A Phase 1/2 Trial of Trametinib and Erlotinib in Patients with EGFR-Mutant Lung Adenocarcinomas and Acquired Resistance to Erlotinib

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.

OneMSK Sites	
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Nassau	All Protocol Activites

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Study Title:	A Phase 1/2 Trial of Trametinib and Erlotinib in Patients with EGFR-Mutant Lung Adenocarcinomas and Acquired Resistance to Erlotinib
Study Objectives:	**Phase 1: Safety Run In** Primary Objective: Determine the safety and tolerability of erlotinib 75mg by mouth once daily with trametinib 1.5mg by mouth once daily for patients with acquired resistance to erlotinib **Phase 2:** Primary Objective: Assess overall response rate (CR+PR) of trametinib when given in combination with erlotinib for patients with EGFR-mutant lung cancers and acquired resistance to erlotinib Secondary Objectives: 1) Measure progression-free survival and overall survival among patients treated with trametinib and erlotinib 2) further define the toxicity profile of the combination **Correlative Studies:** Objectives: 1) Confirm BIM induction with MEK inhibition by assessing BIM protein expression by IHC on serial biopsies 2) Identify changes in protein expression related to apoptosis, EMT and NF1 expression 3) Perform transcriptome analysis (using RNA-seq) on tumor tissue from serial biopsies. 4) Perform next-generation sequencing based mutation testing to identify genetic alterations on tumor tissue from serial biopsies 5) Assess EGFR T790M status on all patients on study.
Patient Population:	Patients with locally advanced or metastatic lung adenocarcinomas with a confirmed EGFR mutation who have developed acquired resistance to EGFR tyrosine kinase inhibitor therapy
Number of patients:	Phase 1: Maximum of 6 patients Phase 2: Maximum of 24 patients (including up to 6 patients from Phase 1)
Inclusion Criteria:	All patients must have: • Pathologic evidence of stage IV or recurrent lung adenocarcinoma that cannot be treated with curative intent • Somatic activating mutation in EGFR • Radiographic progression during treatment with erlotinib. Prior chemotherapy regimens are permitted. • Measurable (RECIST 1.1) indicator lesion not previously irradiated

	• 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
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 due to medications or a medical condition such as Crohn's disease or malabsorption • Pregnant or lactating women • Any type of systemic therapy (chemotherapy or experimental drugs) within 2 weeks of starting treatment on protocol except for a EGFR TKI • Patients who have received prior treatment with MEK inhibitor • Any major surgery or extensive radiotherapy within 21 days of starting treatment on protocol. • A history of clinically significant interstitial lung disease or pneumonitis • Clinically significant cardiac disease including unstable angina, acute myocardial infarction within 6 months from Day 1 of study administration, New York Heart Association Class III or IV congestive heart failure, or symptomatic uncontrolled Arrythmias, prolonged corrected QT interval >480msec, treatment refractory hypertension, presence of a cardiac defibrillator • 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 3 years. Patients who are considered NED from a malignancy may be considered on a case by case basis. • Have a known immediate or delayed hypersensitivity reaction to drugs chemically related to study drug, or excipients or to dimethyl sulfoxide (DMSO). • 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:	Erlotinib and Trametinib

Study Design:

Phase 1: Safety Run In

This portion of the study will assess whether a dose of trametinib 1.5mg by mouth once daily and erlotinib 75mg by mouth once daily is a tolerable and safe dose. Six patients will be enrolled at this dose level and assessed for dose limiting toxicities (DLTs) for 1 full cycle (28 days). Toxicity will be graded according to NCI CTCAE version 4.0. If more than one patient develops a DLT, we will move on to the phase 2 portion of the study and the dose level -1 will be used. If no $\leq$1 DLT is detected, we will move on to the phase 2 portion of the study at dose level 0.

Dose levels	Trametinib Dose	Erlotinib Dose
Dose Level 0	1.5mg PO qdaily	75mg PO qdaily
Dose Level -1	1 mg PO qdaily	100mg PO qdaily

Phase 2:

Once the phase 1 run-in 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 erlotinib in the treatment of patients with EGFR-mutant lung cancers with acquired resistance to erlotinib**.** After screening and registration, patients will be treated with the combination of trametinib and erlotinib. 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. A maximum of 24 patients will be enrolled during this portion of the study.

Correlative studies:

Biopsies will be required within 30 days of start of study treatment and at the time of progression. At prespecified time points and after additional informed consent, patients will have image-guided core needle biopsies with 3-4 cores obtained. At least 2 cores will be immediately frozen in liquid nitrogen and sent to Dr. Rudin's lab. The remaining cores will be fixed in formalin and sent to Surgical Pathology. We will use our genomics core facility for all DNA and RNA extraction and analysis. IHC will be performed to look at expression of specific proteins of interest including: BIM, TGFB2, vimentin, e-cadherin, n-cadherin and neurofibromin. Transcriptome sequencing (RNA-Seq) will be utilized to look at changes in gene expression at various time points of treatment and to identify potential biomarkers of response to combination therapy. IMPACT, our next-generation sequencing based mutation platform that assesses for genetic alterations in 340 cancer-related genes, will be used for molecular analysis.

2.1 OBJECTIVES AND SCIENTIFIC AIMS

Hypothesis: The combination of erlotinib and trametinib is an effective treatment in patients with EGFR mutant lung cancers with acquired resistance to erlotinib monotherapy.

