SWOG CANCER RESEARCH NETWORK

Version Date: March 15, 2019

TO: All National Clinical Trials Network (NCTN) Members; CTSU

FROM: Gretchen Goetz, M.B.A., Lead Protocol Coordinator (Email: ggoetz@swog.org)

RE: **S1507**, "A Phase II Trial of Trametinib with Docetaxel in Patients with KRAS Mutation Positive Non-Small Cell Lung Cancer (NSCLC) and Progressive Disease Following One or Two Prior Systemic Therapies." Study Chairs: Drs. Shirish M. Gadgeel, Jonathan W. Riess, and Philip Mack.

REVISION # 3

Study Chair: Shirish M. Gadgeel, M.D.
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IRB Review Requirements
(√) Expedited review allowed

Protocol changes
(√) Informed Consent changes
(√) Patient notification required
(√) Other: Trametinib dimethyl sulfoxide CAEPR update

Sites using the CIRB as their IRB of record: The protocol and/or informed consent form changes have been approved by the CIRB and must be activated within 30 days of the CIRB posting of this notice.

Sites not using the NCI CIRB: Per CTMB Guidelines, the protocol updates and/or informed consent changes must be approved by local IRBs within 90 days of distribution of this notice.

REVISION #3

This revision has been prepared in response to an RRA from Dr. Helen Chen (helen.chen@nih.gov) received on February 22, 2019. The Action Letter for this RRA is anticipated on March 29, 2019. The above referenced protocol has been revised as follows:

1. The Version Date has been revised in the Protocol and the Model Consent Form.

2. Section 3.4c.1: The trametinib CAEPR has been updated from Version 2.4, dated October 7, 2016 to Version 2.5, dated February 1, 2019. The CAEPR has been updated as follows:

   - The SPEER grades have been updated.
   - The section below utilizes CTCAE 5.0 language unless otherwise noted.

- Increase in Risk Attribution:
  - Changed to Rare but Serious from Also Reported on Trametinib dimethyl sulfoxide Trials But With Insufficient Evidence for Attribution: Papilledema; Thromboembolic event (venous)
  - Changed to Less Likely from Also Reported on Trametinib dimethyl sulfoxide Trials But With Insufficient Evidence for Attribution: Nail changes

- Deleted Risk:
  - Also Reported on Trametinib dimethyl sulfoxide Trials but With Insufficient Evidence for Attribution: Rash pustular; Retinal detachment

- Provided Further Clarification:
  - Footnote# 3 "Edema includes edema, lymphedema, and edema limbs." is now reworded as "Generalized edema includes edema, lymphedema, and edema limbs."
  - Footnote# 5 "Skin and subcutaneous tissue disorders - Other (rash) may include rash, rash acneiform, rosacea, erythematous rash, genital rash, rash macular, exfoliative rash, rash generalized, erythema, rash papular, seborrheic dermatitis, dermatitis psoriasiform, rash follicular, and skin fissures." is now reworded as "Skin and subcutaneous tissue disorders - Other (rash) may include rash, rosacea, erythematous rash, genital rash, rash macular, exfoliative rash, rash generalized, erythema, rash papular, seborrheic dermatitis, dermatitis psoriasiform, rash follicular, skin fissures, and skin chapped."
  - Periorbital edema previously listed under the SKIN AND SUBCUTANEOUS TISSUE DISORDERS SOC *(CTCAE 4.0 language)*, is now reported under the EYE DISORDERS SOC.
  - Vascular disorders - Other (edema) *(CTCAE 4.0 language)* is now reported as Generalized edema under the GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS SOC.
  - Skin and subcutaneous tissue disorders - Other (folliculitis) *(CTCAE 4.0 language)* is now reported as Folliculitis under the INFECTIONS AND INFESTATIONS SOC.
  - Musculoskeletal and connective tissue disorder - Other (rhabdomyolysis) *(CTCAE 4.0 language)* is now reported as Rhabdomyolysis.
  - Enterocolitis is now reported as part of Colitis.
  - Anal hemorrhage, Epistaxis, Lower gastrointestinal hemorrhage, Rectal hemorrhage and Upper gastrointestinal hemorrhage are now reported as parts of Vascular disorders - Other (hemorrhage).
  - Gastrointestinal disorders - Other (oropharyngeal pain) *(CTCAE 4.0 language)* is now reported as Oropharyngeal pain under the RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS SOC.
  - Investigations - Other (blood lactate dehydrogenase increased) *(CTCAE 4.0 language)* is now reported as Blood lactate dehydrogenase increased.
  - Metabolism and nutrition disorders - Other (hyperphosphatemia) *(CTCAE 4.0 language)* is now reported as Hyperphosphatemia.
  - Musculoskeletal and connective tissue disorder - Other (muscle spasm) *(CTCAE 4.0 language)* is now reported as Muscle cramp.

- Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (tumor hemorrhage) *(CTCAE 4.0 language)* is now reported as Tumor hemorrhage.
- Renal and urinary disorders - Other (dysuria) *(CTCAE 4.0 language)* is now reported as Dysuria.
- Skin and subcutaneous tissue disorders - Other (skin fissures) is now reported as part of Skin and subcutaneous tissue disorders - Other (rash).

3. Section 8.1: This section has been updated to state that CTCAE Version 5.0 will be used for Serious Adverse Event (SAE) reporting and CTCAE Version 4.0 will be used for routine toxicity reporting.

4. Section 16.1i: This section has been updated to use CTCAE Version 5.0 terminology.

5. The model consent form risk profile for trametinib dimethyl sulfoxide has been revised as follows:

- Increase in Risk Attribution:
  - Added to Occasional: **Change in or loss of some or all of the finger or toenails**
  - Added to Rare: **Blood clot which may cause swelling, pain, shortness of breath**

- Provided Further Clarification:
  - Sores in mouth which may cause difficulty swallowing (under Occasional) is now reported as Sores in the mouth which may cause difficulty swallowing (under Occasional).
  - High blood pressure (under Occasional) is now reported as High blood pressure which may cause headaches, dizziness, blurred vision (under Occasional).
  - Damage to muscle (under Rare) is now reported as Damage to muscle which may cause muscle pain, dark red urine (under Rare).
  - Damage of the lungs which may cause shortness of breath (under Rare) is now reported as Damage to the lungs which may cause shortness of breath (under Rare).

Patient Notification and Regulatory Considerations

Please note that the information provided below regarding patient notification and amendments to local consent forms reflects SWOG's minimum requirements. Sites should refer to the policies/procedures of the IRB of record to determine whether they have any more stringent requirements.

Patient Notification

Patients must be notified of the changes above that are **bolded**.

Who must be informed?

- Patients currently receiving trametinib dimethyl sulfoxide

How must patients be notified?

- Notification must take place either via the attached Consent Addendum or via formal reconsent. After the changes have been discussed with the patient, the patient should sign and date either the Consent Addendum or the 3/15/19 version of the consent form.

What is the notification deadline and process?

- Patients must be notified by their next scheduled visit or within 90 days after CTSU distribution of this revision, whichever is sooner.
- Sites using the NCI CIRB as their IRB of record: CIRB has approved the attached Consent Addendum; therefore, the Consent Addendum may be utilized immediately to notify patients of these changes.

- Sites not using the NCI CIRB as their IRB of record: This information should be communicated to patients already enrolled on study without waiting for IRB review/approval. This information represents a significant new finding(s) that developed during the course of the research that may relate to a patient's willingness to continue participation. Per the Office for Human Research Protections, the regulations do not require IRB review and approval of statements describing such significant new findings before they are provided to already enrolled patients. If local IRB approval of the Consent Addendum is required before sites may utilize it, the site must still notify patients verbally prior to the notification deadline and notification must be documented in the patient chart. The site must then obtain patient signature on the Consent Addendum or updated consent form once the addendum and/or revised consent is locally approved.

Regulatory Considerations:

Do local consent forms need to be updated?

- No, local consent forms need not be updated because this study is closed to accrual.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL AND INFORMATION OFFICE

PRIVILEGED COMMUNICATION
FOR INVESTIGATIONAL USE ONLY

Activation Date July 18, 2016

SWOG

A PHASE II TRIAL OF TRAMETINIB WITH DOCETAXEL IN PATIENTS WITH KRAS MUTATION POSITIVE NON-SMALL CELL LUNG CANCER (NSCLC) AND PROGRESSIVE DISEASE FOLLOWING ONE OR TWO PRIOR SYSTEMIC THERAPIES

NCT #XXXXX

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AGENTS:

NCI Supplied Investigational Agents:
Trametinib dimethyl sulfoxide (GSK1120212B)
(NSC 763093)

Commercially Supplied Agent:
Docetaxel (NSC 628503)
Filgrastim (r-mehHuG-CSF) (Neupogen®)
(NSC 614629)
Pegfilgrastim (Neulasta™) (NSC 725961)

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CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

To submit site registration documents:	**For patient enrollments:**	**Submit study data:**
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA19103 Phone: 866-651-CTSU Fax: 215-569-0206 Email: CTSURegulatory@ctsu.coccg.org (for submitting regulatory documents only)	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions. Other Tools and Reports: Institutions participating through the CTSU continue to have access to other tools and reports available on the SWOG Workbench. Access this by using your active CTEP-IAM userid and password at the following url: https://crawb.crab.org/TXWB/ctsulogon.aspx

The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password.

For patient eligibility questions contact the SWOG Data Operations Center by phone or email:

206-652-2267
lungquestion@crab.org
For treatment or toxicity related questions contact Dr. Gadgeel or Dr. Riess.

For questions unrelated to patient eligibility, treatment, or data submission contact the CTSU Help Desk by phone or e-mail:

CTSU General Information Line:
888-823-5923
ctsucontact@westat.com

All calls and correspondence will be triaged to the appropriate CTSU representative.

The CTSU Web site is located at https://www.ctsu.org

1.0 OBJECTIVES

1.1 Primary Objective

To evaluate the response rate (confirmed and unconfirmed) to trametinib plus docetaxel in the entire study population of KRAS mutation positive non-small cell lung cancer (NSCLC) patients following one or two prior systemic therapies.

1.2 Secondary Objectives

a. To evaluate if trametinib plus docetaxel is consistent with promise of activity measured by the response rate in G12C KRAS mutation positive NSCLC patients following one or two prior systemic therapies.

b. To assess the response rate of this combination in non-G12C KRAS mutation positive NSCLC patients.

c. To assess progression-free survival within the G12C and non-G12C KRAS positive subgroups and the entire study population.

d. To evaluate the toxicity of the regimen.

e. To assess overall survival within G12C positive patients, non-G12C positive patients, and the entire study population.

1.3 Translational Medicine Objectives

a. To evaluate the response rates in the presence of comutations p53 and LKB1.

b. To bank specimens for future research.

2.0 BACKGROUND

KRAS mutation positive NSCLC

In recent years genetic alterations that bestow a selective proliferative and survival advantage (so called 'driver mutations') have been identified in a subset of cancers, including non-small cell lung cancer (NSCLC). These driver mutations are responsible for both initiation and maintenance of the malignant phenotype. Drugs targeting such driver mutations have led to significant clinical benefit in patients with such tumors.

In NSCLC two genetic alterations that have been successfully targeted for therapeutic benefit and now have approved drugs are mutations in the tyrosine kinase domain of the EGFR (epidermal growth factor receptor) gene and ALK (anaplastic lymphoma kinase) gene rearrangements. *(1, 2)* These results have spurred interest in identifying other genetic alterations that can be targeted.

Mutations in the KRAS gene were identified in NSCLCs over 25 years ago. *(3)* The protein encoded by the KRAS gene functions as a guanosine diphosphate (GDP)/ guanosine triphosphate (GTP) regulated on-off switch that can activate downstream signaling proteins. *(4)* The GDP/GTP cycling is regulated by guanine nucleotide exchange factors that promote formation of active Ras-GTP complex, whereas GTPase activating proteins stimulate GTP hydrolysis and lead to the formation of inactive Ras-GDP. Activated Ras-GTP binds to many

effector proteins and activates them and thus the downstream signaling pathways. Mutated KRAS in cancers result in single amino acid substitutions primarily in codons 12, 13 and 61. Mutated Ras encodes for protein that is insensitive to GTPase and therefore constantly bound to GTP and active, leading to increased activation of downstream signaling proteins. In non-small cell lung cancers, KRAS mutations occur most commonly in adenocarcinomas (25-30%; squamous cell < 5%) and they occur primarily in codon 12 and codon 13. *(5, 6, 7)* Also KRAS mutations are much more common in smokers (25%) than never smokers (6%). Direct inhibition of KRAS for therapeutic benefit has remained elusive. An alternative approach is to inhibit the downstream signaling proteins to effectively inhibit KRAS signaling and thus its oncogenic consequences.

Raf1 was the first effector protein of Ras to be identified. Raf1 signals through a pathway that involves the ERK-MEK signaling cascade. *(8)* The ERK-MEK signaling pathway is the primary mediator of the oncogenic effects of Ras mutations. However Ras mutations also activate other pathways that are important for its oncogenic effects and one of the most important non-ERK-MEK pathways to be activated by Ras is the PI3K pathway. This occurs through the direct interaction of Ras and PI3K. *(9)* The PI3K is known to play a significant role in cell proliferation and survival and it involves the Ser/Thr kinase Akt, protein kinase B and nuclear factor- kappa B (NFkB).

Since ERK-MEK pathway is an important mediator of the oncogenic effects of KRAS, MEK inhibitors were evaluated for the treatment of patients with KRAS mutation positive tumors including NSCLC. Evidence to date has suggested that the benefits of single agent MEK inhibitors are modest. *(10,11)* A plausible explanation for the observed modest activity is the ability of tumors to sustain the malignant phenotype through other pathways activated by mutated KRAS, particularly the PI3K pathway. Pre-clinical studies have shown that tumor cells with Ras or Raf activation resistant to MEK inhibitors have an activated PI3K pathway. *(12,13)* In addition, pre-clinical studies show that MEK inhibition may release the negative feedback loops, leading to activation of AKT and this could limit the anti-tumor effects of MEK inhibitors in KRAS mutation positive tumors. *(14)*

Retrospective clinical data suggest that KRAS-mutation positive NSCLCs are more resistant to chemotherapy drugs. *(15,16)* In addition data presented by Shepherd, et al suggests that benefits of adjuvant chemotherapy may differ based on types of KRAS mutations. Patients with codon 13 KRAS mutation positive NSCLCs had worse outcomes with adjuvant chemotherapy. *(17)* In-vitro studies have shown that addition of MEK inhibitor to chemotherapy can enhance the anti-tumor effects of chemotherapy. *(18)* Recently Janne, et al reported the results of a randomized Phase II study that evaluated the addition of selumitinib (AZD6244), another MEK inhibitor, to docetaxel in patients with KRAS mutation positive progressive NSCLC. *(19)* The addition of AZD6244 led to improved progression free survival (5.3 mo vs. 2.1 mo, p=0.0138) and response rate (37.2% vs. 0%, p < 0.0001). The percentage of patients that were alive and progression free at 6 months was also superior in patients who received the combination, 37.1%, compared to the patients who received docetaxel alone, 15.8% (p=0.0158). The overall survival was numerically superior with the addition of AZD6244 (9.4 mo vs. 5.2 mo) but this did not reach statistical significance (p=0.2069). Adverse events were also higher among patients who received the combination of AZD6244 with docetaxel, particularly neutropenia. Despite the higher rates of adverse events, the patients receiving the combination were able to receive a median of 5 cycles compared to patients receiving docetaxel alone, who received a median of 4 cycles. These data suggest that MEK inhibitors in combination with chemotherapy, specifically docetaxel, have a role in the management of patients with KRAS mutation positive NSCLC. The results of this study have not only generated interest in testing tumors of NSCLC patients for KRAS mutations but also interest in evaluating other MEK inhibitor-based strategies for the treatment of these patients.

Heterogeneity of KRAS mutation cancers

Emerging data suggest that the biologic behavior of KRAS mutation positive tumors is heterogeneous. In colon cancer certain studies have suggested that the negative predictive value of KRAS mutations for benefit from cetuximab varies according to codon 12 or codon 13 mutations. *(20)* As stated earlier a retrospective analyses of adjuvant trials in lung cancer by Shepherd, et al showed that patients with codon 13 mutations had worse outcome with adjuvant chemotherapy. *(21)* This was not observed in patients with codon 12 mutations. In this study 10% of the KRAS mutation positive patients had codon 13 mutations.

