Histologically or cytologically proven diagnosis of advanced lung adenocarcinoma
- KRAS mutation
- Radiographic progression following prior treatment with platinum doublet chemotherapy and prior treatment with a PD-1 inhibitor. Patients who are deemed not eligible for therapy with a PD-1 inhibitor by their treating physician will also be eligible.
- Able to take oral medications

- Measurable disease as per RECIST 1.1. Previously irradiated sites of tumor may be considered measurable if there is radiographic progression at the site subsequent to the time of completing radiation.
- Karnofsky performance status (KPS) ≥ 70%
- Age >18 years old
- Adequate organ function:
    - AST, ALT ≤ 2.5 x ULN - Total bilirubin ≤ 1.5 x ULN -Albumin≥2.5g/dL
    - Creatinine < 1.5 x ULN OR calculated creatinine clearance ≥50mL/min
    - Absolute neutrophil count (ANC) ≥ 1,200 cells/mm^3
    - Hemoglobin≥9.0 g/dL
    - Platelets ≥100,000/mm^3.
    - Amylase and lipase within normal limits (amylase ≤100, lipase ≤78)

- Female patients who:
    - Are postmenopausal for at least 1 year before the screening visit, OR
    - Are surgically sterile, OR
    - If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent through 30 days after the last dose of study drug, or agree to completely abstain from heterosexual intercourse
- Male patients, even if surgically sterilized (i.e., status post-vasectomy), who:
    - Agree to practice effective barrier contraception during the entire study treatment period and through 30 days after the last dose of study drug, or
    - Agree to completely abstain from heterosexual intercourse

6.3 Subject Exclusion Criteria

Patients are to be excluded from the study if they meet any of the following criteria:

- Patients with symptomatic brain metastasis requiring escalating doses of steroids
- Patients with grade 2 or greater diarrhea prior to study initiation despite maximal medical management
- History of acute pancreatitis within 1 year of study entry or history of chronic pancreatitis.
- History of or ongoing alcohol abuse that, in the opinion of the Investigator, would compromise compliance or impart excess risks associated with study participation.
- Pregnant or lactating women
- Any type of systemic therapy (chemotherapy or experimental drugs) within 2 weeks of starting treatment on protocol
- Patients who have received prior treatment with MEK inhibitor
- A history of clinically significant interstitial lung disease or pneumonitis
- Significant uncontrolled or active cardiovascular disease, specifically including, but not restricted to: History of clinically significant (as determined by the treating physician) atrial arrhythmia; or any ventricular arrhythmia, History of congenital long QT syndrome., Abnormal QTc (≥ 450 msec in males and ≥ 470 msec in females), Ejection fraction ≤ 50% as assessed by echocardiogram.

- History of arterial thrombotic disease, specifically including, but not restricted to: Myocardial infarction or unstable angina, cerebrovascular event (CVA) or transient ischemic attack (TIA), Peripheral vascular disease or claudication.
- Uncontrolled hypertension (Diastolic blood pressure > 100 mmHg; Systolic blood pressure > 150 mmHg).
- History of venous thromboembolism (e.g. deep venous thrombosis or pulmonary embolism) within 6 months of study entry. Note: Participants enrolled after this window must be on appropriate therapeutic anticoagulation.
- History of central serous retinopathy or retinal vein occlusion
- Patients with baseline risk factors for central serous retinopathy or retinal vein occlusion such as evidence of new optic disc cupping, evidence of new visual field defects, and intraocular pressure >21 mmHg are excluded from the trial
- History of prior malignancy within 2 years that requires treatment. Patients who are considered NED from a malignancy may be considered on a case by case basis.
- Any other condition that, in the opinion of the investigator, may compromise the safety, compliance of the patient, or would preclude the patient from successful completion of the study

7.0 RECRUITMENT PLAN

A member of the patient's treatment team, the protocol investigator, or research team at the Memorial Sloan Kettering Cancer Center will identify poential research participants. If the investigator is part of the treatment team s/he will screen the patient as to eligibility and will discuss the study and possibility of enrollment in the research study with the patient. The preliminary screen of eligibility will be confirmation of the diagnosis of NSCLC, ascertaining the exact stage of the disease and confirmation of the presence of a KRAS mutation. Potential subjects that meet these basic criteria will be referred by their treating physician to the investigator/research staff of the study.

Minorities and women are well represented in the thoracic oncology clinics and we expect that they will be well represented in the trial accrual. The principal investigator, Kathryn Arbour, will be available to all patients for further questions and information through a contact number which will be provided on the consent form itself.

Additional participants may be identified by several institutional databases. The IMPACT project tests all consented patients for mutations in 410 genes including the KRAS mutation. The protocol is in place to identify all patients with a targetable mutation and to guide them to appropriate clinical trials. Patient identified in this manner will be approached about possible participation in this clinical trial.

During the initial conversation between the investigator/research staff and the patients, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records at MSKCC in order to assess eligibility. They will use the information provided by the patient and/or medical records to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patients during the initial conversation

and medical records review, except for any information that must be maintained for screening log purposes.

8.1 PRETREATMENT EVALUATION

Study eligibility is based on meeting all of the study inclusion criteria and none of the exclusion criteria at screening. The following assessments will be conducted prior to subjects receiving their first dose of Trametinib and Ponatinib on this protocol. All aspects of the screening evaluation (with the exception of radiologic tumor assessments) should be completed within 2 weeks of starting treatment:

- Documented presence of a KRAS mutation
- Full medical history and physical examination
- Baseline tumor assessment: of the CT scan of the chest (and other additional studies based on the patient's known sites of disease).
- Complete vital signs (pulse, blood pressure, temperature, respiratory rate) as well as weight
- 12 lead electrocardiogram (ECG) and echocardiogram within 1 month of study initiation
- Serum pregnancy test for women of child bearing potential
- Complete blood count with differential
- Comprehensive metabolic panel (glucose, blood urea nitrogen, creatinine, sodium, potassium, chloride, bicarbonate, calcium, total protein, albumin, serum bilirubin, alkaline phosphatase, ALT, AST)
- Pancreatic enzymes (amylase, lipase)
- Ophthalmology Exam (See Section 10 for more details)
- Biopsy for baseline tumor tissue (required only for patients in the Phase II portion of the study)

9.0 TREATMENT/INTERVENTION PLAN

9.1.1 Therapeutic Agent-Trametinib

Trametinib is given once daily and should be taken by mouth on an empty stomach, either one hour before or two hours after a meal, at approximately the same time of the day each day

A pill diary will be used to record adherence.

9.1.2 Therapeutic Agent-Ponatinib

Ponatinib is given once daily and should be taken by mouth on an empty stomach, either one hour before or two hours after a meal at approximately the same time of the day each day. A pill diary will be used to record adherence.

9.2 Treatment Arms

All patients will receive Trametinib and Ponatinib in this single-arm study.

9.3 Study design

Table 9.3.1: Cohort dose levels for Trametinib and Ponatinib

Dose levels	Trametinib Dose	Ponatinib Dose

Dose level -3	0.5mg PO q daily	15mg PO q daily
Dose Level -2	1.0 mg PO q daily	15mg PO q daily
Dose Level -1	1.5mg PO q daily	15mg PO q daily
Dose Level 1	2 mg PO q daily	15mg PO q daily
Dose Level 2	2 mg PO q daily	30mg PO q daily

Phase 1: The phase I portion will accrue cohorts of 3-6 patients (maximum enrollment: 18 patients if no de-escalation). Patients will receive Trametinib once daily and Ponatinib once daily as defined by dose level outline in table 9.3.1. Three patients will be enrolled per dose level. Each group of patients enrolled at the same dose level comprises a cohort. Patients in each cohort must complete at 4 weeks of study therapy (28 days) prior to enrollment of the next cohort. Patients will be monitored for toxicity weekly for the first cycle (4 weeks per cycle) and on week 1 of each cycle thereafter. Dose-limited toxicities are described in section 9.4 below. Patients will be monitored for response by CT every 2 cycles (8 weeks). The schedule of evaluations and interventions is described in section 10.0. Patients who do not complete at least 21 out of 28 days of treatment for reasons other than developing a DLT (e.g. withdrawal of consent or progression of disease), will be replaced. Patients will continue to receive treatment until intolerable toxicity or progression of disease.

Phase 2: All patients will receive Trametinib and Ponatinib at the MTD defined during the phase 1 portion of the study. Patients will be monitored for response by CT every 2 cycles (8 weeks). The schedule of evaluations and interventions is described in Section 10.0. Patients will continue to receive treatment until intolerable toxicity or progression of disease.