Phase 1 Trial:

A. Primary Objective: Determine the safety and tolerability of erlotinib 75mg by mouth once daily with trametinib 1.5mg by mouth once daily

Phase 2 Trial:

A. Primary Objectives: Assess overall response rate (CR+PR) of trametinib when given in combination with erlotinib in patients with acquired resistance to erlotinib at 8 weeks (2 cycles)

B. Secondary Objective: Measure progression free survival and overall survival among patients treated with trametinib and erlotinib and further define the toxicity profile of the combination

Correlative Studies:

A. Primary Objective: 1) Determine whether trametinib leads to upregulation of BIM in patients with acquired resistance 2) Identify changes in protein expression related to apoptosis, EMT and NF1 expression 3) Perform transcriptome analysis (using RNA-seq) on tumor tissue from serial biopsies. 4) Perform next-generation sequencing based mutation platform testing to identify genetic alterations on tumor tissue from serial biopsies

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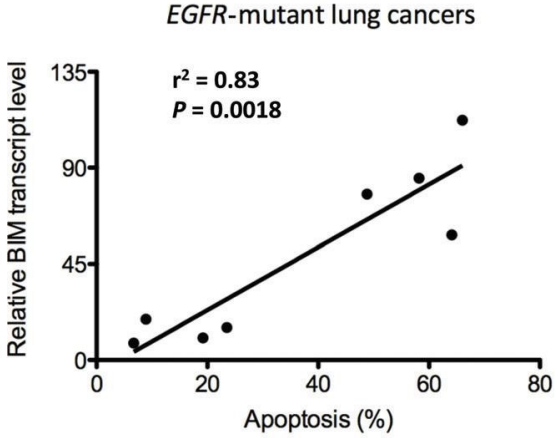
3.0 BACKGROUND AND RATIONALE

3.1 EGFR-mutant lung adenocarcinoma and acquired resistance to EGFR tyrosine Kinase Inhibitors

Twenty percent of patients with metastatic lung adenocarcinoma have somatic activating mutations in the epidermal growth factor receptor (EGFR). Patients with these oncogene-addicted lung adenocarcinomas have a 70% response rate to EGFR-TKI therapy (erlotinib, afatinib, or gefitinib) and a median progression-free survival of 12 months.[4] All of these patients will develop resistance to EGFR TKI therapy and clinical progression. A mechanism of resistance can be identified 82% of the time, with acquisition of EGFR T790M seen most frequently.[5] There are several EGFR T790M targeting EGFR inhibitors currently in clinical development. CO-1686, which targets mutant EGFR including T790M, has a reported overall response rate of 58% in 40 patients with centrally confirmed EGFR T790M tumors.[6] AZD9291, another mutant specific EGFR TKI, has a reported response rate of 64% in 107 patients with EGFR T790M mutant tumors.[7] At this time however, there are currently no approved drugs available for patients with acquired resistance to EGFR TKIs. Therapeutic options are especially limited for patients without acquired EGFR T790M present in their tumors.



Role of BIM and apoptosis

Expression of the apoptotic protein BIM is required for apoptosis triggered by EGFR tyrosine kinase inhibitors (TKIs).[2,8-10] (Figure 1) Treatment with EGFR TKIs induces rapid and sustained increases in the level of BIM, and knockdown of BIM nearly eliminates EGFR TKI-induced cell killing in EGFR-mutant cell lines.[8] Levels of pre- treatment (and post-treatment) BIM predict response to EGFR TKI therapy with an association of both response rate and progression-free survival on EGFR TKI with BIM expression. [2] Similar results were seen when analyzing BIM mRNA expression of patients with EGFR-mutant lung cancers treated in the EURTAC trial.[11] Progression-free survival on erlotinib and overall survival were shorter in those with low BIM expression.[11]

Figure 1: basal BIM RNA levels correlate with apoptosis[2]

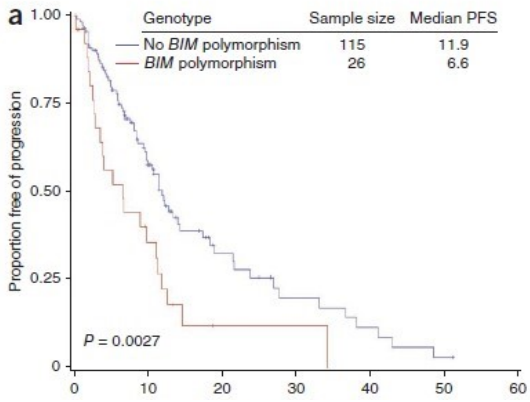


Figure 2: Figure 2: BIM polymorphism predicts PFS w/ EGFR TKI[1]

The importance of BIM was again demonstrated in patients with a BIM deletion polymorphism that results in an isoform of BIM without the crucial BH3 domain that is required for BIM's apoptotic function.[1] The presence of this polymorphism was predictive of a shorter progression free survival with erlotinib re-emphasizing the importance of BIM expression to response to TKI therapy.[1] (Figure 2)

Inhibition of the MEK/ERK pathway is critical for BIM upregulation required for TKI-induced apoptosis. MEK inhibition is sufficient to induce rapid BIM induction by preventing dephosphorylation resulting in BIM accumulation.[10] In EGFR T790M containing cell lines, there is increased phosphorylated ERK in the presence of an EGFR TKI that was attenuated with the addition of a MEK inhibitor.[9] In sensitive EGFR mutant cell lines, the addition of a MEK inhibitor to an EGFR inhibitor may not be additive, but in the resistance setting there is more limited BIM induction and the additive effect of a MEK inhibitor may be more apparent. Song and colleagues evaluated dual MEK and EGFR inhibition which resulted in apoptosis in EGFR resistant, EGFR T790M containing cell lines (H1975) with decreased phospho-ERK and increased BIM expression.[12] Induction of BIM through MEK inhibition has the potential to re-sensitize patients to EGFR TKI irrespective of EGFR T790M status making this a potential treatment strategy in all patients with acquired resistance to EGFR TKI therapy.

Additional support for MEK inhibition in EGFR-mutant lung cancers

In addition to acquisition of EGFR T790M, there are multiple other mechanisms of acquired resistance to EGFR TKI therapy. Histologic transformation including epithelial-mesenchymal transition (EMT) is a mechanism of resistance identified in tumor samples in patients treated with EGFR TKI.[13] ERK/MAPK pathway activation is required for TGF-B2 induced EMT.[14] Inhibition of MEK was able to prevent EMT and augment sensitivity to gefitinib in cell lines resistant to EGFR TKI therapy.[15]

Another mechanism of resistance to EGFR TKI identified is decreased expression of neurofibromin that results in incomplete inhibition of RAS/ERK signaling in the presence of erlotinib.[3] Low NF1 expression was associated with both primary and secondary resistance to EGFR TKIs. Treatment of neurofibromin deficient lung cancers with a trametinib and erlotinib restored sensitivity to erlotinib. (Figure 3).