The heterogeneity of KRAS mutations extends to patients' smoking status. The spectrum of KRAS mutations in lung cancer differs between smokers and never smokers and from those observed in other tumors. *(22,23)* The most common KRAS mutation in lung cancer patients, who are current or former smokers, is a G to T transversion (43%), with the most common amino acid substitution being cysteine (Gly-12Cys or G12C). In contrast, the most common KRAS mutation in lung cancer patients who are never smokers is a G to A transition, with the most common amino acid substitution being aspartate. In an analysis of patients whose tumors were biopsied prospectively on a clinical trial, Ihle, et al reported that patients with Gly-12Cys and Gly-12Val had worse progression free survival than patients with tumors that had other KRAS mutations. *(24)* In addition, based on in vitro analysis, they found that downstream signaling varies based on specific KRAS mutations. Thus, Gly-12Cys and Gly-12Val activated Ral signaling, whereas Gly-12Asp activated PI3K and MEK. The importance of specific amino acid substitutions, in predicting for benefit from specific targeted agents, is further highlighted by recent data from a Phase Ib trial evaluating trametinib, a MEK inhibitor, in combination with docetaxel in two different cohorts of advanced NSCLC patients: KRAS mutation positive (N=25 patients) and KRAS wild type (22 patients). The disease control rate (CR+PR+SD) in both cohorts was about 60%. The disease control rate was 80% among patients with tumors that had G12C mutations (N=10 patients) but only 47% among patients with tumors that had other KRAS mutations (N=15 patients). All patients were treated with granulocyte growth factors since the rate of cytopenias, particularly neutropenia, can be high. Even with the use of colony stimulating factors 23% of the patients had neutropenia and 4% of the patients had febrile neutropenia. The efficacy data suggest that the clinical benefit with a combination of a MEK inhibitor and docetaxel is different in patients with KRAS mutation positive NSCLCs based on the specific amino acid substitution. *(25)*

Heterogeneity in biologic behavior of KRAS mutant tumors may also be related to concomitant genetic alterations. Over the last few years it has been recognized that KRAS-mutation positive NSCLCs could have other genetic alterations, specifically loss of p53 or tumor suppressor gene LKB1. Previous reports suggest that concomitant p53 mutations occur in about 30% of KRAS mutation positive NSCLC and that this rate varies according to smoking status, with a higher rate observed in patients who are current or recent smokers. *(26)* LKB1 is a serine/threonine kinase that is known to have tumor suppressive effect and is inactivated in about 30% of adenocarcinomas. *(27)* Heterozygous germline mutations in LKB1 predisposes to Peutz-Jeghers syndrome. LKB1 through the activation of AMPK regulates mTOR signaling. In addition LKB1 regulates the PI3K/AKT pathway through PTEN. Thus, in tumors with loss of LKB1, the PI3K/AKT/mTOR signaling is activated. In addition, it can be hypothesized that KRAS mutation positive tumors with concomitant loss of LKB1 are highly dependent upon PI3K/Akt/mTOR signaling. This hypothesis is supported by pre-clinical evidence that presence of LKB1 loss of function mutations predict for anti-tumor activity of PI3K pathway inhibitors. *(28)* Recently Skoulidis, et al presented data showing that concomitant mutations in LKB1 and p53 define two non-overlapping subsets of KRAS mutation positive lung adenocarcinomas with distinct intracellular signaling and therefore distinct therapeutic susceptibilities. In addition, they showed that KRAS positive NSCLCs that don't have concomitant mutations in either LKB1 or p53 tend to cluster with one of the two subsets. *(29)* These data suggest that KRAS mutation positive tumors that don't have p53 or LKB1 mutations may also have differential activation of the PI3K pathway.

Chen, et al conducted a co-clinical trial along with the randomized Phase II study, reported by Janne, et al, evaluating the influence of these concomitant genetic alterations on the efficacy of docetaxel + MEK inhibitor combination. *(30)* In this trial they treated genetically engineered mice bearing KRAS-mutation positive NSCLCs with AZD6244 and docetaxel or docetaxel alone. This co-clinical trial found that AZD6244, the MEK inhibitor, enhanced the activity of docetaxel in KRAS mutant tumors and KRAS mutant tumors with p53 loss but it did not do so in KRAS-mutation positive tumors with loss of LKB1. These data suggest that the presence of these concomitant genetic alterations could influence the efficacy of MEK + docetaxel combination as well as the efficacy of MEK + PI3K/AKT pathway inhibitors in KRAS mutation positive NSCLCs.

Trametinib

Trametinib is a potent allosteric and ATP non-competitive inhibitor of MEK1/2. In pre-clinical studies the drug inhibited ERK phosphorylation in all cell lines, however the anti-tumor activity was most often observed in Braf mutant cells lines, variably in KRAS mutant cell lines and seldom in cell lines without Braf or KRAS mutation. The drug has shown clinical activity as a single agent in Braf mutant melanoma and modest activity in KRAS mutant pancreatic cancer (2/26) and KRAS mutant NSCLC (2/22). Trametinib is metabolized predominantly via deacetylation (non-cytochrome P450 [CYP450]-mediated) with secondary oxidation or in combination with glucuronidation biotransformation pathways. *(31)* The deacetylation is likely mediated by hydrolytic esterases, such as carboxylesterases, or amidases. Based on in vitro studies, trametinib is not an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2D6, and CYP3A4. Trametinib has an overall low potential for drug-drug interactions.

In a Phase I trial the MTD (maximum tolerated dose) of trametinib was established as 3 mg every day, but the recommended Phase II dose was chosen at 2mg every day based on tolerability of repeated cycles. *(32)* The relationship between dose and tumor biomarkers such as pERK, Ki67, and p27, were evaluated in patients with BRAF or NRAS mutation-positive metastatic melanoma. *(33)* In general, increasing exposures and/or doses provided greater pharmacodynamic effects. The median change observed at a dose of 2 mg every day was 62% inhibition of pERK, 83% inhibition of Ki67, and a 175% increase in p27.

On May 29, 2013, the U.S. Food and Drug Administration (FDA) approved trametinib for the treatment of patients with unresectable or metastatic melanoma with $BRAF^{V600E}$ or $BRAF^{V600K}$ mutations as detected by an FDA-approved test. *(34)* On January 10, 2014, the Food and Drug Administration granted accelerated approval to trametinib and dabrafenib for use in combination to treat patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation as detected by an FDA-approved test. *(35)*

In a multicenter Phase II study, NSCLC patients with KRAS mutant tumors were randomized 2:1 to receive trametinib (2 mg every day) or docetaxel (75 mg/m^2 IV every 3 weeks). *(36)* A total of 134 pts were randomized to trametinib (89) or docetaxel (45); 129 patients had KRAS-mutant NSCLC. The hazard ratio for PFS was 1.14 (95% CI, 0.75-1.75; *P*=0.5197) with a median PFS of 11.7 versus 11.4 weeks for trametinib versus docetaxel. The overall response rate (ORR) was 12% for trametinib and 12% for docetaxel.

As previously stated encouraging activity in KRAS mutation positive tumors has been reported with the combination of trametinib and docetaxel. *(37)* Cytopenias were common and therefore growth factor support was required. With growth factor support the RP2D is 2 mg daily of trametinib and docetaxel at the dose of 75 mg/m^2 administered every 21 days. The toxicities observed with this combination were GI toxicities, mucositis and fatigue. Efficacy both in KRAS mutation positive and negative tumors was observed with this combination, with preferential activity in the G12C KRAS mutation positive patients.

Trametinib also has been evaluated in other tumors including acute myeloid leukemia/ myelodysplastic syndrome and pancreatic cancer both as single agent and in combination with chemotherapy drugs. Activity with this drug has been observed in these tumors though further studies are required to better define the role of this drug in these tumors.

Based on available AE data from clinical studies involving trametinib to date, the most common toxicities are rash and diarrhea. Rash and diarrhea are common, class-effect toxicities for MEK inhibitors. In addition, visual impairment and left ventricular ejection fraction (LVEF) reduction, although observed at lower frequencies, are also considered class-effect toxicities as they have been observed with trametinib as well as other MEK inhibitors.

Adverse Events (AE) of special interest:
Rash, diarrhea, visual disorders, hepatic disorders, cardiac-related AEs, and pneumonitis are considered AEs of special interest because they are either known class effects (i.e., have been observed with other MEK inhibitors) or are potentially life-threatening. *(38)* The following sections provide integrated summaries for these AEs across different clinical trials, with emphasis on trials using trametinib as monotherapy, especially at the RP2D of 2 mg.

Rash: Rash was a common AE observed across different dose levels and in different combinations. *(39)* At the 2 mg dose, rash was seen in 27% to 78% of patients in different trials. Of the approximately 370 subjects with rash AEs at the 2 mg monotherapy dose (including crossover subjects) in five studies, the majority of rash AEs were Grades 1 or 2 (24% to 73%); 0% to 9% of patients experienced Grade 3 rash AEs, and four patients had a Grade 4 rash AE.

In a randomized Phase III trial of trametinib vs. chemotherapy, the overall incidence of skin toxicity (including rash, dermatitis, acneiform rash, palmar-plantar erythrodysesthesia syndrome, and erythema) was 87% in patients treated with trametinib and 13% in chemotherapy-treated patients. Severe skin toxicity occurred in 12% of patients on the trametinib arm, most commonly for secondary infections of the skin The median time to onset of skin toxicity was 15 days (range: 1 to 221 days), and median time to resolution was 48 days (range: 1 to 282 days). Dose reduction was required in 12% for skin toxicities, and permanent discontinuation of trametinib was required in 1% of patients.

Diarrhea: At the 2 mg monotherapy dose, 33% to 58% of patients in five trials had diarrhea. *(40)* Of the approximately 320 subjects (including crossover subjects) with diarrhea at this dose, the majority of diarrhea AEs were Grade 1 or 2 in severity (33% to 56% of all study patients); 17 patients had Grade 3 diarrhea, and none had Grade 4 diarrhea.

Visual disorders: At the 2 mg monotherapy dose, 4% to 21% of the patients in five trials experienced visual disorders. *(41)* Of the 85 total subjects (including crossover subjects) experiencing visual disorders at this dose level, the majority of visual disorders were Grades 1 or 2 (4% to 20% of all study patients); six patients experienced Grade 3 visual disorders, and one patient experienced a Grade 4 visual disorder.

- *Retinal Pigment Epithelial Detachment (RPED):* Also known as chorioretinopathy, RPED is a visual impairment due to fluid accumulation under the retina and causes blurry vision. There were five cases of RPED, previously termed central serous retinopathy, reported from the integrated trametinib safety population consisting of subjects treated with trametinib 2 mg once daily from five studies. *(42)* As of 23 June 2013, 14 cases of RPED were reported across the entire trametinib program amongst subjects treated with trametinib either as monotherapy or in combination with other anti-cancer agents (including cases from a MEK/BRAF combination study).

  Retinal vein occlusion (RVO): As of 23 June 2013, a total of four cases of RVO were reported across the entire trametinib program (including one case from a MEK/BRAF combination study). *(43)* All cases of RVO occurred in one eye only. Study drug was stopped at time of diagnosis in all cases. There was a decrease of visual acuity in two subjects with central RVO (CRVO) while the other two subjects had no meaningful decrease of visual acuity. In the two subjects with CRVO, local treatment with intravitreal injections of anti-VEGF antibodies was initiated within 2 weeks after RVO diagnosis, and visual acuity improved in one subject and restored to baseline conditions in another subject, at the time of the data cutoff. Three of these four cases were considered related to study treatment by the investigators.

Hepatic disorders: Abnormalities of liver enzymes and bilirubin have been observed with administration of trametinib. *(44)* However, assessment of these cases was often confounded by co-morbid conditions (such as biliary obstruction), concomitant use of other potentially hepatotoxic drugs, and liver metastases. At the 2 mg monotherapy dose, 8% to 34% of patients in five trials had LFT abnormalities. Of the 96 total patients (including crossovers) with LFT changes, the majority were Grade 1 or 2 in severity (4% to 20% of all study patients); 26 had Grade 3 events, and 6 patients had Grade 4 events.

Cardiac-related AEs: At the 2 mg monotherapy dose, 3% to 21% of the subjects in six studies had cardiac-related AEs. *(45)* Of the 65 total subjects (including crossover subjects) experiencing cardiac-related AEs at the 2 mg monotherapy dose in five of the studies, the majority of cardiac-related AEs were Grades 1 or 2 in severity (0% to 16% of all study subjects); 18 subjects had Grade 3 cardiac-related AEs, and no subjects had Grade 4 cardiac-related AEs in any study. No subject in one study, which evaluated the effect of repeat oral dosing of trametinib 2 mg QD on cardiac repolarization in subjects with solid tumors, had cardiac-related AEs. One study subject receiving trametinib 2 mg QD had Grade 5 (fatal) acute cardiac failure, with evidence of massive tumor invasion of the heart; this AE was considered not drug-related by the investigator.

In the Phase III trial of trametinib vs. chemotherapy in patients with melanoma (MEK114267), cardiomyopathy (defined as cardiac failure, left ventricular dysfunction, or decreased LVEF) occurred in 7% (14/211) of patients treated with trametinib, and in no patients in the chemotherapy arm. Cardiomyopathy was identified within the first month of treatment in five of these 14 patients; median onset of cardiomyopathy was 63 days (range: 16 to 156 days). Cardiomyopathy resolved in 10 of these 14 (71%) patients. Cardiac monitoring should be included in trametinib protocols, to include LVEF assessment by echocardiogram or MUGA scan at baseline, one month after initiation of trametinib and then at 2- to 3-month intervals while on treatment. Refer to dose modification guidelines for cardiac AEs in the event of LVEF decline or symptomatic cardiac AEs.

Pneumonitis: At the 2 mg monotherapy dose, 0% to 4% of the subjects in five studies had pneumonitis. *(46)* Of the nine total subjects (including crossovers) experiencing pneumonitis AEs at this dose, three subjects had Grade 1 or 2 pneumonitis and six subjects had Grade 3 pneumonitis.

Embryofetal toxicity: Based on its mechanism of action, trametinib can cause fetal harm when administered to a pregnant woman. Trametinib was embryotoxic and abortifacient in rabbits at doses greater than or equal to those resulting in exposures approximately 0.3 times the human exposure at the recommended clinical dose. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

Incidence of common AEs reported from a Phase III trial of trametinib vs. chemotherapy in patients with advanced melanoma:

Patients with abnormal LVEF, history of acute coronary syndrome within 6 months, or current evidence of Class II or greater congestive heart failure (New York Heart Association) were excluded from this trial. Selected adverse reactions (AR) occurring in patients receiving trametinib as compared to patients in the chemotherapy arm are listed as below:

Table: Selected adverse reactions (ARs) occurring in ≥ 10% of patients receiving trametinib AND at a higher incidence than in the chemotherapy arm (high in the trametinib arm compared with chemotherapy by ≥ 5% in overall incidence or by ≥ 2% Grade 3 or 4 AEs)

	Trametinib (n=211)		Chemotherapy (n=99)	
Adverse Reactions	**All Grades**	**Grades 3 and 4**	**All Grades**	**Grades 3 and 4**
Skin and subcutaneous tissue disorders				
Rash	57	8	10	0
Dermatitis acneiform	19	<1	1	0
Dry skin	11	0	0	0
Pruritis	10	2	1	0
Paronychia	10	0	1	0
Gastrointestinal disorders				
Diarrhea	43	0	16	2
Stomatitis	15	2	2	0
Abdominal pain	13	1	5	1
Vascular disorders				
Lymphedema	32	1	4	0
Hypertension	15	12	7	3
Hemorrhage	13	<1	0	0

Table: Percent-patient incidence of laboratory abnormalities occurring at a higher incidence in patients treated with trametinib versus chemotherapy (between-arm difference of ≥ 5% [all grades] or ≥ 2% [Grades 3 or 4])

	Trametinib (n=211)		Chemotherapy (n=99)	
Preferred term	**All Grades**	**Grades 3 and 4**	**All Grades**	**Grades 3 and 4**
Increased aspartate aminotransferase (AST)	60	2	16	1
Increased alanine aminotransferase (ALT)	39	3	20	3
Hypoalbuminemia	42	2	23	1
Anemia	38	2	26	3
Increased alkaline phosphatase	24	2	18	3

Other clinically important adverse reactions observed in ≤ 10% of patients (n=329) treated with trametinib were: nervous system disorders (dizziness, dysgeusia), ocular disorders (blurred vision, dry eye), infections and infestations (folliculitis, rash pustular, cellulitis), cardiac disorders (bradycardia), gastrointestinal disorders (xerostomia), and musculoskeletal and connective tissue disorders (rhabdomyolysis).

Rationale

KRAS mutation positive NSCLC is a distinct biologic subset of NSCLC that has eluded effective targeted therapy. KRAS mutations occur in about 25% of NSCLCs. At the present time there is no approved therapy for this specific NSCLC patient population. In addition, some studies suggest that presence of KRAS mutations may predict for poor prognosis and inferior outcomes with chemotherapy. It is therefore imperative that novel therapies are evaluated in this specific NSCLC patient population. Trametinib may be one of the most effective MEK inhibitors. Though another trial has shown improvement in outcomes with the combination of docetaxel and MEK inhibitor, this single arm Phase II trial will attempt to assess the activity of the combination of docetaxel with trametinib in KRAS mutation positive NSCLC.

An important consideration in evaluating treatment strategies is that KRAS mutation positive NSCLCs can have different biologic outcomes and consequence based on the specific KRAS mutations due to differential downstream signaling. For example, Gly (12Cys), the most common KRAS mutation in patients with lung cancer, is highly associated with tobacco carcinogenesis and complex genotypes which result from cigarette smoking and appears to have distinct clinical and pathological characteristics. In this regard, heterogeneity in the biology of KRAS-mutated cancers may also occur due to concomitant genetic alterations (co-mutations) such as KB1 loss and p53 loss. Therapeutic strategies based on these factors are therefore of considerable interest, and this study will attempt to provide an estimate of efficacy with this combination in the different subsets of KRAS mutation positive NSCLC.