9.4 **Dose Limiting Toxicities:**

The NCI Common Terminology Criteria for Adverse Events Version 4.0 (NCI CTCAE) will be used to grade toxicities during the trial. Dose limiting toxicities (DLTs) are defined as any of the following events occurring during the first cycle of treatment (i.e. 4 weeks) that are, in the opinion of the treatment physician, possibly, probably, or definitely related to the investigational regimen:

- Death related to the investigational regimen
- Any toxicities for which the dose modification tables (in section 11) recommends discontinuation or dose reduction of Trametinib or Ponatinib
- Hematologic toxicities including:
  - Grade=4 neutropenia lasting >5 days
  - Grade=4 thrombocytopenia (<25,000/mm3)
  - Grade= 3 thrombocytopenia with evidence of clinically significant bleeding
  - Grade=4 anemia
- Non-hematologic toxicities include:
  - Grade ≥ 3 AST, ALT, alkaline phosphatase, total bilirubin, amylase, or lipase
  - Grade 3 diarrhea, nausea, vomiting that lasts >72 hours despite optimal maximum supportive care
  - Grade 4 diarrhea, nausea, vomiting

- Any other non-hematologic grade ≥3 major organ toxicity not described in section 11, specifically renal toxicity
- Central serous retinopathy or retinal vein occlusion
- Arterial or venous thrombotic event

Patients in each cohort must complete the first four weeks of study therapy prior to enrollment of subsequent cohorts as outlined in Table 9.4.1.The MTD will be defined at the highest dose where not more than 1 of the 6 patients develops a DLT. Dose levels are outlined in Table 9.3.1 above

Table 9.4.1: Dose Escalation Schema

# of patients with DLT at a given dose level	Escalation decision rule
0 of 3	Enter the next cohort (3 patients) at the next dose level
1 of 3	Enter next cohort (3 patients) at the same dose level • If 0 of 3 experience DLT, proceed to the next dose level • If 1 or more experience DLT, dose escalation stopped. 3 additional patients will be entered at the next lowest dose level is only 3 patients were treated previously at that dose level
≥ 2 of 3	Dose escalation stopped. 3 additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose level
≤ 1 of 6 at the highest dose level	Recommended phase II dose. 6 patients must be entered at the recommended phase II dose prior to proceeding to the phase II study

9.5 **Supportive Care**

Palliative and supportive care for disease related symptoms may be administered at the investigator's discretion and according to available American Society of Clinical Oncology (ASCO) guidelines. All concomitant medications and blood products, as well as interventions (thoracentesis, paracentesis, etc) will be recorded in the patient's medical records.

9.6 **Correlative Studies:** Biopsies will be required prior to start of study treatment, 28 +/- 7 days after initiation of study drug and at the time of progression for patients participating in the Phase II portion of the trial. This biopsy is mandatory unless there is a safety reason not to perform. For example, if due to the location of the tumor, the biopsy is high risk as decided by treating physician. At prespecified time points, patients will have image-guided core needle biopsies with 3-4 cores obtained. Blood will also be used to obtain germline DNA for next-generation sequencing based testing if not obtained previously. One fixed core will be used for immunohistochemistry to determine protein expression for transcripts of interest, including: pERK, pFRS2 and pAKT.

Plasma will be collected during pretreatment evaluation and at the time of each radiographic assessment for ctDNA analysis (for Phase I and Phase II patients).

1) Samples should be sent same day, ambient with overnight delivery via FedEx to:
   a. Translational Research Laboratory
      Dana-Farber Cancer Institute
      Attn. Bryan Ulrich (e-mail: Bryan_Ulrich@DFCI.HARVARD.EDU)
      360 Longwood Ave. / LC4202
      Boston, MA 02215

2) Samples can be shipped Monday through Thursday, but not on Fridays, weekends and holidays. Samples can be kept at room temperature, onsite, until Dana-Farber Cancer Institute can receive the samples for processing (i.e. Friday blood draws should be shipped Monday).

Samples are to be de-identified, labeled without PHI identifiers, and shipped with requisition form, cooling gel packs in Styrofoam container and cardboard shipping box with appropriate absorbent materials and dangerous goods warning label.

10.1 EVALUATION DURING TREATMENT/INTERVENTION

Table 10.1 outlines the schedule of assessments. If the subject is unable to have a study assessment taken within the defined time window due to an event outside of his or her control (e.g. clinic closure, personal emergency, inclement weather, vacation) the assessment should be performed as close as possible to the required schedule. Subjects will return to the study site within 30 days after their last dose of Trametinib and Ponatinib to complete end of study assessments outlined below. Additional follow up will occur for subjects with AEs related to study treatment that are ongoing at the time of this visit and for subjects with SAEs related to study treatment that occur after the time of this visit.

Table 10.1 Study Calendar

1 cycle=28 days	Screening	Cycle 1			Cycle 2	Cycle 3+	At progression/ Off Study
	Within 2 weeks unless otherwise noted	C1D1	C1D8	C1D15	C2D1	Day 1	
Informed Consent[11]	X						
Medical History	X	X	X	X	X	X	X
Concurrent Medication Reconciliation	X	X	X	X	X	X	X
Physical Exam[1]	X	X	X	X	X	X	X

Ophthalmology Exam[2]	X				X		
Complete Blood Count w/ differential[1]	X	X		X	X	X	X
Serum Chemistries [1,3]	X	X		X	X	X	X
Pancreatic Enzymes[4]	X	X		X	X	X	X
12 lead EKG[5]	X				X	X	
Echocardiogram[6]	X				X[6]		
Adverse Events Evaluation[1]	X	X	X	X	X	X	X
Radiologic Tumor Assessments[7]	X					X	X
B-HCG[8]	X						
Tumor Tissue[9]	X				X		X
Research blood for		X				X	X

1. Study Assessments (physical exams, vitals, weight, CBC, CMP, adverse events evaluation) will be repeated C1D1, C1D15 (first cycle), then monthly subsequently. C1 assessments have a window of +/- 3 days; C2 onward assessments have a window of +/- 2 weeks. In addition, on C1D8, patients will have study assessments including physical exam, adverse event evaluation.
2. Baseline Opthalmic exam will include visual acuity, visual field examination, tonometry, slit lamp biomicroscopyof the anterior segment (with special attention to inflammation) and the posterior segment, and indirect funduscopic examination with special attention to possible retinal abnormalities. Exams are required at screening, cycle 2 day 1 +/- 2 week, and cycle 6 day 1 +/- 4 weeks. Additional ophthalmic exams will be performed if symptomaticallywarranted.
3. Serum chemistries includes glucose, blood urea nitrogen, creatinine, sodium, potassium, chloride, bicarbonate, calcium, phosphorus, total protein, albumin, serum bilirubin, alkaline phosphatase, ALT, AST4. Pancreatic enzyme analysis includes amylase and lipase
5. A single 12 lead ECG should be performed at screening and day 1 of every cycle +/- 2 weeks.
6. Echocardiogram should be performed at screening, after 4 weeks, and every 12 weeks thereafter (+/- 2 weeks)
7. Response to therapywill be assessed byinterval imaging studies every 2 cycles (8 weeks) +/- 2 weeks with response evaluated using RECIST version 1.1. Radiologic imaging will include a CT chest +/- abdomen/pelvis depending on sites of disease with or without contrast and CT/MRI brain (if screening CT/MRI brain identified brain metastases). Screening radiologic tumor assessments are required within 4 weeks of start of treatment. If an appropriate imaging studyis performed earlyfor any reason (i.e. hospitalization), it can be used for disease assessment. CT scans should be completed if the patient comes off study for any reason other than progression. If a CT scan was completed within the last 8 weeks, it will not need to be repeated.8. B-HCG testing (serum or urine) should be performed onlyin women of child bearing potential. Follow up of elevated B-HCG will be determined in accordance to MSKCC policy.
9. Tumor biopsywill be performed within 1 month of treatment initiation, at day 28+/-7 days after initiation of study drugs, and at time of progression +/- 4 weeks for patients in the Phase II portion of the study.
10. Blood for plasma ctDNAtesting to be collected before treatment on Cycle 1 Day 1 and every 8 weeks thereafter. One 10mL Streck tube of blood will be drawn with each blood draw.
11. Informed Consent can be obtained up to 28 days prior to Screening.