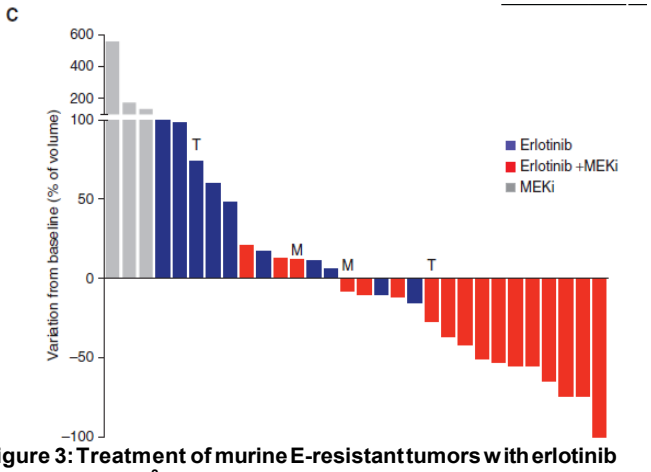


Figure 3: Treatment of murine E-resistant tumors with erlotinib MEK and E+MEK[3]: Waterfall plot showing tumor response of the final 4 weeks of combined treatment with EGFR and MEK inhibitors (red bars), the EGFR inhibitor alone (blue bars) or MEK inhibitor alone (grey). Each bar represents one individual tumor, with data expressed relative to the tumor volume measured prior to the 4-weeks treatment round, showing progressive disease (PD), stable disease (SD), partial response (PR) or complete response (CR). Tumor mRNA was sequenced for the presence of EGFR-T790M and analysed for *Met* expression; T790M-positive tumors are marked with an T, and tumors showing a >4-fold *Met* expression are marked with an M.

<u>Preliminary data and Rationale for Dose Selection:</u>

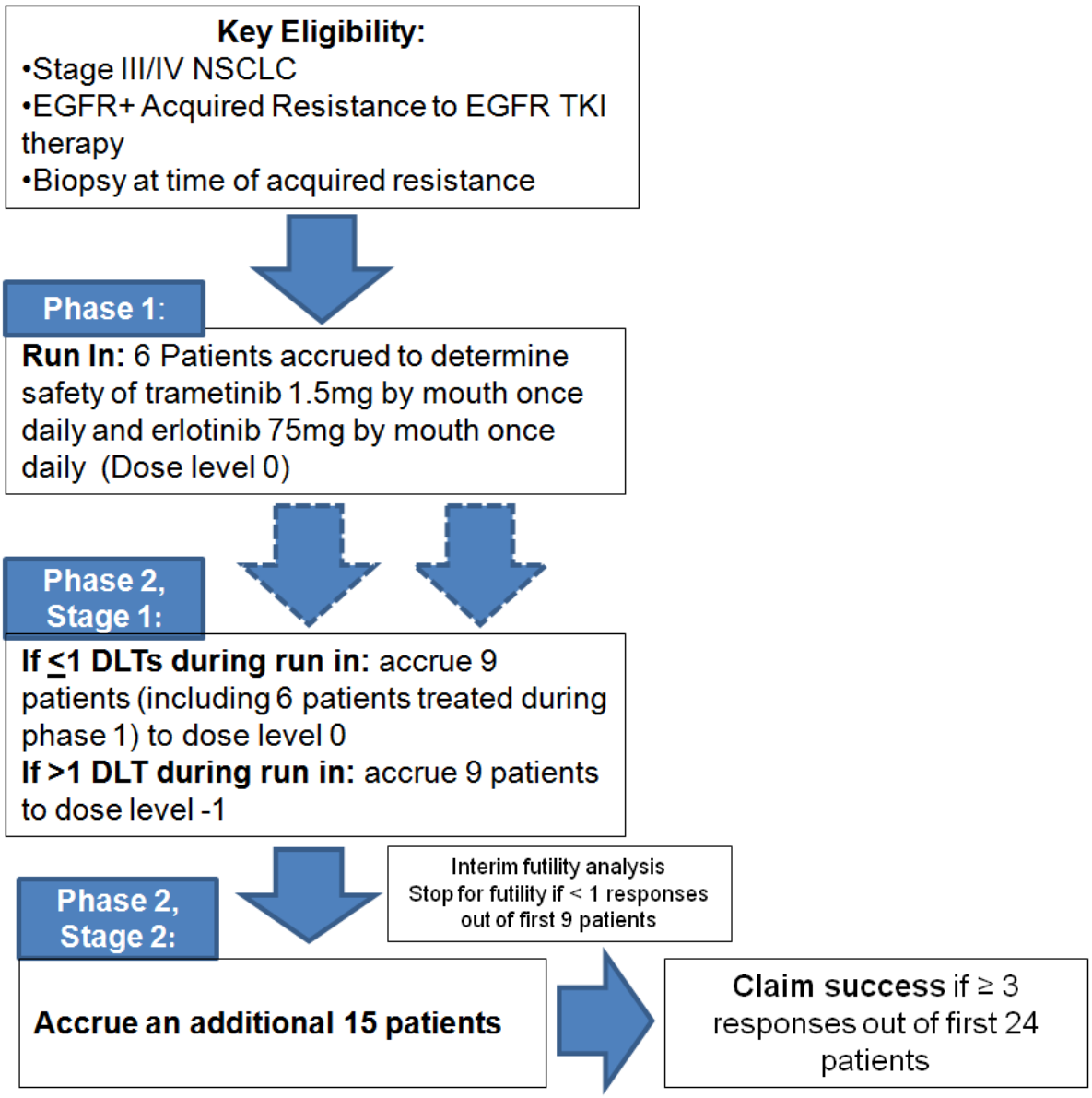
Trametinib is approved for the treatment of BRAF-mutant melanomas at a dose of 2mg orally daily. A phase 1 study of trametinib and erlotinib was conducted in patients with solid tumors (NCT01192165). Twenty-two patients were treated and 3 dose-limiting toxicities were seen: 1 DLT of diarrhea at the dose of trametinib 1mg with erlotinib 100mg and 2 DLTs of diarrhea and mucositis with trametinib 1.5mg with erlotinib 100mg. Most common side effects (>30% of all patients), any grade, were diarrhea, rash, fatigue, nausea, vomiting, anorexia, hypokalemia and anemia. The maximum tolerated dose level of the combination was determined to be trametinib 1mg daily and erlotinib 100mg daily. No partial or complete responses were seen in this unselected population. Prophylactic antidiarrheals were not utilized on protocol.