Inclusion of Women and Minorities

This study was designed to include women and minorities, but was not designed to measure differences of intervention effects. The anticipated accrual in the ethnicity/race and sex categories is shown in the table below.

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/Alaska Native	0	0	0	0	0
Asian	1	2	0	0	3
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	2	2	0	0	4
White	24	21	0	1	46
More Than One Race					
Total	27	25	0	1	53

3.0 DRUG INFORMATION

Investigator Brochures

For information regarding Investigator Brochures, please refer to SWOG Policy 15.

For this study, docetaxel, filgrastim, and pegfilgrastim are commercially available; therefore, Investigator Brochures are not applicable for these drugs. Information about commercial drugs is publicly available in the prescribing information and other resources.

For this study, trametinib is investigational and is being provided under an IND held by the National Cancer Institute. The Investigator Brochure may be obtained by contacting the NCI's Pharmaceutical Management Branch (PMB) at 240/276-6575.

3.1 Docetaxel (NSC 628503)

a. PHARMACOLOGY

Mechanism of Action: Docetaxel promotes the assembly of microtubules and stabilizes their formation by inhibiting depolymerization. This stabilization creates a microtubule which is non-functional. Cell death is promoted by the disruption of normal cell shape, motility, attachment, and intracellular transport. Docetaxel is cytotoxic predominately in the s-phase of the cell cycle.

b. PHARMACOKINETICS

1. Absorption: Intravenous administration of docetaxel results in 100% bioavailability. Area under the curve (AUC) of docetaxel was dose proportional following doses of 70 mg/m2 to 115 mg/m2 with infusion times of 1 to 2 hours.

2. Distribution: The initial rapid decline represents distribution to the peripheral compartments and the late (terminal) phase is due, in part, to a relatively slow efflux of docetaxel from the peripheral compartment. Mean steady state volume of distribution was 113 L. In vitro studies showed that docetaxel is about 94% protein bound, mainly to α1-acid glycoprotein, albumin, and lipoproteins.

3. Metabolism: Docetaxel is primarily metabolized in the liver by cytochrome P450 3A4 and 3A5 isoenzymes (CYP3A4/5).

4. Elimination: Docetaxel elimination follows a three compartment model with an initial distribution half-life of 3 to 5 minutes, an intermediate elimination half-life of 36 to 60 minutes, and a terminal half-life of 10 to 18 hours. Mean total body clearance was 21 L/h/m^2.Approximately 6% of unchanged drug is eliminated by the kidney in 24 hours, with the majority (80%) of excretion occurring in feces at 7 days.

c. ADVERSE EFFECTS

1. Possible Side Effects of Docetaxel: The most common adverse effects occurring in > 20% of people receiving docetaxel include: fluid retention, alopecia, nail disorders, skin reactions (rash, pruritis), nausea, vomiting, diarrhea, constipation, mucositis, infections, anemia, asthenia, neutropenia, neuropathy, fever, amenorrhea, erythema of the extremities with edema, pain and lacrimation with or without conjunctivitis.

Adverse effects occurring in ≤ 20% of people receiving docetaxel include: cutaneous skin reactions, abdominal pain, thrombocytopenia, febrile neutropenia, hepatotoxicity, venous thromboembolism, pulmonary embolism, myalgia, anorexia, dysgeusia, dyspnea, and cardiac dysrhythmias.

Rare (< 3%) but potentially serious adverse effects include: hypersensitivity reactions (rash/erythema, hypotension, wheezing, shortness of breath, swelling of the face or throat), acute myeloid leukemia, and interstitial lung disease or pneumonia.

Patients receiving docetaxel infusions may experience alcohol intoxication from the ethanol included in the formulation.

Refer to the current FDA-approved package insert for the most comprehensive and up to date information on adverse reactions.

2. Pregnancy and Lactation: Pregnancy Category D. Excretion in breast milk is unknown and breast feeding is not recommended during treatment.

3. Drug Interactions: Cytochrome P450 3A4/5 inducers, inhibitors, or substrates may alter docetaxel metabolism. In patients receiving treatment with docetaxel, close monitoring for toxicity and a docetaxel dose reduction could be considered if systemic administration of a potent CYP3A inhibitor cannot be avoided. Patients should use caution with sleep aids or narcotic analgesics due to possible additive sedation from the alcohol present in the docetaxel formulation. Due to potential drug interactions, a complete patient medication list, including docetaxel, should be screened prior to initiation of and during treatment with docetaxel (see Section 8.0). Toxicities to be Monitored and Dosage Modifications.

d. DOSING & ADMINISTRATION

See treatment plan in Section 7.0.

e. HOW SUPPLIED

Docetaxel is commercially available and will not be supplied. Refer to the current FDA-approved package insert.

f. STORAGE, PREPARATION & STABILITY

Refer to the current FDA-approved package insert.

3.2 Filgrastim (r-metHuG-CSF) (Neupogen®) (NSC 614629)

a. PHARMACOLOGY

Mechanism of Action: Filgrastim stimulates the production, maturation, and activation of neutrophils; filgrastim activates neutrophils to increase both their migration and cytotoxicity.

b. PHARMACOKINETICS

1. Absorption: First-order pharmacokinetic modeling with maximum serum concentration reached within 2 to 8 hours after subcutaneous injection

2. Distribution: Average Vd 150 mL/kg

3. Metabolism: Unknown

4. Elimination: Renal and neutrophil receptor-mediated, elimination half-life is approximately 3.5 hours

c. ADVERSE EFFECTS

1. Possible Side Effects of Filgrastim: Refer to the current FDA-approved package insert for the most comprehensive and up to date information on adverse reactions.

Most frequent adverse reactions reported are skeletal pain (> 20%).

2. Pregnancy and Lactation: Category C, filgrastim should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Animal studies have demonstrated adverse effects and fetal loss. Filgrastim has been shown to cross the placenta in humans. There are no adequate and well-controlled studies in pregnant women. Excretion in breast milk unknown/use caution.

3. Drug Interactions: Drug interactions between filgrastim and other drugs have not been fully evaluated. Drugs which may potentiate the release of neutrophils, such as lithium, should be used with caution.

Increased hematopoietic activity of the bone marrow in response to growth factor therapy has been associated with transient positive bone-imaging changes. This should be considered when interpreting bone-imaging results.

Filgrastim should not be administered on the same day with anticancer chemotherapeutic agent(s) with leukocyte suppressive properties.

Filgrastim is contraindicated in patients with hypersensitivity to *E.coli*-derived proteins, filgrastim, or any component of the product

d. DOSING & ADMINISTRATION

1. Dosing – See Section 7.0 Treatment Plan

2. Refer to the current FDA-approved package insert for drug administration.

e. PREPARATION, STORAGE & STABILITY

Refer to the current FDA-approved package insert for storage, stability and special handling information.

f. HOW SUPPLIED

Filgrastim is commercially available and will not be supplied. Refer to the current FDA-approved package insert.

3.3 Pegfilgrastim (Neulasta™) (NSC 725961)

a. PHARMACOLOGY

Mechanism of Action: Similar to filgrastim, pegfilgrastim is a colony-stimulating factor that acts on hematopoietic cells by binding to specific cell surface receptors, thereby stimulating proliferation, differentiation, commitment, and end-cell functional activation. Studies on cellular proliferation, receptor binding, and neutrophil function demonstrate that filgrastim and pegfilgrastim have the same mechanism of action.

b. PHARMACOKINETICS

1. Absorption: Similar to filgrastim, first-order pharmacokinetic modeling is expected with maximum serum concentration reached within 2 to 8 hours after subcutaneous injection

2. Distribution: Similar to filgrastim, volume of distribution of averaged at 150 mL/kg

3. Metabolism: Unknown

4. Elimination: Neutrophil receptor binding is an important component of the clearance of pegfilgrastim, and serum clearance is directly related to the number of neutrophils. Pegfilgrastim has reduced renal clearance and prolonged persistence in vivo as compared with filgrastim. The half-life of pegfilgrastim ranges from 15 to 80 hours after subcutaneous injection.

c. ADVERSE EFFECTS

1. Possible Side Effects of Pegfilgrastim: Refer to the current FDA-approved package insert for the most comprehensive and up to date information on adverse reactions. Most frequent adverse reactions are skeletal pain (< 20%).

2. Pregnancy and Lactation: Category C, pegfilgrastim should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Animal studies have demonstrated adverse effects and fetal loss. Pegfilgrastim has been shown to cross the placenta in humans. There are no adequate and well-controlled studies in pregnant women. Excretion in breast milk unknown/use caution.

3. Drug Interactions: Drug interactions between filgrastim and other drugs have not been fully evaluated. Drugs such as lithium may potentiate the release of neutrophils; ensure that patients receiving lithium and pegfilgrastim have more frequent monitoring of neutrophil counts.

Pegfilgrastim should not be administered on the same day with anticancer chemotherapeutic agent(s) with leukocyte suppressive properties.

Pegfilgrastim is contraindicated in patients with hypersensitivity to *E.coli*-derived proteins, filgrastim, or any component of the product.

d. DOSING & ADMINISTRATION

1. Dosing – See Section 7.0 Treatment Plan

2. Refer to the current FDA-approved package insert for drug administration.

e. PREPARATION, STORAGE & STABILITY

Refer to the current FDA-approved package insert for storage, stability and special handling information.

f. HOW SUPPLIED

Pegfilgrastim is commercially available and will not be supplied. Refer to the current FDA-approved package insert.

3.4 Trametinib Dimethyl Sulfoxide (GSK1120212B) (NSC-763093)

a. PHARMACOLOGY

Mechanism of Action: Trametinib is a reversible, highly selective allosteric inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2. Tumor cells commonly have hyperactivated extracellular signal-related kinase (ERK) pathways in which MEK is a critical component. Trametinib interferes with cellular signal-transduction and inhibits proliferation by inducing cell apoptosis, with selective activity towards B-RAF serine/threonine protein kinase (BRAF) and v-ras oncogene homolog GTPase (RAS) mutant cancer cell lines and hematopoietic cancer cells from acute myeloid leukemia (AML) and chronic myeloid leukemia (CML) origins.

b. PHARMACOKINETICS

1. Absorption: Peak plasma concentrations are observed at 1.5 hours following single dose oral administration of trametinib under fasted conditions in humans. Administration of trametinib with a high-fat, high-calorie meal resulted in a 70% decrease in the maximum concentration (Cmax) and 10% decrease in the area under the concentration curve (AUC) compared to fasted conditions. Therefore, it is recommended that trametinib be administered under fasting conditions. The absolute oral bioavailability of a 2 mg tablet is moderate to high (72%) relative to a co-administered IV microdose (5 micrograms).

2. Distribution: Trametinib is highly bound to plasma proteins (97.4%), and has a high volume of distribution (Vd) of 1060 L.

3. Metabolism: Following single dose oral administration in humans, approximately 50% of plasma radioactivity is present as the parent compound. Trametinib is primarily metabolized via deacetylation mediated by hydrolytic esterases, such as carboxylesterases or amidases, with secondary oxidation or in combination with glucuronidation biotransformation pathways. The high absolute bioavailability and low clearance relative to liver blood flow (3.21 L/hr) suggest low hepatic extraction of trametinib in addition to low first-pass metabolism.

4. Elimination: Trametinib has a long terminal half-life of 5.3 days and accumulates with repeat once daily dosing. Fecal excretion is the major route of elimination accounting for >80% of excreted radioactivity recovered. Urinary excretion accounted for <19% of excreted radioactivity recovered (< 10% of the radioactive dose).

c. ADVERSE EFFECTS

1. **Comprehensive Adverse Events and Potential Risks list (CAEPR) for Trametinib dimethyl sulfoxide (GSK1120212B, NSC 763093)**

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 1111 patients.* Below is the CAEPR for Trametinib (GSK1120212B).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.5, February 1, 2019[1]

Adverse Events with Possible Relationship to Trametinib (GSK1120212B) (CTCAE 5.0 Term) [n= 1111]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
CARDIAC DISORDERS			
		Heart failure	
		Left ventricular systolic dysfunction	
	Sinus bradycardia		
EYE DISORDERS			
	Blurred vision		
	Dry eye		
		Eye disorders - Other (chorioretinopathy also known as retinal pigment	

Adverse Events with Possible Relationship to Trametinib (GSK1120212B) (CTCAE 5.0 Term) [n= 1111]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		epithelial detachment)	
		Eye disorders - Other (retinal vein occlusion)	
	Eye disorders - Other (visual disorders)[2]		
		Papilledema	
	Periorbital edema		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
		Colitis	
		Colonic perforation	
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 3)***
	Dry mouth		***Dry mouth (Gr 2)***
	Dyspepsia		***Dyspepsia (Gr 2)***
	Mucositis oral		***Mucositis oral (Gr 3)***
Nausea			***Nausea (Gr 3)***
	Vomiting		***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		***Chills (Gr 2)***
	Edema face		
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
Generalized edema[3]			***Generalized edema[3] (Gr 2)***
IMMUNE SYSTEM DISORDERS			
	Allergic reaction[4]		
INFECTIONS AND INFESTATIONS			
	Folliculitis		***Folliculitis (Gr 2)***
	Lung infection		
	Paronychia		***Paronychia (Gr 2)***
	Skin infection		***Skin infection (Gr 2)***
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 3)***
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr 2)***

Adverse Events with Possible Relationship to Trametinib (GSK1120212B) (CTCAE 5.0 Term) [n= 1111]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 3)***
	CPK increased		
	Ejection fraction decreased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 3)***
	Dehydration		***Dehydration (Gr 3)***
	Hypoalbuminemia		
	Hypomagnesemia		***Hypomagnesemia (Gr 2)***
	Hyponatremia		***Hyponatremia (Gr 3)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Back pain		***Back pain (Gr 2)***
	Pain in extremity		***Pain in extremity (Gr 2)***
		Rhabdomyolysis	
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Headache		***Headache (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 3)***
		Pneumonitis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		***Alopecia (Gr 2)***
	Dry skin		***Dry skin (Gr 2)***
	Nail changes		
		Palmar-plantar erythrodysesthesia syndrome	
	Pruritus		***Pruritus (Gr 2)***
Skin and subcutaneous tissue disorders - Other (rash)[5]			***Skin and subcutaneous tissue disorders - Other (rash)[5] (Gr 3)***
VASCULAR DISORDERS			
	Hypertension		***Hypertension (Gr 3)***

Adverse Events with Possible Relationship to Trametinib (GSK1120212B) (CTCAE 5.0 Term) [n= 1111]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Thromboembolic event (venous)	
	Vascular disorders - Other (hemorrhage)[6]		

[1] This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2] Visual disorders include visual disturbance that can be associated with conjunctival hemorrhage, corneal graft rejection, cyclitis, eye nevus, halo vision, iritis, macular edema, retinal hemorrhage, visual acuity reduced, visual impairment, and vitreous detachment.

[3] Generalized edema includes edema, lymphedema, and edema limbs.

[4] Hypersensitivity (allergic reactions) may present with symptoms such as fever, rash, increased liver function tests, and visual disturbances.

[5] Skin and subcutaneous tissue disorders - Other (rash) may include rash, rosacea, erythematous rash, genital rash, rash macular, exfoliative rash, rash generalized, erythema, rash papular, seborrhoeic dermatitis, dermatitis psoriasiform, rash follicular, skin fissures, and skin chapped.

[6] The majority of hemorrhage events were mild. Major events, defined as symptomatic bleeding in a critical area or organ (e.g., eye, GI hemorrhage, GU hemorrhage, respiratory hemorrhage), and fatal intracranial hemorrhages have been reported.