After completion of the study drug, the patients will be followed for overall survival data. This data will be obtained by review of the MSKCC electronic medical record.

11.0 TOXICITIES/SIDE EFFECTS

Toxicity grading will be performed in accordance with NCI CTCAE version 4.0. If toxicities are encountered, dosing adjustments will be made based on the likely causative agent as outlined below. If toxicities continue despite dose reductions and it is clear by the nature of the side effect

which is the causative agent, the treating physician may choose to discontinue the causative agent and may continue the patient on the other drug as monotherapy. During cycle 1 of phase 1 portion, doses of drugs will not be dose reduced unless a DLT has been declared.

11.1 Management of Trametinib related toxicities:

Toxicities with Trametinib that are likely (>20%) include:

- Fatigue
- Rash
- Diarrhea
- Nausea/Vomiting
- Leg or arm swelling
- Constipation
- Decreased appetite
- Decreased red block cell count leading to fatigue

Toxicities with Trametinib that are less likely (<20%) include:

- dehydration
- Cough
- Shortness of breath
- Itching
- Abdominal pain
- Dry skin
- Fever/chills
- Dizziness
- Pain in the bones
- Difficulty sleeping
- Dry mouth
- Headache
- Increases in blood pressure
- Loss of hair
- Headaches
- Blurry vision
- Changes or infection in fingernails

Side effects of Trametinib that are rare, but serious include:

- Changes in the eye that can cause blindness or serious vision problems (Chorioretinopathy or central serous retinopathy (CSR), retinal vein occlusion (RVO), Retinal Detachment)
- Impaired heart function (decreased in cardiac ejection fraction)
- Liver failure or abnormalities in the liver function blood tests
- Pneumonitis
- Infections in the lung or urinary tract

Trametinib Dose Modifications

The tables below outline the dose levels to be used for any necessary Trametinib dose modification:

Dose Reduction	Trametinib Dose/Schedule
-1	1.5mg QD
-2	1mg QD

-3	0.5mg QD

A maximum of two Trametinib dose level reductions are allowed. If a third dose level reduction is required, treatment will be permanently discontinued. If dose reduction beyond dose level -3 is required (0.5mg), treatment will be permanently discontinued.

Trametinib Dose Modification for Toxicities Not Specified in Subsequent Sections

Trametinib Treatment Modification for Clinically Significant Toxicities Deemed Related to Trametinib (This section is not for specific AEs such as rash, pneumonitis, diarrhea, liver chemistry, QTc prolongation, or visual changes. Refer to other sections for these specific AEs).		
CTCAE v4 Grade	**Dose Modification**	**Management Guideline**
Grade 1	Continue Trametinib at current dose level.	Monitor as clinically indicated. Provide supportive care according to institutional standards
Grade 2	• Consider interrupting treatment until resolution to grade 1 or baseline. • Upon resolution, restart treatment at current dose level.	
Grade 3	• Interrupt Trametinib if clinically indicated • When toxicity resolves to Grade 1 or baseline, restart Trametinib **reduced by one dose level**. • If the Grade 3 toxicity recurs, interrupt Trametinib; When toxicity resolves to grade ≤1, restart Trametinib **reduced by another dose level**	
Grade 4	• Interrupt treatment until resolution to grade ≤1 Upon resolution to grade ≤1, restart with one level of dose reduction. • It toxicity does not resolve to ≤1 or baseline, permanently discontinue Trametinib.	
Trametinib should be discontinued if treatment delay is ≥28 days due to toxicities. If the investigator concludes that continued Trametinib will benefit a patient, the study PI may be consulted for the possibility of resuming Trametinib, provided that toxicities have resolved to grade ≤1.		

11.2 Management of Ponatinib related toxicities:

Toxicities with Ponatinib that are likely (>20%) include:

- Low blood counts including white blood cells, red blood cells, and platelets
- Increased serum lipase
- Increase in liver enzymes (AST and/or ALT)
- Abdominal pain
- Nausea
- Vomiting
- Constipation
- Diarrhea
- Decreased appetite
- Fever
- Fatigue
- Weakness
- Pain

- Headache
- Dry skin
- Skin rash
- High blood pressure
- Shortness of breath
- Fluid retention
- Pain that may occur in the joints, muscles, bone, back, or limbs

Toxicities with Ponatinib that are less likely (<20%) include:

- Pancreatitis
- Stroke
- Heart attack
- Irregular heart rhythm including atrial fibrillation, supraventricular tachycardia, or bradycardia
- Impaired heart function (decreased in cardiac ejection fraction)
- Increase in bilirubin
- Hyperglycemia
- Hyperuricemia
- Electrolyte disturbances including hyponatremia, hypokalemia, hypophosphatemia, hypocalcemia and/or hypophosphatemia
- Heartburn, indigestion, or upset stomach
- Mucositis
- Bloating
- Weight loss
- Muscle cramps and pain
- Dizziness
- Cough
- Upper respiratory infection
- Pneumonia
- Sepsis
- Febrile neutropenia
- Cranial or peripheral neuropathy
- Peripheral vascular disease
- Insomnia
- Voice impairment such as hoarseness

Side effects of Ponatinib that are rare, but serious include:

- Venous thromboembolic events (DVT, PE)
- Liver failure or abnormalities in the liver function blood tests
- Changes in the eye that can cause blindness or serious vision problems (including macular edema, retinal vein occlusion, and retinal hemorrhage)
- Bleeding events
- Pleural effusion
- Pericardial effusion

Ponatinib Dose Modifications

The tables below outlines the dose levels to be used for any necessary Ponatinib dose modification:

Dose Reduction	Trametinib Dose/Schedule

-1	15mg QD

A maximum of one Ponatinib dose level reductions are allowed. If a third dose level reduction is required, treatment will be permanently discontinued. If dose reduction beyond dose level -1 is required (15mg), treatment will be permanently discontinued.

Ponatinib Dose Modification for Toxicities Not Specified in Subsequent Sections

Ponatinib Treatment Modification for Clinically Significant Toxicities Deemed Related to Ponatinib (This section is not for specific AEs such as liver chemistry, pancreatitis, and hematologic toxicity. Refer to other sections for these specific AEs).		
CTCAE v4 Grade	**Dose Modification**	**Management Guideline**
Grade 1	Continue Ponatinib at current dose level.	Monitor as clinically indicated. Provide supportive care according to institutional standards
Grade 2	• Consider interrupting treatment until resolution to grade 1 or baseline. • Upon resolution, restart treatment at current dose level.	
Grade 3	• Interrupt Ponatinib if clinically indicated • When toxicity resolves to Grade 1 or baseline, restart Ponatinib **reduced by one dose level** (15mg) • If the Grade 3 toxicity recurs, interrupt Ponatinib; When toxicity resolves to grade ≤1, restart Trametinib **reduced by another dose level**	
Grade 4	• Interrupt treatment until resolution to grade ≤1 Upon resolution to grade ≤1, restart with one level of dose reduction. • It toxicity does not resolve to ≤1 or baseline, permanently discontinue Ponatinib	
Ponatinib should be discontinued if treatment delay is ≥28 days due to toxicities. If the investigator concludes that continued Ponatinib will benefit a patient, the study PI may be consulted for the possibility of resuming Ponatinib, provided that toxicities have resolved to grade ≤1.		

11.3 Specific Dose Modifications:

11.3.1 Rash

Rash is a frequent AE observed in patients receiving Trametinib (package insert). Recommendations for supportive care and guidelines for dose modifications for rash are based on experience with other MEK inhibitors[18,19]. Patients should be informed that skin toxicity is likely during treatment with Trametinib. Skin toxicity can take the form of dry skin, rash, acneiform eruption, and hair/nail changes. Prophylactic treatment of the skin for Phase I participants with the recommendations below may prevent or reduce skin toxicity. Participants enrolled into the Phase II portion of the study will be required to follow the guidelines below for supportive care of rash.

Patients with significant skin toxicity will be referred to dermatology for management. Any treatment provided must be documented in the participants medical record. For more severe cases, oral corticosteroids may be administered. Patients who fail to respond to these measures may have Trametinib interrupted, dose reduced, or discontinued.

