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FROM: NICOLE COPELAND

PROTOCOL SECTION

DATE: DECEMBER 26, 2017

RE: PROTOCOL GOG-0229O—AMENDMENT 7

PROTOCOL TITLE: A RANDOMIZED PHASE II STUDY WITH A SAFETY LEAD-IN TO ASSESS THE ANTITUMOR EFFICACY OF THE MEK INHIBITOR TRAMETINIB ALONE OR IN COMBINATION WITH GSK2141795, AN AKT INHIBITOR, IN PATIENTS WITH RECURRENT OR PERSISTENT ENDOMETRIAL CANCER

NCI Version Date 11/08/2017

Study Chair: Shannon N. Westin, MD, MPH; (713)794-4314; E-mail: swestin@mdanderson.org

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IRB Recommendations

( ) No review required
(X) Expedited review; however, site IRB requirements take precedence
( ) Full board review
SUMMARY OF CHANGES

NCI Protocol #: GOG-0229O
Local Protocol #: GOG-0229O

NCI Version Date: November 8, 2017
Protocol Date: November 8, 2017

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<td>11.5, 11.6</td>
<td><strong>New Sections 11.5 PTEN assessment and 11.6 Analysis of Genes have been added; subsequent section has been renumbered.</strong></td>
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<td>Appendix IX</td>
<td><strong>A new Appendix IX, “Translational research laboratory testing procedures,” has been added, which details revised translational research lab testing procedures and provides the new Translational Objective. It is hypothesized that a comprehensive assessment of PI3K/AKT and RAS/RAF/MEK pathway aberrations, as well as additional pathways of interest, will provide potential markers for response to therapy with trametinib and GSK2141795.</strong></td>
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PROTOCOL GOG-02290
A RANDOMIZED PHASE II STUDY WITH A SAFETY LEAD-IN TO ASSESS THE ANTITUMOR EFFICACY OF THE MEK INHIBITOR TRAMETINIB ALONE OR IN COMBINATION WITH GSK2141795, AN AKT INHIBITOR, IN PATIENTS WITH RECURRENT OR PERSISTENT ENDOMETRIAL CANCER NCT #01935973

NCI VERSION DATE: November 8, 2017
Includes Amendments 1-7

POINTS:
PER CAPITA – 20
MEMBERSHIP – 3

TR PER CAPITA – Award based on specimen submission with 1 point for each FFPE and whole blood (MAX = 5 points).
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Lead Organization: NRG / NRG Oncology (05/12/14)

Participating Organizations (05/12/14)
ALLIANCE / Alliance for Clinical Trials in Oncology
ECOG-ACRIN / ECOG-ACRIN Cancer Research Group
SWOG / SWOG

STUDY CHAIR
SHANNON N. WESTIN, MD, MPH
MD ANDERSON CANCER CENTER
GYN ONCOLOGY AND REPRODUCTIVE MEDICINE
1155 Herman Pressler Blvd
Unit 1362
Houston, TX 77030
PH: (713)794-4314
FAX: (713) 792-7586
EMAIL: swestin@mdanderson.org

STUDY CO-CHAIR
ROBERT L. COLEMAN, MD
See GOG Website

STATISTICIAN
MICHAEL SILL, PHD
See GOG Website

TR CO-CHAIR
PANAGIOTIS KONSTANTINOPULIS MD, PHD
See GOG Website

TR SCIENTIST
HEATHER A LANKES, PhD, MPH
See GOG Website

PATHOLOGIST
See GOG Website

NURSE CONTACT
PAULA ROGERS, RN
See GOG Website

NCI-Supplied Agents: Trametinib dimethyl sulfoxide (GSK1120212B) (NSC #763093), GSK2141795 (NSC #767034), GlaxoSmithKline

IND #: 118640
IND Sponsor: DCTD, NCI

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OPEN TO PATIENT ENTRY SEPTEMBER 30, 2013

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NCI Version Date: November 8, 2017

PARTICIPATING INSTITUTIONS (Phase I Safety Lead-In)(07/28/14)

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CA011/UNIVERSITY OF SOUTHERN CALIFORNIA
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VA009/UNIVERSITY OF VIRGINIA
IL057/UNIVERSITY OF CHICAGO
OH029/CASE WESTERN RESERVE UNIVERSITY
RI012/WOMEN & INFANTS HOSPITAL
CT005/THE HOSPITAL OF CENTRAL CONNECTICUT
CT009/HARTFORD HOSPITAL
GA020/ MEDICAL COLLEGE OF GEORGIA
NC042/ CAROLINAS MEDICAL CENTER
SC008/MEDICAL UNIVERSITY OF SOUTH CAROLINA
**CONTACT INFORMATION**

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<thead>
<tr>
<th>To submit site registration documents:</th>
<th>For patient enrollments:</th>
<th>Submit study data</th>
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<tr>
<td>CTSU Regulatory Office</td>
<td>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 <a href="https://www.ctsu.org/OPEN_SYSTEM/">https://www.ctsu.org/OPEN_SYSTEM/</a> or <a href="https://OPEN.ctsu.org">https://OPEN.ctsu.org</a>. Contact the CTSU Help Desk with any OPEN-related questions at <a href="mailto:ctsucontact@westat.com">ctsucontact@westat.com</a>.</td>
<td>Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions.</td>
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<tr>
<td>1818 Market Street, Suite 1100</td>
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</tr>
<tr>
<td>Philadelphia, PA 19103</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phone – 1-866-651-CTSU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fax – 215-569-0206</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Email: <a href="mailto:CTSURegulatory@ctsu.coccg.org">CTSURegulatory@ctsu.coccg.org</a></td>
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A RANDOMIZED PHASE II STUDY WITH A SAFETY LEAD-IN TO ASSESS THE ANTITUMOR EFFICACY OF THE MEK INHIBITOR TRAMETINIB ALONE OR IN COMBINATION WITH GSK2141795, AN AKT INHIBITOR, IN PATIENTS WITH RECURRENT OR PERSISTENT ENDOMETRIAL CANCER

RECURRENT or PERSISTENT ENDOMETRIAL CANCER MEASURABLE DISEASE AND 1-2 PRIOR CHEMOTHERAPY REGIMENS

SAFETY LEAD IN
Safety Lead In #1: 12-15 patients deemed unsafe
Safety Lead In #2: design to evaluate regimen in 6 to 12 patients
Treated with Regimen II (below)
Evaluation of dose-limiting toxicities in cycle 1 to determine safety
If Regimen II is safe – proceed to randomized study

KRAS mutation status on primary or recurrent tumor (required)

Stratification by KRAS mutation

KRAS wildtype  KRAS mutant

RANDOMIZATION

REGIMEN I
Trametinib 2.0 mg PO Daily
(One cycle = 28 days)

REGIMEN II
PENDING MTD determination
in Safety Lead In #2
(One cycle = 28 days)

Assess response every 8 weeks by RECIST 1.1
Continue until disease progression or adverse events prohibit further therapy
Patients on Regimen I may cross over to Regimen II at progression
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8.1 Antitumor Effect – Solid Tumors

9.0 DURATION OF STUDY

9.1 Patients will receive therapy until disease progression or intolerable toxicity.
9.2 All patients will be treated (with completion of all required case report forms)
9.3 A patient is considered off study therapy when the patient has progressed or died,

10.0 STUDY MONITORING & REPORTING PROCEDURES

10.1 Adverse Event Reporting For An Investigational Agent (CTEP IND) (05/12/14)
10.2 Medidata Rave Data Submission and Reporting (05/12/14)
10.3 GOG Data Management Forms (12/23/13) (07/28/14)

11.0 STATISTICAL CONSIDERATIONS

11.1 Parameters employed to evaluate treatment efficacy and toxicity are:
11.2 The anticipated annual accrual is approximately 50 patients.
11.3 Study Plan (05/12/14) (07/28/14)
11.4 Secondary and Exploratory Analyses
11.5 PTEN assessment
11.6 Analysis of Genes
11.7 Minority Accrual

12.0 BIBLIOGRAPHY

Appendix I - General Chemotherapy Guidelines:
Appendix II - Congestive Heart Failure – New York Heart Association Criteria
Appendix III - PATIENT PILL CALENDAR: REGIMEN I
Appendix IV - PATIENT PILL CALENDAR: REGIMEN II
Appendix V - Translational Research Specimen Procedures (12/23/13)(07/28/14)
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Appendix VIII – CT Scan Date Calculator (12/23/13)
APPENDIX IX – TRANSLATIONAL RESEARCH LABORATORY
1.0 OBJECTIVES

1.1 Primary Objectives

Phase 2:

1.11 To assess the relative activity of trametinib (MEK inhibitor) alone or in combination with GSK2141795 (AKT inhibitor) for patients with recurrent or persistent endometrial cancer by progression-free survival.

1.12 To determine the frequency and severity of adverse events as assessed by CTCAE.

Safety Assessment Lead-In:

1.13 To determine the tolerability of the combination regimen of trametinib and GSK2141795 through determination of dose-limiting toxicity in a two-stage safety lead-in study. (07/28/14)

1.2 Secondary Objectives

1.21 To estimate the association between baseline KRAS status and clinical activity (e.g. response and PFS) for patients with recurrent or persistent endometrial cancer who are treated with trametinib alone or in combination with GSK2141795.

1.22 To estimate overall survival (OS) of patients with recurrent or persistent endometrial cancer treated with trametinib therapy alone (excluding patients who cross over) and trametinib/GSK2141795 combination therapy in the two subgroups of patients defined above.

1.23 Prognostic factors will be examined for associations with patients who do not crossover.

1.24 To estimate objective response and response duration associated with trametinib therapy and trametinib/GSK2141795 combination therapy in the two subgroups of patients defined above.

1.25 To estimate the relative proportion of patients responding or have 6-month PFS on the therapies administered on this study with those studies that may serve as a historical control. In the event that Regimen II is rejected, Regimen I may be assessed for possible activity against this historical dataset.

1.3 Exploratory Objectives
Note: Testing of banked samples will not occur until an amendment to this treatment protocol (or separate correlative science protocol) is reviewed and approved in accordance with National Clinical Trials Network (NCTN) policies.

1.31 To estimate the association between baseline genomic biomarkers in the PI3K/AKT pathway and clinical activity (e.g. response and PFS) in two subgroups of patients defined above with recurrent or persistent endometrial cancer who are treated with trametinib alone or in combination with GSK2141795.
2.0 BACKGROUND AND RATIONALE

2.1 Introduction

2.11 Endometrial Cancer

Endometrial cancer is the most common of all uterine malignancies and is the most common gynecologic malignancy in the United States. In 2012, the American Cancer Society estimated there would be 47,130 new cases and 8,010 deaths from endometrial cancer\(^1\). Fortunately, the majority of patients are diagnosed at an early stage and may be cured by surgery with or without adjuvant radiotherapy\(^2\). However, approximately 25% of early stage and more than 50% of advanced stage cancers will recur. Further, the median survival after recurrence is 10 months and the 5-year survival for patients who have recurred is <15%. This stems from the limited options that are available for the majority of patients with distant disease.

Currently the GOG is screening a number of cytotoxic and biologic agents in this regard. Clinical activity of cytotoxics has been documented with doxorubicin, cisplatin, ifosfamide and paclitaxel\(^3\). In addition, combinations of these agents have been documented to have significant clinical activity in this setting\(^4\)\(^-\)\(^8\).

Nonetheless, most recurrent patients will not be cured by salvage therapy and will go onto other programs with much lower anticipated response. This represents an important unmet need in endometrial cancer care. In this regard, the GOG is evaluating a series of single agent biologic agents. In this queue, trastuzumab (0181-B), thalidomide (0229-B), gefitinib (0229-C), GW-572016 (lapatinib, 0229-D), bevacizumab (0229E), aflibercept (0229F), bevacizumab/temsirolimus (0229-G), AZD6244 (0229-H), brivanib (0229-I), cediranib (0229-J), AMG386 (0229-L), BIBF1120 (0229-K), and dalantercept (0229-N) have been studied or are still accruing patients.

2.12 Relevance of RAF/MEK/ERK pathway in recurrent endometrial cancer

The RAF-MEK-ERK pathway plays a critical role in multiple cellular functions. Activation of the pathway can result from activation/mutations of the upstream receptor tyrosine kinases (RTKs) and RAS, or upregulation/mutations in RAF and MEK. Upon activation, RAF acts as the MAPK kinase and activates MAPKK (MEK1/2), which in turn catalyze activation of the effectors ERK1/ERK2. Once activated, ERK1/2 translocate into the nucleus and phosphorylate a number of effector proteins and transcriptional factors that regulate cell proliferation, motility, differentiation, and survival\(^9\).
Mutated, oncogenic forms of RAS are found in 50% of colon and >90% of pancreatic cancers as well as many other types of cancers\textsuperscript{10}. Recently, BRAF gene mutations have been identified in more than 60% of malignant melanomas, as well as in other tumor types\textsuperscript{7}. These mutations in BRAF result in a constitutively active MAP kinase cascade. Studies of primary tumor samples and cell lines have also shown constitutive activation or over activation of the MAP kinase pathway in cancers of the pancreas, colon, lung, ovary, and kidney\textsuperscript{11}. Thus, there is a strong correlation between cancers and an overactive MAP kinase pathway resulting from genetic mutations.