Adverse events reported on trametinib dimethyl sulfoxide (GSK1120212B) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that trametinib dimethyl sulfoxide (GSK1120212B) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Disseminated intravascular coagulation; Febrile neutropenia; Leukocytosis
CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Myocardial infarction; Restrictive cardiomyopathy; Sinus tachycardia
EYE DISORDERS - Corneal ulcer; Eyelid function disorder; Flashing lights; Floaters; Glaucoma; Photophobia
GASTROINTESTINAL DISORDERS - Ascites; Duodenal ulcer; Esophageal necrosis; Esophageal ulcer; Esophagitis; Gastric hemorrhage; Gastric ulcer; Gastritis; Gastrointestinal disorders - Other (intestinal obstruction); Gastrointestinal disorders - Other (pneumatosis intestinalis); Gastrointestinal fistula; Gingival pain; Hemorrhoidal hemorrhage; Ileus; Obstruction gastric; Pancreatitis; Small intestinal obstruction

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Flu like symptoms; General disorders and administration site conditions - Other (axillary pain); Localized edema; Malaise; Non-cardiac chest pain; Pain
HEPATOBILIARY DISORDERS - Cholecystitis; Hepatic failure; Hepatic pain; Hepatobiliary disorders - Other (hepatic encephalopathy)
INFECTIONS AND INFESTATIONS - Biliary tract infection; Catheter related infection; Device related infection; Endocarditis infective; Enterocolitis infectious; Hepatitis viral; Infections and infestations - Other (abscess limb); Infections and infestations - Other (necrotizing fasciitis); Infections and infestations - Other (oral infection); Pharyngitis; Sepsis; Upper respiratory infection; Urinary tract infection
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising
INVESTIGATIONS - Blood bilirubin increased; Blood lactate dehydrogenase increased; Creatinine increased; Electrocardiogram QT corrected interval prolonged; GGT increased; Lipase increased; Lymphocyte count decreased; Platelet count decreased; Serum amylase increased; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Hyperglycemia; Hyperkalemia; Hyperphosphatemia; Hyperuricemia; Hypocalcemia; Hypoglycemia; Hypokalemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Generalized muscle weakness; Muscle cramp; Musculoskeletal and connective tissue disorder - Other (compression fracture); Myalgia; Neck pain
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor hemorrhage; Tumor pain
NERVOUS SYSTEM DISORDERS - Dysgeusia; Encephalopathy; Intracranial hemorrhage; Lethargy; Nervous system disorders - Other (diplopia); Seizure; Somnolence; Stroke; Syncope; Transient ischemic attacks
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Delirium; Depression; Hallucinations; Insomnia; Personality change
RENAL AND URINARY DISORDERS - Acute kidney injury; Cystitis noninfective; Dysuria; Hematuria; Proteinuria; Urinary incontinence
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Vaginal fistula; Vaginal hemorrhage
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Hypoxia; Laryngeal edema; Oropharyngeal pain; Pleural effusion; Pneumothorax; Productive cough; Pulmonary hypertension; Respiratory failure; Sinus disorder
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Bullous dermatitis; Photosensitivity; Purpura; Skin and subcutaneous tissue disorders - Other (erythema nodosum); Skin ulceration; Urticaria
VASCULAR DISORDERS - Hematoma; Hot flashes; Hypotension

Note: Trametinib (GSK1120212B) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

2. Pregnancy and Lactation: There are no adequate and well-controlled studies of trametinib in pregnant women. Animal studies have shown reproductive toxicity, decreased maternal and fetal weight, fetal

malformations, and early termination of pregnancy. Therefore, trametinib should not be administered to pregnant women. Women of childbearing potential should use effective methods of contraception during therapy and for 4 months following discontinuation. If trametinib is used during pregnancy, or if the subject becomes pregnant while taking trametinib, the subject should be informed of the potential hazard to the fetus. It is not known whether trametinib is excreted in human milk. Because of the potential for drugs to be excreted in human milk, the risk to the nursing infant cannot be excluded and therefore trametinib should not be administered to nursing mothers.

3. Drug Interactions: *In vitro* studies suggest that trametinib may be a substrate for CYP3A4 metabolism and consideration should be used when trametinib is given in combination with a strong CYP3A4 inducer or inhibitor. Trametinib is a weak CYP2C8 inhibitor and may affect medications that are substrates of CYP2C8. Trametinib is not a substrate for human P-glycoprotein (Pgp), breast cancer resistance protein (BCRP), OATP1B1, or OATP1B2 transporters.

   Patients who are taking concomitant medications that have the potential to interact with trametinib may continue taking them, but should be monitored for additional toxicities.

d. DOSING & ADMINISTRATION

1. Dosing – See Section 7.0 Treatment Plan

2. Administration Instructions: Administer orally, on an empty stomach, either 1 hour before or 2 hours after food.

e. PREPARATION, STORAGE & STABILITY

Store tablets at 2°C – 8°C in the original bottle(s). Bottle(s) should be protected from light and moisture. Shelf life surveillance of the intact bottles is ongoing.

Patient Storage Instructions:
- Study drug can be transported home in the bottle(s) that were dispensed to the patient at room temperature. Avoid exposing the bottle(s) to prolonged temperature extremes (ie.do not leave bottle(s) in a hot car while doing errands)
- At home, store the study drug in the refrigerator, 2°C – 8°C (36°F - 46°F). Do not freeze the bottles.
- Keep the tablets in the original bottle(s). Do not remove tablets from the bottle(s) and put them in a pill box or daily dispenser.
- Keep desiccant cylinder in the bottles in order to keep tablets dry.

f. HOW SUPPLIED

1. Novartis supplies and CTEP, NCI, DCTD distributes 0.5 mg and 2 mg (as free base) tablets.

   Investigationally labeled bottles each contain 32 tablets packaged in high density polyethylene bottles with child-resistant closures including an induction seal liner.

The tablet core contains mannitol, microcrystalline cellulose, hypromellose, croscarmellose sodium, magnesium stearate (non-animal), colloidal silicon dioxide and sodium lauryl sulfate.

- 0.5 mg tablets are yellow, modified oval, biconvex and film-coated. Aqueous film coating consists of Opadry Yellow 03B120006 (hypromellose, titanium dioxide, polyethylene glycol, iron oxide yellow).

- 2 mg tablets are pink, round, biconvex and film-coated. Aqueous film coating consists of Opadry Pink YS-1-14762-A (hypromellose, titanium dioxide, polyethylene glycol, polysorbate 80, iron oxide red).

Each commercially-labeled bottle contains 30 tablets with a desiccant.

The tablet core contains mannitol, microcrystalline cellulose, hypromellose, croscarmellose sodium, magnesium stearate (non-animal), colloidal silicon dioxide and sodium lauryl sulfate.

- 0.5 mg tablets are yellow, modified oval, biconvex and film-coated with 'GS' debossed on one face and 'TFC' on the opposing face. Aqueous film coating consists of hypromellose, titanium dioxide, polyethylene glycol, iron oxide yellow.

- 2 mg tablets are pink, round, biconvex and film-coated with 'GS' debossed on one face and 'HMJ' on the opposing face. Aqueous film coating consists of hypromellose, titanium dioxide, polyethylene glycol, polysorbate 80, iron oxide red.

2. Supplied by: Trametinib is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI. Trametinib is provided to the NCI under a Collaborative Agreement between Novartis and the DCTD, NCI.

3. Drug Ordering: NCI supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP assigned protocol number must be used for ordering all CTEP supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Drug may be requested by submitting agent requests through the PMB Online Agent Ordering Processing (OAOP) application (https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM)

account (https://eapps-ctep.nci.nih.gov/iam/) and the maintenance of an "active" account status and a "current" password.

4. Drug Returns: All unused drug supplies should be returned to the PMB. When it is necessary to return study drug (e.g. sealed vials remaining when expired vials are recovered by the PMB), investigators should return the study drug to the PMB using the NCI Return Agent Form available on the NCI home page (http://ctep.cancer.gov).

5. Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition and return of all drugs received from the PMB using the Drug Accountability Record Form available on the NCI home page (http://ctep.cancer.gov).

6. Contact Information: Questions about drug orders, transfers, returns or accountability should be addressed to the PMB by calling 240/276-6575 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time or by emailing PMBAfterHours@mail.nih.gov anytime.

4.0 STAGING CRITERIA

Patients must have recurrent or Stage IV disease as outlined below (AJCC Cancer Staging Manual, 7th Edition, 2010):

Stage IV	Any T	Any N	M1a
	Any T	Any N	M1b

Primary Tumor (T)

TX	Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)*
T1a	Tumor 2 cm or less in greatest dimension
T1b	Tumor more than 2 cm but 3 cm or less in greatest dimension

T2 Tumor more than 3 cm but 7 cm or less or tumor with any of the following features (T2 tumors with these features are classified T2a if 5 cm or less); Involves main bronchus, 2 cm or more distal to the carina; Invades visceral pleura (PL1 or PL2); Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung

T2a Tumor more than 3 cm but 5 cm or less in greatest dimension
T2b Tumor more than 5 cm but 7 cm or less in greatest dimension
T3 Tumor more than 7 cm or one that directly invades any of the following: parietal pleural (PL3) chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumor in the main bronchus (less than 2 cm distal to the carina* but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumor nodule(s) in the same lobe
T4 Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, separate tumor nodule(s) in a different ipsilateral lobe

* The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximally to the main bronchus, is also classified as T1a.

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastases
N1 Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2 Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3 Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

Distant Metastasis (M)

M0 No distant metastasis
M1 Distant metastasis
M1a Separate tumor nodule(s) in a contralateral lobe tumor with pleural nodules or malignant pleural (or pericardial) effusion **
M1b Distant metastasis

** Most pleural (and pericardial) effusions with lung cancer are due to tumor. In a few patients, however, multiple cytopathologic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is non-bloody and is not an exudate. Where these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient should be classified as M0.

5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a patient to be considered eligible for registration. Use the spaces provided to confirm a patient's eligibility. For each criterion requiring test results and dates, please record this information on the Onstudy Form and submit via Medidata Rave® (see Section 14.0). Any potential eligibility issues should be addressed to the Data Operations Center in Seattle at 206/652-2267 or lungquestion@crab.org prior to registration.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday 4 weeks later would be considered Day 28. This allows for efficient patient scheduling without exceeding the guidelines. **If Day 14 or 28 falls on a weekend or holiday, the limit may be extended to the next working day.**

5.1 Disease Related Criteria

a. Patients must have pathologically confirmed KRAS mutation (at codon 12, 13 and 61) positive non-small cell lung cancer (NSCLC) that is Stage IV or recurrent. The specific subtype of KRAS mutation must be known. KRAS mutation and subtype testing must have been performed in a CLIA certified laboratory. CLIA certified commercially available tests are acceptable.

b. Patients must have measurable disease (see Section 10.1) documented by CT or MRI within 28 days prior to registration. The CT from a combined PET/CT may be used only if it is of diagnostic quality as defined in Section 10.1a. Non-measurable disease must be assessed within 42 days prior to registration. All known sites of disease must be assessed and documented on the Baseline Tumor Assessment Form (RECIST 1.1).

c. Patients must not have known brain metastases, leptomeningeal carcinomatosis or spinal cord compression unless: (1) metastases have been locally treated (including SBRT, WBRT, and surgical resection) and have remained clinically controlled and asymptomatic for at least 14 days following treatment and prior to registration, AND (2) patient has no residual neurological dysfunction and has been off corticosteroids for at least 2 days prior to registration.

5.2 Prior/Concurrent Therapy Criteria

a. Patients must have documented progressive cancer following at least one but no more than two prior regimens of systemic therapy for lung cancer, one of which must have been platinum based combination chemotherapy.

Treatment with an immune therapy or targeted therapy for advanced disease will be considered a separate regimen and will count toward the prior regimens.

Maintenance therapy will not be counted as a separate regimen.

Adjuvant chemotherapy or chemotherapy administered as part of concurrent chemotherapy and radiation therapy for the treatment of lung cancer will not count as a prior regimen of systemic therapy as long as recurrence of patient's lung cancer occurred more than 12 months after the last day of chemotherapy.

b. Patients must not have received any chemotherapy, biologic agent, or any investigational agent within 14 days prior to registration. Patients must have recovered from any adverse events to CTCAE Grade 0-1 prior to registration.

c. Prior treatment with an anti-PD-1 or anti-PDL1 is not required.

d. Patients must not have received prior docetaxel. Patients must not have received therapy with a drug known to be either a MEK inhibitor or a PI3K/AKT/mTOR pathway inhibitor.

e. Patients must have recovered from any adverse effects from prior therapy (except alopecia) to ≤ CTCAE Grade 1 prior to registration.

f. Patients may have had prior radiation therapy as long as it has not affected greater than 25% of the bone marrow and at least one measurable lesion is outside the area of prior radiation (see Section 18.3). At least 7 days must have elapsed since last radiation treatment. Patients must have recovered from any adverse events from prior radiation therapy to ≤ CTCAE Grade 1.

g. Patients must not have had a major surgery within 28 days prior to registration. Patients must have recovered from any adverse effects of prior surgery to the satisfaction of the treating physician. Biopsies and central IV access placement are not considered major surgery.

h. Because the composition, PK, and metabolism of many herbal supplements are unknown, the concurrent use of all herbal supplements is prohibited during the study (including but not limited to St. John's Wort, kava, ephedra [ma huang], ginko biloba, dehydroepiandrosterone [DHEA], yohimbe, saw palmetto, or ginseng).

5.3 Clinical/Laboratory Criteria

a. Patients must have Zubrod performance status of 0-2 (see Section 10.4

b. Patients must have adequate bone marrow function as evidenced by all of the following: ANC ≥ 1500/mcL; platelet count ≥ 100,000/mcL; and hemoglobin ≥ 9 grams/dl. These results must be obtained within 28 days prior to registration.

c. Patients must have adequate liver function as evidenced by the following: total bilirubin ≤ 1.5 x institutional upper limit of normal (IULN), and AST and ALT ≤ 2.5 x IULN (or ≤ 5 x IULN for patients with known liver metastases). These results must be obtained within 28 days prior to registration.

d. Patients must have adequate renal function as evidenced by ONE of the following: serum creatinine ≤ 1.5 x IULN OR measured or calculated creatinine clearance ≥ 40 mL/min. This result must have been obtained within 28 days prior to registration.

$$\text{Calculated creatinine clearance} = \frac{(140 - \text{age}) \times \text{wt (kg)} \times 0.85 \text{ (if female)}}{72 \times \text{creatinine (mg/dl)}}$$

e. Patients must be able to swallow oral medications and must not have a gastro-intestinal disorder with diarrhea as a major symptom or that may alter absorption such as malabsorption syndromes or gastric resection.

f. Patient must not have prior history of interstitial lung disease or pneumonitis.

g. Patients must not have history of significant co-morbid illness inclusive of but not restricted to New York Heart Association Class II, congestive cardiac failure, uncontrolled hypertension, history of myocardial infarction, unstable angina, coronary angioplasty, stenting or cerebrovascular accident within 6 months prior to registration or any other illness that in the assessment of the treating physician would compromise the ability of the patient to participate in this study.

h. Patients must have QTC interval ≤ 480 msec (using the Bazett's formula) on electrocardiogram performed within 42 days prior to registration. History or evidence of current clinically significant uncontrolled arrhythmias are not eligible. However, patients with controlled atrial fibrillation for > 30 days prior to randomization are eligible. Patients must not have atrial fibrillation > Grade 2 on the screening ECG. Patients with CTCAE Grade 1-2 atrial fibrillation on their screening ECG must have a second ECG performed prior to registration and more than 30 days from the screening ECG (either before or after) with the most recent ECG showing stable or improving grade of atrial fibrillation.

i. Patients must have a left ventricular ejection fraction (LVEF) ≥ institutional lower limit of normal (ILLN) by ECHO or MUGA within 42 days prior to registration.

j. Patients must not have untreated or unresolved retinopathy or have a history (or current evidence) of retinal vein occlusion determined by an ophthalmology exam within 42 days prior to registration.

k. Patients must not have an immediate or delayed hypersensitivity reaction or idiosyncracy to drugs chemically related to trametinib, or excipients, or to dimethyl sulfoxide (DMSO) or other agents used in the study.

l. Patients must not have a known history of active hepatitis B or C infection (defined as presence of Hep B sAg and/or Hep B DNA and/or Hep C RNA) because docetaxel and trametinib can cause hepatotoxicity and can jeopardize patients with hepatitis. Also, because docetaxel and trametinib can cause significant cytopenias, patients must not have a known history of HIV seropositivity.

m. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, *in situ* cervical cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease free for three years. Patients with localized prostate cancer who are being followed by an active surveillance program are also eligible.

n. Patients must not be pregnant or nursing due to the risk of fetal or nursing infant harm. Women/men of reproductive potential must have agreed to use an effective contraceptive method (hormonal or barrier method of birth control; abstinence) prior to study entry, during the study participation and for 4 months after the last dose of the drug. A woman is considered to be of "reproductive potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures.

5.4 Specimen Submission Criteria

a. Patients must be offered optional participation in banking of specimens for future research as described in Section 15.1.

5.5 Regulatory Criteria

a. Patients must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines

b. As a part of the OPEN registration process (see Section 13.3 for OPEN access instructions) the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.

6.0 STRATIFICATION FACTORS

Patients will be stratified by type of KRAS mutation: G12C vs non-G12C.

7.0 TREATMENT PLAN

For treatment or dose modification questions, please contact Dr. Shirish M. Gadgeel at 313/576-8753 or email at gadgeels@karmanos.org or contact Dr. Jonathan Riess at 916/734-3772 or jonathan.riess@ucdmc.ucdavis.org. For dosing principles or questions, please consult the SWOG Policy #38 "Dosing Principles for Patients on Clinical Trials" at http://swog.org (then click on "Policies and Manuals" under the "Visitors" menu and choose Policy 38).

7.1 Pre-Medication

Patients receiving therapy with docetaxel must receive appropriate pre-medications consisting of dexamethasone and anti-emetics. The exact schedule and dose for these pre-medications should be according to local practices.