Guidelines for Supportive Care of Rash	
Type of Care	**Recommendations**
Prevention/Prophylaxis[a]	• Avoid unnecessary exposure to sunlight. • Apply broad-spectrum sunscreen (containing titanium dioxide or zinc oxide) with a skin protection factor (SPF) ≥15 at least twice daily. • Use thick, alcohol-free emollient cream (*e.g.*, glycerine and cetomacrogol cream) on dry areas of the body at least twice daily. • Topical steroids and antibiotics should be applied at least twice daily, starting on Day 1 of study treatment, to affected body areas such as face, chest, and upper back.
Symptomatic Care[b]	• 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 systemic or topical antibiotics.
[a] Rash prophylaxis is recommended for the first 6 weeks of study treatment. [b] Patients who develop rash/skin toxicities should be seen by a qualified dermatologist and should receive evaluation for symptomatic/supportive care management.	

Trametinib Dose Modification Guidelines and Management for Rash		
Rash Severity	**Management Guideline**	**Dose Modification**
Grade 1	• Initiate prophylactic and symptomatic treatment measures.[1]	Continue Trametinib at same dose level.
Grade 2	Initiate prophylactic and symptomatic treatment measures.[1]	Continue at same dose level. If rash persists or worsens over 14 days consider dose reduction of Trametinib by one dose level at discretion of investigator.
Grade 3		Suggest withholding Trametinib until toxicity is grade ≤2. If rash persists or worsens over 14 days, consider dose reduction at discretion of investigator.[2]
Grade 4		Withhold Trametinib until toxicity is grade ≤2. Restart with Trametinib reduced by one dose level.[2] If No recovery to ≤ grade 2 within 4 weeks, permanently discontinue Trametinib
1. Rash prophylaxis is recommended for the first 6 weeks of study treatment. See above table. 2. Trametinib may be escalated to previous dose level if no rash is evident 4 weeks after restarting study treatment.		

11.3.2 **Diarrhea**

Episodes of diarrhea have occurred in patients receiving Trametinib and Ponatinib, though less commonly (package insert). Other frequent causes of diarrhea may include concomitant medications (*e.g.*, stool softeners, laxatives, antacids, *etc.*), infections by *C. difficile* or other pathogens, or partial bowel obstruction. Those conditions should be excluded, as clinically indicated.

Guidelines regarding management and dose modification for diarrhea considered related to Trametinib and/or Ponatinib are provided in the table below.

Management and Trametinib Dose Modification Guidelines for Diarrhea		
CTCAE Grade	**Adverse Event Management**	**Action and Dose Modification**
Grade 1 or 2	• Diet: Stop all lactose containing products; eat small meals, BRAT-diet (bananas, rice, apples, toast) recommended. • Hydration: 8-10 large glasses of clear liquids per day (*e.g.*, Gatorade or broth). • Loperamide[1]: Initially 4 mg, followed by 2 mg every 4 hours or after every unformed stool; maximum 16 mg/day. Continue until diarrhea-free for 12 hours. • Lomotil[1]: 2.5-5mg of diphenoxylate up to 4x a day; maximum 20mg/daily. Continue until diarrhea-free for 12 hours. • Diarrhea >24 hours: Loperamide 2 mg every 2 hours; maximum 16 mg/day. Consider adding oral antibiotics.	• Continue Trametinib and/or Ponatinib at same dose. Initiate adverse event management

Management and Trametinib Dose Modification Guidelines for Diarrhea		
CTCAE Grade	**Adverse Event Management**	**Action and Dose Modification**
Grade 3 diarrhea	• Clinical evaluation mandatory. • Loperamide[1]: Initially 4 mg, followed by 2 mg every 4 hours or after every unformed stool; maximum 16 mg/day. Continue until diarrhea-free for 12 hours. • Lomotil[1]: 2.5-5mg of diphenoxylate up to 4x a day; maximum 20mg/daily. Continue until diarrhea-free for 12 hours. • Oral antibiotics and second-line therapies if clinically indicated • Hydration: Intravenous fluids if clinically indicated. • Antibiotics (oral or intravenous) if clinically indicated. • Intervention should be continued until the subject is diarrhea-free for ≥24 hours. • Intervention may require hospitalization for subjects at risk of life-threatening complications.	• Interrupt Trametinib and/or Ponatinib until diarrhea resolves to ≤ grade 2. • Restart treatment at same dose or with a dose reduction at discretion of investigator.[2]
Grade 4		• Withhold Trametinib and/or Ponatinib until toxicity is grade <=2. Initiate adverse event management. Discontinue permanently or restart with a dose reduction at the discretion of the investigator.[2]
1. Loperamide and Lomotil should be made available prior to start of study treatment so loperamide administration can begin at the first signs of diarrhea. 2. Escalation of Trametinib and/or Ponatinib to previous dose level is allowed after consultation with the medical monitor and in the absence of another episode of complicated or severe diarrhea in the 4 weeks subsequent to dose reduction.		

11.3.3 Pancreatitis and elevation of Lipase:

Pancreatitis (symptomatic abdominal pain associated with pancreatic enzyme elevation) and/or elevations in lipase and amylase are known AEs associated with Ponatinib. Pancreatitis was reported in 7% of patients in the phase 2 study of Ponatinib and 12% in the phase 1 dose-escalation study. Most cases of pancreatitis or elevated pancreatic enzymes occur within the first month of treatment with Ponatinib. The events are generally uncomplicated and reversible and can be managed with a brief interruption of treatment and standard medical therapies. Almost all patients are able to continue on with Ponatinib treatment at the same or a reduced dose once the event has improved to grade 1 or resolved. Patients with low-grade (1 or 2) elevation in amylase can be continued without dose reduction but should be monitored closely with serial enzyme level determination.

Table 11.3.3 Dose modification for Pancreatitis

CTCAE Grade	Action and Dose Modification
Asymptomatic Grade 1 or Grade 2 elevation or serum lipase	• Consider interruption or dose reduction of Ponatinib
Asymptomatic Grade 3 or Grade 4 elevation or serum lipase (>2 x ULN) or asymptomatic radiologic pancreatitis (grade 2 pancreatitis)	• Occurrence at 30mg: hold until event is ≤ grade 1, or has returned to baseline. Resume at 15mg • Occurrence at 15mg: discontinue study drug Any Recurrence at any dose level, discontinue Ponatinib
Symptomatic grade 3 pancreatitis (severe pain, vomiting, medical intervention indicated [eg analgesia, nutritional support])	• Occurrence at 30mg: hold until complete resolution of symptoms and after recovery of lipase elevation to ≤ grade 1 (<1.5X ULN), or has returned to baseline. Resume at 15mg • Occurrence at 15mg: discontinue study drug
Grade 4 pancreatitis	Permanently discontinue Ponatinib

11.3.4 **Hepatotoxicity**

Hepatotoxicity, most commonly manifested by reversible transaminase and alkaline phosphatase elevation and hyperbilirubinemia, has been observed with Ponatinib. Monitoring of hepatic function is recommended and management of laboratory abnormalities should be managed with dose interruption and/or dose reduction according to grade of toxicity.

CTCAE Grade	Action and Dose Modification
Elevation of liver transaminase >3 x ULND (grade 2 or higher)	• Occurrence at 30mg: hold until event is ≤ grade 1, or has returned to baseline. Resume at 15mg • Occurrence at 15mg: discontinue study drug
Elevation of AST or ALT >3 x ULN concurrent with an elevation of bilirubin >2 x ULN and alkaline phosphatase <2 x ULN	Permanently discontinue Ponatinib

11.3.5 **Pneumonitis**

Pneumonitis has been observed in patients receiving Trametinib. To reduce the risk of pneumonitis, patients will be monitored closely for symptoms and evaluated with imaging. Dose modification and supportive care guidelines for pneumonitis are described in the tables below.