The importance of ERK pathway has been firmly established. Pollock and colleagues reported frequent activating mutations in the fibroblast growth factor receptor 2 gene in 16% of endometrioid carcinomas\textsuperscript{12}. Mutations in a more proximal component of the ERK signaling pathway, KRAS, are seen in 13-26% of endometrial cancers. Further, aberrations may be found in the RTK, which activates this pathway. Detailed analysis of 116 primary endometrioid endometrial cancer revealed FGFR2 mutations are mutually exclusive with KRAS mutation\textsuperscript{12}. Furthermore, FGFR2 or KRAS mutations frequently occur alongside PTEN inactivation.

2.13 Relevance of PI3K/AKT pathway in recurrent endometrial cancer

The PI3K pathway is important in the pathogenesis of endometrial cancer, evidenced by the finding that up to 80% of endometrial cancers will have an aberration in this pathway. Deleterious PTEN mutations are present in 30-50% of endometrial cancers, leading to PTEN protein dysfunction\textsuperscript{13-15}. Loss of the tumor suppressor PTEN leads to constitutive activation of AKT, which, in turn leads to up-regulation of downstream AKT targets including mammalian target of rapamycin (mTOR). PIK3CA is the oncogene that encodes the p110alpha catalytic subunit of PI3K, while the tumor suppressor PTEN dephosphorylates and inactivates phosphatidylinositolsthat are phosphorylated by PI3K. Mutations in the PIK3CA (activating) and PTEN (deleterious) genes, along with other genomic aberrations, lead to frequent activation of PI3K pathway signaling in endometrial cancer, making the pro-oncogenic PI3K pathway an attractive target for therapy in these tumors. Phosphorylation of membrane phosphatidylinositolsthat by PI3K plays a pivotal role in cell proliferation, differentiation, senescence, cytoskeletal organization, motility, metastasis, invasion, angiogenesis, and cell survival\textsuperscript{16-19}.

Activating mutations of PIK3CA are present in approximately 30-40% of endometrial cancers, further demonstrating that the PI3K pathway is important in the pathogenesis of endometrial cancer\textsuperscript{14,15}. PIK3CA mutations, like PTEN loss, lead to constitutive activation of PI3K pathway signaling. Other aberrant events in endometrial cancer reduce inhibitory input into the pathway and thus increase signaling through the PI3K pathway. Activating AKT1 mutations that, like PIK3CA and PTEN mutations, lead to constitutive activation of PI3K pathway signaling, have
recently been identified in breast and colorectal cancers and may also play a role in the pathogenesis of endometrial cancer\textsuperscript{19,20}. Taken together, these data indicate that the PI3K pathway is frequently activated in endometrial cancer, and this justifies exploration of this pathway as a therapeutic target in this disease. Indeed, we and other groups have previously completed clinical trials that have demonstrated efficacy for mTOR inhibitors such as everolimus, temsirolimus and ridaforolimus in the treatment of women with advanced endometrial cancer. Our institution has completed a Phase II single agent everolimus study demonstrating 21% confirmed clinical benefit (stable disease by imaging at 20 weeks of treatment) in patients with previously treated, measurable, recurrent endometrial cancer\textsuperscript{21}. Prior treatment with chemotherapy, though, appears to impact the single agent response of mTOR agents (aka rapalog’s), as was observed in two trials evaluating the efficacy of temsirolimus in chemotherapy naïve (RR: 24%) and chemotherapy exposed (RR: 4%), suggesting compensatory mechanisms in the pathway or other pathways (e.g. Ras) may be selected for following cytotoxic exposure\textsuperscript{22}. Indeed, activating mutations in KRAS (which are identified in 10-30% of endometrial cancers\textsuperscript{14,15,23}) have been shown to be dominant predictors of resistance to targeted therapies (e.g. erlotinib, cetuximab, PI3K inhibitors) in lung and colorectal cancers\textsuperscript{24-26}. As such, emerging data implicate that the combination of PI3K and RAS/RAF pathway (e.g. MEK) inhibitors may be necessary for optimal growth inhibition of tumors that possess KRAS mutations\textsuperscript{26}. Of note, PI3K aberrations investigated in archival specimens in each of the clinical studies did not correlate with clinical activity, highlighting the need for contemporary tissue evaluation.

Inhibitors of mTOR have been the only clinically available inhibitors of PI3K signaling for some time. However, several factors limit the antitumor activity of mTOR inhibitors. First, the PI3K pathway can be visualized as a pyramid, with PI3K at the apex and multiple signaling branches downstream from PI3K that PI3K utilizes to mediate its effects, only one of which is mTOR. Thus, while PI3K inhibition can cause a complete blockade of PI3K pathway signaling, the effects of mTOR inhibition can be bypassed by other signaling branches downstream from PI3K. Second, feedback loops that likely play a normal role in the maintenance of PI3K pathway homeostasis are now known to be induced by most mTOR (TORC1) inhibitors. These feedback loops paradoxically result in upstream activation of AKT and therefore potentially blunt the antitumor efficacy of mTOR inhibition\textsuperscript{27}. In contrast, novel PI3K and AKT inhibitors have been demonstrated to inhibit these feedback loops. Thus, novel PI3K and AKT inhibitors lead to more comprehensive inhibition of PI3K pathway signaling than rapalog mTOR inhibitors, and this is likely to translate into more potent tumor growth inhibition. Furthermore, targeting multiple related pathways has the potential to achieve great tumor response.
Based on our data in 196 patients with endometrial cancers as well as other published studies, we have determined the approximate percentage of mutations in the PI3K and KRAS pathways among this group of patients\textsuperscript{28}. Given the very closely related coexistence of PIK3CA, PTEN and AKT1 in the PI3K pathway, the hierarchical position of KRAS in the distinct RAS/RAF/MAPK signaling pathway and the apparent dominance of KRAS mutations in terms of implying resistance to many kinase-targeted therapies, we hypothesize that endometrial cancer defined by PIK3CA, PTEN and KRAS mutations can be condensed into 2 major subgroups in terms of signaling deregulation and responsiveness to PI3K and RAS/RAF pathway-targeted therapies alone and in combination. The frequencies of the 2 major subgroups are as follows: Wild-type PTEN/PIK3CA/AKT1 or mutations in this pathway without KRAS mutations (80%), and KRAS mutations alone or in combination with other mutations (20%).

Thus, we have the following hypotheses:

1. Targeting the PI3K/AKT and RAS/RAF/MEK pathways will achieve clinical activity in recurrent endometrial cancer.

2. Response to therapies targeting the PI3K/AKT and RAS/RAF/MEK pathways will vary based on presence/absence of aberrations in those pathways.

### 2.2 Trametinib Dimethyl Sulfoxide (GSK1120212B)

Trametinib is a potent and highly selective inhibitor of MEK1 activation and kinase activity. Trametinib is one of the several MEK inhibitors in clinical development. Experience to date indicates that MEK is a valid target. In a phase III trial comparing trametinib with dacarbazine or paclitaxel in patients with BRAF V600E or V600K mutant metastatic melanoma, trametinib demonstrated a significantly better response rate, progression-free survival, and overall survival\textsuperscript{29}. However, single agent activities are limited. Extensive research is underway to identify the patient selection markers and develop rational combination strategies. Preclinical studies have provided strong rationale and proof of principle for combination of MEK inhibitors with RTK inhibitors (EGFR or IGF-1R)\textsuperscript{30,31}, PI3K/AKT inhibitors\textsuperscript{26,32}, and mTOR inhibitors. On the other hand, the optimal dose/schedule and patient selection criteria for combination regimens have not been defined. Phase 1 results for a number of combinations have been reported: Phase 1 AZD6244 + MK2206\textsuperscript{33}, phase 1 GDC-0973 + GDC-094 (MEK + PI3K inhibitor)\textsuperscript{34}.

### 2.2.1 Mechanisms of Action and Preclinical Data with Trametinib

Trametinib is a dimethyl sulfoxide (DMSO) solvate compound (ratio 1:1) with potent, allostERIC and ATP non-competitive inhibition of MEK1/2
Trametinib inhibited MEK1/2 kinase activity and prevented RAF-dependent MEK phosphorylation (S217 for MEK1), producing prolonged pERK1/2 inhibition. Trametinib showed better potency against unphosphorylated MEK1/2 (u-MEK1/2) when compared with preactivated diphosphorylated MEK (pp-MEK), suggesting that u-MEK affords a higher affinity binding site for trametinib than does pp-MEK.

The specificity of trametinib was confirmed against a panel of 183 kinases, including MEK5 (the closest kinase homolog to MEK1/2), CRAF, BRAF, ERK1, and ERK2. Trametinib demonstrated equal potency against activated MEK1- and MEK2-mediated phosphorylation of ERK (sequence identity of 85% across the whole protein and 100% in the active site for humans). Trametinib demonstrated preferential inhibition of RAF-mediated MEK1 activation (IC\textsubscript{50} = 0.60 nM) over pMEK1 kinase activity (IC\textsubscript{50} = 13 nM).

BRAF-mutant Colo205, A375P F11s, and HT-29 human tumor xenograft mouse models showed the most significant mean tumor growth inhibition (TGI) (80% to 87%) at 3.0 mg/kg trametinib, with multiple complete and partial tumor regressions. In the Colo205 model, tumor regression was observed even at a dose of 0.3 mg/kg. Two KRAS-mutant xenograft models, HCT-116 and A549, also showed significant TGI (83% and 75%) but without significant tumor regressions. As predicted by cell proliferation assays, tumor xenograft lines with wild-type (wt) RAF/RAS (PC3, BxPC3, and BT474) were much less sensitive, showing only modest TGI (44-46%) with no tumor regressions.

Pharmacodynamic studies were performed in mice treated with trametinib for 14 days. In the A375P F11s xenograft model, the first dose of trametinib (3 mg/kg) significantly reduced pERK for more than 8 hours on Day 1. pERK inhibition was more sustained (over 24 hours) after the Day 7 dose, probably due to an increase in the steady-state levels of trametinib after repeated doses. The average C\textsubscript{max} in blood was 1,410 nM on Day 7, with an estimated half-life (t\textsubscript{1/2}) of 33 hours. In addition, immunohistochemistry (IHC) also confirmed inhibition of cell proliferation (reduced Ki67) and G1 cell cycle arrest (elevated p27Kip1/CDKN1B) following 4 days of treatment.

### 2.22 Clinical Pharmacokinetics (PK) and Activity of Trametinib

**FTIH Phase 1 Trial of Trametinib Monotherapy (MEK111054)**

There are 3 parts in this ongoing study. Part 1: The dose-escalation portion involves administration of trametinib (repeat doses of 0.125 mg to 4.0 mg) to patients with solid tumors or lymphoma in one of three schedules - (1) QD for 21 days followed by 7 days without drug, (2) loading dose on Day 1 or Day 1-2, followed by QD with the designated dose, or (3) QD dosing
without a drug holiday. Part 2: cohort expansion at the recommended phase 2 dose (RP2D) for pancreatic cancer, melanoma, NSCLC, CRC, or any BRAF mutation-positive cancer. Part 3: expansion to characterize the biologically active range of trametinib via analysis of pharmacodynamic biomarkers (biopsies or FDG-PET).

The dose escalation part and some of the cohort expansion components have been completed. The MTD of trametinib was established as 3 mg QD, but the recommended phase 2 dose (RP2D) was chosen at 2 mg QD based on tolerability of repeated cycles\textsuperscript{38}.

2.222 \textit{PK and metabolism of trametinib:}

PK measurements were conducted under fasting conditions. After a single dose (Day 1), AUC\textsubscript{0-24} and C\textsubscript{max} values were dose-proportional up to 6 mg, lower than dose proportional following 8 mg, and greater than dose proportional following the 10 mg dose. Median T\textsubscript{max} was 1.5 hours.