We hypothesize that effective MEK inhibition with trametinib will circumvent acquired resistance to erlotinib therapy. We would therefore like to first conduct a phase 1 safety run in with a higher dose of MEK inhibitor (trametinib 1.5mg once daily) with a reduced dose of erlotinib at 75mg once daily. This dose had not been tested during the previous phase 1 study described above. It is our hypothesis that a lower dose (75mg) of erlotinib would allow us to maximize the dose of trametinib given. We will also utilize prophylactic anti-diarrheal medications to minimize toxicities. Six patients will be accrued to this portion of the study. If zero to one patient experiences a toxicity with these doses, we will move to the phase 2 portion of the study. If two or more patients develop a DLT at this higher dose of trametinib, we will use trametinib 1mg daily with erlotinib 100mg daily during the phase 2 portion of the study.

4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.2 Design

This is a phase 1 safety run-in/phase 2 single arm, open labeled, single institution study of erlotinib and trametinib in patients with EGFR mutant lung cancer and acquired resistance to erlotinib therapy



Dose levels	Trametinib Dose	Erlotinib Dose
Dose Level 0	1.5mg PO qdaily	75mg PO qdaily
Dose Level -1	1 mg PO qdaily	100mg PO qdaily

4.3 Intervention

Phase 1: Safety Run in

This portion of the study will assess whether a dose of trametinib 1.5mg by mouth once daily and erlotinib 75mg by mouth once daily is a safe dose. Up to six patients will need to be enrolled at this dose level and assessed for dose limiting toxicities (DLTs) for 1 full cycle (28 days). Toxicity will be graded according to NCI CTCAE version 4.0. If more than one patient develops a DLT, we

will move on to the phase 2 portion of the study and the dose level -1 will be used. Dose level -1 was already deemed safe in a previous phase 1 study (NCT01192165). If ≤1 DLT is detected, we will move on to the phase 2 portion of the study at dose level 0. Two to six patients will be enrolled in the phase 1 portion.

Dose levels	Trametinib Dose	Erlotinib Dose
Dose Level 0	1.5mg PO qdaily	75mg PO qdaily
Dose Level -1	1 mg PO qdaily	100mg PO qdaily

Phase 2:

Once the run-in 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 erlotinib in the treatment of patients with EGFR-mutant lung cancers with acquired resistance to erlotinib**.** After screening and registration, patients will be treated with the combination of trametinib and erlotinib. 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. A maximum of 24 patients will be enrolled in the phase 2 study. Dosing for the phase 2 portion of the study will depend on the results from the run In Phase 1 Portion. If 0-1 DLTs occur, and dose level 0 is used in the phase 2 portion, the patients treated in the phase 1 portion at dose level 0 will be included in the phase 2 portion.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1 **Trametinib**

Drug: Trametinib ()

Classification: MEK inhibitor

Composition, Formulation, and storage: all study medication will be stored and inventoried in accordance with applicable state and federal regulations.

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: Novartis will provide each investigator with adequate supplies of trametinib which will be supplied at 0.5 mg and 1mg (as free base) tablets. Tablets are packaged in high density polyethylene bottles with child resistant closures including an induction seal liner. The enclosed paperboard carton is required for additional light protection.

- 0.5mg tablets are white or yellow, modified oval, biconvex and film-coated.
- 1mg tablets are white, round, biconvex, film-coated tablets

Schedule, route of administration, and dosing: Subjects will receive trametinib 1.5mg by mouth once daily or 1mg by mouth once daily depending on the results of the phase 1 Run In. 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

Stability and Storage: Store tablets at 2C-25C in the original bottle. Bottles should be stored in the manufacturer's package carton for light protection. Protect from moisture. Shelf life studies of trametinib dimethyl sulfoxide are ongoing.

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 must also be recorded. At completion of the study, to satisfy regulatory requirements regarding drug accountability, all unused trametinib will be reconciled and destroyed in accordance with applicable state and federal regulations.

Inactive Ingredients: Tablet Core: colloidal silicon dioxide, croscarmellose sodium, hypromellose, magnesium stearate (vegetable source), mannitol, microcrystalline cellulose, sodium lauryl sulfate. Coating: hypromellose, iron oxide red (2-mg tablets), iron oxide yellow (0.5-mg tablets), polyethylene glycol, polysorbate 80 (2-mg tablets), titanium dioxide.

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

5.2 **Erlotinib**

Drug: Erlotinib (Tarceva)

Classification: quinazolinamine that inhibits the intracellular phosphorylation of tyrosine kinase associated with the epidermal growth factor receptor

Chemical Name: N-(3-ethynylphenyl)-6,7-bis(2-m ethoxyethoxy)4-quinazolinamine

Erlotinib Tablets: Erlotinib will be commercially supplied.