CTCAE Grade	Adverse Event Management	Action and Trametinib Dose Modification

Grade 1	• CT scan (high-resolution with lung windows) recommended • Clinical evaluation and laboratory work-up for infection • Monitoring of oxygenation via pulse-oximetry recommended • Consultation of pulmonologist recommended	• Continue Trametinib at current dose if clinically indicated.
Grade 2	• CT scan (high-resolution with lung windows) • Clinical evaluation and laboratory work-up for infection • Consult pulmonologist • Pulmonary function tests –if < normal, repeat every 8 weeks until ≥ normal • Bronchoscopy with biopsy and/or BAL recommended • Symptomatic therapy including corticosteroids if clinically indicated	• Interrupt Trametinib until recovery to grade ≤1 • Consider restarting with Trametinib reduced by one dose level • Escalation to previous dose level after 4 weeks and consultation with medical monitor possible • If no recovery to grade ≤1 within 4 weeks, permanently discontinue study treatment
Grade 3	• CT scan (high-resolution with lung windows) • Clinical evaluation and laboratory work-up for infection • Consult pulmonologist • Pulmonary function tests-if < normal, repeat every 8 weeks until ≥ normal • Bronchoscopy with biopsy and/or BAL if possible • Symptomatic therapy including corticosteroids as clinically indicated	• Interrupt Trametinib until recovery to grade ≤1 • After consultation with PI, study treatment may be restarted reduced by one dose level • If no recovery to grade ≤1 within 4 weeks, permanently discontinue study treatment
Grade 4	• Same as grade 3	• Permanently discontinue Trametinib

11.3.6 **Reduced Left Ventricular Ejection Fraction**

Decreases of the left ventricular ejection fraction (LVEF) have been observed in patients receiving Trametinib and Ponatinib. Therefore, echocardiograms must be performed in regular intervals outlined in the Study Calendar. The same procedure (either ECHO or MUGA, although ECHO is preferred) should be performed at baseline and at follow-up visits

Trametinib and Ponatinib Dose Modification Guidelines and Stopping Criteria for LVEF Decrease		
Clinic	**LVEF-drop (%) or CTCAE grade**	**Action and Dose Modification**
Asymptomatic	Absolute decrease of >10% in LVEF compared to baseline and ejection fraction below the institution's LLN.	• Interrupt Trametinib and Ponatinib and repeat ECHO within 2 weeks.[a] • If the LVEF **recovers** within 4 weeks (defined as LVEF ≥LLN and absolute decrease ≤10% compared to baseline): – Consult with the Trametinib medical monitor, Ponatinib medial monitor, and PI and request approval for restart. – Restart treatment with Trametinib at reduced dose by one dose level and Ponatinib reduced by one dose level[b] – Repeat ECHO 2, 4, and 12 weeks after re-start; continue in intervals of 12 weeks thereafter. • If LVEF **does not** recover within 4 weeks: – Consult with cardiologist. – Permanently discontinue Trametinib and Ponatinib. – Report as SAE – Repeat ECHO after 2, 4, 8, 12, and 16 weeks or until resolution.
Symptomatic[b]	• Grade 3: resting LVEF 39-20% or >20% absolute reduction from baseline • Grade 4: Resting LVEF ≤20%.	• **Permanently discontinue Trametinib and Ponatinib** • **Report as SAE.** • **Consult with cardiologist.** • Repeat ECHO after 2, 4, 8, 12, and 16 weeks or until resolution.

[a] If ECHO does not show LVEF recovery after 2 weeks, repeat ECHO 2 weeks later.

[b] Escalation of Trametinib and Ponatinib to previous dose level can be considered if LVEF remains stable for 4 weeks after restarting both agents. Approval from PI is required.

[C]Symptoms may include: dyspnea, orthopnea, and other signs and symptoms of pulmonary congestion and edema.

11.3.5 QTc Prolongation

QTc prolongation has been observed in patients receiving Trametinib. Therefore, 12 lead EKGs must be performed in regular intervals outlined in the Study Calendar.

Trametinib Withholding and Stopping Criteria for QTc Prolongation	
Prolongation*	**Action and Dose Modification**
• QTcB ≥501 msec, or • Uncorrected QT >600 msec, or • QTcB >530 msec for subjects with bundle branch block	• Interrupt study treatment until QTcB prolongation resolves to grade 1 or baseline. • Test electrolytes (K, Ca, Phos, and Mg). If abnormal, replete to normal limits. • Review concomitant medication usage for a prolonged QTc • If the QTc prolongation resolves to grade 1 or baseline, Trametinib may be resumed at current dose level • **If the event does not resolve, permanently discontinue study treatment.** • **If the event recurs, permanently discontinue study treatment.**
Abbreviations: msec = milliseconds; QTcB = QT interval on electrocardiogram corrected using the Bazett's formula * Based on average QTc value of triplicate ECGs. For example, if an ECG demonstrates a prolonged QT interval, obtain two or more ECGs over a brief period, and then use the averaged QTc values of the three ECGs to determine if study treatments should be interrupted or discontinued.	

11.3.6 Arterial Thrombotic and Occlusive Events

In patients suspected of developing any arterial thrombotic occlusive event, Ponatinib should be immediately interrupted. Patients should be discontinued form Ponatinib in the event of MI, unstable angina, cerebrovascular accident, or TIA, or revascularization procedures. For all other arterial thrombotic occlusive events, dose modification guidelines are outlined in table below.

CTCAE Grade	**Action and Ponatinib Dose Modification**
	Vascular Occlusion: other cardiovascular and cerebrovascular events
Grade 1	• Consider interruption or dose reduction of Ponatinib until the event resolves
Grade 2	First occurrence at any dose level: • Hold until event is < grade 1 or has returned to baseline. Resume at current dose level Recurrence at 30mg: discontinue study drug Recurrence at 15mg: discontinue study drug
Grade 3 or 4	• Permanently discontinue Ponatinib
	Other vascular occlusions including peripheral vascular events
Grade 1	• Consider interruption or dose reduction of Ponatinib until the event resolves

Grade 2	First occurrence at any dose level: • Hold until event is ≤ grade 1 or has returned to baseline. Resume at current dose level • Resume at 30mg • Recurrence at 30mg: hold until event is ≤ grade 1, or has returned to baseline. Resume at 15mg • Recurrence at 15mg: discontinue study drug
Grade 3	• Occurrence at 30mg: hold until event is ≤ grade 1, or has returned to baseline. Resume at 15mg • Occurrence at 15mg: discontinue study drug • Any Recurrence at any dose level, discontinue Ponatinib
Grade 4	• Permanently discontinue Ponatinib

[a]"Recurrence" means the second vascular occlusive event (VOE), not necessarily recurrence of the same VOE, is encountered by a patient at any dose level.

[b]"Occurrence" means the first time an AE is encountered by a patient at a given dose level

Note: patients should be discontinued from Ponatinib in the even of a myocardial infarction (MI), unstable angina, cerebrovascular accident or transient ischemic attack (TIA) or revascularization procedures.

11.3.7 Venous Thromboembolic Events

Venous thromboembolic events have been observed in patients receiving Ponatinib Patients should be discontinued from Ponatinib in the event of life-threatening pulmonary embolism or retinal vein thrombosis

CTCAE Grade	Action and Ponatinib Dose Modification
	Venous Thromboembolic Events
Grade 1	• Consider interruption or dose reduction of Ponatinib until the event resolves
Grade 2	First occurrence at any dose level: • Hold until event is ≤ grade 1 or has returned to baseline. Resume at current dose level • Recurrence at 30mg: hold until event is ≤ grade 1, or has returned to baseline. Resume at 15mg Recurrence at 15mg: discontinue study drug
Grade 3	• Occurrence at 30mg: hold until event is ≤ grade 1, or has returned to baseline. Resume at 15mg • Occurrence at 15mg: discontinue study drug • Any Recurrence at any dose level, discontinue Ponatinib
Grade 4	Permanently discontinue Ponatinib

11.3.8 Visual Changes

Episodes of visual changes have been observed in patients receiving Trametinib. The causal relationship between a change in vision and the study treatment should be carefully explored and an ophthalmologist should be consulted. Patients are required to have a standard ophthalmic exam performed by an ophthalmologist at baseline and follow up exams as outlined in study calendar. The exam will include indirect funduscopic examination, visual acuity (corrected), visual field examination, tonometry, and direct funduscopy. Special attention should be given to retinal (*e.g.*, CSR) or retinal vein abnormalities (*e.g.*, RVO).