7.2 Treatment

Patients will receive the following therapy:

Agent	Dose	Route	Day	Schedule*
Trametinib	2 mg	PO	1-21	Daily
Docetaxel	75 mg/m^2	IV	1	Each cycle
Pegfilgrastim/filgrastim**				

* 1 cycle = 21 days

** As long as the patient is receiving docetaxel at the dose of 75mg/m^2, patient must receive pegfilgrastim or filgrastim following each cycle. Dosing and administration must be performed in accordance with ASCO and NCCN guidelines. Current guidelines from both NCCN and ASCO state that prophylactic use of myeloid growth factors is justified if the expected risk of febrile neutropenia is 20%. In previous studies of MEK inhibitors with docetaxel the risk of febrile neutropenia was around 20%.

Docetaxel treatment will be administered on an outpatient basis.

On the day of treatment with docetaxel patients must have a neutrophil count of ≥ 1,500/mcL and platelet count of ≥ 100,000/mcL. If counts do not recover to required level in 21 days then docetaxel must be discontinued. No specific changes are required for anemia. This should be managed according to local guidelines.

Patients must not receive any other therapy for NSCLC while receiving treatment on this trial. Patients must not receive any other investigational agent while receiving treatment on this trial. Bisphosphonates and denusomab for bone metastases are permitted.

7.3 Drug Compliance Documentation

The study medication will be given in accordance with the protocol and the instructions of a site investigator. Patients will be asked to bring the remaining trial medication at the end of each cycle to the investigator site for a compliance check. The remaining tablets will be counted by the investigator/site staff and recorded at the investigator site. Discrepancies between the number of tablets remaining and the calculated number of tablets the patients should have taken must be documented and explained. At the end of each cycle, any remaining medication will be collected. If the patient is eligible for further treatment, a new bottle of study medication must be dispensed.

Drug compliance will be recorded by patients in the Intake Calendar (see Appendix 18.1). Institutional CRAs will review and ascertain patient adherence with protocol therapy at the end of treatment for each cycle. Calendar should be kept in the patient's clinic chart.

7.4 Full CDUS Reporting Requirement

Because this study contains an investigational drug for which CTEP holds the IND, it falls under CTEP requirements for full reporting. This involves required submission of cycle-specific toxicity and dose information (see Section 14.4b, the **S1507** Treatment Form, and the **S1507** Adverse Event Form). A cycle is defined as 21 days.

7.5 Criteria for Removal from Protocol Treatment

a. Progression of disease or symptomatic deterioration (as defined in Section 10.2e).

b. Unacceptable toxicity.

c. Delay of both agents > 3 weeks beyond scheduled treatment for any reason.

d. The patients may withdraw from the study at any time for any reason.

e. The investigator can withdraw a patient from the study in the event of serious and persistent non-compliance that jeopardizes the patient's safety or renders study results for this patient unacceptable.

7.6 Discontinuation of Treatment

All reasons for discontinuation of treatment must be documented in the Off Treatment Notice.

7.7 Follow-Up Period

All patients will be followed until death or 3 years after registration, whichever occurs first.

8.0 TOXICITIES TO BE MONITORED AND DOSE MODIFICATIONS

8.1 NCI Common Terminology Criteria for Adverse Events

Two different versions of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be used on this study.

a. Serious Adverse Event (SAE) reporting

The CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5.0 will be utilized for SAE reporting only. The CTCAE Version 5.0 can be downloaded from the CTEP home page (https://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 5.0.

b. Routine toxicity reporting

This study will utilize the CTCAE Version 4.0 for routine toxicity reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP home page (https://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0.

8.2 General Dose Modification Guidelines

a. Missed doses are to be omitted rather than made up.

b. If multiple toxicities are experienced, dose modifications will be based on the toxicity requiring the largest dose reduction.

c. The treating physician can reduce the dose of only one of the two drugs if the toxicity is felt to be related to only one of the drugs.

d. Reductions are based on the dose given in the preceding cycle and are based on toxicities observed since the prior toxicity evaluation.

e. If both drugs are held > 21 days, patient must be removed from protocol treatment. If one drug is held for > 21 days then that drug should be permanently discontinued and the other drug could be continued as long as the treating physician believes the patient is deriving clinical benefit.

f. If trametinib is discontinued due to toxicity, patient may remain on docetaxel as long as docetaxel is well tolerated and according to the treating physician the patient is still deriving benefit. If docetaxel is discontinued due to toxicity, patient may remain on trametinib as long as trametinib is well tolerated and according to the treating physician the patient is still deriving benefit.

8.3 Dose Modifications

a. Dose Modifications for Docetaxel and Trametinib

Trametinib dose levels	Docetaxel dose levels
Level 0: 2 mg	Level 0: 75 mg/m^2
Level -1: 1.5 mg	Level -1: 60 mg/m^2
Level -2: 1 mg	Level -2: 50 mg/m^2

Note: Except where indicated below, no dose escalations are allowed.

On the day of docetaxel administration patient must not have a > Grade 1 toxicity attributable to docetaxel.

Maximum of 2 dose reductions for trametinib are allowed. If further dose reduction is required the drug must be discontinued.

Dose modification and AE guidelines are outlined in the sections below for AEs that are deemed possibly related to trametinib or docetaxel:

- AEs not otherwise specified
- Rash
- Visual changes
- Diarrhea
- Liver chemistry elevation
- Ejection fraction changes
- Prolonged QTc
- Hypertension
- Nausea and vomiting
- Cytopenias
- Pneumonitis

b. Trametinib or Docetaxel Dose Modification for Toxicities Not Specified in Subsequent Sections

Trametinib or docetaxel Treatment Modification for Clinically Significant Toxicities Deemed Related to the specific drug (This section is not for specific AEs such as hypertension, rash, ejection fraction changes, pneumonitis, diarrhea, liver chemistry, QTc prolongation, or visual changes. Refer to other sections for these specific AEs).		
CTCAE v4 Grade	**Management Guideline**	**Dose Modification**
Grade 1	Monitor as clinically indicated. Provide supportive care according to institutional standards.	Continue trametinib and docetaxel at current dose level.
Grade 2 (tolerable)		• Interrupt treatment until resolution to Grade 1 or baseline. If it is clear that the toxicity is related to only 1 drug then the other drug may be continued. • Upon resolution, restart treatment with both drugs at current dose level.
Grade 2 (intolerable) and Grade 3		• Interrupt treatment until resolution to Grade 1 or baseline. • Upon resolution to baseline or Grade 1, restart with one level of dose reduction for both drugs. • If the Grade 3 toxicity recurs, interrupt trametinib and/or docetaxel; When toxicity resolves to Grade 1 or baseline, restart trametinib and/or docetaxel **reduced by another dose level.** • If it is clear that the toxicity is from one drug then the other drug may be continued at the same dose level and interruption of the other drug is not necessary.
Grade 4		If event resolves to Grade 1 or baseline discuss potential continuation of trametinib/docetaxel with Medical Monitor; if continuation of treatment

Trametinib or docetaxel Treatment Modification for Clinically Significant Toxicities Deemed Related to the specific drug (This section is not for specific AEs such as hypertension, rash, ejection fraction changes, pneumonitis, diarrhea, liver chemistry, QTc prolongation, or visual changes. Refer to other sections for these specific AEs).		
CTCAE v4 Grade	**Management Guideline**	**Dose Modification**
		agreed then restart trametinib/docetaxel at dose **reduced by one dose level**. If event does not resolve, permanently discontinue trametinib/docetaxel. If it is clear that the toxicity is from one drug then the other drug may be continued at the same dose level and interruption of the other drug is not necessary.

c. Rash

Rash is a frequent AE observed in patients receiving trametinib. *(47)* Recommendations for supportive care and guidelines for dose modifications for rash are based on experience with other MEK inhibitors and EGFR inhibitors. *(48, 49)* **No modifications in docetaxel dose or schedule are necessary for trametinib related rash.**

The institutional standards for the management of skin-related AEs can differ from these guidelines. In this case, best clinical judgment should be applied and a consultation with the study chair or the CTEP Medical Monitor may be required.

Guidelines for Supportive Care of Rash	
Type of Care	**Action**
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 body areas such as face, chest, and upper back. • Use 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).

Guidelines for Supportive Care of Rash	
Type of Care	**Action**
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 physician 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] • Use moderate strength topical steroid.[2] • Reassess after 2 weeks.	• Continue trametinib. • If rash does not recover to baseline within 2 weeks despite best supportive care, **reduce trametinib by one dose level**.[3]
Grade 2	• Initiate prophylactic and symptomatic treatment measures.[1] • Use moderate strength topical steroid.[2] • Reassess after 2 weeks.	• **Reduce trametinib by one dose level.** • If rash recovers to ≤ Grade 1 within 2 weeks, increase dose to previous dose level. • If no recovery to ≤ Grade 1 within 2 weeks, interrupt trametinib until recovery to ≤ Grade 1. • **Restart trametinib at reduced dose level**.[3]
Grade ≥3	• Use moderate strength topical steroids PLUS oral methyl-prednisolone dose pack.[2] • Consult dermatologist.	• Interrupt trametinib until rash recovers to ≤ Grade 1. • **Restart with trametinib reduced by one dose level.**[3,4] • 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. 2. Moderate-strength topical steroids: Hydrocortisone 2.5% cream or fluticasone propionate 0.5% cream. 3. Approval of CTEP Medical Monitor is required to restart study treatment after >4 weeks of interruption. 4. Trametinib may be escalated to previous dose level if no rash is evident 4 weeks after restarting study treatment.		

d. Visual Changes

Trametinib is known to be associated with visual adverse events. An ophthalmologist should be consulted if changes in vision develop. However, if the visual changes are clearly unrelated to study treatment (e.g., allergic conjunctivitis), then monitor closely as it may be reasonable to defer ophthalmic examination. Special attention should be given to retinal findings (e.g., retinal pigment epithelial detachment (RPED) or retinovascular abnormalities (i.e., branch or central retinal vein occlusions [RVO]).

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

No modifications in dose or schedule of docetaxel is necessary if patient develops visual changes from trametinib. If it is not clear whether docetaxel has contributed to the toxicity then the guidelines in Section 8.3b ("Trametinib or Docetaxel Dose Modification for Toxicities Not Specified in Subsequent Sections") should be followed.

Management and Trametinib Dose Modification for Visual Changes and/or Ophthalmic Examination Findings		
Event CTCAE Grade	**Management Guideline**	**Dose Modification**
Grade 1*	• Consult ophthalmologist within 7 days of onset.	• If dilated fundus examination cannot be performed within 7 days of onset, hold trametinib until RPED and RVO can be excluded by retina specialist/ophthalmologist. • If RPED and RVO excluded, continue/or restart trametinib at same dose level. • If RPED suspected/diagnosed: See RPED dose modification table below (following this table); **report as SAE**. • If RVO diagnosed: **Permanently discontinue trametinib and report as SAE**.
Grade 2 and Grade 3	• Consult ophthalmologist immediately.	• Hold trametinib • If RPED or RVO excluded, restart trametinib at same dose level after visual AE is ≤ Grade 1. If no recovery within 3 weeks, discontinue trametinib • If RPED diagnosed: See RPED dose modification table below; **report as SAE**. • If RVO: **Permanently discontinue trametinib and report as SAE**.
Grade 4	• Consult ophthalmologist immediately. • Report as SAE.	• Hold Trametinib • If RPED/RVO excluded, may restart trametinib at same or reduced dose after discussion with the CTEP Medical Monitor. • **If RVO or RPED, permanently discontinue trametinib**.
Abbreviations: RPED = retinal pigment epithelial detachments; 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.		

Trametinib Dose Modification for RPED	
Event CTCAE Grade	**Action and Dose Modification**
Grade 1 RPED (Asymptomatic; clinical or diagnostic observations only)	• Continue treatment with retinal evaluation monthly until resolution. If RPED worsens, follow instructions below.
Grade 2-3 RPED (Symptomatic with mild to moderate decrease in visual acuity; limiting instrumental ADL)	• Interrupt trametinib. • Retinal evaluation monthly. • If improved to ≤ Grade 1, restart trametinib with one dose level reduction (reduced by 0.5 mg) or discontinue in patients taking trametinib 1 mg daily. • If no recovery within 4 weeks permanently discontinue trametinib

e. Diarrhea

Episodes of diarrhea have occurred in patients receiving trametinib. *(50)* Other frequent causes of diarrhea including concomitant medications (e.g., stool softeners, laxatives, antacids, etc.), infections by C. difficile or other pathogens, or partial bowel obstruction should be clinically excluded.

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

Diarrhea may also occur with docetaxel. Therefore docetaxel modifications are also included in the table below.

Management and Trametinib/Docetaxel Dose Modification Guidelines for Diarrhea		
CTCAE Grade	**Adverse Event Management**	**Action and Dose Modification**
Uncomplicated Diarrhea,[1] 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[3]: 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. • Diarrhea >24 hours: Loperamide 2 mg every 2 hours; maximum 16 mg/day. Consider adding oral antibiotics. • Diarrhea >48 hous: Loperamide 2 mg every 2 hours; maximum 16 mg/day. Add budesonide or other second-line therapies (otreotide, or tincture of opium) and oral antibiotics.	• Continue trametinib/docetaxel. • If diarrhea is Grade 2 for > 48 h, interrupt trametinib and docetaxel until diarrhea resolves to Grade ≤1. • Restart trametinid and docetaxel at the same dose level • If treatment delay is >21 days, discontinue trametinib/docetaxel.

Management and Trametinib/Docetaxel Dose Modification Guidelines for Diarrhea		
CTCAE Grade	**Adverse Event Management**	**Action and Dose Modification**
Uncomplicated Diarrhea,[1] Grade 3 or 4 **Any Complicated Diarrhea[2]**	• Clinical evaluation mandatory. • Loperamide[3]: 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. • 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 docetaxel until diarrhea resolves to ≤ Grade 1. • Restart with trametinib and docetaxel reduced by one dose level.[4] • If 3 dose reductions of study treatment are clinically indicated, **permanently discontinue trametinib and docetaxel**. • If treatment delay is >21 days weeks, discontinue trametinib and docetaxel.
1. **Uncomplicated diarrhea** defined by the absence of symptoms such as cramping, nausea/vomiting ≥ Grade 2, decreased performance status, pyrexia, sepsis, neutropenia ≥ Grade 3, frank bleeding, and/or dehydration requiring intravenous fluid substitution. 2. **Complicated diarrhea** defined by the presence of symptoms such as cramping, nausea/vomiting ≥ Grade 2, decreased performance status, pyrexia, sepsis, neutropenia ≥ Grade 3, frank bleeding, and/or dehydration requiring intravenous fluid substitution. 3. Loperamide should be made available prior to start of study treatment so loperamide administration can begin at the first signs of diarrhea. 4. 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. Escalation of docetaxel is not allowed.		

f. Liver Chemistry Changes

It is recommended that docetaxel modifications be made according to package insert and institutional guidelines. A general recommendation is to hold docetaxel if the patient has developed Grade 2 elevation in liver enzymes or elevation in bilirubin, which is associated with greater than 50% of the bilirubin being direct. Restart docetaxel at the next lower dose once the liver enzymes have returned to Grade 1 and the direct bilirubin has normalized

Trametinib Dose Modification for Liver Function Test Abnormalities	
Event	**Treatment modifications and assessment/monitoring**
ALT ≥3x ULN but <5x ULN and TB <2x ULN, without symptoms considered related to liver injury or hypersensitivity and who can be monitored weekly for 4 weeks	• May continue study drug. • Report as SAE if CTEP-AERS reporting criteria is met. • If liver chemistry stopping criteria are met any time, proceed as described below. MONITORING: Repeat LFT (ALT, AST, ALK, bilirubin) until they return to normal/baseline or stabilise (LFT may be every 2 weeks after 4 weeks if ALT <3x ULN and TB <2 ULN).
Criteria for discontinuing study drug: When any of the liver stopping criteria below is met, discontinue trametinib 1. ALT ≥3xULN and bilirubin ≥2x ULN or >35% direct bilirubin [1, 2] 2. ALT ≥ 3xULN and INR >1.5, if INR measured[2] (INR threshold does not apply if patient is on anticoagulant) 3. ALT ≥5x ULN 4. ALT ≥3x ULN persists for ≥4 weeks 5. ALT ≥3x ULN and cannot be monitored weekly for 4 weeks 6. ALT ≥3x ULN associated with symptoms[3] (new or worsening) believed to be related to liver injury or hypersensitivity	• Immediately discontinue study treatment. • Do not restart/rechallenge unless approved by CTEP trametinib medical monitor. • Report as SAE if: 1) CTEP-AERS reporting criteria are met, or 2) patients meet criteria 1-2. • Perform liver event ASSESSMENT AND WORKUP (see below). • Monitor the patient until liver chemistries resolve, stabilize, or return to baseline (see MONITORING below). • If applicable, provide details on required follow up assessments (e.g., follow up for overall survival or disease recurrence or progression).
	MONITORING: *In patients stopping for criteria 1-2 (with abnormal TB and INR, indicating potentially more significant liver toxicities):* • Repeat liver chemistries (ALT, AST, ALK, bilirubin) and perform liver event follow-up assessments within 24 hours. • Monitor subjects twice weekly until LFT return to normal/baseline or stabilize. • A specialist or hepatology consultation is recommended. *In patients stopping for criteria 2-6:* • Repeat LFT and perform liver event follow up assessments within 24-72

Trametinib Dose Modification for Liver Function Test Abnormalities	
Event	**Treatment modifications and assessment/monitoring**
	hrs • Monitor subjects weekly until LFTs return to normal/baseline or stabilize. ASSESSMENT and WORKUP: • Viral hepatitis serology.[4] • If possible, obtain blood sample for PK analysis.[5] • Serum CPK and LDH. • Fractionate bilirubin, if total bilirubin ≥2x ULN. • CBC with differential to assess eosinophilia. • Record clinical symptoms of liver injury, or hypersensitivity on AE CRF. • Record concomitant medications (including acetaminophen, herbal remedies, other over the counter medications). • Record alcohol use. *Additional work up for patient stopping for criteria 1-2 (with abnormal TB and INR, indicating potentially more significant liver toxicities)*: • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct HPLC assay (in subjects with likely acetaminophen use in the preceding). • If there is underlying chronic hepatitis B (e.g. positive hepatitis B surface antigen): quantitative hepatitis B DNA and hepatitis delta antibody.[6] • Liver imaging (ultrasound, MRI, CT) and /or liver biopsy.
Footnotes: 1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation testing is unavailable, record presence of detectable urinary bilirubin on dipstick, which indicates direct bilirubin elevations and suggesting liver injury. 2. All events of ALT ≥3xULN and bilirubin ≥2xULN (>35% direct bilirubin) or ALT ≥3x ULN and INR >1.5 (if INR measured) may indicate severe liver injury (possible "Hy's Law"). INR measurement is not required, and the threshold value stated will not apply to subjects receiving anticoagulants. 3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia) 4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B	

Trametinib Dose Modification for Liver Function Test Abnormalities	
Event	**Treatment modifications and assessment/monitoring**
Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody 5. PK sample is desired if feasible. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Not required for single-dose studies 6. If hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed) (Le Gal *et al.*, 2005).	

g. Reduced Left Ventricular Ejection Fraction

Decreases of the left ventricular ejection fraction (LVEF) have been observed in patients receiving trametinib.