6.1 CRITERIA FOR SUBJECT ELIGIBILITY

6.2 Subject Inclusion Criteria

All patients must have:

- Pathologic evidence of advanced stage IV or recurrent lung adenocarcinoma reviewed at MSKCC
- Somatic activating mutation in EGFR Radiographic progression during treatment with erlotinib or any other EGFR TKI therapies.
- Any number of prior chemotherapy regimens is permitted.
- Measurable (RECIST 1.1) indicator lesion not previously irradiated
- KPS ≥ 70%
- Age >18 years old
- Must have undergone biopsy after development of acquired resistance to erlotinib with available archived tissue (equivalent of ≥ 10 unstained slides)
- Left ventricular Ejection Fraction ≥ the lower limit of normal by ECHO or MUGA
- Adequate organ function:
  - **-** AST, ALT ≤ 2.5 x ULN

- - Total bilirubin ≤ 1.5 x ULN
- -Albumin≥2.6g/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

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 due to medications or a medical condition such as Crohn's disease or malabsorption
- Pregnant or lactating women
- Any type of systemic therapy (chemotherapy or experimental drugs) within 2 weeks of starting treatment on protocol except for a EGFR TKI
- Patients who have received prior treatment with a MEK inhibitor
- Any major surgery or extensive radiotherapy within 21 days of starting treatment on protocol.
- A history of clinically significant interstitial lung disease or pneumonitis
- Clinically significant cardiac disease including unstable angina, acute myocardial infarction within 6 months from Day 1 of study administration, New York Heart Association Class III or IV congestive heart failure, or symptomatic uncontrolled Arrythmias, prolonged corrected QT interval >480msec, treatment refractory hypertension, presence of a cardiac defibrillator
- 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 3 years. Patients who are considered NED from a malignancy may be considered on a case by case basis.
- Have a known immediate or delayed hypersensitivity reaction to drugs chemically related to study drug, or excipients or to dimethyl sulfoxide (DMSO).
- 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

7.1 RECRUITMENT PLAN

A member of the patient's treatment team, the protocol investigator, or research team at Memorial Sloan Kettering Cancer Center will identify potential research participants. If the investigator is a part of the treatment team, s/he will screen the patient as to eligibility, and will discuss the study and the possibility of enrollment in the research study with the patient. The preliminary screen of eligibility will be confirmation for the diagnosis of the following:

• Patients with EGFR mutant lung cancers with progression of disease on Erlotinib therapy

Potential subjects that meet these basic criteria will be referred by their treatment physician to the investigator, co-investigators, or research staff of the study. Minority 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, **Dr. Helena Yu**, will be available to all patients for further questions and information through a contact number which will be provided on the consent form itself.

8.1 PRETREATMENT EVALUATION

Study eligibility is based on meeting all of the study inclusion criteria and none of the exclusion criteria at screening and on Study Day 1 before study treatment administration. The following assessments will be conducted prior to subjects receiving their first dose of trametinib on this protocol. All aspects of the screening evaluation should be completed within 4 weeks of starting treatment:

- Documented presence of a somatic activating EGFR 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 sites of disease). Tumor burden must be measurable using RECIST 1.1.
- Complete vital signs (pulse, blood pressure, temperature, respiratory rate) as well as weight and height
- 12 lead electrocardiogram (ECG) and echocardiogram within 1 month of study initiation
- Performance status
- Serum pregnancy test for women with 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)
- Ophthalmology Exam (See Section 10 for more details)
- Archival Tumor Tissue

9.0 TREATMENT/INTERVENTION PLAN

Erlotinib will be commercially obtained. Investigators should reference the current approved prescribing information. A pill diary will be used to track adherence. Erlotinib is administered daily, at approximately the same time of day every day. Erlotinib should be taken on an empty stomach (at least 1 hour before, or 2 hours after the ingestion of food). If vomiting occurs during the course of treatment, patients should not take an additional dose of erlotinib that day. The patient should resume treatment with the next scheduled dose. If more than 12 hours have elapsed, that day's dose should be omitted, and the patients should continue treatment with the next scheduled dose. A pill diary will be used to record adherence.

9.1.2 Therapeutic Agent-Trametinib

Trametinib will be supplied for the purposes of this trial by Novartis. Trametinib is given once daily and can be taken with or without food 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 erlotinib in this single-arm study.

9.3 Study design

Phase 1 (safety run-in): This portion of the study will assess whether a dose of trametinib 1.5mg by mouth once daily and erlotinib 75mg by mouth once daily is a safe dose. Six patients will need to be enrolled at this dose level and assessed for dose limiting toxicities (DLTs) for 1 full cycle (28 days). Toxicity will be graded according to NCI CTCAE version 4.0. If more than one patient develops a DLT, we will move on to the phase 2 portion of the study and the dose level -1 will be used. Dose level -1 of trametinib 1mg daily and erlotinib 100mg daily was already established to be safe and tolerable in a previous phase 1 study. If ≤1 DLTs are detected, we will move on to the phase 2 portion of the study at dose level 0.

Dose levels	Trametinib Dose	Erlotinib Dose
Dose Level 0	1.5mg PO qdaily	75mg PO qdaily
Dose Level -1	1 mg PO qdaily	100mg PO qdaily

Phase 2: All patients will receive erlotinib and trametinib at the dose level defined during the phase 1 portion of the study. Patients will be monitored for response by CT every 2 cycles (8 weeks). The first 8 week response will be considered the primary objective outcome for this portion of the study. The schedule of evaluations and interventions is described in Section 10.0.

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 cycles 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
- Hematologic toxicities including:
  - Grade=4 neutropenia lasting >5 days
  - Grade=4 thrombocytopenia (<25,000/mm3)
  - Grade≥ thrombocytopenia with evidence of clinically significant bleeding
  - Grade=4 anemia
- Non-hematologic toxicities include:
  - Grade ≥ 3 AST, ALT, alkaline phosphatase or total bilirubin
  - 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
  - central serous retinopathy or retinal vein occlusion

9.5 Correlative Studies:

Biopsies will be required prior to start of study treatment and at the time of progression. At prespecified time points, and after additional informed consent, patients will

have image-guided core needle biopsies with 3-4 cores obtained. At least 2 cores will be immediately frozen in liquid nitrogen and sent to Dr. Rudin's lab.

The remaining cores will be fixed in formalin and sent to Surgical Pathology. Blood will also be used for IMPACT testing for next-generation sequencing based testing if not obtained previously.