Guidelines regarding event management and dose reduction for visual changes considered to be related to study treatment are provided in the table below

Management and Trametinib Dose Modification for Visual Changes		
Event **CTCAE Grade**	**Management Guideline**	**Dose Modification**
Grade 1 Asymptomatic or symptomatic but not limiting ADL; intervention not indicated.	• Consult ophthalmologist within 7 days of onset. • Exclude CSR or RVO. • Consult retinal specialist if available in case of CSR or RVO. • Continue follow up examination(s) (by retinal specialist if available) for CSR and RVO.	• Continue Trametinib at the same dose level until ophthalmologic examination can be conducted.* • If ophthalmologic examination cannot be performed within 7 days of onset, interrupt Trametinib until CSR and RVO can be excluded and symptoms resolve. • If CSR and RVO excluded restart Trametinib at same dose level. • If CSR: Interrupt Trametinib until symptoms resolve and exam (by retinal specialist if available) shows resolution. May restart Trametinib with one dose level reduction. • If RVO: **Permanently discontinue Trametinib**.
Grade 2 and 3 Grade 2 defined as: Symptomatic with moderate decrease in visual acuity (20/40 or better; limiting instrumental ADL; local or non-invasive intervention indicated.) Grade 3 defined as: Symptomatic with marked decrease in visual acuity or marked visual field defect (worse than 20/40 but better than 20/200); severe pain or medically significant; operative intervention indicated.	• Consult ophthalmologist immediately. • Exclude CSR and RVO. • Consult retinal specialist in case of RVO or CSR for follow-up exam. • Continue follow up examination(s) (by retinal specialist if available) for CSR and RVO	• Interrupt Trametinib until signs and symptoms have resolved to baseline. • If CSR and RVO excluded and symptoms resolved to baseline, restart Trametinib reduced by one dose level. • If CSR: Interrupt Trametinib until symptoms resolve and exam (by retinal specialist if available) shows resolution. If CSR resolves restart Trametinib **reduced by one dose level**. • If RVO: **Permanently discontinue study treatment**.
Grade 4 Sight-threatening consequences; urgent intervention indicated; blindness (20/200 or worse).	• Consult ophthalmologist immediately. • Exclude CSR and RVO. • Continue follow up examination(s) (by retinal specialist if available) for CSR and RVO.	**Permanently discontinue Trametinib.**

Management and Trametinib Dose Modification for Visual Changes		
Event CTCAE Grade	**Management Guideline**	**Dose Modification**
Abbreviations: CSR = central serous retinopathy; RVO = retinal vein occlusion; SAE = serious adverse event * If visual changes are clearly unrelated to study treatment (*e.g.*, allergic conjunctivitis), monitor closely but ophthalmic examination is not required. * If ocular toxicities do not resolve within 21 days, permanently discontinue Trametinib.		

11.3.9 Hypertension

Hypertension has occurred in patients taking Trametinib and Ponatinib. Blood pressure should be monitored at each visit. Hypertension (HTN) by at least two blood pressure measurements should be graded according to CTCAE version 4.0. For participants who develop HTN or worsening HTN during study treatment, anti-hypertensive medication should be initiated or optimized to achieve target blood pressure before interruption or dose reduction of the study treatment at the discretion of the investigator. If hypertension is persistent despite adequate anti-hypertensive therapy including titration of anti-hypertensive medication or introduction of additional anti-hypertensive medications, or if grade 4 HTN develops, dose interruption and reduction is recommended according to Dose Modification Guidelines below.

Management and Dose Modification Guidelines for Hypertension

Hypertension	Action and Dose Modification
(Scenario A) • Asymptomatic and persistent[a] SBP of ≥140 and <160 mmHg, or DBP ≥90 and <100 mmHg, or • Clinically significant increase in DBP of 20 mmHg (but DBP still <100 mmHg).	• Continue Trametinib and Ponatinib at the current dose • Adjust current or initiate new antihypertensive medication • Titrate antihypertensive medication(s) during the next 2 weeks as indicated to achieve well-controlled[b] BP • If BP is not well controlled within 2 weeks, consider referral to a specialist and go to scenario (B).
(Scenario B) • Asymptomatic SBP ≥160 mmHg, or DBP ≥100 mmHg, or • Failure to achieve well-controlled BP within 2 weeks in Scenario A	• Interrupt both Trametinib and Ponatinib if clinically indicated • Adjust current or initiate new antihypertensive medication(s) • Titrate antihypertensive medication(s) during the next 2 weeks to achieve well-controlled BP • Once BP is well controlled[b], restart Trametinib and Ponatinib, both **reduced by one dose level[c]**
(Scenario C) • Symptomatic[d] hypertension or • Persistent SBP ≥160 mmHg, or DBP ≥100 mmHg, despite antihypertensive medication and dose reduction of Trametinib	• Interrupt Trametinib and Ponatinib • Adjust current or initiate new antihypertensive medication(s) • Titrate antihypertensive medication during the next 2 weeks to achieve well-controlled BP • Referral to a specialist for further evaluation and follow-up is recommended • Once BP is well controlled, restart Trametinib and Ponatinib, both **reduced by one dose level[c]**
(Scenario D) • Refractory hypertension unresponsive to above interventions or having hypertensive crisis.	• **Permanently discontinue Trametinib and Ponatinib** • Continue follow-up per protocol.

Abbreviations: BP = blood pressure; DBP = diastolic blood pressure; mmHg = millimetres mercury; SBP = systolic blood pressure;

a. Hypertension detected in two separate readings during up to three consecutive visits
b. Well-controlled blood pressure defined as SBP ≤140 mm Hg and DBP ≤90 mm Hg in two separate readings during up to three consecutive visits.
c. Escalation of Trametinib and Ponatinib to previous dose level can be considered if BPs remains well-controlled for 4 weeks after restarting of Trametinib and Ponatinib. Approval from PI is required.

d. Symptomatic hypertension defined as hypertension aggravated by symptoms (e.g., headache, light - headedness, vertigo, tinnitus, episodes of fainting) that resolve after the blood pressure is controlled within the normal range.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

The same method of assessment (i.e. CT or MRI) and the same technique (i.e. with or without contrast) should be used to characterize each identified and reported lesion at baseline and every two cycles (+/- 1 week). A designated radiologist at MSKCC will interpret the study CTs or MRIs according to RECIST 1.1 criteria. The same radiologist/physician should perform the evaluation for the entire duration of the study.

Tumor response will be assessed using RECIST 1 and confirmation of PR and CR is required. A CT scan of the chest +/- abdomen/pelvis will be performed to demonstrate all known areas of measurable disease. The baseline study will occur no more than 4 weeks prior to first study drug administration. A CT scan with contrast will be the preferred method and modality of imaging. A CT scan without contrast or MRI can be used in patients with contraindications to radiographic contrast media used in CT scans. All patients must have at least one measurable disease lesion by CT or MRI.

All measurable lesions, up to a maximum of 5 lesions total, representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size, should be representative of all involved organs, and should lend themselves to reproducible repeat measurements. All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Definitions of response in target and non-target lesions are described in table 12.1. Table 12.2 provides overall responses for all possible combination of tumor responses in target and non-target lesions.

Table 12.1 Evaluations of Target Lesions	
Complete response (CR):	Disappearance of all target lesions
Partial Response (PR):	At least a 30% decrease in the sum of the diameters of the target lesions
Progressive Disease (PD):	At least a 20% increase in the sum of the diameters of the target lesions or the appearance of one or more new lesions
Stable Disease (SD):	Neither sufficient shrinkage or qualify to PR nor sufficient increase to qualify for PD

Table 12.2 Evaluations of Non-Target Lesions	
Complete response (CR):	Disappearance of all non-target lesions
Incomplete response/stable disease (SD):	Persistence of one or more non-target lesions
Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesion

Table 12.3 Best Overall Response			
Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Incomplete/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Discontinuation of treatment: Early death is defined as having no repeat tumor assessments following initiation of study therapy resulting from death of the patient due to disease or treatment. Patients with global deterioration of health status requiring discontinuation of treatment without objective disease progression will be recorded as "symptomatic deterioration". Every effort will be made to document objective progression after discontinuation of treatment.

Evaluation of Best Overall Response: The best overall response is the best response recorded from the start of treatment until disease progression, as defined in **Table 12.3.** Patients who remain on trial will be followed for 6 months to determine best overall response rate

Evaluation of Toxicity: All patients who receive at least one dose of treatment with Trametinib and Ponatinib will be evaluable for toxicity.

Progression Free Survival (PFS): Duration of time from first treatment to time of progression or death, whichever occurs first.

Overall Survival (OS): Duration of time from first treatment to time of death

13.0 CRITERIA FOR REMOVAL FROM STUDY

Patients may withdraw from the study at any time. Patients who discontinue early should return within 30 days of the last dose of the study drugs for a follow-up evaluation (+/- 14 days). Any assessments listed for the final visit in Table 10.1 will be performed at that time.

Patients will be discontinued from treatment and from the study should they experience any of the following

- Dose limiting toxicity in the phase 1 portion
- disease progression (defined by RECIST 1.1)

Other reasons for study discontinuation include but are not limited to:

- change in patient eligibility
- non-compliance with defined treatment plan
- protocol violation
- Investigator's decision based on patient's best interest
- Withdrawal of consent
- Severe, unexpected toxicities/side effects
- lost follow up

Patients who are discontinued from the phase I portion for reasons other than DLT without completing at least 21 of 28 days of therapy will be replaced.