After repeat doses (Day 15), trametinib accumulated with a mean accumulation ratio of 6.6 at the RP2D of 2 mg QD. Between-subject variability in exposure ranged from 27-50\% for C\textsubscript{max} and 20-41\% for AUC\textsubscript{0-24} across all dosing regimens. The effective t\textsubscript{1/2} was approximately 4.5 days, and steady state was reached by approximately Day 15. Trametinib had a small peak: trough ratio of ~2\textsuperscript{38}. At 2 mg QD on Day 15, mean AUC\textsubscript{0-24} was 376 ng\cdot h/mL and C\textsubscript{max} 23 ng/mL, and the mean trough concentrations ranged from 10.0 to 18.9 ng/mL. The long half life and small peak: trough ratio of trametinib allowed constant target inhibition within a narrow range of exposure.

2.223 \textit{Drug-drug interactions:}

Trametinib is metabolized predominantly via deacetylation (non-cytochrome P450 [CYP450]-mediated) with secondary oxidation or in combination with glucuronidation biotransformation pathways\textsuperscript{37}. The deacetylation is likely mediated by hydrolytic esterases, such as carboxylesterases, or amidases. Based on \textit{in vitro} studies, trametinib is not an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2D6, and CYP3A4. Although trametinib was found to be an \textit{in vitro} inhibitor of CYP2C8, CYP2C9, and 2C19; inducer of CYP3A4; and inhibitor of transporters (OATP1B1, OATP1B3, P-glycoprotein [P-gp], and breast cancer resistance protein [BCRP]), its low efficacious dose, and low clinical systemic concentration (22.2 ng/mL or 0.04 mcM at 2 mg) relative to the \textit{in vitro} inhibition/induction potency suggests an overall low potential for drug-drug interactions.
2.224 Pharmacodynamic effect and biomarkers:

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\(^\text{37}\). In general, increasing exposures and/or doses provided greater pharmacodynamic effects. The median change observed at a dose of 2 mg QD was 62% inhibition of pERK, 83% inhibition of Ki67, and a 175% increase in p27.

2.23 Antitumor Activity of Trametinib Monotherapy

In the FTIH phase 1 trial, 14 patients with BRAF-mutant melanoma received trametinib at 2 mg QD (2 mg/day continuously, or 2 mg for 21 days followed by a 1 week break). The overall objective response rate (ORR) was 43% (6/14), including 2 complete responses (CRs)\(^\text{37}\). In 9 patients with BRAF wt melanoma, 2 patients achieved a partial response (PR), and 3 stable disease (SD)\(^\text{38}\). In 26 evaluable pancreatic cancer patients, there were 2 PRs (1 PR was KRAS mutation-positive) and 11 SD (2 achieved ≥20% tumor reduction)\(^\text{39}\). Among the 27 CRC patients (without selection of RAS or RAF mutations), 8 SD were observed.

In a phase 3 trial, patients with unresectable stage IIIC or IV cutaneous melanoma with a BRAF V600E or V600K mutation were randomized (2:1) to trametinib (2 mg, PO, QD) or chemotherapy (dacarbazine or paclitaxel)\(^\text{29}\). There were 322 patients in the intention-to-treat (ITT) population, of whom 273 (85%) were in the primary efficacy population (patients with BRAF\(^\text{V600E}\)-positive cancer who did not have brain metastases at baseline). In the ITT analyses, the ORR was 22% in the trametinib group and 8% in the chemotherapy group; the median duration of PFS was 4.8 months in the trametinib group as compared with 1.5 months in the chemotherapy group; and the 6-month OS rate was 81% in the trametinib group and 67% in the chemotherapy group.

2.231 Antitumor Activity of Trametinib in Cancer Other Than Melanoma

In a phase 1/2 monotherapy study, acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) patients were given trametinib at dose levels from 1-2 mg QD. Drug-related AEs in 45 patients were similar to that observed in patients with solid tumors, and 2 mg PO QD was selected for further investigation in this patient population. Twelve patients (23%) withdrew due to an AE, including cardiac failure (2) and infection (2). Efficacy was reported in 39 patients\(^\text{29}\). The best response in 13 patients with KRAS or NRAS mutations included 3 CRs (23%), 7 SD (54%), and 1 PD (progressive disease) (5%). In 26 patients with wild-type RAS or an unknown mutation, there were 2 PRs (8%).

2.24 Trametinib Safety Profile
A Comprehensive Adverse Events and Potential Risks (CAEPR) list using NCI Common Terminology Criteria for Adverse Events (CTCAE) terms is included in Section 4 of the protocol.

Due to limited experience in human subjects, there is currently incomplete information available about the relationship of AEs and administration of trametinib. 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.

AEs 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.

Rash: Rash was a common AE observed across different dose levels and in different combinations. The majority of rash observed with trametinib was acneiform and appeared to occur most frequently on the face, scalp, chest, and upper back. At the 2 mg dose, rash was seen in 48% to 91% of patients in different trials. The majority of rash AEs were grades 1 or 2 (68% to 80%); 1% to 18% of patients experienced grade 3 rash AEs, and one patient had a grade 4 rash AE.

Diarrhea: At the 2 mg monotherapy dose, 28% to 58% of patients in three trials had diarrhea. Of 219 patients with diarrhea at this dose, the majority of diarrhea AEs were grade 1 or 2 in severity (28% to 56% of all study patients); 6 patients had grade 3 diarrhea, and none had grade 4 diarrhea.

Visual disorders: At the 2 mg monotherapy dose, 6% to 21% of the patients in three trials experienced visual disorders. Of the 62 total patients experiencing visual disorders at this dose level, the majority of visual disorders were grades 1 or 2 (6% to 20% of all study patients); five patients experienced grade 3 visual disorders, and one patient experienced a grade 4 visual disorder.

- **Central Serous Retinopathy (CSR):** CSR is a class side effect of MEK inhibitors. As of 22 May 2012, 13 cases of CSR have been reported amongst approximately 1,600 patients treated with trametinib, either as monotherapy or in combination with other anti-cancer agents: two cases of grade 1, eight cases of grade 2, and three cases of grade 3. All 13 resolved.

- **Retinal Vein Occlusion (RVO):** As of 22 May 2012, four cases of RVO have been observed with trametinib. All four cases occurred...
in one eye only, and study drug was stopped at time of diagnosis in all cases. There was a decrease in visual acuity in two patients with central RVO (CRVO), while the other two patients experienced no meaningful decrease of visual acuity. Three of the 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. 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, 10% to 19% of patients in three trials had hepatic disorders. Of the 56 total patients experiencing hepatic disorders, the majority were grade 1 or 2 in severity (7% to 15% of all study patients); 12 patients had grade 3 hepatic disorders, and 3 patients had grade 4 hepatic disorders.

**Cardiac-related AEs**: At the 2 mg monotherapy dose in three trials, 3% to 21% of patients had cardiac-related AEs. Of the 43 total patients experiencing cardiac-related AEs, the majority were grade 1 or 2 in severity (4% to 16% of all study patients); six patients at this trametinib dose level had grade 3 cardiac-related AEs (three left ventricular dysfunction, two decreased LVEF, and one ventricular dilatation), and one patient experienced a grade 4 cardiac-related AE (cardiogenic shock). One patient died of 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 3 trial of trametinib vs. chemotherapy in patients with melanoma (MEK114267), patients were monitored by serial echocardiogram or MUGA scans. As of 23 June 2012, among 211 patients on the trametinib arm, 17 cardiac-related AEs were reported and included: decreased LVEF (ten grade 1-2, and two grade 3), left ventricular dysfunction (two grade 2, and two grade 3), and one grade 3 cardiac failure. No cardiac-related AEs have been observed on the chemotherapy arm of the study. Cardiac-related AEs leading to permanent discontinuation of study drug included decreased LVEF (n=2), left ventricular dysfunction (n=2), cardiac failure (n=1), myocardial infarction (n=1), and tachycardia (n=1). There was also one death due to cardiogenic shock secondary to ischemic heart disease, but it was not considered related to trametinib.

**Pneumonitis**: As of the Investigator Brochure’s cut-off date, 20 cases of pneumonitis were reported in subjects treated with trametinib, either as monotherapy or in combination with other anti-cancer agents, in six studies: five cases of grade 1, five cases of grade 2, nine cases of grade 3, and one case of grade 4.
2.3 GSK2141795

GSK2141795 is a novel member of the N-alkyl pyrazole class of orally available kinase inhibitors and has been shown to be a potent, ATP competitive, pan-AKT (a serine/threonine protein kinase with 3 isoforms, AKT1, AKT2 and AKT3) inhibitor, with potency (Ki) values for human AKT1, 2 and 3 kinases being 0.066, 1.4 and 1.5 nM, respectively. GSK2141795 exhibited a time-dependent inhibition of AKT with a dissociation half-life of 20 minutes. In vitro, GSK2141795 caused a concentration- and time-dependent reduction in phosphorylation of multiple proteins downstream of AKT such as glycogen synthase kinase 3 (GSK-3), an insulin-regulated inhibitor of the mTORC1 protein kinase (PRAS40), Forkhead gene product (FOXO) and caspase 9. Treatment of tumor cells with GSK2141795 resulted in a concentration-dependent increase in the nuclear translocation of the FOXO transcription factor as a functional consequence of reduced phosphorylation of FOXO. GSK2141795 inhibited the proliferation of a range of tumor cell lines from multiple histologies including breast, hematological, colon, ovarian and prostate (EC50 <1 nM). AKT signaling was inhibited in cell lines both sensitive and less sensitive to GSK2141795, suggesting that resistance to GSK2141795 is not due to a lack of AKT kinase inhibition. GSK2141795 induced cell cycle arrest at G1 or apoptosis in a concentration-dependent manner depending on the cellular context.

There are 3 ongoing clinical pharmacology studies for GSK2141795. PCS112689 is a first-time-in-human (FTIH), dose-escalation study in subjects with cancer to characterize the safety, pharmacokinetic, and pharmacodynamic profiles of GSK2141795. PCS113124 is an open-label, multiple-dose, dose-escalation study designed to explore the potential dose response relationship between the pharmacokinetics of GSK2141795 and [18F] FDG PET pharmacodynamic markers of glucose metabolism in tumor tissue. TAC113886 is a dose-escalation, open-label study to determine the recommended Phase II dose and regimen for the combination of the orally administered MEK inhibitor TRAMETINIB and the orally administered AKT kinase inhibitor GSK2141795.

2.31 Pharmacokinetics (PK)

Single-dose (Day 1) PK parameters of GSK2141795 were evaluated in the first-time-in-human (FTIH) study (PCS112689). Preliminary data indicated that plasma concentrations for GSK2141795 were measurable for all subjects over the 72 hours after a single dose over the dose range tested (10 mg to 150 mg). In addition, drug concentrations were measurable on Day 8, suggesting that GSK2141795 can still be found in the plasma at least 1 week after a single dose of study drug over the dose range tested (75 mg to 100 mg). While the exposure for the 100 mg and 150 mg doses were similar following a single dose, drug exposure following multiple doses was approximately in proportion to dose. GSK2141795 accumulated 2.5- to 8.4-fold with repeat daily dosing. Mean area under the concentration-time curve [AUC_{0-24}] and maximum plasma concentration (C_{max}) values generally increased in a dose-proportional manner, although there was variability among subjects.
Median time to reach peak concentration ($T_{\text{max}}$) across doses was 3 hours and ranged from 0 to 4 hours. The mean value for the effective half-life of elimination ($t_{\text{1/2, eff}}$), across subjects was 3.0 days and ranged from approximately 1.3 to 5.5 days.

2.32 Maximum Tolerated Dose (MTD) and Recommended Phase 2 Dose (RP2D)

The MTD of single-agent GSK2141795 is 75 mg once-daily as determined by the FTIH study. The RP2D of single-agent GSK2141795 has not been determined.

2.33 Potential Drug-Drug Interactions

*In vitro* data indicate that GSK2141795 is a CYP3A4 substrate. Drugs that potently inhibit CYP3A4 could lead to increased GSK2141795 exposure in subjects, and should either be prohibited or used with caution. Drugs which are strong inducers of CYP3A and may result in lower exposures of GSK2141795 should also be prohibited. GSK2141795 also appears to be a moderate *in vitro* inhibitor of CYP2C8 ($50\%$ inhibitory concentration $[\text{IC}_{50}]$ 3 mcM) and CYP3A4 ($\text{IC}_{50}$ 11 mcM). Drugs that are substrates of CYP3A4 or CYP2C8 with a narrow therapeutic index may be prohibited. Drugs that are sensitive substrates of CYP3A4 or CYP2C8 should be used with caution.

2.34 Safety Profile

A Comprehensive Adverse Events and Potential Risks (CAEPR) list using NCI Common Terminology Criteria for Adverse Events (CTCAE) terms is included in Section 4 of the protocol.