Therefore, ECHO/MUGAs 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 visit(s).

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/MUGA 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 CTEP trametinib medical monitor and request approval for restart. – Restart treatment with trametinib at reduced dose by one dose level.[b] – Repeat ECHO/MUGA 2, 4, 8, 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/MUGA after 2, 4, 8, 12, and 16 weeks or until resolution. – Consult with the CTEP trametinib medical monitor.[c]
Symptomatic[b]	• Grade 3: resting LVEF 39-20% or >20% absolute reduction from baseline	• **Permanently discontinue trametinib**. • **Report as SAE**. • **Consult with cardiologist**. • Repeat ECHO/MUGA 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**
	• Grade 4: Resting LVEF ≤20%.	
[a] If ECHO/MUGA does not show LVEF recovery after 2 weeks, repeat ECHO/MUGA 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 the CTEP trametinib medical monitor is required. [c] Symptoms may include: dyspnea, orthopnea, and other signs and symptoms of pulmonary congestion and edema.		

h. QTc Prolongation

Docetaxel may be continued in patients with QTc prolongation.

Trametinib Withholding and Stopping Criteria for QTc Prolongation	
QTc Prolongation[a]	**Action and Dose Modification**
• QTcB ≥501 msec, or • Uncorrected QT >600 msec, or • QTcB >530 msec for patients with bundle branch block	• Interrupt study treatment until QTcB prolongation resolves to Grade 1 or baseline. • Test serum potassium, calcium, phosphorus, and magnesium. If abnormal, correct per routine clinical practice to within normal limits. • Review concomitant medication usage for a prolonged QTc. • Restart at current dose level.[b] • **If the event does not resolve or recurs after restarting, permanently discontinue study treatment.**
Abbreviations: msec = milliseconds; QTcB = QT interval on electrocardiogram corrected using Bazett's formula [a] 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. [b] if the QTc prolongation resolves to Grade 1 or baseline, the patient may resume study treatment if the investigator and the CTEP trametinib medical monitor agree that the subject will benefit from further treatment.	

i. Hypertension

Increases in blood pressure (BP) have been observed in patients receiving trametinib. Recommendations for BP monitoring and management are provided below. No changes in docetaxel are necessary.

Management and Trametinib Dose Modification for Hypertension		
Event	**Management Guideline**	**Dose Modification**
Definitions used in the table: - Persistent hypertension: Hypertension detected in two separate readings during up to three subsequent visits. - Well-controlled hypertension: Blood pressure of SBP ≤140 mmHg and DBP ≤90 mmHg in two separate readings during up to three subsequent visits. - Symptomatic hypertension: Hypertension associated with symptoms (*e.g.*, headache, light-headedness, vertigo, tinnitus, episodes of fainting or other symptoms indicative of hypertension) that resolve after the blood pressure is controlled within the normal range. - Asymptomatic hypertension: SBP >140 mmHg and/or DBP >90 mmHg in the absence of the above symptoms.		
(Scenario A) Asymptomatic and persistent SBP of ≥140 and <160 mmHg, or DBP ≥90 and <100 mmHg, or Clinically significant increase in DBP of 20 mmHg (but still below 100 mmHg).	• Adjust current or initiate new antihypertensive medication(s). • Titrate antihypertensive medication(s) during the next 2 weeks to achieve well-controlled BP. If BP is not well-controlled within 2 weeks, consider referral to a specialist and go to scenario (B).	Continue trametinib at the current dose.
(Scenario B) Asymptomatic SBP ≥160 mmHg, or DBP ≥100 mmHg, or Failure to achieve well-controlled BP within 2 weeks in Scenario A.	• Adjust current or initiate new antihypertensive medication(s). • Titrate antihypertensive medication(s) during the next 2 weeks to achieve well-controlled BP.	• Interrupt trametinib if clinically indicated. • Once BP is well-controlled, restart trametinib **reduced by one dose level**.[a]
(Scenario C) Symptomatic hypertension or Persistent SBP ≥160 mmHg, or DBP ≥100 mmHg, despite antihypertensive medication and dose reduction of trametinib	• Adjust current or initiate new antihypertensive medication(s). • Titrate antihypertensive medication(s) during the next 2 weeks to achieve well-controlled BP. • Referral to a specialist for further evaluation and follow-up is recommended.	• Interrupt trametinib. • Once BP is well-controlled, restart trametinib **reduced by one dose level**.[a]
(Scenario D) Refractory hypertension unresponsive to above interventions or hypertensive crisis.	Continue follow-up per protocol.	**Permanently discontinue trametinib**.
a. Escalation of trametinib to previous dose level can be considered if BPs remain well controlled for 4 weeks after restarting of trametinib. Approval from Medical Monitor is required.		

j. Nausea and Vomiting

Appropriate prophylactic anti-emetics should be prescribed.

Nausea and Vomiting Grade	Modification
Nausea 1	Antiemetic treatment*, if deemed necessary by treating physician.
Nausea 2 and/or Vomiting 1-2	Give antiemetic treatment*. Hold trametinib if Grade 2 vomiting or Grade 2 nausea persists for 3 or more consecutive days despite optimal supportive care. Resume treatment at next reduced dose level when recovered to ≤ Grade 1. If nausea and vomiting have not resolved to Grade 1 in 21 days then trametinib should be discontinued (see Section 8.2e).
Vomiting 3 or 4 or Nausea 3 or 4	Give antiemetic treatment*. Hold trametinib until recovery to ≤ Grade 1 or baseline then resume treatment at next reduced dose level. If ≥ Grade 3 nausea or vomiting does not resolve to ≤ Grade 1 within 21 days of stopping treatment and despite optimal supportive care, discontinue trametinib (see Section 8.2e).

* Antiemetic treatment should follow the recommendations given in the Consensus Statement of the Antiemetic Subcommittee of the Multinational Association of Supportive Care in Cancer (MASCC): Prevention of chemotherapy- and radiotherapy-induced emesis: Results of the Perugia Consensus Conference (R06-0986).

k. Cytopenias

Patients must receive pegfilgrastim or filgrastim. **On the day of treatment with docetaxel patients must have a neutrophil count of ≥ 1,500/mcl and platelet count of ≥ 100,000/mcL. If counts do not recover to required level in 21 days then docetaxel must be discontinued. No specific changes are required for anemia. This should be managed according to local guidelines.**

Neutropenia or Thrombocytopenia	Modification
1	No change required in trametinib. Reduce docetaxel to next dose level if counts have not recovered to required levels by Day 1 of next cycle.
2	Same as Grade 1. Reduce docetaxel and trametinib to next dose level if counts have not recovered to required levels by Day 1 of next cycle.
3 or 4	Hold trametinib and docetaxel. Resume treatment at next reduced dose level once the toxicity improves to **≤ Grade 2**. If ≥ Grade 3 neutropenia or thrombocytopenia does not resolve to ≤ Grade 2 within 21 days of stopping treatment discontinue protocol treatment (see Section 8.2e).

l. Pneumonitis

Pneumonitis is known to occur with trametinib and docetaxel. Patients should undergo appropriate assessment to determine if there is another cause for the pneumonitis.

Pnuemonitis Grade	Guidelines/Modification
1	Continue treatment with both drugs. Patient may need to be followed more closely.
2 or 3	Interrupt both drugs. Once toxicity resolves to ≤ Grade 1 can restart both drugs at the next lower dose. If toxicity does not resolve in 21 days then study drugs should be discontinued (see Section 8.2e).
4	Permanently discontinue study therapy.

8.4 Dose Modification Contacts

For treatment or dose modification questions, please contact Dr. Shirish M. Gadgeel at 313/576-8753 or email at gadgeels@karmanos.org or contact Dr. Jonathan Riess at 916/734-3772 or jonathan.riess@ucdmc.ucdavis.org.

8.5 Adverse Event Reporting

Toxicities (including suspected reactions) that meet the expedited reporting criteria as outlined in Section 16.0 of the protocol must be reported to the Operations Office, Study Chair and NCI via CTEP-AERS, and to the IRB per local IRB requirements.

9.0 STUDY CALENDAR

REQUIRED STUDIES	Pre-Reg ®	Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5 £			Cycle 6			Off Protocol Treatment	After off treatment, prior to prog ≠	F/U after prog β
		W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W			
		1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3			
PHYSICAL																						
History and Physical Exam	X	X	X	X	X			X			X			X			X				X	X
Weight and Performance Status	X	X			X			X			X			X			X				X	X
Toxicity Notation		X	X	X	X			X			X			X			X					
Pill Count (see Section 7.3)					X			X			X			X			X					
Baseline Abnormalities Assessment		X																				
Disease Assessment €	X							X						X							X	
Ophthalmology exam ¿	X																					
LABORATORY																						
CBC/Differential/Platelets	X	X	X	X	X			X			X			X			X					
Bilirubin	X	X	X	X	X			X			X			X			X					
AST and ALT	X	X	X	X	X			X			X			X			X					
Serum creatinine / Calculated creatinine clearance	X	X	X	X	X			X			X			X			X					
SCANS																						
CT or MRI for disease assessment €	X							X						X							X	
Electrocardiogram Ω	X	X			X			X			X											
Echocardiogram or MUGA ۞	X													X ۞								

REQUIRED STUDIES	Pre-Reg ®	Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5 £			Cycle 6			Off Protocol Treatment	After off treatment, prior to prog ≠	F/U after prog β
		W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W			
		1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3			
SPECIMEN SUBMISSION																						
Archived Tissue Ш		X																				
Buffy coat and plasma ¥		X						X												X		
TREATMENT																						
Trametinib ±		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Docetaxel ƨ		X			X			X			X			X			X					
Filgrastim or Pegfilgrastim ƨ		X			X			X			X			X			X					

Footnotes

£ Protocol treatment and parameters will continue at the intervals indicated for Cycles 5 and 6 until patient has met any of the criteria in Section 7.5.

Ω Electrocardiograms must be done within 42 days prior to registration then the first day of each cycle for the first four cycles, and then as often as clinically indicated to assess QT interval (see Section 8.3j).

€ Disease assessment, including CT or MRI, must be performed after every 6 weeks.

® See Section 5.0 for additional information and required values

± Daily oral dosing (see Section 7.2)

≠ After off treatment prior to disease progression, scans for disease assessment and physical assessments (with lab tests performed at the discretion of the treating investigator) must take place every six weeks until progression.

β After off treatment following disease progression, physical assessments (with lab tests performed at the discretion of the treating investigator) must take place every six months until three years from the time of registration.

Ш If patient consents, submit within 30 days after registration (see Section 15.1 for details).

ƨ If docetaxel is given at 75 mg/m^2, filgrastim or pegfilgrastim administration is mandatory per Section 7.2.

۞ Echocardiogram or MUGA must be done within 42 days prior to registration then every 12 weeks to assess LVEF. The same modality (ECHO or MUGA) should be used at all timepoints.

¿ Ophthalmology exam must be performed within 42 days prior to registration (see Section 5.3j) and, if clinically indicated (see Section 8.3d), during study to assess visual changes. Ophthalmology exam should include Ocular Coherence Tomography, fundoscopy, tonometry, visual field examination, and corrected visual acuity assessments.

¥ If patient consents, draw blood prior to treatment on Cycle 1 Day 1, at Cycle 3 visit, and when patient is removed from protocol treatment (see Section 15.1 for details).

10.0 CRITERIA FOR EVALUATION AND ENDPOINT ANALYSIS

10.1 Measurability of Lesions

a. **Measurable disease:** Measurable disease is defined differently for lymph nodes compared with other disease and will be addressed in a separate section below.

1. Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 2.0 cm by chest x-ray, by ≥ 1.0 cm with CT or MRI scans, or ≥ 1.0 cm with calipers by clinical exam. All tumor measurements must be recorded in decimal fractions of centimeters (or millimeters).

   The defined measurability of lesions on CT scan is based on the assumption that CT slice thickness is 0.5 cm or less. If CT scans have slice thickness greater than 0.5 cm, the minimum size for a measurable lesion should be twice the slice thickness.

2. A malignant lymph node is to be considered pathologically enlarged and measurable if it measures ≥ 1.5 cm in **SHORT AXIS** (greatest diameter perpendicular to the long axis of the lymph node) when assessed by scan (CT scan slice recommended being no greater than 0.5 cm).

b. **Non-measurable disease**: All other lesions (or sites of disease), including small lesions (longest diameter < 1.0 cm or pathologic lymph nodes with ≥ 1.0 cm to < 1.5 cm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered non-measurable as are previously radiated lesions that have not progressed.

c. **Notes on measurability**

1. For CT and MRIs, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should by performed with breath-hold scanning techniques, if possible.

2. PET-CT: At present, the low dose or attenuation correction CT portion of a PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT, then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT.

3. Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

4. Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition simple cysts.

5. If a target lesion becomes very small some radiologists indicate that it is too small to measure. If the lesion is actually still present, a default measurement of 0.5 cm should be applied. If the radiologist believes the lesion has gone, a default measurement of 0.0cm should be recorded.

10.2 Objective Status at Each Disease Evaluation

Objective Status is to be recorded at each evaluation. All measurable lesions up to a maximum of 2 lesions per organ 5 lesions in total, representative of all involved organs, should be identified as ***target*** lesions at baseline. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as ***non-target*** lesions. Measurements must be provided for target measurable lesions, while presence or absence must be noted for non-target measurable and non-measurable disease.

For studies that use disease progression as an endpoint, whole body scanning at specific intervals is necessary to determine that progression is NOT present outside of the "target" areas. Therefore, in these studies it is not acceptable to image only the "target" areas of the body in follow-up scans. For study-specific imaging requirements, see the Study Calendar in Section 9.0.

a. **Complete Response (CR):** Complete disappearance of all target and non-target lesions (with the exception of lymph nodes mentioned below). No new lesions. No disease related symptoms. Any lymph nodes (whether target or non-target) must have reduction in short axis to < 1.0 cm. All disease must be assessed using the same technique as baseline.

b. **Partial Response (PR):** Applies only to patients with at least one measurable lesion. Greater than or equal to 30% decrease under baseline of the sum of appropriate diameters of all target measurable lesions. No unequivocal progression of non-measurable disease. No new lesions. All target measurable lesions must be assessed using the same techniques as baseline.

c. **Stable:** Does not qualify for CR, PR, Progression or Symptomatic Deterioration. All target measurable lesions must be assessed using the same techniques as baseline.

d. **Progression**: One or more of the following must occur: 20% increase in the sum of appropriate diameters of target measurable lesions over smallest sum observed (over baseline if no decrease during therapy) using the same techniques as baseline, as well as an absolute increase of at least 0.5 cm. Unequivocal progression of non-measurable disease in the opinion of the treating physician (an explanation must be provided). Appearance of any new lesion/site. Death due to disease without prior documentation of progression and without symptomatic deterioration (see Section 10.2e).

Notes regarding new lesions: FDG-PET imaging can complement regular scans in identifying new lesions according to the following algorithm.

1. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of progression based on a new lesion.