14.0 BIOSTATISTICS

Phase 1:

Primary Objective:

To determine maximum tolerated dose of combination of Ponatinib and Trametinib in patients with KRAS mutated non-small cell lung cancer (NSCLC).

Endpoints: maximum tolerated doses for combination. The MTD will be defined as the dose that does not exceed an acceptable threshold of toxicity. Dose limiting toxicity is a binary outcome where a patient either experiences a DLT or not. DLT is defined as any of the toxicity described in Section 9 of the attached protocol that occurs during the first cycle of treatment with Trametinib and Ponatinib.

Methods: A standard 3+3 design will be used to find the maximum tolerated dose (MTD). Patients who are discontinued before completing at least 21 out of 28 days of therapy for reasons other than development of a DLT (progression of disease or withdrawal of consent) will be replaced. There will be three set dose levels using the FDA approved dose of Trametinib with escalating dose (33%, 66%) of the FDA approved dose of Ponatinib (45mg once daily). In addition, three doses of Trametinib (75%, 50% and 25% of FDA approved dose) are reserved for de-escalation is dose level 1 is determined to be too toxic.

Dose levels	Trametinib Dose	Ponatinib Dose
Dose level -3	0.5mg PO q daily	15mg PO q daily
Dose Level -2	1.0 mg PO q daily	15mg PO q daily
Dose Level -1	1.5mg PO q daily	15mg PO q daily
Dose Level 1	2 mg PO q daily	15mg PO q daily
Dose Level 2	2 mg PO q daily	30mg PO q daily

The dose escalation scheme is as follows:

1. If none of the initial three patients at a given dose level experience DLT, the next dose level will be studied.

2. If one of the initial three patients at a given dose level experiences DLT, three additional patients will be treated at the same dose level. Escalation will continue only if there was been no additional DLT observed.
3. If two or more patients experience DLT at a given dose, the previous dose will be declared the MTD. Should two or more patients experience the DLT at dose level 1, the dose level -1 will be studied.
4. If only three patients were treated at a dose under consideration as the MTD, an additional three patients will be treated at that level to confirm previous results.

The MTD will be the phase 2 recommended dose. However, if the target toxicity level is not exceeded at the dose level 2, then the dose level 2 will be used at the phase II recommended dose. At the completion of the phase 1 portion, 6 patients will have been treated at the MTD. Considering the doses reserved for de-escalation, a minimum of 8 and a maximum of 30 patients will be included. If only does levels 1-2 are used, the maximum number of patients is 12. Given an expected accrual rate of 2 patients per month, the phase I portion of the study will be completed in about 9 months if no de-escalation doses are used and in a maximum of 18 months otherwise.

Following the completion of this phase, individual toxicities will be tabulated and the information will be summarized using descriptive statistics.

Phase 2:

Primary Objective: To determine the ORR of the combination of Trametinib and Ponatinib in patients with KRAS mutant lung cancer.

Secondary Objective: To determine the progression free survival and overall survival and determine the safety and tolerability of the combination.

Methods: A Simon optimal two-stage trial design will be utilized to assess the primary endpoint of response rate (RECIST 1.1 CR+PR). This study will test the null hypothesis of 10% response rate against the alternative hypothesis of 30% response rate for patients with progressive disease following at least two prior lines of therapy. A null hypothesis of 10% was chosen as this represents the established response rate for second line chemotherapy (Docetaxel[2,20]) in this setting. Subsequently, an alternative hypothesis of 30% was chosen for this study. The design chosen has a 10% type I error (falsely accepting a non-promising therapy), 10% type II error (falsely rejecting a promising therapy), for 90% power. The study would enroll 15 patients in the first stage. If one or more responses are seen, then the study would expand to 25 patients. To declare Ponatinib and Trametinib at this dose and schedule as promising, there would need to be at least 5 confirmed partial responses in 25 response evaluable patients. Patients must receive at least 21 days of therapy to be considered evaluable for response. Patients discontinued from the study before 6 month after treatment initiation without observed response (CR/PR) will be counted as non-responders. Overall survival and progression free survival will be estimated using the Kaplan-Meier method, with the follow-up starting at the initiation of therapy. Patients will be censored at the time of the last on-study evaluation if they do not experience the event of interest. Safety and tolerability will be summarized using descriptive statistics. The toxicities and the adverse events will be assessed for each patient according to the NCI CTCAE version 4.1 criteria. All correlative aims are exploratory and will be hypothesis-generating only.

Up to 6 patients treated at MTD in phase I, if evaluable for response, will be included in the phase II part. Therefore, 9 or 19 additional patients are needed for phase II. Given an expected accrual rate of 2 patients per month, the accrual to the phase 2 portion of the study will be completed in about 10 months.

Correlative analysis:

Serial biopsies will be performed in the pre-treatment phase, 4 weeks after starting therapy, and at the time of progression (3 biopsies per patient) for patients enrolled in the Phase II portion of the study. Levels of pERK will be assessed by immunohistochemistry (IHC) to evaluate degree of MAPK pathway inhibition. pAKT will be assessed by IHC as a marker of PI3K pathway inhibition. pFRS2 will also be assessed by IHC as a marker of FGFR1 inhibition. Plasma testing for ddPCR testing of presence of KRAS ctDNA (continuous measure) will be collected at the time of each radiographic assessment for patients in both the Phase I and Phase II portion of the study. The longitudinal measures of these biomarkers and their changes over time will be summarized by medians and ranges. The individual patient measures will be plotted to reveal any trends. The presence of concurrent genetic alterations identified on routine molecular profiling will also be described by response status using 2-by-2 tables. Correlative studies will be performed only on patients in the Phase II portion. Sample size of the correlative studies will therefore include a maximum of 19 patients since 6 patients treated at the MTD in the Phase I portion will not have the necessary studies performed.

15.1 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.2 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

15.3 Randomization

No randomization will occur.

16.1 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team. The data collected for this study will be entered into a secure database (Clinical Research Database CRDB). Source documentation will be available to

support the computerized patient record. The principal investigator will maintain ultimate responsibility for the clinical trial.

16.2 Quality Assurance

Weekly meetings will occur to monitor patient accrual and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow up will be monitored periodically throughout the study period and potential problem will be brought to the attention of the study team for discussion and action. Random sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times a year, and more frequently if indicated.

16.3 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: *http://mskweb2.mskcc.org/irb/index.htm*

There are several different mechanisms bywhich clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

17.1 PROTECTION OF HUMAN SUBJECTS

Prior to the enrollment of each patient, the risks, benefits, and objectives of the study will be reviewed with the participant, including a discussion of the possible toxicities and side effects. Alternative, non-protocol, treatment options will be discussed with the patient. It will be reviewed that participation in this clinical trial is voluntary and that the patient may withdraw consent at any time. The study is designed with careful safety monitoring for toxicity including physician visits. Specific guidelines for symptom management are in place to protect the study participants.

Human Subjects Involvement and Characteristics: All patients at MSKCC who meet the inclusion criteria will be eligible to enroll. Patients eligible will be 18 years of age or older with a KPS of 70% or greater. Both men and women and members of all ethnic groups will be eligible for this trial. Pregnant and breast feeding women are excluded from this study. This protocol does not include children because the number of children is expected to be limited for the patient population expected to be accrued onto this study. Also the majority of children are already accessed by a nationwide pediatric cancer research network. This statement is based on exclusion 4b of the NIH policy and guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects.

Consent process: All patients at MSKCC who meet the inclusion criteria will be eligible. Participation in the trial is voluntary. All patients will be required to sign a statement of informed consent, which must conform to IRB guidelines. The informed consent procedure is described in Section 18.0.

Possible Toxicities: There are risks associated with treatment as described in Section 11.0.

Benefits: The combination of Trametinib and Ponatinib has the potential to be effective and induce tumor response in patients with KRAS mutant NSCLC.

Costs: Patients will be charged (insurance billed) for physician visits, routine laboratory tests, and radiologic studies required for monitoring their condition. The patients will not be billed for the study drugs, Trametinib or Ponatinib. The research studies will be covered with separate research funding and no charges associated with research will be billed to the patient. Repeat biopsy on day 28 and progression of disease on study will not be charged to the patient.

Alternatives: The alternative to this trial would be treatment with chemotherapy or participation in an alternative clinical trial.