Based on available adverse event (AE) data from 151 subjects dosed as of the data cut-off date of May 6, 2012, the most common toxicities of GSK2141795 monotherapy or in combination with trametinib are gastrointestinal (GI)-related (diarrhea, nausea, and vomiting) and fatigue (Investigator’s Brochure, 2012). Hyperglycemia, hypoglycemia, mucositis, and rash are also commonly observed. In addition, three cases of hypothyroidism have been noted.

**GI-related AEs**

Interim medical history, continuous assessment of AEs, physical examination, and clinical laboratory assessments will be used to identify and assess toxicity in the GI tract. Supportive therapy will be provided according to standard medical practice. Treatment will be discontinued for clinically significant toxicity.

**Diarrhea:** This is the most frequent drug-related AE in patients receiving GSK2141795. Most diarrhea events reported were Grade 1 and 2. Based on current data, the majority of cases of diarrhea occur within the first 3 to 4 weeks of starting the drug. In most cases, diarrhea resolves with
interruption of GSK2141795 dosing and implementation of supportive treatment. Based on preliminary data, re-challenge with a reduced dose of GSK2141795 is tolerated. Early diarrhea management for subjects taking GSK2141795 is critical and must be initiated as soon as the first episode of diarrhea has occurred. Supportive care interventions should include dietary modifications, anti-diarrheal medications, and supplementary intravenous hydration as needed.

**Mucosal inflammation:** Mucositis has been observed as a dose-limiting toxicity (DLT).

Early intervention for signs and symptoms of mucosal inflammation is recommended and encouraged. Based on preliminary data, dose interruption followed by dose reduction on re-challenge can ameliorate symptoms. Supportive care interventions should include good oral hygiene, adequate pain control, prevention of superinfection, and maintenance of adequate hydration with supplementary intravenous hydration as needed.

**Cutaneous AEs**
Rash may or may not be associated with pruritus. Preliminary data suggest that drug interruption and dose reduction upon re-challenge ameliorate the symptoms. Rash management should focus on symptom relief and maintenance of an intact integument. Dermatology consult is recommended when clinically appropriate. Topical steroid creams have been found to provide some relief from symptoms. Treatment will be dose reduced or discontinued for clinically significant toxicity not adequately controlled by supportive care measures.

**Glucose Abnormalities**

**Hyperglycemia:** Hyperglycemia occurred in patients receiving ≥75 mg/day with the majority of events occurring at doses exceeding the maximum tolerated dose (MTD) of 75 mg/day. Treatment-related grade 3 or grade 4 events were observed at 75 mg, 100 mg, and 150 mg daily doses. The frequency and severity of hyperglycemia AEs is reduced at the 75mg/day dose as compared with higher doses. It is not clear if oral anti-hyperglycemic drugs are useful to ameliorate the hyperglycemia, although both intravenous and sliding scale insulin have been helpful.

To reduce the risk of hyperglycemia, patients with abnormal fasting glucose values at screening will be excluded. In addition, patients with Type 1 diabetes will also be excluded; however, patients with Type 2 diabetes will be allowed if diagnosed ≥6 months prior to enrollment, and if presenting with hemoglobin A1C (HbA1C) ≤8% at screening. Patients will have glucose and insulin monitored during the study. If hyperglycemia is observed, supportive therapy will be provided according
Treatment will be dose reduced or discontinued for clinically significant toxicity that cannot be adequately managed medically.

**Hypoglycemia:** Asymptomatic hypoglycemia occurred in patients receiving ≥75 mg/day. Treatment-related grade 3 or grade 4 events were observed at 75 mg and 100 mg daily doses. The mechanism of hypoglycemia is currently unknown. Careful monitoring of glucose levels and encouragement of adequate oral intake are recommended.

**Thyroid Events**
Reversible minimal to mild hypertrophy of follicular cells was seen in the thyroid glands of dogs given 5 mg/kg/day for 4 weeks. The relationship to GSK2141795 and clinical significance are unknown, although three cases of drug-related hypothyroidism have been reported. Continued monitoring for thyroid function (thyroid-stimulating hormone laboratory testing) will be incorporated in all clinical protocols. Supportive therapy will be provided according to standard medical practice, and treatment will be discontinued if necessary.

**Other Glandular Events**
In both rats and dogs, several glandular structures (salivary, nasal, mammary, and Brunner’s glands) had reversible reductions in secretory content and/or apoptosis of individual acinar cells. The mechanism for this finding is not understood, although it may result in dry mouth, a toxicity that has been reported in some patients. Frequent monitoring with medical history, physical examination, and clinical laboratory assessments will be done. If clinically significant toxicity is observed, supportive therapy will be provided according to standard medical practice, and treatment will be discontinued if necessary.

### 2.4 Clinical Experience with the Combination of Trametinib + GSK2141795 (AKT inhibitor) (TAC113886) (07/28/14)

Twenty-three patients with advanced solid tumors received the combination using a zone-based escalation procedure enabling evaluation of multiple combination doses in parallel cohorts (Kurzrock et al., 2011). While the RP2D for single agent trametinib and GSK2141795 are 2 mg/d and 75 mg/d, dose reductions were required for the combination. DLTs include grade 2 AST and ALT elevation, and grade 3 chest pain with sustained ventricular tachycardia; all DLTs were reversible with drug interruption. The most common AEs (≥10%) included nausea (26%), AST elevation (22%; grade 3/4, 9%), fatigue (22%) and rash (22%). Three MTDs were defined for variable dose ratios: 2 mg trametinib + 25 mg GSK2141795; 0.5 mg trametinib + 75 mg GSK2141795; and 1.5 mg trametinib + 50 mg GSK2141795. Three of 13 evaluable patients (unselected) had tumor shrinkage of 8% (ovarian), 16% (endometrial), and 17% (ovarian) after 8 weeks on study. The dose regime of 1.5 mg trametinib + 50 mg GSK2141795...
will be considered for further development. Additional trials to explore alternate schedules (e.g., intermittent) and pharmacodynamic markers are ongoing.

As of March 13, 2014, 14 patients were enrolled in the initial safety lead in study of the continuous dosing regimen. Fourteen patients have completed the dose limiting toxicity window. Among evaluable patients, 7 dose-limiting toxicities have occurred requiring dose reduction to dose level -1 including: 1) grade 3 hypertension > 7 days (n=2), 2) grade 3 mucositis (n=2), 3) grade 3 dehydration, G3 acute kidney injury (n=1), and 4) grade 3 rash lasting > 7 days (n=2). Five of the patients had complete resolution of toxicity and were restarted on dose level -1. Two of the patients came off study because of significant residual toxicity. Given the degree of toxicity, we recommend an immediate dose level modification to dose level -1 for all patients currently on trial. In addition, we added an additional safety lead in to assess the toxicity of an alternative dosing regimen for the combination arm prior to proceeding with the randomized phase II portion.

2.5 Translational Research

Given the high proportion of PI3K/AKT and RAS/RAF/MEK pathway aberrations found in endometrial cancer, targeting these pathways holds great promise for improving outcomes for this aggressive disease. Our group and others have found that the presence of mutations in the PI3K/AKT pathway incur sensitivity to the antitumor effects of PI3K pathway directed agents. In addition, the presence of KRAS mutations are dominant predictors of resistance to targeted therapies (erlotinib, cetuximab) in colorectal and lung cancers\textsuperscript{24,25}. Emerging data in endometrial cancer and other solid tumors suggest that combination therapy with PI3K pathway and RAS/RAF pathway inhibitors may be necessary for improved outcomes\textsuperscript{26}. We hypothesize that a comprehensive assessment of PI3K/AKT and RAS/RAF/MEK pathway aberrations will predict response to therapy with the AKT inhibitor, GSK2141795, alone or in combination with the MEK inhibitor TRAMETINIB.

The majority of current clinical trials of targeted therapy in gynecologic malignancies include all patients, regardless of molecular profile. In order to avoid incorrect classification of an agent as inactive, it is essential that patients who are likely to benefit from a given therapy are identified at initial assessment in clinical trials. The proposed trial will stratify subjects based on key molecular alterations that have the potential to predict response and resistance to agents targeting the PI3K/AKT and RAS/RAF/MEK pathways. The use of multiple platforms will allow analysis of interaction of biomarkers of importance.

The validation of this clinical trial design has potential to direct future trial design of targeted therapies in all gynecologic malignancies. Successful implementation could result in a paradigm shift for this cooperative group, directly impacting patient care and development of multiple different agents.
2.6 Inclusion of Women and Minorities

The Gynecologic Oncology Group and GOG participating institutions will not exclude potential subjects from participating in this or any study solely on the basis of ethnic origin or socioeconomic status. Every attempt will be made to enter all eligible patients into this protocol and therefore address the study objectives in a patient population representative of the entire endometrial cancer population treated by participating institutions.
3.0 PATIENT ELIGIBILITY

3.1 Eligibility Criteria

3.11 Patients must have recurrent or persistent endometrial carcinoma, which is refractory to curative therapy or established treatments. Histologic confirmation of the original primary tumor is required.

Patients with the following histologic epithelial cell types are eligible: Endometrioid adenocarcinoma, serous adenocarcinoma, undifferentiated carcinoma, mixed epithelial carcinoma, uterine clear cell carcinoma, and adenocarcinoma not otherwise specified (N.O.S.). (05/12/14) (07/28/14)

3.12 Formalin-fixed, paraffin-embedded tumor tissue must be submitted to Baylor College of Medicine (BCM) – Cancer Genetics Laboratory for CLIA-certified KRAS mutation testing (see section 7.1). Results must be reported on the eligibility checklist during registration in order to receive treatment assignment. (07/28/14)

Note: If CLIA-certified KRAS mutation tumor testing is available from local or other source (e.g., Foundation Medicine) this report can be submitted to SDC to meet this requirement. (12/23/13)

3.13 All patients must have measurable disease. Measurable disease is defined by RECIST (version 1.1). Measurable disease is defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded). Each lesion must be ≥ 10 mm when measured by CT, MRI or caliper measurement by clinical exam; or ≥ 20 mm when measured by chest x-ray. Lymph nodes must be > 15 mm in short axis when measured by CT or MRI (See section 8).

3.14 Patients must have at least one “target lesion” to be used to assess response on this protocol as defined by RECIST version 1.1 (Section 8.1). Tumors within a previously irradiated field will be designated as “non-target” lesions unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy.

3.15 Patients must have a GOG Performance Status of 0 or 1.

3.16 Recovery from effects of recent surgery, radiotherapy, or chemotherapy

3.161 Patients should be free of active infection requiring antibiotics (with the exception of uncomplicated UTI).
Any hormonal therapy directed at the malignant tumor must be discontinued at least one week prior to registration.

Any other prior therapy directed at the malignant tumor, including chemotherapy and immunotherapy, must be discontinued at least three weeks prior to registration. Any investigational agent must be discontinued at least 30 days prior to registration.

Any prior radiation therapy must be discontinued at least four weeks prior to registration.

At least 4 weeks must have elapsed since the patient underwent any major surgery (e.g., major: laparotomy, laparoscopy). There is no delay in treatment for minor procedures (e.g., tumor core biopsy).

### Prior Therapy

Patients must have had one prior chemotherapeutic regimen for management of endometrial carcinoma. Initial treatment may include chemotherapy, chemotherapy and radiation therapy, or consolidation/maintenance therapy. Chemotherapy administered in conjunction with primary radiation as a radio-sensitizer WILL be counted as a systemic chemotherapy regimen.

Patients are allowed to receive, but are not required to receive, one additional cytotoxic regimen for management of recurrent or persistent disease.

Patients MAY HAVE received non-cytotoxic (biologic or targeted) agent(s) as part of initial treatment and/or for management of recurrent or persistent disease, with the below stated exceptions (see NOTE below). Prior hormonal therapy is allowed, but must be discontinued at least one week prior to registration.

**NOTE:** Prior therapy with PI3K inhibitors, AKT inhibitors and/or mTor inhibitors (e.g., everolimus, temsirolimus) is NOT allowed. Prior therapy with MEK inhibitors (e.g., AZD6244 or selumetinib) is NOT allowed.

Patients must have adequate:

**NOTE:**

ULN = institutional/laboratory upper limit of normal

LLN = institutional/laboratory lower limit of normal

### Bone marrow function:

- Absolute neutrophil count (ANC) ≥1,500/mcl
- Platelets ≥ 100,000/mcl
- Hemoglobin ≥ 9 g/dl.