DNA/RNA will be extracted from one flash-frozen core using an AllPrep® DNA/RNA mini kit (Qiagen). RNA quality will be assessed at the MSKCC integrative genomics (iGO) core facility using an Agilent Bioanalyzer 2100 platform. We will perform RNA-seq on all patients with sufficient tissue from the phase 2 cohort, to quantify changes in gene expression at various time points of treatment and to identify potential biomarkers of response to combination therapy. Extracted RNA (5ug) will be submitted to Genewiz for single-end 75bp reads on a HiSeq 2500 instrument. RNA samples that are limiting in quality/amount will be amplified using the Ovation® RNA-seq System V2 kit (NuGen) and submitted for RNA-seq as cDNA. We expect RNA yields from core biopsies to be limiting, thus we will not perform rRNA depletion prior to submission of samples. Analysis of RNA-seq data will be performed at the MSKCC Bioinformatics core facility. Remaining RNA will be frozen at -80C for validation of genes of interest highlight by RNA-seq data. Validation will be performed using either RT-PCR or through the construction of a custom nanostring nCounter panel that includes genes of interest. One fixed core will be used for immunohistochemistry to determine protein expression for transcripts of interest, including: BIM, cleaved caspase 3, TGFB2, vimentin, e-cadherin, n-cadherin and neurofibromin. MSK-IMPACT, our next-generation sequencing based mutation platform that assesses for genetic alterations in 340 cancer-related genes will be used for molecular analysis.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

Tables 10.1 outlines the schedule of assessments applied to patients. 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. More frequent assessments should be obtained if clinically indicated. Subjects will return to the study site within 30 days after their last dose of trametinib and erlotinib 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 4 weeks unless otherwise noted	C1D1	C1D7	C1D8	C1 D15	C2D1	C3+D1	
Informed Consent	X							
Medical History	X	X		X	X	X	X	X
Concurrent Medication Reconciliation	X	X		X	X	X	X	X
Physical Exam/Performance status[1]	X	X			X	X	X	X
OphthalmologyExam[2]	X					X		
Vital Signs and Weight[1]	X	X			X	X	X	X
Complete Blood Count w/ differential[1]	X	X			X	X	X	X
Comprehensive Metabolic Panel (CMP)[1,3]	X	X			X	X	X	X
12 lead EKG[4]	X	X				X	X	
Echocardiogram[5]	X						X[5]	
Adverse Events Evaluation[1]	X	X		X	X	X	X	X
Radiologic Tumor Assessments[6]	X						X	X
MRI brain/disease assessment	X							
B-HCG[7]	X							
Tumor Tissue[8]	X							X
IMPACT Bloods[9]	x							

[1]Study Assessments (physical exams, vitals, weight, CBC, CMP, adverse events evaluation) will be repeated C1D1, C1D8, C1D15 (first cycle), then monthly subsequently. C1 assessments have a window of +/- 3 days, C2 onward assessments have a window of +/- 2 weeks.
[2]Baseline Opthalmic exam will include visual acuity, visual field examination, tonometry, slit lamp biomicroscopy of 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, month 1 +/- 2 week, and month 6 +/- 4 weeks. Additional ophthalmic exams will be performed if symptomatically warranted.
[3]CMP includes glucose, blood urea nitrogen, creatinine, sodium, potassium, chloride, bicarbonate, calcium, total protein, albumin, serum bilirubin, alkaline phosphatase, ALT, AST
[4]A single 12 lead ECG should be performed at screening and day 1 of every cycle +/- 2 weeks.
[5]Echocardiogram should be performed at screening and every three cycles +/- 2 weeks
[6]Response to therapy will be assessed by interval 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 sties of disease with or without contrast. If an appropriate imaging study is performed early for 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.

[7] B-HCG testing (serum or urine) should be performed only in women of child bearing potential.
[8]Tumor biopsy will be performed within 3 months of study initiation (unless archived tissue is available from a biopsy obtained after progression on erlotinib)and at time
of progression +/- 4 weeks. Both patients on the phase 1 and phase 2 portion of the study will have biopsies performed.
[9]IMPACT bloods will be drawn at screening for next-generation sequencing based testing.

11.0 TOXICITIES/SIDE EFFECTS

Adverse events occurring in patients treated with trametinib and erlotinib may be 1) overlapping toxicities seen in both agents (i.e. rash, diarrhea, and pneumonitis); 2) toxicities typically associated with trametinib (i.e. visual disturbance, QTc prolongations) or 3) toxicities typically associated with erlotinib. However, toxicities with individual agents may be potentiated in the combination or unanticipated AEs may occur. The dose modifications may involve one or both agents, and should be based on the nature, severity, and attributions of the AEs. General guidelines are provided below. For safety and adverse event reporting, see **Section 17.0.**

While AEs may be thought to be related to individual agents for purposes of dose modifications, all toxicities will be considered related to combination therapy for description of AE profile.

11.1 **Management of Erlotinib-Related Toxicities:**

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

- Fatigue
- Rash
- Diarrhea
- Decreased appetite
- Nausea/Vomiting

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

- Cough
- Shortness of breath
- Mucositis
- Abdominal Pain
- Changes in hair or nails
- Liver Toxicity

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

- Pneumonitis
- Acute renal failure
- Stevens Johnson Syndrome
- Liver failure
- Conjunctivitis
- GI bleeding/perforation

The table below outlines the dose levels to be used for any necessary **erlotinib** dose modification:

If Dose level 0 of erlotinib (75mg daily) in the Phase 1 run-in is used for the phase 2 study:

Dose Reduction	Erlotinib Dose/Schedule
0	75mg QD
1	50mg QD
2	25mg QD

If dose level -1 of erlotinib (100mg daily) in the Phase 1 run-in is used for the phase 2 study:

Dose Reduction	Erlotinib Dose/Schedule
0	100mg QD
1	75mg QD
2	50mg QD

A maximum of two erlotinib dose level reductions are allowed. If a third dose level reduction is required, study treatment will be permanently discontinued.