2. No FDG-PET at baseline and a positive FDG-PET at follow-up corresponding to a potential new site of disease must have a confirmation by anatomical assessment (e.g. CT, MRI, x-ray) as new site

of disease to be considered progressive disease. In such a case, the date of progressive disease will be the date of the initial abnormal FDG-PET.

e. **Symptomatic deterioration**: Global deterioration of health status requiring discontinuation of treatment without objective evidence of progression. Efforts should be made to obtain objective evidence of progression after discontinuation.

f. **Assessment inadequate, objective status unknown**. Progression or symptomatic deterioration has not been documented, and one or more target measurable lesions have not been assessed or inconsistent assessment methods were used.

g. Objective status notes:

1. Non-measurable and non-target measurable disease do not affect Objective Status in determination of CR (must be absent--a patient who otherwise has a CR, but who has non-measurable or non-target measurable disease present or not assessed, will be classified as having a PR). However, non-measurable and non-target lesions are included in determination of progression (if new sites of disease develop or if unequivocal progression occurs in the opinion of the treating physician).

2. An objective status of PR or stable cannot follow one of CR. Stable can follow PR only in the rare case that tumor increases too little to qualify as progression, but enough that a previously documented 30% decrease no longer holds.

3. In cases for which initial flare reaction is possible (hypercalcemia, increased bone pain, erythema of skin lesions), objective status is not progression unless either symptoms persist beyond 4 weeks or there is additional evidence of progression.

4. Lesions that appear to increase in size due to presence of necrotic tissue will not be considered to have progressed.

5. For bone disease documented on bone scan only, increased uptake does not constitute unequivocal progression. However, increase in the soft tissue component of a lesion as measured by CT or MRI would constitute progression.

6. Appearance of new pleural effusions does not constitute unequivocal progression unless cytologically proven of neoplastic origin, since some effusions are a toxicity related to therapy or other medical conditions. Increase in the size of an existing effusion does not constitute unequivocal progression, since the fluid status of the patient could alter the size of the effusion.

7. If CR determination depends on a lesion for which the status is unclear by the required tests, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate.

10.3 Best Response

This is calculated from the sequence of objective statuses.

a. CR: Two or more objective statuses of CR a minimum of four weeks apart documented before progression or symptomatic deterioration.

b. PR: Two or more objective statuses of PR or better a minimum of four weeks apart documented before progression or symptomatic deterioration, but not qualifying as CR.

c. Unconfirmed CR: One objective status of CR documented before progression or symptomatic deterioration but not qualifying as CR or PR.

d. Unconfirmed PR: One objective status of PR documented before progression or symptomatic deterioration but not qualifying as CR, PR or unconfirmed CR.

e. Stable/no response: At least one objective status of stable/no response documented at least 6 weeks after registration and before progression or symptomatic deterioration, but not qualifying as anything else above.

f. Increasing disease: Objective status of progression within 12 weeks of registration, not qualifying as anything else above.

g. Symptomatic deterioration: Objective status of symptomatic deterioration within 12 weeks of registration, not qualifying as anything else above.

h. Inadequate assessment, response unknown: Progression or symptomatic deterioration greater than 12 weeks after registration and no other response category applies.

10.4 Performance Status

Patients will be graded according to the Zubrod Performance Status Scale.

POINT	**DESCRIPTION**
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

10.5 Time to Death

From date of registration to date of death due to any cause. Patients last known to be alive are censored at date of last contact.

10.6 Progression-Free Survival

From date of registration to date of first documentation of progression or symptomatic deterioration (as defined above), or death due to any cause. Patients last known to be alive without report of progression are censored at date of last disease assessment.

11.0 STATISTICAL CONSIDERATIONS

11.1 Sample size with Power Justification

The primary objective of this study is to evaluate the response rate (confirmed and unconfirmed complete and partial responses) in all KRAS mutant patients (both those with G12C mutations and those with non-G12C mutations). An important secondary outcome is to evaluate the response rate in the subset of patients with a G12C mutation. It is assumed that this regimen will not warrant further investigation in this setting if the true response rate is ≤ 17% and that a true response rate ≥ 37% would be of considerable interest.

A two-stage design will be implemented as follows. Initially, 30 patients will be enrolled. If necessary, the study may be temporarily closed while response data matures. We will test the alternative of a 37% response rate among the first 30 patients enrolled at the 0.02 level. If five or fewer responses are observed, then we will perform the same test within the G12C stratum. The G12C stratum will remain open until at least 9 G12C patients have been enrolled. Assuming 15 of the initial 30 patients have a G12C mutation, then 0-1 responses are observed among the 15 G12C patients the study will be closed to further accrual with the conclusion that this regimen is not active in this setting. If 2 or more responses are observed among the 15 G12C patients, but fewer than 5 responses overall, then the study will be reopened to G12C patients only. However, if at least 6 responses are observed among all 30 patients, then the study will be reopened to all KRAS mutation patients.

If the second stage is reopened to all KRAS patients, then an additional 15 patients will be enrolled for a total accrual of 45 patients. If at least 13 responses are observed, the conclusion would be that this regimen warrants further investigation in this setting, assuming other factors, such as progression-free survival, overall survival, and toxicity, also appear favorable. This design has 90% power (probability of concluding the regimen warrants further investigation when the true response rate is 37%) and a type I error of 3% (probability of concluding the regimen warrants further investigation when the true response rate is 17%).

If less than 25 of the total 45 eligible patients enrolled have a G12C mutation, accrual to the G12C stratum will be expanded for up to an additional 5 G12C patients for a total sample size of 50. If at least 8 responses are observed among the 25 patients in the G12C subset, this would be considered evidence that this regimen warrants further investigation in the G12C mutation population, regardless of the conclusion in the overall population. This subset analysis has 76% power with a type I error of 5%.

If the second stage is reopened to the G12C stratum only, an additional 20 G12C patients will be enrolled for a total sample size of 50. Assuming the total number of G12C patients is 35, if at least 11 responses are observed this will be considered evidence that

this regimen warrant further investigation in the G12C mutation population only. This subset analysis has 80% power with a type I error of 3%.
The following Table illustrates the decisions rules:

N Overall (G12C + non-G12C)	CR/PR	N G12C	CR/PR	Decision
30	0-5	15	0-1	Close study and conclude regimen inactive in this setting
30	0-5	15	2+	Close the study to non-G12C. Enroll an additional 20 G12C patients.
30	6+			Enroll 15-20 additional patients
45	13+			Conclude regimen warrants further investigation
45	6-12	25	8+	Conclude regimen warrants further analysis, but only in G12C subset
45	6-12	25	≤ 7	Conclude regimen inactive in this setting
If second stage only continues in G12C				
		35	11+	Conclude regimen warrants further analysis, but only in G12C subset
		35	≤ 10	Conclude regimen inactive in this setting

11.2 Secondary Objectives

Progression-Free Survival and Overall Survival estimates will be calculated using the method of Kaplan-Meier. 95% confidence for the medians will be constructed using the method of Brookmeyer-Crowley. With 50 patients, PFS (or OS) at a particular time point (e.g. 6 months) can be estimated to within ± 14% with 95% confidence. With 25 patients in each subgroup (G12C and non-G12C), response and PFS and OS at a particular time point can be estimated to within ± 20% with 95% confidence.

With 50 patients, any adverse event with at least a 5% chance of occurring is likely to be seen at least once (92% probability). Toxicity rates can be estimated to within ± 14% with 95% confidence.

Translational Medicine Objectives:

The primary translational medicine objectives are to assess: a) if the presence of dysfunctional p53 in KRAS mutant tumors will favor responses compared to patients without p53 dysfunction, and b) if the presence of LKB1 disruption in KRAS mutant tumors is associated with a lower response rate compared with tumors without presence of LKB1 disruption.

Assuming 50 eligible patients will be enrolled and that p53 and LKB1 results will be available for 80% of the patients, then 40 eligible patients will be included in this analysis. It is further assumed that 30% (~12 patients) will be determined to have p53 loss and 30% (~12 patients) will be determined to have LKB1 loss.

If we assume a 17% response rate in both the G12C and non-G12C groups, and further assume no correlation between G12C status and p53 loss (i.e. equal numbers in each group), then if the response rate for patients without p53 loss is 10% and the response

rate for patients with p53 loss is 55%, we would have 80% power to detect this difference using a one-sided binomial test of proportions with an alpha of 0.05. The response rate will be estimated by LKB1 disruption status (yes/no), along with 95% confidence intervals around the estimated proportions. This analysis will evaluate if disruption in LKB1 is associated with a lower probability of response. With 12 LKB1+ and 28 LKB1- patients, the response rate can be estimated to within at least ±28% and ±19% with 95% confidence, respectively.

11.3 Accrual

Assuming a 5% ineligibility rate, approximately 53 patients will need to be accrued in order to enroll 50 eligible patients. Assuming an estimated accrual rate of 6 patients per month, and further assuming no temporary closure between the first and second stage of accrual, this study would require approximately 9 months to reach full accrual

11.4 Data and Safety Monitoring

There is no formal data and safety monitoring committee for this study. Toxicity and accrual are primarily monitored by the Study Chair, Study Statistician and the Disease Committee Chair. Endpoint monitoring is done by the Study Statistician and Study Coordinator. The Adverse Event Coordinator at the Operations Office and the SAE Physician Reviewer are notified immediately whenever a serious adverse event is reported using the NCI CTEP-AERS system (see Section 16.0 for details). The Adverse Event Coordinator then provides the Study Chair and Study Statisticians a cumulative report of all SAEs within 24 hours with the most recent event highlighted. Regular monitoring of all adverse events is performed monthly by the Study Chair and Study Statistician(s). The Study Chair and Study Statistician(s) receive monthly reports summarizing all adverse events and serious adverse events. In addition, the Study Chair and Study Statistician(s) receive a monthly summary of treatment status for patients on the study. Accrual reports are generated weekly and formal toxicity reports are available to all SWOG group members are generated every 6 months.

12.0 DISCIPLINE REVIEW

There is no discipline review for this study.

13.0 REGISTRATION GUIDELINES

13.1 Registration Timing

Patients must be registered prior to initiation of treatment (no more than three working days prior to planned start of treatment).

13.2 Investigator/Site Registration

Prior to the recruitment of a patient for this study, investigators must be registered members of a Cooperative Group. Each investigator must have an NCI investigator number and must maintain an “active” investigator registration status through the annual submission of a complete investigator registration packet to CTEP.

a. CTEP Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed ***Statement of Investigator Form*** (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed ***Supplemental Investigator Data Form*** (IDF)
- a completed ***Financial Disclosure Form*** (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at <http://ctep.cancer.gov/investigatorResources/investigator_registration.htm>.

For questions, please contact the ***CTEP Investigator Registration Help Desk*** by email at <pmbregpend@ctep.nci.nih.gov>.

b. CTEP Associate Registration Procedures

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' website.

Additional information can be found on the CTEP website at <http://ctep.cancer.gov/branches/pmb/associate_registration.htm>. For questions, please contact the ***CTEP Associate Registration Help Desk*** by email at <ctepreghelp@ctep.nci.nih.gov>.

c. CTSU Registration Procedures

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU members' website by entering credentials at https://www.ctsu.org. For sites under the CIRB initiative, IRB data will automatically load to RSS.

Note: Sites participating on the NCI CIRB initiative and accepting CIRB approval for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory Office for initial, continuing or amendment review. This information will be provided to the CTSU Regulatory Office from the CIRB at the time the site's Signatory Institution accepts the CIRB approval. The Signatory site may be contacted by the CTSU Regulatory Office or asked to complete information verifying the participating institutions on the study. Other site registration requirements (i.e., laboratory certifications, protocol-specific training certifications, or modality credentialing) must be submitted to the CTSU Regulatory Office or compliance communicated per protocol instructions.

1. Downloading Site Registration Documents:

   Site registration forms may be downloaded from the **S1507** protocol page located on the CTSU members' website.
   - Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
   - Click on the Protocols tab in the upper left of your screen
   - Click on the By Lead organization folder to expand
   - Click on the SWOG link to expand, then select **S1507**.
   - Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided.

2. Requirements for **S1507** Site Registration:

   - CTSU IRB Certification (for sites not participating via the NCI CIRB)
   - CTSU IRB/Regulatory Approval Transmittal Sheet (for sites not participating via the NCI CIRB)

3. Submitting Regulatory Documents:

   Submit completed forms along with a copy of your IRB Approval *and Model Informed Consent* to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

   CTSU Regulatory Office
   1818 Market Street, Suite 1100
   Philadelphia, PA 19103
   Phone: 1-866-651-2878
   Fax: 215-569-0206
   E-mail: CTSURegulatory@ctsu.coccg.org (for regulatory document submission only)

4. Checking Your Site's Registration Status:

   Check the status of your site's registration packets by querying the RSS site registration status page of the members' section of the CTSU website. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)
   - Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
   - Click on the Regulatory tab at the top of your screen

- Click on the Site Registration tab

Enter your 5-character CTEP Institution Code and click on Go

13.3 OPEN Registration Requirements

The individual registering the patient must have completed the appropriate SWOG Registration Worksheet. The completed form must be referred to during the registration but should not be submitted as part of the patient data.

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at < https://eapps-ctep.nci.nih.gov/iam/index.jsp >) and a 'Registrar' role on either the LPO or participating organization roster.

OPEN will also ask additional questions that are not present on the SWOG Registration Worksheet. The individual registering the patient must be prepared to provide answers to the following questions:

a. Institution CTEP ID

b. Protocol Number

c. Registration Step

d. Treating Investigator

e. Credit Investigator

f. Patient Initials

g. Patient's Date of Birth

h. Patient SSN (SSN is desired, but optional. Do not enter invalid numbers.)

i. Country of Residence

j. ZIP Code

k. Gender (select one):
- Female Gender
- Male Gender

l. Ethnicity (select one):
- Hispanic or Latino
- Not Hispanic or Latino
- Unknown

m. Method of Payment (select one):
- Private Insurance
- Medicare
- Medicare and Private Insurance
- Medicaid
- Medicaid and Medicare
- Military or Veterans Sponsored NOS

- Military Sponsored (Including Champus & Tricare)
- Veterans Sponsored
- Self Pay (No Insurance)
- No Means of Payment (No Insurance)
- Other
- Unknown

n. Race (select all that apply):
- American Indian or Alaska Native
- Asian
- Black or African American
- Native Hawaiian or other Pacific Islander
- White
- Unknown

13.4 Registration Procedures

a. All site staff will use OPEN to enroll patients to this study. OPEN is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient in the Rave database. OPEN can be accessed at https://open.ctsu.org, from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org, or from the OPEN Patient Registration link on the SWOG CRA Workbench.

b. Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes and the affirmation of eligibility on the Registration Worksheet has been signed by the registering investigator or another investigator designate. Site staff should refer to Section 5.0 to verify eligibility.

- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

c. The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

d. Further instructional information is provided on the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 888/823-5923 or ctsucontact@westat.com.

13.5 Exceptions to SWOG registration policies will not be permitted.

a. Patients must meet all eligibility requirements.

b. Institutions must be identified as approved for registration.

c. Registrations may not be cancelled.

d. Late registrations (after initiation of treatment) will not be accepted.

14.0 DATA SUBMISSION SCHEDULE

14.1 Data Submission Requirement

Data must be submitted according to the protocol requirements for **ALL** patients registered, whether or not assigned treatment is administered, including patients deemed to be ineligible. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible

14.2 Master Forms

Master forms can be found on the protocol abstract page on the SWOG website (www.swog.org) and (with the exception of the sample consent form and the Registration Worksheet) must be submitted on-line via the Web; see Section 14.3a for details.

14.3 Data Submission Procedures

a. Data collection for this study will be done exclusively through the Medidata Rave® clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, you must have an active CTEP-IAM account (check at https://eapps-ctep.nci.nih.gov/iam/index.jsp) and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on either the LPO or participating organization roster at the enrolling site.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the “accept” link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members’ website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU help Desk at 888/823-5923 or by e-mail at ctsucontact@westat.com

b. You may also access Rave® via the SWOG CRA Workbench. Go to the SWOG web site (http://swog.org) and logon to the Members Area using your SWOG Roster ID Number and password. After you have logged on, click on *Workbenches*, then *CRA Workbench* to access the home page for the CRA Workbench and follow the link to Rave® provided in the left-hand navigation panel.

To access the CRA Workbench the following must be done (in order):

1. You are entered into the SWOG Roster and issued a SWOG Roster ID Number,
2. You are associated as an investigator or CRA/RN at the institution where the patient is being treated or followed,
3. Your Web User Administrator has added you as a web user and has given you the appropriate system permissions to view data for that institution.

For assistance with points 1 and 2 call the Operations Office at 210/614-8808. For point 3, contact your local Web User Administrator (refer to the "Who is my Web User Administrator?" function on the swog.org Members logon page).

For difficulties with the CRA Workbench, please email technicalquestion@crab.org.

c. Institutions participating through the Cancer Trials Support Unit (CTSU) please refer to the CTSU Participation Table.

14.4 Data Submission Overview and Timepoints

a. WITHIN 7 DAYS AFTER REGISTRATION:

Submit the following:

S1507 Onstudy Form

Baseline Tumor Assessment Form

Baseline Abnormalities Form

Pathology Report*

KRAS mutation status report (if not part of pathology report)* Report must document that KRAS mutation status was determined in a CLIA certified lab.