3.182 Renal function:
- Creatinine ≤ 1.5 x ULN OR calculated creatinine clearance (Cockcroft-Gault formula) ≥ 50 ml/min OR 24-hour urine creatinine clearance ≥ 50 ml/min

3.183 Hepatic function:
- Bilirubin ≤ 1.5 x ULN
- AST and ALT ≤ 2.5 x ULN
- Alkaline phosphatase ≤ 2.5 x ULN
- Albumin ≥ 2.5 g/dL

3.184 Endocrine function:
- Fasting glucose < 160 mg/dL
- Hemoglobin A1C (HbA1C) ≤ 8 if patient has diabetes.
- TSH within institutional/laboratory normal limits

3.185 Cardiac function: Left ventricular ejection fraction (LVEF) greater than or equal to LLN by ECHO or MUGA.

3.186 Coagulation Factors: International normalized ratio (INR) and partial thromboplastin time (PTT) ≤ 1.5 x ULN.

3.1861 For patients on Coumadin, INR/PT/PTT must be > 1.5 ULN. (05/12/14)(07/28/14)

3.187 Hemodynamic parameters: (07/28/14)
  - Systolic blood pressure < 140 mmHg
  - Diastolic blood pressure < 90 mmHg

3.188 All prior treatment-related toxicities must be CTCAE v4 grade ≤ 1 (except alopecia) at the time of randomization.

3.19 Patients with abnormal fasting glucose values at screening will be excluded (fasting glucose ≥ 160). In addition, patients with Type 1 diabetes will also be excluded; however, patients with Type 2 diabetes will be allowed if diagnosed ≥6 months prior to enrollment, and if presenting with hemoglobin A1C (HbA1C) ≤ 8% at screening. (12/23/13)

3.110 Patients must be able to swallow and retain orally-administered medication and must not have any clinically significant gastrointestinal abnormalities that may alter absorption such as malabsorption syndrome or major resection of the stomach or bowels.
The effects of trametinib on the developing human fetus are unknown. For this reason and because MEK inhibitors as well as GSK2141795 are known to be teratogenic, women of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation AND for 4 months following discontinuation. Women of child-bearing potential must have a negative serum pregnancy test within 14 days prior to randomization. Should a woman become pregnant or suspect she is pregnant while she is participating in this study, she should inform her treating physician immediately.

Patients must meet pre-entry requirements as specified in section 7.0.

Patients must be 18 years or older. Because no dosing or adverse event data are currently available on the use of trametinib in combination with GSK2141795 in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

Patients must have signed an approved informed consent and authorization permitting release of personal health information.

3.2 Ineligibility Criteria

3.20 Patients who have had prior therapy with GSK2141795 or any other PI3K/AKT/MTOR pathway inhibitor.

3.21 Patients who have prior therapy with trametinib or any other MEK inhibitor.

3.22 Patients who have mucinous, squamous, sarcomas, or carcinosarcomas. (12/23/13) (05/12/14)

3.23 Patient with a history of other invasive malignancies, with the exception of non-melanoma skin cancer are excluded if there is any evidence of other malignancy being present within the last three years. Patients are also excluded if their previous cancer treatment contraindicates this protocol eligibility.

3.24 Patients with symptomatic or untreated leptomeningeal or brain metastasis or spinal cord compression.

3.25 Patients with a history of interstitial lung disease or pneumonitis.

3.26 Patients with known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to the trametinib, GSK2141795 or dimethyl sulfoxide (DMSO).
Current use of a prohibited medication. The following medications or non-drug therapies are prohibited:

- Other anti-cancer therapy while on study treatment.
- Concurrent treatment with bisphosphonates is permitted; however, treatment must be initiated prior to the first dose of study therapy. Prophylactic use of bisphosphonates in patients without bone disease is not permitted, except for the treatment of osteoporosis.
- 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], gingko biloba, dehydroepiandrosterone [DHEA], yohimbe, saw palmetto, or ginseng).

In vitro data indicate that GSK2141795 is a CYP3A4 substrate. Drugs that potently inhibit CYP3A4 could lead to increased GSK2141795 exposure in subjects, and are prohibited. Drugs which are strong inducers of CYP3A and may result in lower exposures of GSK2141795 should also be prohibited.

GSK2141795 also appears to be a moderate in vitro inhibitor of CYP2C8 (50% inhibitory concentration [IC₅₀] 3 mcM) and CYP3A4 (IC₅₀ 11 mcM). Drugs that are substrates of CYP3A4 or CYP2C8 with a narrow therapeutic index may be prohibited (see Table 1 below). Drugs that are sensitive substrates of CYP3A4 or CYP2C8 should be used with caution.

Trametinib may be an inhibitor of CYP2C8 in vivo. Caution should be exercised when dosing trametinib concurrently with medications with narrow therapeutic windows that are substrates of CYP2C8.

In vitro studies suggest that the metabolism of trametinib is mediated predominantly by non-CYP-mediated processes and possibly by CYP3A4. Therefore, drugs that potently inhibit or induce CYP3A4 should be administered with caution, as they may alter exposure to trametinib.

Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated list such as http://medicine.iupui.edu/clinpharm/ddis/table.aspx; medical reference texts such as the Physicians’ Desk Reference may also provide this information. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product.
The following medications (including but not limited to) are prohibited during the study:

<table>
<thead>
<tr>
<th>CYP3A Substrate</th>
<th>Therapeutic Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>cisapride</td>
<td>Hypnotics and Sedatives</td>
</tr>
<tr>
<td>pimozide</td>
<td>Antidepressant, Antipsychotics, Anti-anxiety agents</td>
</tr>
<tr>
<td>astemizole</td>
<td>Antihistamine</td>
</tr>
</tbody>
</table>

**BCRP Substrate**

<table>
<thead>
<tr>
<th>drug</th>
<th>Therapeutic Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>rosuvastatin, sulfasalazine</td>
<td>HMG-CoA Reductase Inhibitors, gastrointestinal agents</td>
</tr>
</tbody>
</table>

**PROHIBITED – strong inducers/inhibitors of CYP3A4**

<table>
<thead>
<tr>
<th>Strong CYP3A4 Inhibitor/Inducer</th>
<th>Therapeutic Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>clarithromycin, telithromycin, rifamycin class agents (<em>e.g.</em>, rifampin, rifabutin, rifapentine), troleandomycin</td>
<td>Antibiotics</td>
</tr>
<tr>
<td>itraconazole, ketoconazole</td>
<td>Antifungals</td>
</tr>
<tr>
<td>nefazodone</td>
<td>Antidepressants</td>
</tr>
<tr>
<td>atazanvir, delavirdine, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, nevirapine</td>
<td>Antivirals</td>
</tr>
<tr>
<td>carbamazepine, phenobarbital, phenytoin</td>
<td>Anticonvulsants</td>
</tr>
</tbody>
</table>

The following medications (including but not limited to) that may alter the concentrations of trametinib or GSK2141795 or have their elimination altered by trametinib or GSK2141795 should be administered **WITH CAUTION**:

**USE WITH CAUTION – Drugs Potentially Affecting trametinib or GSK2141795 concentrations**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Therapeutic Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>quinidine, diltiazem, verapamil</td>
<td>Antiarrhythmics:</td>
</tr>
<tr>
<td>fluvoxamine, fluoxetine, paroxetine, nefazodone</td>
<td>Antidepressants:</td>
</tr>
<tr>
<td>aprepitant, cimetidine</td>
<td>Antiemetics</td>
</tr>
<tr>
<td>fluconazole, terbinafine, voriconazole</td>
<td>Antifungals</td>
</tr>
<tr>
<td>ciprofloxacin, erythromycin, isoniazid</td>
<td>Anti-infectives</td>
</tr>
<tr>
<td>mibefradil, diltiazem, verapamil</td>
<td>Calcium Channel Blockers</td>
</tr>
<tr>
<td>aprepitant, oxandrolone, tizanidine, gemfibrozil</td>
<td>Miscellaneous</td>
</tr>
</tbody>
</table>
### USE WITH CAUTION – Drugs that may inhibit P-gp and BCRP

<table>
<thead>
<tr>
<th>Drug</th>
<th>Therapeutic Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>valsapodar</td>
<td>Miscellaneous</td>
</tr>
<tr>
<td>atorvastatin</td>
<td>HMG-CoA Reductase Inhibitors</td>
</tr>
<tr>
<td>carvedilol</td>
<td>Congestive Heart Failure</td>
</tr>
<tr>
<td>methadone</td>
<td>Analgesic</td>
</tr>
<tr>
<td>meperidine</td>
<td>Narcotic</td>
</tr>
<tr>
<td>omeprazole</td>
<td>Proton Pump Inhibitor</td>
</tr>
</tbody>
</table>

### USE WITH CAUTION – Drugs that may have their concentrations altered by trametinib or GSK2141795

<table>
<thead>
<tr>
<th>Drug</th>
<th>Therapeutic Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>repaglinide, rosiglitazone, pioglitazone</td>
<td>Antidiabetics</td>
</tr>
<tr>
<td>alfentanil, fentanyl</td>
<td>Analgesics</td>
</tr>
<tr>
<td>quinidine</td>
<td>Antiarrhythmics</td>
</tr>
<tr>
<td>cilostazol</td>
<td>Anticoagulants and Antiplatelets</td>
</tr>
<tr>
<td>astemizole</td>
<td>Antihistamines</td>
</tr>
<tr>
<td>diergotamine, ergotamine, eletriptan</td>
<td>Antimigraine agents</td>
</tr>
<tr>
<td>pimozide</td>
<td>Antipsychotics</td>
</tr>
<tr>
<td>buspirone</td>
<td>Anxiolytics</td>
</tr>
<tr>
<td>felodipine</td>
<td>Calcium Channel Blockers</td>
</tr>
<tr>
<td>sildenafil, tadalafil, vardenafil</td>
<td>Erectile Dysfunction agents</td>
</tr>
<tr>
<td>cerivastatin, ovastatin, simvastatin, atorvastatin</td>
<td>HMG-CoA Reductase Inhibitors</td>
</tr>
<tr>
<td>alprazolam, diazepam, midazolam, triazolam</td>
<td>Hypnotics and Sedatives</td>
</tr>
<tr>
<td>cyclosporine, sirolimus, tacrolimus</td>
<td>Immunosuppressive agents</td>
</tr>
<tr>
<td>cisapride</td>
<td>Prokinetic agents</td>
</tr>
<tr>
<td>cyclosporine, torsemide, chloroquine, zopiclone</td>
<td>Miscellaneous</td>
</tr>
<tr>
<td>eplerenone</td>
<td>Selective Aldosterone Blockers</td>
</tr>
<tr>
<td>chloroquine, zopiclone</td>
<td>Thiazolidinediones</td>
</tr>
</tbody>
</table>

Use of repaglinide, rosiglitazone and/or pioglitazone is permitted only after consultation with the CTEP Medical Monitor.

#### 3.29 Known Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV) infection (unless cleared) will be excluded.

HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with trametinib and GSK2141795. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate
studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.

3.30 History or current evidence/risk of retinal vein occlusion (RVO)  
(07/28/14)

3.31 History or evidence of cardiovascular risk including any of the following:

- LVEF<LLN.
- A QT interval corrected for heart rate using the Bazett’s formula (QTcB) ≥ 480 msec.
- History or evidence of current clinically significant uncontrolled arrhythmias (exception: patients with controlled atrial fibrillation for >30 days prior to registration are eligible).
- History of acute coronary syndromes (including myocardial infarction and unstable angina), coronary angioplasty, or stenting within 6 months prior to registration.
- History or evidence of current ≥ Class II congestive heart failure as defined by the New York Heart Association (NYHA) functional classification system.
- Treatment-refractory hypertension defined as a blood pressure of systolic >140 mmHg or diastolic >90 mmHg which cannot be controlled by anti-hypertensive therapy. (12/23/13) (05/12/14)
- Patients with intra-cardiac defibrillators or permanent pacemakers (05/12/14)
- Known cardiac metastases.

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

3.33 Patients who are pregnant or nursing. Animal reproductive studies have not been conducted with trametinib or GSK2141795. Therefore, the study drug must not be administered to pregnant women or nursing mothers. Women of childbearing potential should be advised to avoid pregnancy and use effective methods of contraception. If a patient becomes pregnant while the patient receives trametinib and/or GSK2141795, the potential hazard to the fetus should be explained to the patient.
4.0 STUDY MODALITIES

4.1 GSK2141795 (NSC #767034)

4.11 Chemical Name: N-[(1S)-2-amino-1-[(3,4-difluorophenyl) methyl] ethyl]-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide

4.12 Other Names: GSK2141795C

4.13 Classification: pan-AKT inhibitor

4.14 Molecular Formula: C_{18}H_{16}Cl_{2}F_{2}N_{4}O_{2}; Molecular Weight: 429.25 g/mol

4.15 Approximate Solubility: Very slightly soluble in water at room temperature (0.18 mg/mL). Solubility decreases as pH increases; for example solubility in gastric fluid at 37° C is >11 mg/mL.