Erlotinib Dose Modification for Toxicities Not Specified in Subsequent Sections

<table>
<tr><td colspan="3">Erlotinib Treatment Modification for Clinically Significant Toxicities Deemed Related to Erlotinib
(This section is <u>not</u> for specific AEs such as rash, pneumonitis, or diarrhea. Refer to <u>other</u> sections for these specific AEs).</td></tr>
<tr><th>CTCAE v4 Grade</th><th>Dose Modification</th><th>Management Guideline</th></tr>
<tr><td>Grade 1</td><td>Continue erlotinib at current dose level.</td><td rowspan="4">Monitor as clinically indicated. Provide supportive care according to institutional standards</td></tr>
<tr><td>Grade 2</td><td>• Consider interrupting treatment until resolution to grade 1 or baseline.
• Upon resolution, restart treatment at current dose level.</td></tr>
<tr><td>Grade 3</td><td rowspan="2">• Interrupt treatment until resolution to grade ≤2 Upon resolution to grade ≤2, restart with one level of dose reduction
• If the Grade 3 toxicity recurs, interrupt erlotinib; When toxicity resolves to grade ≤2, restart erlotinib reduced by another dose level</td></tr>
<tr><td>Grade 4</td></tr>
<tr><td colspan="3">Erlotinib should be discontinued if treatment delay is <u>≥</u>21 days due to toxicities. If the investigator concludes that continued erlotinib will benefit a patient, the study PI may be consulted for the possibility of resuming erlotinib provided that toxicities have resolved to grade ≤2.</td></tr>
</table>

11.2 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 outlines the dose levels to be used for any necessary trametinib dose modification:

If Dose level 0 of trametinib (1.5mg daily) in the Phase 1 run-in is used for the phase 2 study:

Dose Reduction	Trametinib Dose/Schedule
0	1.5mg QD
1	1mg QD
2	0.5mg QD

If dose level -1 of trametinib (1 mg daily) in the Phase 1 run-in is used for the phase 2 study:

Dose Level	Trametinib Dose/Schedule
0	1mg QD
1	0.5mg QD
2	0.25mg QD

A maximum of two trametinib dose level reductions are allowed. If a third dose level reduction is required, 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 ≥21 days due to toxicities. If the investigator concludes that continued trametinib will benefit a patient, the study PI and GSK medical monitor may be consulted for the possibility of resuming trametinib, 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 and erlotinib (package insert). Recommendations for supportive care and guidelines for dose modifications for rash are based on experience with other MEK inhibitors and EGFR inhibitors.[16,17] Patients should be informed that skin toxicity is expected during treatment with erlotinib and trametinib. Skin toxicity can take the form of dry skin, rash, acneiform eruption, and hair/nail changes. Prophylactic treatment of the skin with the recommendations below may prevent or reduce skin toxicity.

Patients with significant skin toxicity will be referred to dermatology for management. Recommended treatments may include topical therapy such as hydrocortisone cream or clindamycin gel. If needed, oral minocycline or oral doxycycline may be combined with topical therapy. For more severe cases, oral corticosteroids may be administered. Patients who fail to respond to these measures may have erlotinib and or 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. • Consider mild-strength topical steroid (hydrocortisone 1% cream) or topical antibiotic (*e.g.*, clindamycin) or oral antibiotics (*e.g.*, doxycycline 100 mg BID, minocycline 100 mg BID).
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/Erlotinib Dose Modification Guidelines and Management for Rash		
Rash Severity	**Management Guideline**	**Dose Modification**
Grade 1	• Initiate prophylactic and symptomatic treatment measures.[1]	Continue trametinib and erlotinib at same dose level.

Trametinib/Erlotinib Dose Modification Guidelines and Management for Rash		
Rash Severity	**Management Guideline**	**Dose Modification**
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 and/or erlotinib by one dose level at discretion of investigator.
Grade 3		Suggest withholding erlotinib and/or 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 and/or erlotinib until toxicity is grade ≤2. Restart with trametinib and or erlotinib reduced by one dose level.[2] If No recovery to ≤ grade 2 within 4 weeks, permanently discontinue trametinib and/or erlotinib.
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 erlotinib (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.

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

Management and Trametinib /Erlotinib 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 (banana, 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 erlotinib at same dose. Initiate adverse event management
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 erlotinib 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 erlotinib 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 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 **Pneumonitis**

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

CTCAE Grade	Adverse Event Management	Action and 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/erlotinib 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/erlotinib until recovery to grade ≤1 • Consider restarting with trametinib/erlotinib 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/erlotinib until recovery to grade ≤1 • After consultation with medical monitor, 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/erlotinib

11.3.4 **Reduced Left Ventricular Ejection Fraction**

Decreases of the left ventricular ejection fraction (LVEF) have been observed in patients receiving trametinib. Therefore, ECHOs 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 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 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 and PI and request approval for restart. – Restart treatment with trametinib at reduced dose 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. – Report as SAE – Repeat ECHO after 2, 4, 8, 12, and 16 weeks or until resolution.

Trametinib Dose Modification Guidelines and Stopping Criteria for LVEF Decrease		
Clinic	**LVEF-drop (%) or CTCAE grade**	**Action and Dose Modification**
Symptomatic[b]	• Grade 3: resting LVEF 39-20% or >20% absolute reduction from baseline • Grade 4: Resting LVEF ≤20%.	• **Permanently discontinue trametinib.** • **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 to previous dose level can be considered if LVEF remains stable for 4 weeks after restarting of trametinib. Approval from GSK Medical Monitor 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, 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.**

Trametinib Withholding and Stopping Criteria for QTc Prolongation	
Prolongation*	**Action and Dose Modification**
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 **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 as clinically warranted. 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**
Any grade of CRS or RVO should be reported as SAE		
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**.

Management and Trametinib Dose Modification for Visual Changes		
Event **CTCAE Grade**	**Management Guideline**	**Dose Modification**
Any grade of CRS or RVO should be reported as SAE		
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. • <u>If CSR</u>: Interrupt trametinib until symptoms resolve and exam (by retinal specialist if available) shows resolution**.** If CSR resolves restart trametinib **reduced by one dose level**. • <u>If RVO</u>: **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.**
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.		