Submit radiology reports from all scans performed to assess disease at baseline.

* NOTE: Upload these reports via the Source Documentation: Baseline form in Rave®.

b. WITHIN 7 DAYS AFTER EACH CYCLE (1 CYCLE = 21 DAYS) OF TREATMENT:

Submit the following:

S1507 Treatment Form

S1507 Adverse Event Form

c. WITHIN 30 DAYS AFTER REGISTRATION, IF PATIENT CONSENTS:

Submit tissue as described in Section 15.1.

d. WITHIN 14 DAYS AFTER EACH DISEASE ASSESSMENT:

Submit the following:

Follow Up Tumor Assessment Form

Radiology reports (Upload these reports via the Source Documentation: Follow-Up form in Rave®.)

e. WITHIN 14 DAYS AFTER DISCONTINUATION OF TREATMENT:

Submit the following:

Off Treatment Notice

S1507 Treatment Form

S1507 Adverse Event Form

f. WITHIN 14 DAYS AFTER PROGRESSION/RELAPSE:

Submit the following:

Follow Up Tumor Assessment Form

Lung Carcinoma First Site(s) of Progression or Relapse Form

All radiology reports used to document progression (Upload via the Source Documentation: Follow-Up form in Rave®)

If the patient was off protocol treatment, also submit the Advanced NSCLS Follow-Up Form

g. ONCE OFF ALL PROTOCOL TREATMENT, SUBMIT EVERY 6 MONTHS FOR UP TO 3 YEARS FROM THE DATE OF REGISTRATION:

Submit the following:

Advanced NSCLC Follow Up Form

Late Effects Form (if prior to treatment for progression or relapse or a second primary, and prior to non-protocol treatment, the patient experiences any severe [Grade ≥ 3] long term toxicity that has not been previously reported)

h. WITHIN 4 WEEKS AFTER KNOWLEDGE OF DEATH:

Submit the Notice of Death. If the patient was still on protocol treatment, also submit the forms listed in Section 14.4e. If the patient was off protocol treatment, also submit the Advanced NSCLC Follow-Up Form.

15.0 SPECIAL INSTRUCTIONS

15.1 Translational Medicine and Banking

Patients must be offered the opportunity to participate in banking of specimens for future research. Collection of specimens is critical to the interpretation of this study and should be acquired if at all possible. If the patient consents, specimens must be submitted as described in this section.

a. Archived Tumor Tissue (Optional for patient)

The translational medicine studies described in Section 18.2 will be prioritized for the future use of banked speicmens. Any specimens that remain after the completion of these studies will continue to be banked and may be used for other future research.

Within 30 days after registration, submit the following:

One or two paraffin-embedded tissue blocks containing formalin fixed tumor or needle aspirate slides from time of diagnosis (or subsequent, but prior to therapy). It is not necessary to perform an additional biopsy for this purpose. Paraffin blocks may be processed according to standard institutional protocols. If blocks are unavailable, 6-8 unstained slides are acceptable alternatives.

Cytology (i.e., fine-needle aspirations) can be accepted only if they are paraffin embedded as cell blocks.

FFPE blocks and slides must be shipped at ambient temperature.

b. Buffy Coat and Plasma (Optional for patient)

Buffy coat and plasma will be banked for future research.

Draw approximately 10 mL blood in 1-2 lavender (EDTA) tubes at the following three time points:

- After registration, prior to treatment on Cycle 1 Day 1
- Cycle 3 visit
- when patient is removed from protocol treatment

Blood should be placed on wet ice immediately after collection and processed as soon as possible (preferably within 2 hours). Centrifuge vacutainer tubes at approximately 800 x g for 10 minutes (preferably in a refrigerated centrifuge, if available). Immediately after centrifugation, carefully transfer plasma to a new 15 mL conical tube using a pipette, being careful not to aspirate the interface between the plasma and the platelets (buffy coat layer). Set aside original purple top tubes for later processing. Then centrifuge plasma a second time at 1200 x g for 10 minutes. After the second centrifugation, aliquot plasma in 500 ul aliquots into 6-10 labeled 1.8-2.0 ml cryovials, being careful not to disturb the pellet in the bottom of the tube. The buffy coat, a whitish layer of cells between the plasma and red blood cell layers, should be collected from the original purple top tube(s) and transferred into 2 labeled 1.8-2.0 ml cryovials (contamination with RBC not a concern). Freeze cryovials immediately and store at or below -70° until shipping.

Blood products may be batch shipped. They must be shipped by overnight delivery on dry ice (please do not ship on a Friday).

c. Specimen Tracking System

All specimen submissions for this study must be entered and tracked using the SWOG online Specimen Tracking system. SWOG members may log on the online system via the CRA Workbench. To access the CRA Workbench, go to the SWOG Web site (http://swog.org) and logon to the Members Area. After you have logged on using your SWOG roster ID number and password, click on the *CRA Workbench* link to access the home page for CRA Workbench website. Non- SWOG users may log into SpecTrack using their CTSU UserID and password on the SpecTrack login page located at https://crawb.crab.org/SpecTrack/Logon.aspx (select the option “SWOG – SWOG – CTSU”). SpecTrack start-up instructions (both written and demo) are available after signing in to SpecTrack.

A copy of the Shipment Packing List produced by the online Specimen Tracking system should be printed and placed in the pocket of the specimen bag if it has one, or in a separate resealable bag. The Specimen Submission Form is NOT required when the online system is used.

ALL SPECIMENS MUST BE LOGGED VIA THIS SYSTEM; THERE ARE NO EXCEPTIONS.

To report technical problems with Specimen Tracking, such as database errors or connectivity issues, please send an email to technicalquestion@crab.org. For procedural help with logging and shipping specimens, there is an introduction to the system on the Specimen Tracking main page (http://dnet.crab.org/SpecTrack/Documents/Instructions.pdf); or contact the Data Operations Center at 206/652-2267 to be routed to the Data Coordinator for further assistance.

In the online specimen tracking system, the appropriate SWOG laboratory for submission of all specimens for this study is:

Lab #111: UC Davis SWOG Translational Medicine Lab
Phone: 916/734-0821
Contact: Leslie Solis, M.S.

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, No. 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

Drug Accountability

An investigator is required to maintain adequate records of the disposition of investigational drugs according to procedures and requirements governing the use of investigational new drugs as described in the Code of Federal Regulations 21 CFR 312.

Publication and Industry Contact

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award apply to the use of the Agent in this study:

1. Agent(s) may not be used outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be

maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

   a. NCI will provide all Collaborators with written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations which would tend to restrict NCI's participation in the proposed combination protocol.

   b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.

   c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to the Collaborator(s) for Phase III studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to the Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably

at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/media presentation should be sent to:

E-mail: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to the Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of the Collaborator's confidential/proprietary information.

Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol and patient-specific CDUS data will be submitted quarterly to CTEP by electronic means, either by FTP burst of data or via the CDS web application. Reports are due January 31, April 30, July 31 and October 31. The SWOG Data Operations center will submit data using the CDUS instructions that can be found on the CTEP website (http://ctep.cancer.gov/reporting/cdus.html).

Confidentiality

Please note that the information contained in this protocol is considered confidential and should not be used or shared beyond the purposes of completing protocol requirements until or unless additional permission is obtained.

16.1 Adverse Event Reporting Requirements

a. Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. The following guidelines prescribe expedited adverse event reporting for this protocol.

b. Reporting method

This study requires that expedited adverse events be reported using the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov. A CTEP-AERS report must be submitted to the SWOG Operations Office electronically via the CTEP-AERS Web-based application located at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm

c. When to report an event in an expedited manner

Some adverse events require 24-hour notification (refer to Table 16.1) via CTEP-AERS.

When the adverse event requires expedited reporting, submit the report within the number of calendar days of learning of the event, as specified in Table 16.1.

In the rare event when internet connectivity is disrupted a 24-hour notification is made to NCI by telephone at 301-897-7497. An electronic report MUST be submitted immediately upon re-establishment of internet connection.

Any supporting documentation requested by CTEP should be submitted in accordance with instructions provided by the CTEP-AERS system.

d. Other recipients of adverse event reports

The SWOG Operations Office will forward reports and documentation to the appropriate regulatory agencies and drug companies as required.

Adverse events determined to be reportable to the Institutional Review Board responsible for oversight of the patient must be reported according to local policy and procedures.

e. **Expedited reporting for investigational agents**

Expedited reporting is required if the patient has received at least one dose of the investigational agent(s) as part of the trial. Reporting requirements are provided in Table 16.1. The investigational agent used in this study is trametinib. If there is any question about the reportability of an adverse event or if on-line CTEP-AERS cannot be used, please telephone or email the SAE Specialist at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

Table 16.1:
Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under a CTEP IND within 30 Days of the Last Administration of the Investigational Agent/Intervention[1] trametinib

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

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

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) 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 subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

May 5, 2011

f. **Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Late Phase 2 and Phase 3 Studies Utilizing an Agent under a CTEP IND:**

1) **Group-specific instructions**

Submission of the on-line CTEP-AERS report plus any necessary amendments generally completes the reporting requirements. In addition, you may be asked to submit supporting clinical data to the Operations Offices in order to complete the evaluation of the event. If requested, the supporting data should be sent within **5 calendar days** by fax to 210-614-0006. Supporting clinical data submitted should include:

- Printed copy of the first page of the CTEP-AERS Report.
- Copies of clinical sourced documentation of the event.
- If applicable, and they have not yet been submitted to the SWOG Data Operations Center copies of Off Treatment Notice and/or Notice of Death.

g. **Expedited reporting for commercial agents**

Commercial reporting requirements are provided in Table 16.2. The commercial agent used in this study is docetaxel. If there is any question about the reportability of an adverse event or if on-line CTEP-AERS cannot be used, please telephone or email the SAE Program at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

Table 16.2. Expedited reporting requirements for adverse events experienced within 30 days of the last administration of docetaxel

Attribution	Grade 4		Grade 5[a]	
	Unexpected	Expected	Unexpected	Expected
Unrelated or Unlikely			**CTEP-AERS**	**CTEP-AERS**
Possible, Probable, Definite	**CTEP-AERS**		**CTEP-AERS**	**CTEP-AERS**

CTEP-AERS: Indicates an expedited report is to be submitted via CTEP-AERS within 10 calendar days of learning of the event[b].

[a] This includes all deaths within 30 days of the last dose of treatment with a commercial agent(s), regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent(s) and is attributed (possibly, probably, or definitely) to the agent(s) and is not due to cancer recurrence must be reported according to the instructions above.

[b] Submission of the on-line CTEP-AERS report plus any necessary amendments generally completes the reporting requirements. You may, however, be asked to submit supporting clinical data to the Operations Office in order to complete the evaluation of the event. If requested, the specified data should be sent within 5 calendar days by fax to 210-614-0006.

h. Reporting Secondary Malignancy, including AML/ALL/MDS

1. A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

   CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND to be reported via CTEP-AERS. Three options are available to describe the event.

   - Leukemia secondary to oncology chemotherapy (e.g., Acute Myelocytic Leukemia [AML])
   - Myelodysplastic syndrome (MDS)
   - Treatment-related secondary malignancy

   Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

   Second Malignancy: A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS unless otherwise specified.

   For more information see:
   http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf

2. Supporting documentation should be submitted to CTEP in accordance with instructions provided by the CTEP-AERS system. A copy of the report and the following supporting documentation must also be submitted to SWOG Operations Office within 30 days by fax to 210-614-0006 or mail to the address below:

   - a copy of the pathology report confirming the AML/ALL /MDS diagnosis
   - (if available) a copy of the cytogenetics report

   SWOG
   ATTN: SAE Program
   4201 Medical Drive, Suite 250
   San Antonio, Texas 78229

   NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the report must be submitted for the most recent trial.

i. **Reporting Pregnancy, Pregnancy Loss, and Death Neonatal**

1. Pregnancy Study participants who become pregnant while on study; that pregnancy should be reported in an expedited manner via CTEP-AERS as Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)" under the Pregnancy, puerperium and perinatal conditions SOC.

   Additionally, the pregnancy outcome for patients on study should be reported via CTEP-AERS at the time the outcome becomes known, accompanied by the same Pregnancy Report Form used for the initial report.

2. Pregnancy Loss Pregnancy loss is defined in CTCAE as "Death in utero." Pregnancy loss should be reported expeditiously as Grade 4 "Pregnancy loss" under the Pregnancy, puerperium and perinatal conditions SOC.

   A Pregnancy loss should **NOT** be reported as a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEP-AERS recognizes this event as a patient death.

3. Death Neonatal Death neonatal is defined in CTCAE as "Newborn death occurring during the first 28 days after birth. A neonatal death should be reported expeditiously as Grade 4 "Death neonatal" under the General disorders and administration SOC.

   Neonatal death should **NOT** be reported as a Grade 5 event under the General disorders and administration SOC as currently CTEP-AERS recognizes this event as a patient death.

NOTE: When submitting CTEP-AERS reports for "Pregnancy, "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form should also be completed and faxed with any additional medical information to 301-230-0159. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

The Pregnancy Information Form is available at:
http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm.

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18.0 APPENDIX

18.1 Intake Calendar - Trametinib

SWOG Patient ID_____ Patient Initials (L, F, M) _____ **SWOG Study #S1507**

Institution/Affiliate _____ Physician _____

Instructions for the participant:
This is a monthly calendar on which you are to record the number of tablets you take each day. Be sure you have enough calendars to last until your next appointment. If you develop any side effects from the tablets, mark this on the calendar on the day you note the effect. Bring your calendars with you each time you have an appointment.

If you have questions contact: _____ Telephone: _____

Your next appointment is: _____

Special instructions:

Month: **Year:**

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday

Patient Signature:_____

18.2 Translational Medicine Methodology

p53, STK11 and KRAS mutation analysis: Tumor TP53, STK11 and KRAS mutation status will be determined in all consenting patients with sufficient tumor in real time (within 2 weeks of receipt of tissue). Mutation analysis will be performed by Genoptix using the Nexcourse NSCLC assay under oversight from the UC Davis Comprehensive Cancer Center by Dr. Philip Mack. The Genoptix next-generation sequencing panel uses capture-based technology to measure mutations, copy number variance and fusion events in 25 NSCLC-specific cancer genes. Using the Illumina HiSeq2000 platform, hybrid-capture–selected libraries are sequenced to high uniform depth (targeting >500× coverage by non-PCR duplicate read pairs, with >99% of exons at coverage >100×). Protocols and reagents have been optimized to assure even coverage and robust performance for a wide variety of specimens. Sequence data are processed using a customized analysis pipeline designed to accurately detect multiple classes of genomic alterations: base substitutions, indels, focal gene amplifications, homozygous gene deletions and selected gene fusions in routine clinical specimens. All testing is done in a CLIA-certified, CAP-accredited laboratory. Overall substitution detection performance is high; >99% of base substitutions expected to be present at mutant allele frequencies (MAF) ≥ 10% are successfully detected (1,036/1,036), as are 99% of substitutions at MAF < 10% (1,013/1,021) In addition, high specificity is maintained with a positive predictive value (PPV, the fraction of substitution calls in the pools traceable to a substitution in a constituent cell line) >99% (2,577/2,579, with two false-positive calls at MAF < 5%). At 250× median coverage, >99% of base substitutions present at MAF ≥ 10% are successfully detected (1,035/1,036), as are 98% of substitutions at 5% ≤ MAF ≤ 10% (601/614). Furthermore, PPV remains high (>99%) across the full coverage range. A high correlation between expected and observed MAFs at test sites remains, highlighting the quantitative nature of the optimized NGS-based test. Overall, indel detection is also high: 98% (92/94) of indels at MAF ≥ 20% are successfully detected, as well as 97% (71/73) of indels at 10% ≤ MAF ≤ 20% and 88% (53/60) of indels at 5% ≤ MAF ≤ 10%. In addition to TP53, STK11 and KRAS, the assay will also interrogate AKT1 activating mutations and PTEN deleterious abnormalities. Genoptix operates under strict adherence to the WHO's good clinical laboratory practice (GCLP) guidelines, and all work will be performed in their CLIA-licensed CAP-accredited facilities. Additionally, Genoptix will perform p53 IHC using their validated commercial assay and a partnership has been formed with MolecularMD to evaluate LKB1 (STK11) by IHC. The IHC assays are essential to identify abnormalities that result in loss of expression. Patient specimen materials from this trial will not be assayed until CTEP has reviewed all assay information.

18.3 Bone Marrow Distribution in the Adult

Anatomic Site	% Total Red Marrow
Head	13.1
Cranium	12.0
Mandible	1.1
Upper Limbs	8.3
2 Humerus	2.0
2 Scapula	4.8
2 Clavicle	1.5
Sternum	2.3
Ribs	7.9
Vertebrae	42.3
Cervical	3.4
Thoracic	14.1
Lumbar	10.9
Sacrum	13.9
Lower Limb Girdle	26.1
2 Os Coxae	22.0
2 Femoral Head & Neck	4.0

(Extracted from Phys Med Biol 5:255, 1961)