4.16 Mode of Action: GSK2141795 is an ATP competitive pan-AKT inhibitor. AKT, a serine/threonine protein kinase with three isoforms, is active in several pathways that regulate survival, proliferation, tissue invasion and metabolism. Since AKT-mediated pathways are important in tumor proliferation and survival, AKT kinases are promising targets for therapeutic intervention. Hyperactivation of the AKT pathway can also correlate with chemotherapy resistance and poorer prognosis.

4.17 Description: white to off-white powder

4.18 How Supplied: GSK2141795 capsules are supplied by GlaxoSmithKline and distributed by the DCTD, NCI. The 25 mg capsule is a size 2 Swedish orange opaque body and Swedish orange opaque cap with no markings. The capsule contains active pharmaceutical ingredient, microcrystalline cellulose, and magnesium stearate. The capsules are packaged in white high density polyethylene (HDPE) bottles with white plastic, induction-seal, child-resistant caps. Each bottle contains 35 capsules.

GSK does not have stability data to support repackaging GSK2141795 capsules. Capsules must be dispensed in the original container.

4.19 Storage: Store bottles at 2-8° C (36-46° F).

4.10 Stability: Shelf life studies of GSK2141795 are on-going.

4.11 Route of Administration: Oral administration. Capsules must be taken fasting 1 hour following a meal and 2 hours before the next meal.
4.112 **Potential Drug Interactions**: *In vitro* data suggest GSK2141795 is a substrate of CYP450 3A4. Potent inhibitors and inducers of 3A4 are prohibited. GSK2141795 appears to be a moderate inhibitor of CYP 2C8 and 3A4 by *in vitro* testing. Drugs that are substrates of these isoenzymes should be used with caution and ones with a narrow therapeutic index should be avoided.

GSK2141795 is a substrate of p-glycoprotein (P-gp) and breast cancer resistant protein (BCRP). It is also an inhibitor of BCRP and OATP1B1. Administration of sensitive BCRP substrates should be prohibited, such as topotecan.

4.113 **Comprehensive Adverse Events and Potential Risks list (CAEPR)** for GSK2141795 (NSC 767034) (05/12/14)

The Comprehensive Adverse Event 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 via CTEP-AERS (except as noted below).

Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements'

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.

<table>
<thead>
<tr>
<th>Adverse Events with Possible Relationship to GSK2141795 (CTCAE 4.0 Term) [n= 150]</th>
<th>Likely (&gt;20%)</th>
<th>Less Likely (&lt;=20%)</th>
<th>Rare but Serious (&lt;3%)</th>
<th>Specific Protocol Exceptions to Expedited Reporting (SPEER)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GASTROINTESTINAL DISORDERS</td>
<td></td>
<td></td>
<td></td>
<td>Diarrhea (Gr 2)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esophagitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td></td>
<td></td>
<td>Nausea (Gr 2)</td>
</tr>
<tr>
<td>Gastrointestinal mucositis²</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td></td>
<td></td>
<td>Vomiting (Gr 2)</td>
</tr>
<tr>
<td>GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS</td>
<td></td>
<td></td>
<td></td>
<td>Fatigue (Gr 2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>METABOLISM AND NUTRITION DISORDERS</td>
<td></td>
<td></td>
<td></td>
<td>Anorexia (Gr 2)</td>
</tr>
<tr>
<td>Anorexia</td>
<td></td>
<td></td>
<td></td>
<td>Hyperglycemia (Gr 2)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS</td>
<td></td>
<td></td>
<td></td>
<td>Respiratory mucositis³</td>
</tr>
<tr>
<td>Respiratory mucositis³</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SKIN AND SUBCUTANEOUS TISSUE DISORDERS</td>
<td></td>
<td></td>
<td></td>
<td>Rash maculo-papular</td>
</tr>
</tbody>
</table>

Version 2.1, July 26, 2013¹
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.

Gastrointestinal mucositis may include Anal mucositis, Mucositis oral, Rectal mucositis, or Small intestinal mucositis under the GASTROINTESTINAL DISORDERS SOC.

Respiratory mucositis may include Laryngeal mucositis, Pharyngeal mucositis, or Tracheal mucositis under the RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS SOC.

Also reported on GSK2141795 trials but with the relationship to GSK2141795 still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Leukocytosis
CARDIAC DISORDERS - Cardiac arrest, Left ventricular systolic dysfunction, Ventricular tachycardia
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Non-cardiac chest pain
HEPATOBILIARY DISORDERS - Hepatic failure
INFECTIONS AND INFESTATIONS - Wound infection
INVESTIGATIONS - Alanine aminotransferase increased; Alkaline phosphatase increased; Aspartate aminotransferase increased; Ejection fraction decreased; GGT increased
METABOLISM AND NUTRITION DISORDERS - Hypokalemia; Hyponatremia, Hypophosphatemia
NERVOUS SYSTEM DISORDERS - Dysgeusia; Dysphasia
RENAL AND URINARY DISORDERS - Acute kidney injury
VASCULAR DISORDERS - Thromboembolic event

Note: GSK2141795 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.

4.2 Trametinib dimethyl sulfoxide (GSK1120212B) (NSC #763093)(07/18/15)

4.21 Chemical Name: Acetamide, N-[3-[3-cy clopropyl-5-[(2-fluoro-4-iodophenyl)amino]-3,4,6,7-tetrahydro-6,8-dimethyl-2,4,7-trioxopyrido[4,3-D]pyrimidin-1(2H)-yl]phenyl]-, dimethylsulfoxide solvate (1:1)

4.22 Other Names: trametinib, JTP-74057, JTP-78296, JTP-75303, GSK1120212

4.23 Classification: MEK inhibitor

4.24 Molecular Formula: C_{26}H_{23}FIN_{5}O_{4} • C_{2}H_{6}OS

4.25 Molecular Weight: 693.54 (dimethyl sulfoxide solvate)
615.41 (anhydrous parent) 429.25 g/mol

4.26 **Approximate Solubility:** Trametinib dimethyl sulfoxide is almost insoluble in water (<0.0001 mg/mL at 25° C)

4.27 **Mode of Action:** Trametinib dimethyl sulfoxide is a reversible, highly selective, allosteric inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2. Tumor cells commonly have hyper-activated extracellular signal-related kinase (ERK) pathways in which MEK is a critical component. Trametinib dimethyl sulfoxide inhibits activation of MEK by RAF kinases and MEK kinases.

4.28 **Description:** Trametinib dimethyl sulfoxide is a white to almost white powder.

4.29 **How Supplied:** GlaxoSmithKline supplies and CTEP, NCI, DCTD distributes 0.5 mg and 2 mg (as free base) tablets. Tablets are packaged in high density polyethylene bottles with child-resistant closures including an induction seal liner. Each bottle contains 32 tablets.

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 white or 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).

4.210 **Storage:** Store tablets at 2°C -8°C in the original bottle. Do not repackage tablets or remove desiccant. Bottles should be protected from light and moisture.

4.211 **Stability:** Shelf life studies of trametinib dimethyl sulfoxide are ongoing.

4.212 **Route of Administration:** Oral. Take by mouth on an empty stomach, either one hour before or two hours after a meal.

4.213 **Potential Drug Interactions:** *In vitro* studies suggest that trametinib dimethyl sulfoxide may be a substrate for CYP3A4 metabolism and therefore consideration should be used when given in combination with potent CYP3A4 inducers or inhibitors. Trametinib dimethyl sulfoxide is a weak CYP2C8 inhibitor and may significantly alter the clinical effects of narrow therapeutic drugs that are metabolized by CYP2C8.
Trametinib dimethyl sulfoxide is not a substrate for human Pgp, BCRP, OATP1B1 or OATP1B2 transporters.

### 4.214 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Trametinib dimethyl sulfoxide (GSK1120212B, NSC 763093) (05/12/14) (12/14/15)

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](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf) for further clarification. Frequency is provided based on 968 patients. Below is the CAEPR for Trametinib dimethyl sulfoxide (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 2.3, October 26, 2015

<table>
<thead>
<tr>
<th>Likely (&gt;20%)</th>
<th>Less Likely (&lt;=20%)</th>
<th>Rare but Serious (&lt;3%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BLOOD AND LYMPHATIC SYSTEM DISORDERS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td></td>
<td>Anemia (Gr 2)</td>
</tr>
<tr>
<td><strong>CARDIAC DISORDERS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heart failure</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Left ventricular systolic dysfunction</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sinus bradycardia</td>
<td></td>
</tr>
<tr>
<td><strong>EYE DISORDERS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blurred vision</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry eye</td>
<td>Eye disorders - Other (chorioretinopathy also known as retinal pigment epithelial detachment)</td>
<td></td>
</tr>
<tr>
<td>Eye disorders - Other (visual disorders)²</td>
<td>Eye disorders - Other (retinal vein occlusion)</td>
<td></td>
</tr>
<tr>
<td><strong>GASTROINTESTINAL DISORDERS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td></td>
<td>Abdominal pain (Gr 2)</td>
</tr>
<tr>
<td>Constipation</td>
<td>Constipation (Gr 2)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Diarrhea (Gr 3)</td>
<td></td>
</tr>
<tr>
<td>Dry mouth</td>
<td>Dry mouth (Gr 2)</td>
<td></td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>Dyspepsia (Gr 2)</td>
<td></td>
</tr>
<tr>
<td>Mucositis oral</td>
<td>Mucositis oral (Gr 2)</td>
<td></td>
</tr>
<tr>
<td>Adverse Events with Possible Relationship to Trametinib dimethyl sulfoxide (GSK1120212B) (CTCAE 4.0 Term) [n= 968]</td>
<td>Specific Protocol Exceptions to Expedited Reporting (SPEER)</td>
<td></td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
<td>---------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Likely (&gt;20%)</td>
<td>Less Likely (&lt;=20%)</td>
<td>Rare but Serious (&lt;3%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>Nausea (Gr 3)</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>Vomiting (Gr 3)</td>
<td></td>
</tr>
<tr>
<td><strong>GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chills</td>
<td>Chills (Gr 2)</td>
<td></td>
</tr>
<tr>
<td>Edema face</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>Fatigue (Gr 3)</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>Fever (Gr 2)</td>
<td></td>
</tr>
<tr>
<td><strong>IMMUNE SYSTEM DISORDERS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergic reaction</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>INFECTIONS AND INFESTATIONS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paronychia</td>
<td>Paronychia (Gr 2)</td>
<td></td>
</tr>
<tr>
<td>Skin infection</td>
<td>Skin infection (Gr 2)</td>
<td></td>
</tr>
<tr>
<td><strong>INVESTIGATIONS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>Alanine aminotransferase increased (Gr 2)</td>
<td></td>
</tr>
<tr>
<td>Alkaline phosphatase increased Aspartate aminotransferase increased</td>
<td>Alkaline phosphatase increased (Gr 2) Aspartate aminotransferase increased (Gr 2)</td>
<td></td>
</tr>
<tr>
<td>CPK increased Ejection fraction decreased</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>METABOLISM AND NUTRITION DISORDERS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td>Anorexia (Gr 2)</td>
<td></td>
</tr>
<tr>
<td>Dehydration</td>
<td>Dehydration (Gr 3)</td>
<td></td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>Hypomagnesemia (Gr 2)</td>
<td></td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>Hyponatremia (Gr 3)</td>
<td></td>
</tr>
<tr>
<td><strong>MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>Back pain (Gr 2)</td>
<td></td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>Pain in extremity (Gr 2)</td>
<td></td>
</tr>
<tr>
<td><strong>NERVOUS SYSTEM DISORDERS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>Dizziness (Gr 2)</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>Headache (Gr 2)</td>
<td></td>
</tr>
<tr>
<td><strong>RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>Cough (Gr 2)</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>Dyspnea (Gr 2)</td>
<td></td>
</tr>
<tr>
<td>Pneumonitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SKIN AND SUBCUTANEOUS TISSUE DISORDERS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>Alopecia (Gr 2)</td>
<td></td>
</tr>
<tr>
<td>Dry skin</td>
<td>Dry skin (Gr 2)</td>
<td></td>
</tr>
<tr>
<td>Palmar-plantar erythrodysesthesia syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Periorbital edema</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>Pruritus (Gr 2)</td>
<td></td>
</tr>
<tr>
<td>Likely (&gt;20%)</td>
<td>Less Likely (&lt;=20%)</td>
<td>Rare but Serious (&lt;3%)</td>
</tr>
<tr>
<td>--------------</td>
<td>---------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td><strong>VASCULAR DISORDERS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders - Other (rash)⁴</td>
<td>Skin and subcutaneous tissue disorders - Other (folliculitis)</td>
<td></td>
</tr>
<tr>
<td>Vascular disorders - Other (edema)⁵</td>
<td>Hypertension</td>
<td>Hypertension (Gr 2)</td>
</tr>
<tr>
<td>Vascular disorders - Other (hemorrhage)⁶</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹This 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.