11.3.7 Hypertension

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 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 trametinib 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 **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 • 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 **reduced by one dose level[c]**
(Scenario D) • Refractory hypertension unresponsive to above interventions, or having hypertensive crisis.	• **Permanently discontinue trametinib** • 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 to previous dose level can be considered if BPs remain well-controlled for 4 weeks after restarting of trametinib. Approval from GSK Medical Monitor 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 1.1. Confirmation of response will not need to be 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 sumo 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 ore 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

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.**

Evaluation of Toxicity: All patients who receive at least one dose of treatment with erlotinib and trametinib 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. Other reasons for study discontinuation include but are not limited to:

- Change in patient eligibility
- Non-compliance with the defined treatment plan
- Protocol violation
- Investigator's decision based on patient's best interest
- Withdrawal of consent
- Severe, unexpected toxicities/side effects
- Lost to follow up
- Death
- Progression of disease (defined by RECIST 1.1)

For the Phase 1 portion of the study, patients who withdraw from the study for reasons other than DLT without completing a full treatment cycle will be replaced.

14.0 BIOSTATISTICS

Phase 1: Safety Run In

Primary Objective: To determine the safety and tolerability of the combination of erlotinib 75mg by mouth once daily with trametinib 1.5mg by mouth once daily in patients with EGFR mutant lung cancer and acquired resistance to EGFR tyrosine kinase inhibitors.

Endpoints: Identify any dose limiting toxicities of the combination. A dose limiting toxicity is a binary

outcome where a patient either experiences a DLT or not. DLT is defined as any of the toxicities described in Section 9 that occurs within one cycle after initiation of treatment with erlotinib and trametinib.

Method: Up to six patients will be enrolled at dose level 0 (trametinib 1.5mg by mouth once daily and erlotinib 75mg by mouth once daily) and assessed for dose limiting toxicities (DLTs) for 1 full cycle (28 days). Toxicity will be graded according to NCI CTCAE version 4.0. If more than one patient develops a DLT, we will move on to the phase 2 portion of the study and the dose level -1 will be used. If $\leq$1 DLTs are detected, we will move on to the phase 2 portion of the study at dose level 0.

If 0-1 DLTs occur, and dose level 0 is used in the phase 2, the patients accrued during the phase 1 portion of the study will be followed for response assessment and included in the phase 2 portion of the study. Given an expected accrual rate of 2 patients per month, the accrual to the phase 1 portion of the study will be completed in about 3 months. Two to six patients will be enrolled in the phase 1 portion of the study.

Dose levels	Trametinib Dose	Erlotinib Dose
Dose Level 0	1.5mg PO qdaily	75mg PO qdaily
Dose Level -1	1 mg PO qdaily	100mg PO qdaily

Phase 2:

Primary Objective: To determine the ORR of the combination of erlotinib and trametinib in patients with EGFR mutant lung cancer and acquired resistance to EGFR tyrosine kinase inhibitors

Secondary Objective: To determine the progression free survival and overall survival and further assess the toxicity of trametinib and erlotinib

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 5% response rate against the alternative hypothesis of 25% response rate for patients with acquired resistance. A null hypothesis of 5% was chosen because all eligible patients have demonstrated progression and lack of response to erlotinib. The most effective treatment for both EGFR T790M positive and negative patients is afatinib and cetuximab which has a response rate of 29% but results in significant adverse events[18]. Subsequently, an alternative hypothesis of 25% 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. In the first stage of this design, 9 patients will be treated. If 0 responses are seen in the first 9 patients, the trial will be stopped and declared negative. If at least 1 response is observed, than an additional 15 patients will be accrued to the second stage. At the end of the study, if 3 or more patients have a response out of a total of 24 patients enrolled, the combination of trametinib and erlotinib will be considered worthy of further investigation. Overall survival and time to progression 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 4.0 criteria. All correlative aims are exploratory and will be hypothesis-generating only.

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 6-12 months.

Correlatives: For the correlative studies, the analysis is primarily exploratory and hypothesis generating. Correlative studies will be performed on all patients participating in both the phase 1 and 2 portions of this clinical trial.

Method: EGFR T790M status will be determined for the biopsy samples obtained at the time of acquired resistance to EGFR TKI monotherapy. The portion of patients with T790M mutation will be calculated along with the exact 95% confidence interval. The expression of proteins such as BIM, TGFB2, vimentin, e-cadherin, n-cadherin, and neurofibromin will be quantified using immunohistochemical (IHC) staining in the biopsy tissue obtained and reported as a proportion of patients with each IHC score. Results will be summarized at each time point using descriptive statistics (mean +/- std). Graphical methods will be used to evaluate the way protein expression changes during the course of treatment.

15.1 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.2 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

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.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. Registrations must be submitted via the PPR Electronic Registration System (http://ppr/). The completed signature page of the written consent/RA or verbal script/RA, a completed Eligibility Checklist and other relevant documents must be uploaded via the PPR Electronic Registration System.

15.3 Randomization

There will be no randomization in this phase 2 study.

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 erlotinib has the potential to be effective and induce tumor response in patients with EGFR mutant lung cancer and acquired resistance to erlotinib.

Costs: Patients will be charged (insurance billed) for physician visits, erlotinib, routine laboratory tests, and radiologic studies required for monitoring their condition. The patients will not be billed for the study drug, trametinib. 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 progression of disease on study will not be charged to the patient.

Alternatives: The alternative to this trial would be treatment with chemotherapy with or without continuation of erlotinib 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 (e.g. qualified monitors from Novartis(the manufacturer of trametinib), 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).

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

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

17.2.1 Adverse Event Reporting to Novartis

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided the main 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.

Any SAEs experienced after this 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE 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.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. 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 by fax within 24 hours to the oncology Novartis Drug Safety and Epidemiology (DS&E) department - Fax: (877-778-9739). The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Follow-up information is sent to the same contact(s) to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original 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.

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 recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis Drug Safety and Epidemiology Department (DS&E). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Warnings and precautions

Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed

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.

19.0 REFERENCES

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20.0 APPENDICES

Pill diary