Confidentiality: Every effort will be made to maintain patient confidentiality. Research and hospital records are confidential. Patients' names and any other identifying information will not be used in reports or publications resulting from this study. Other authorized agencies and appropriate internal personnel (e.g. qualified monitors from MSKCC) and external personnel, its authorized agents, the FDA (and/or other governmental agencies) may review patient records as required.

Patient Safety: Patients are monitored by physicians and oncology nurses who are very familiar with clinical trials. In the case of an adverse reaction, immediate medical attention is available. In the evenings and weekends, we have a 24 hour urgent care facility for outpatients. The PI or co-PI will also be available at all times to organize any necessary intervention.

Monitoring of data to ensure safety: The study is to be monitored by the institutional IRB. This incorporates an independent data and safety monitoring board established by arrangement with the National Cancer Institute. The analysis of safety will include all patients. Adverse events, including all toxic effects of treatment, will be tabulated individually and summarized by severity and causality.

17.2 Privacy

MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

The consent indicates that individualized de identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have received approval from MSK will be allowed to access this information which will not include protected health information, such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with other qualified researchers.

17.3 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant starts investigational treatment/intervention. SAE reporting is required for 30-days after the participant's last investigational treatment/intervention. Any event that occur after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (i.e., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be submitted within 5 calendar days of the event. All other SAEs must be submitted within 30 calendar days of the event.

The report should contain the following information:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment(s)
- If the AE was expected
- Detailed text that includes the following
    - An explanation of how the AE was handled
    - A description of the participant's condition
    - Indication if the participant remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

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17.3.1 Novartis reporting

All Serious Adverse Events ("SAE") required to be reported pursuant to the Protocol shall be provided to Novartis and its representatives by Institution or Principal Investigator within 24 hours of learning of the event as well as provide any additional reports agreed upon by the Institution or Principal Investigator and Novartis contact below. The Institution or Principal Investigator will have the primary responsibility of reporting adverse events ("AE") to regulatory authorities.

Copies of IND Safety reports submitted to the FDA by the institution under the Institution's IND will be shared with the contact below so that these reports can be evaluated and included in the package insert or Novartis IND safety submissions as required to ensure safety of other patients who are receiving the product form Novartis for sponsored trials.

The principal investigator has the obligation to report all serious adverse events to the FDA (if applicable), IRB, and Novartis Pharmaceuticals Drug Safety and Epidemiology Department (DS&E) ***(For patients taking Novartis drugs)***.

All events reported to the FDA by the investigator are to be filed utilizing the Form FDA 3500A (MedWatch Form), if applicable.

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until at least 30 days after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence. Information about all SAEs is collected and recorded on a Serious Adverse Event Report Form. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and **send the completed, signed form along with the Novartis provided fax cover sheet to the Novartis Oncology Drug Safety and Epidemiology (DS&E) department by fax (fax: 877-778-9739) within 24 hours.**

Any additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Any SAEs experienced after the 30-day safety evaluation follow-up period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment.

Follow-up information is submitted in the same way as the original SAE Report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis Drug Safety and Epidemiology (DS&E) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

17.2.1.1 Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be reported by the investigator to the Novartis Oncology Drug Safety and Epidemiology Department (DS&E) by fax **(fax: 877-778-9739)**. Pregnancy follow-up should include an assessment of the possible relationship to the study treatment and any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

17.3.2 Takeda Reporting

All Serious Adverse Events ("SAE") are also required to be reported pursuant to the Protocol shall be provided to Takeda and its representatives by Institution or Principal Investigator within 24 hours of learning of the event as well as provide any additional reports agreed upon by the Institution or Principal Investigator and Takeda contact above. The Institution or Principal Investigator will have the primary responsibility of reporting adverse events ("AE") to regulatory authorities.

Copies of IND Safety reports submitted to the FDA by the institution under the Institution's IND will be shared with the contact below so that these reports can be evaluated and included in the package insert or Takeda IND safety submissions as required to ensure safety of other patients who are receiving the product form Takeda for sponsored trials.

Adverse Events may be spontaneously identified by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures. Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event.

Adverse Events which are **serious** must be reported to Takeda Pharmacovigilance (or designee) from the first dose of ponatinib up to and including 30 days after administration of the last dose of ponatinib. Any SAE that occurs at any time after completion of ponatinib treatment or after the designated follow-up period that the sponsor-investigator and/or sub-investigator considers to be related to any study drug must be reported to Takeda Pharmacovigilance (or designee). In addition, new primary malignancies that occur during the follow-up periods must be reported, regardless of causality to study regimen, for a minimum of three years after the last dose of the investigational product, starting from the first dose of study drug. All new cases of primary malignancy must be reported to Takeda Pharmacovigilance (or designee).

Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the trial are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (e.g., surgery was performed earlier or later than planned). All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness (es).

Since this is an investigator-initiated study, the principal investigator Dr. Arbour also referred to as the sponsor-investigator, is responsible for reporting serious adverse events (SAEs) to any regulatory agency and to the sponsor- investigator's EC or IRB.

Regardless of expectedness or causality, all SAEs must also be reported in English to Takeda Pharmacovigilance or designee:

Fatal and Life Threatening SAEs within 24 hours of the sponsor-investigator's observation or awareness of the event

All other serious (non-fatal/non-life threatening) events within 4 calendar days of the sponsor-investigator's observation or awareness of the event

The Sponsor will send all SAE reports to Takeda Pharmacovigilance (or designee) within 24 hours but no later than 4 calendar days as per any agreements.

Follow-up information on the SAE may be requested by Takeda Pharmacovigilance (or designee).

In the event that this is a multisite study, the sponsor-investigator is responsible to ensure that the SAE reports are sent to Takeda Pharmacovigilance (or designee) from all sites participating in the study. Sub-investigators must report all SAEs to the sponsor-investigator so that the sponsor-investigator can meet his/her foregoing reporting obligations to the required regulatory agencies and to Takeda Pharmacovigilance, unless otherwise agreed between the sponsor-investigator and sub-investigator(s).

Relationship to all study drugs for each SAE will be determined by the investigator or sub-investigator by responding yes or no to the question: Is there a reasonable possibility that the AE is associated with the study drug(s)?

US and Canada

Toll-Free Fax #: 1-800-963-6290

E-mail: takedaoncocases@cognizant.com

All other countries (Rest of World)

Fax #: 1 202 315 3560

For IND/IDE protocols: The SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the IND Office.

17.2.2.1 Product Complaints or Medication Errors (Including Overdose)

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact Takeda Pharmacovigilance or designee (see below) and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Takeda Quality representative.

A medication error is a preventable event that involves an identifiable patient and that leads to inappropriate medication use, which may result in patient harm. While overdoses and underdoses constitute medication errors, doses missed inadvertently by a patient do not. Investigators must record all medication errors (including overdose) on the appropriate form. Individuals who identify a potential medication error situation should immediately contact Takeda (see below) and report the event.

For Product Complaints or Medication Errors (Including Overdose), contact Takeda Pharmacovigilance

For ADCETRIS or PIPELINE Products:

Phone: 1-844-ONC-TKDA(1-844-662-8532)

Email: GlobalOncologyMedInfo@takeda.com

Fax: 1-800-881-6092, Hours Mon – Fri, 9 a.m. – 7 p.m. ET

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE form should be completed and sent to Takeda Pharmacovigilance (refer to Section 17.2.2).

17.2.2.2 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a female patient becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study drug. The sponsor-investigator must fax a completed Pregnancy Form to the Takeda Pharmacovigilance or designee immediately (see Section 17.2.1). The pregnancy must be followed for the final pregnancy outcome (i.e., delivery, still birth, miscarriage) and Takeda Pharmacovigilance or designee will request this information from the sponsor-investigator.

Suggested Pregnancy Reporting Form:
Pregnancy Report Form (a sample will be provided by Takeda)

Safety contact:

The Principal Investigator will provide Novartis or its contacts above with copies of the IND safety report every 6 months in the format of a line listing with details regarding the reports that were submitted to the FDA. Individual submissions will be provided to Novartis upon request.

The Principal Investigator will also provide Takeda or its contacts above with copies of the IND safety report every 6 months in the format of a line listing with details regarding the reports that were submitted to the FDA. Individual submissions will be provided to Takeda upon request.

18.1 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

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20.0 APPENDICES

20.1 Trametinib Prescribing Information

20.2 Ponatinib Prescribing Information