²Visual disorders include visual disturbance that can be associated with retinal hemorrhage, corneal graft rejection, cyclitis, eye nevus, halo vision, intraocular pressure increased, macular edema, visual acuity reduced, and vitreous detachment.

³Hypersensitivity (allergic reactions) may present with symptoms such as fever, rash, increased liver function tests, and visual disturbances.

⁴Skin 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, seborrhoeic dermatitis, dermatitis psoriasiform, rash follicular, and skin fissures.

⁵Edema includes edema, lymphedema, and edema limbs.

⁶The 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

**EYE DISORDERS** - Eye disorders - Other (corneal graft rejection); Eye disorders - Other (cyclitis); Eye disorders - Other (eye nevus); Eye disorders - Other (intraocular pressure increased); Eye disorders - Other (iritis); Eye disorders - Other (vitreous detachment); Eyelid function disorder; Flashing lights; Floaters; Glaucoma; Papilledema; Photophobia

**GASTROINTESTINAL DISORDERS** - Ascites; Colitis; Enterocolitis; Esophagitis; Gastric ulcer; Gastritis; Gastrointestinal disorders - Other (obstruction gastric); Gastrointestinal disorders - Other (oropharyngeal pain); Gastrointestinal disorders - Other (pneumatosis intestinalis); Gastrointestinal fistula; Pancreatitis; Small intestinal obstruction

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GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Flu-like symptoms; General disorders and administration site conditions - Other (axillary pain); General disorders and administration site conditions - Other (pneumatosis); Pain
HEPATOBILIARY DISORDERS - Cholecystitis; Hepatic pain
INFECTIONS AND INFESTATIONS - Biliary tract infection; Device related infection; Enterocolitis infectious; Infections and infestations - Other (abscess limb); Pharyngitis; Upper respiratory infection
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising
INVESTIGATIONS - Blood bilirubin increased; Creatinine increased; Electrocardiogram QT corrected interval prolonged; GGT increased; Lipase increased; Platelet count decreased; Serum amylase increased
METABOLISM AND NUTRITION DISORDERS - Hyperglycemia; Hyperkalemia; Hyperuricemia; Hypocalcemia; Hypoglycemia; Hypokalemia; Metabolism and nutrition disorders - Other (hyperphosphatemia)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Musculoskeletal and connective tissue disorder - Other (compression fracture); Musculoskeletal and connective tissue disorder - Other (muscle spasm); Myalgia; Neck pain
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (tumor hemorrhage); Tumor pain
NERVOUS SYSTEM DISORDERS - Dysequisia; Encephalopathy; Intracranial hemorrhage; Lethargy; Nervous system disorders - Other (diplopia); Seizure; Stroke; Syncope; Transient ischemic attacks
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Depression; Insomnia; Personality change
RENAL AND URINARY DISORDERS - Acute kidney injury; Renal and urinary disorders - Other (dysuria); Urinary incontinence
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Vaginal fistula
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Pleural effusion; Pneumothorax; Productive cough; Pulmonary hypertension; Respiratory failure; Sinus disorder
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Bullous dermatitis; Photosensitivity; Skin and subcutaneous tissue disorders - Other (erythema nodosum); Skin ulceration; Urticaria
VASCULAR DISORDERS - Hot flashes; Hypotension; Thromboembolic event (venous)

Note: Trametinib dimethyl sulfoxide (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.

4.3 Preparation, Handling, and Storage
Investigational products (trametinib and GSK2141795) must be dispensed or administered according to procedures described herein. Only subjects enrolled in the study may receive investigational products. Only authorized site staff may supply or administer investigational products. All investigational products must be stored in a secure area with access limited to the investigator and authorized site staff. Trametinib is to be stored at 25°C (77°F), protected from moisture and light, and are to be stored in the original containers supplied by GSK. GSK2141795 is to be stored at a temperature between 2-8°C (36-46°F) in the original containers supplied by GSK. Whole bottles of investigational products are dispensed at each 4 week visit. Maintenance of a temperature log (manual or automated) is required.

Neither trametinib nor GSK2141795 are expected to pose significant occupational safety risk to site staff under normal conditions of use and administration. A Material Safety Data Sheet (MSDS) describing occupational hazards and
recommended handling precautions is available upon request from GSK, or will be provided to the investigator where this is required by local laws.

All used, unused or expired drug should be destroyed according to the sponsor’s standard operating procedures, and their disposition should be recorded on the NCI Investigational Agent Accountability Record Form.

### 4.4 Agent Ordering and Agent Accountability

#### 4.41 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.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order 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. For questions about drug orders, transfers, returns, or accountability, call (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

#### 4.42 Agent Inventory Records

- The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record Form (DARF). (See the NCI Investigator’s Handbook for Procedures for Drug Accountability and Storage.)

### 4.5 Pathology Requirements

#### 4.51 Eligibility Criteria: Patients must have recurrent or persistent endometrial cancer.

Patients with the following histologic epithelial cell types are eligible: Endometrioid adenocarcinoma, serous adenocarcinoma, undifferentiated
carcinoma, mixed epithelial carcinoma, uterine clear cell carcinoma, adenocarcinoma not otherwise specified (N.O.S.). (07/28/14)

4.52 Requirements: At least one representative stained slide (or slides) documenting the primary site, histologic cell type, and grade will be required. At least one representative H&E stained slide demonstrating recurrent disease will be required only if histologically documented.

4.53 Requirements: FFPE tissue for KRAS mutational analysis from primary, metastatic or recurrent specimen is required prior to stratification and treatment assignment.
5.0  TREATMENT PLAN AND ENTRY/RANDOMIZATION PROCEDURE

5.1  Registration Procedures (05/12/14)

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>.

5.11  CTEP Associate Registration Procedures / CTEP-IAM Account

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>.
5.12 CTSU Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

5.121 IRB Approval:

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.

5.122 Downloading Site Registration Documents:

Site registration forms may be downloaded from the GOG-0229O protocol page located on the CTSU members’ website. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.

- 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 NCTN NRG link to expand, then select trial protocol # 0229O
- Click on the Site Registration Documents link

5.123 Requirements For GOG-0229O 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)
- CTSU RT Facilities Inventory Form

NOTE: Per NCI policy all institutions that participate on protocols with a radiation therapy component must participate in IROC Houston monitoring program. If this form has been previously submitted to CTSU it does not need to be resubmitted unless updates have occurred at the RT facility

5.124 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.cojcc.org (for regulatory document submission only)

5.125 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

5.2 Patient Entry and Registration (07/28/14)

For the first 15 patients treated on Regimen II during the safety lead-in, the GOG Statistical and Data Center’s web-based patient reservation system (available at the GOG web menu page) will be used, in which slots for particular patients are reserved. Reservations are not transferrable to other patients, and if the patient is not enrolled within the required timeframe, the reservation is then cancelled and the slot is then made available to other patients and sites. If all slots are reserved, patients can be added to a waiting list.

After the “safety lead-in” patients have been evaluated for safety on Regimen II, all site staff will use OPEN to enroll patients on both Regimen I and II to this study. OPEN can be accessed on the GOG web menu page and clicking on the OPEN link.

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.
All site staff will use OPEN to enroll patients to this study. It 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 or from the OPEN tab on the CTSU members’ side of the website at https://www.ctsu.org.

Prior to accessing OPEN, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes. Site staff should use the registration forms provided on the group web site as a tool to verify eligibility.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

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

Access requirements for OPEN:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user id and password) used for the CTSU members' web site.
- To perform registrations, the site user must have been assigned the 'Registrar' role on the GOG or CTSU roster.
- To perform registrations you must have an equivalent 'Registrar' role on the Lead Group roster. Role assignments are handled through the Groups in which you are a member.

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

Further instructional information is provided on the CTSU members' web site OPEN tab or within the OPEN URL. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

5.3 Treatment Plan (12/23/13) (07/28/14)

5.3.1 This is phase II trial of trametinib alone or in combination with GSK2141795 in patients with persistent or recurrent endometrial cancer. Prior to starting the study, patients will submit archived FFPE primary, metastatic or recurrent tumor tissue for identification of genomic profile. All molecular testing will be done in a CLIA-compliant manner. Patients will be stratified based on genomic profile into two distinct subgroups defined as
a. Tumors WITHOUT KRAS mutations with or without PI3K, AKT, PTEN mutations (approximately 80% of patients)
b. Tumors WITH KRAS mutations with or without PI3K, AKT, PTEN mutations (approximately 20% of patients)

The following mutations will classify a tumor as KRAS mutant:

<table>
<thead>
<tr>
<th>Gene</th>
<th>Mutation</th>
<th>Amino Acid Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAS</td>
<td>12GGT&gt;AGT</td>
<td>G12S</td>
</tr>
<tr>
<td>KRAS</td>
<td>12GGT&gt;GAT</td>
<td>G12D</td>
</tr>
<tr>
<td>KRAS</td>
<td>12GGT&gt;GTT</td>
<td>G12V</td>
</tr>
<tr>
<td>KRAS</td>
<td>12GGT&gt;TGT</td>
<td>G12C</td>
</tr>
<tr>
<td>KRAS</td>
<td>12GGT&gt;GCT</td>
<td>G12A</td>
</tr>
<tr>
<td>KRAS</td>
<td>12GGT&gt;CGT</td>
<td>G12R</td>
</tr>
<tr>
<td>KRAS</td>
<td>13GGC&gt;GAC</td>
<td>G13D</td>
</tr>
<tr>
<td>KRAS</td>
<td>61CAA&gt;CAT</td>
<td>Q61H</td>
</tr>
<tr>
<td>KRAS</td>
<td>61CAA&gt;CTA</td>
<td>Q61L</td>
</tr>
<tr>
<td>KRAS</td>
<td>61CAA&gt;CGA</td>
<td>Q61R</td>
</tr>
<tr>
<td>KRAS</td>
<td>61CAA&gt;CAC</td>
<td>Q61H</td>
</tr>
</tbody>
</table>

Only the patient’s mutational status with regard to KRAS needs to be determined before stratification and treatment assignment.

After stratification, patients will be randomized to receive trametinib alone or in combination with GSK2141795, daily dosing for 28 days, on a continuous schedule. Response assessment will be performed every 8 weeks according to RECIST 1.1. At the time of progression, patients in the trametinib alone arm will be allowed to cross over to the combination arm.

Patients that progress on the combination arm will be removed from the study therapy.

The study includes a safety assessment lead-in, in which the dose limiting toxicities of the study agents will be assessed over cycle 1 for patients enrolled on Regimen II. Further accrual will be held until Regimen II is deemed safe. Based on early results and results from additional phase I trials of the combination of trametinib and GSK2141795, the dosing schedule of the two agents may be adjusted to intermittent dosing of GSK2141795. Once experience with the combination is obtained, the trial accrual may be expanded to all GOG institutions.

During the safety assessment lead in, all enrolling sites will be required to participate in a regularly scheduled teleconference with the Study Chair and Phase I Subcommittee Chair, and their assigned delegates. Conference
calls during Phase II will be at the discretion of the Study Chair and the Chair of the Developmental Therapeutics Committee of the GOG.

As of March 13, 2014, the original continuous dosing combination arm was deemed too toxic for further exploration in the endometrial cancer population. Thus, an additional safety lead in is planned to assess the safety and tolerability of alternative dosing regimens. (07/28/14)

5.32 **Regimen I:** Trametinib 2 mg (one 2 mg tablet) daily

**Oral administration guidelines:** Take by mouth on an empty stomach, either one hour before or two hours after a meal.

Patients will be given a Patient Medication Calendar to complete daily (Appendix III). The Patient Medication Calendar should be reviewed prior to the start of each cycle.

**Regimen II:** Trametinib 1.5 mg (three, 0.5 mg tablets) daily and GSK2141795 50 mg (two, 25 mg) daily.

**NOTE:** As of March 13, 2014 – all patients on the initial safety lead in of Regimen II will be on dose level -1: Trametinib 1.0mg (two, 0.5mg tablets) daily and GSK2141795 25mg (one, 25mg capsule) daily.

**NOTE:** As of March 13, 2014, all patients on the safety lead-in of the continuous combination dosing were dose reduced to dose level -1. There will be no further dose reductions allowed on this arm of the trial.

A second safety lead in will be performed with the following dose levels:

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>GSK2141795 Dose/Schedule</th>
<th>Trametinib Dose/Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25 mg QD</td>
<td>1.5 mg QD</td>
</tr>
<tr>
<td>-1</td>
<td>25 mg QD</td>
<td>1 mg QD</td>
</tr>
</tbody>
</table>

The phase II doses of Regimen II will be revised contingent on the completion of the additional safety lead in. (07/28/14)

**Oral administration guidelines:** Trametinib tablets must be taken on an empty stomach 1 hour before or 2 hours after a meal. GSK2141795 capsules must be taken fasting 1 hour following a meal and 2 hours before the next meal.

1. Take trametinib tablets on an empty stomach (at least 2 hours after any food).
2. One hour later, eat a meal followed by 60 minutes of fasting prior to taking GSK2141795 capsules. Water is allowed during this fasting period.

3. Remain upright for 30 minutes after taking the last capsule of GSK2141795 to avoid stomach irritation.

4. Fast for 2 hours after ingestion of the last capsule of GSK2141795. Water is allowed during this fasting period.

Patients will be given a Patient Medication Calendar to complete daily (Appendix IV). The Patient Medication Calendar should be reviewed prior to the start of each cycle. (12/23/13)

5. Oral steroids should be used with caution and subjects monitored for steroid-induced hyperglycemia. Short courses (up to a maximum of 14 days) of oral corticosteroids intended to treat study treatment related rash or diarrhea are allowed. Budesonide is recommended for supportive care of diarrhea. Subjects will be instructed to inform the investigator before taking any of these or any other medications. Investigators (or their appropriate designee) will be expected to review concomitant medications with the subject at each clinical visit.

5.34 See Section 3.27 and 3.28 for potential drug interactions and medications that are prohibited and medications that should be used with caution.

5.35 Chemotherapy Guidelines: See the GOG Chemotherapy Guidelines (Appendix I).

5.36 If side effects are not severe, a patient may remain on a study agent indefinitely until evidence of disease progression or unacceptable toxicity.

5.4 Criteria for Removal From Treatment

5.41 Inability to tolerate the lowest doses of trametinib or trametinib plus GSK2141795.

5.42 Patients may withdraw from the study at any time for any reason. Patients with evidence of disease progression or significant side effects will be removed from study. Patients randomized to Regimen I with disease progression can crossover to Regimen II.

5.5 Safety Lead-in

A review of safety will occur after the first 12 evaluable patients on Regimen II are treated and complete one 28 day cycle (including starting cycle 2 within the DLT constraints below) or have a DLT prior to completing the first cycle. Within the safety lead-in, patients who do not have a DLT and who do not complete cycle 1 will be replaced. All patients that received any treatment will be considered
evaluable for a DLT, unless they withdraw from the trial for reasons other than toxicity.

The formal decision rule can also be found in Section 11.3. If 3 or fewer patients out of 12 experience DLTs in cycle 1 (including treatment delays for cycle 2 of greater than 2 weeks due to toxicities), then the regimen will be deemed safe for administration in the phase II study. If 4 or more patients out of 12 experience DLTs, then the regimen will be declared unsafe.

5.51 A Dose Limiting Toxicity (DLT) is defined as either hematologic or non-hematologic toxicity [assessed in accordance with the current version of NCI Common Terminology Criteria, CTCAE], occurring during cycle 1 of therapy, which cause any of the following: (12/23/13)

5.511 Hematologic Toxicity:

5.5111 Dose delay of greater than 14 days due to failure to recover counts. (12/23/13) (05/12/14)

5.5112 Study treatment-related febrile neutropenia.

5.5113 Grade 4 neutropenia lasting >7 days

5.5114 Study treatment related Grade 4 thrombocytopenia or clinically significant bleeding with Grade 3 thrombocytopenia.

5.512 Non-hematologic Toxicity

5.5121 Study treatment-related grade 3 or Grade 4 non-hematologic toxicity (excluding anorexia, constipation, fatigue, hypersensitivity/allergic reactions, Grade 4 nausea and vomiting ≤ 48 hours with maximum medical management, Grade 3 electrolyte imbalance, including hypocalcemia, hypokalemia, hypomagnesemia, hyponatremia, and hypophosphatemia as a result of diarrhea, Grade 3 dehydration as a result of nausea and vomiting, Grade 3 rash that does not decrease the ADL or recovers to Grade 1 within one week, and Grade 3 hypertension that can be controlled within one week). (07/28/14)

5.5122 Grade 4 nausea and vomiting for >48 hours despite maximum medical management is a DLT.
5.5123 Grade 4 electrolyte imbalance that can be replaced within 48 hours to grade 2 or less should not be considered a DLT.

5.513 Treatment delay of greater than 14 days.

5.514 Any drug related death.
6.0 TREATMENT MODIFICATIONS (12/23/13) (07/28/14)

Regimen I

The table below outlines the dose levels to be used for any necessary trametinib dose modifications:

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Trametinib Dose/Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2 mg QD</td>
</tr>
<tr>
<td>-1</td>
<td>1.5 mg QD</td>
</tr>
<tr>
<td>-2</td>
<td>1 mg QD</td>
</tr>
</tbody>
</table>

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

Regimen II

Table of dose levels of GSK2141795 when used in combination with trametinib

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>GSK2141795 Dose/Schedule</th>
<th>Trametinib Dose/Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50 mg QD</td>
<td>1.5 mg QD</td>
</tr>
<tr>
<td>(-1)</td>
<td>25 mg QD</td>
<td>1 mg QD</td>
</tr>
</tbody>
</table>

NOTE: After high toxicity experienced with the first safety lead in, new dose levels were created. Below are the current recommendations for dose modifications

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>GSK2141795 Dose/Schedule</th>
<th>Trametinib Dose/Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>25 mg QD</td>
<td>1.5 mg QD</td>
</tr>
<tr>
<td>(-1A)</td>
<td>25 mg QD</td>
<td>1 mg QD</td>
</tr>
</tbody>
</table>

If the toxicity modifications listed below indicate need for dose reduction but there is no lower dose available, the patient will be instructed to stop both agents until resolution of toxicity.

NOTE: AEs occurring in patients treated with GSK2141795 + trametinib may be related to 1) overlapping toxicities between the two agents (e.g., rash and diarrhea); 2) toxicities typically associated with trametinib (e.g., visual disturbance) or GSK2141795 (e.g., hyperglycemia or hypoglycemia). However, toxicities associated with individual agents may be potentiated in the combination, or unanticipated AEs may occur.

The dose modifications may involve one or both agents, and should be based on the nature, severity and attributions of the AEs. General guidelines are provided below. CTEP drug monitors should be consulted if there are questions about the attribution of AEs and how the doses should be modified.
A maximum of one trametinib dose level reductions is allowed. If a second dose level reduction is required, treatment will be permanently discontinued.

No GSK2141795 dose level reductions are allowed. If the dose of GSK2141795 is too toxic, the treatment will be discontinued.

6.1 Hematologic Toxicity – Regimen I and II

6.11 Hematologic toxicity is not expected in this study. Guidelines to ensure patient safety are indicated below.

6.12 Treatment decisions will be based on the absolute neutrophil count (ANC) rather than the total white cell count (WBC).

6.13 Subsequent cycles of therapy will not begin until the ANC is $\geq 1500$ cells/mcl and the platelet count is $\geq 100,000$/mcl. Therapy will be delayed for a maximum of three weeks until these values are achieved. Patients who fail to recover adequate counts within a three-week delay will be removed from study but follow-up will continue.

6.2 Non-Hematologic Toxicity

6.21 Trametinib and GSK2141795 Dose Modification for Toxicities Not Specified in Subsequent Sections

<table>
<thead>
<tr>
<th>CTCAE v4 Grade</th>
<th>Management Guideline</th>
<th>Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Monitor as clinically indicated.</td>
<td>Continue at current dose level.</td>
</tr>
</tbody>
</table>
| Grade 2 (tolerable) | Provide supportive care according to institutional standards | • Consider withholding treatment until resolution to grade 1 or baseline.  
• Upon resolution, restart treatment at current dose level. |
| Grade 2 (intolerable) or 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 of both agents  
• If the Grade 3 toxicity recurs, permanently discontinue treatment |
| Grade 4        | | Permanently discontinue treatment. |

Treatment should be discontinued if treatment delay is $>14$ days due to toxicities.

6.22 Dose Modification Guidelines for Rash (12/23/13)

Two types of rashes may be seen with the trametinib + GSK2141795 combination:
1. Acneiform rash, typically associated with MEK inhibitor therapy (trametinib).

2. Maculo-papular rash often associated with pruritus (GSK2141795).

   If the diagnosis is unclear, a biopsy and photographs should be obtained as well as a dermatology consult. In addition, if the investigator feels the rash is not consistent with a MEK inhibitor-associated acneiform rash and is ≥ Grade 2, a skin punch biopsy should be performed.

   **In general, topical and oral antibiotics (e.g., doxycycline or minocycline) play a larger role in management of the MEK inhibitor acneiform rash, while topical and oral steroids are more relevant to the management of the AKT inhibitor maculo-papular rash.**

<table>
<thead>
<tr>
<th>Guidelines for Supportive Care of Rash</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Care</strong></td>
</tr>
<tr>
<td>Prevention/Prophylaxis&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Symptomatic Care&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
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</tr>
</tbody>
</table>

<sup>a</sup> Rash prophylaxis is recommended for the first 6 weeks of study treatment.

<sup>b</sup> Patients who develop rash/skin toxicities should be seen by a qualified physician and should receive evaluation for symptomatic/supportive care management.

<table>
<thead>
<tr>
<th>Dose Modification Guidelines and Management for Rash</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rash Severity</strong></td>
</tr>
<tr>
<td>Grade 1</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
### Dose Modification Guidelines and Management for Rash

<table>
<thead>
<tr>
<th>Rash Severity</th>
<th>Management Guideline</th>
<th>Dose Modification</th>
</tr>
</thead>
</table>
| Grade 2       | • Initiate prophylactic and symptomatic treatment measures.\(^1\)  
• Use moderate strength topical steroid.\(^2\)  
• Reassess after 2 weeks. | • Continue treatment  
• **Reduce trametinib or both agents by one dose level.**  
• If rash recovers to \(\leq\) grade 1 within 2 weeks, increase dose(s) to previous dose level.  
• If no recovery to \(\leq\) grade 1 within 2 weeks, interrupt treatment until recovery to \(\leq\) grade 1.  
• **Restart trametinib or both agents at reduced dose level.** |
| Grade \(\geq 3\) | • Use moderate strength topical steroids PLUS oral methylprednisolone dose pack.\(^2\)  
• Consult dermatologist. | • Interrupt trametinib or both agents until rash recovers to \(\leq\) grade 1.  
• **Restart with trametinib or both agents with one dose level reduction\(^3\)**  
• If no recovery to \(\leq\) grade 2 within 3 weeks, **permanently discontinue both agents** (resumption of trametinib or GSK2141795 alone may be considered based on toxicity-benefit consideration and after consultation with CTEP). |

1. Rash prophylaxis is recommended for the first 6 weeks of study treatment (refer to guidelines above).  
2. Moderate-strength topical steroids: Hydrocortisone 2.5% cream or fluticasone propionate 0.5% cream.  
3. Trametinib or GSK2141795 may be escalated to previous dose level if no rash is evident 4 weeks after restarting study treatment.

6.23 Trametinib Dose Modifications for **Visual Changes** (05/12/14)

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)). For events of visual changes regardless of severity but for which an ophthalmic examination is conducted, a blood sample for PK analysis is encouraged when feasible, and the blood sample should be drawn as close as possible to the time of the event.

The ophthalmology exam will include best corrected visual acuity, visual field examination, tonometry, slit lamp biomicroscopic examination, and indirect fundoscopy. Optical coherence tomography is recommended at scheduled visits and if retinal abnormalities are suspected. Other types of ancillary testing including visual field examination, fundus photography,
and fluorescein angiography may also be indicated as determined by clinical exam.

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

<table>
<thead>
<tr>
<th>Event CTCAE Grade</th>
<th>Management Guideline</th>
<th>Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1*</td>
<td>Consult ophthalmologist within 7 days of onset.</td>
<td>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/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.</td>
</tr>
<tr>
<td>Grade 2 and Grade 3</td>
<td>Consult ophthalmologist immediately.</td>
<td>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.</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Consult ophthalmologist immediately. Report as SAE.</td>
<td>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.</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Event CTCAE Grade</th>
<th>Action and Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 RPED (Asymptomatic; clinical or diagnostic observations only)</td>
<td>Continue treatment with retinal evaluation monthly until resolution. If RPED worsens, follow instructions below.</td>
</tr>
</tbody>
</table>
Trametinib Dose Modification for RPED

<table>
<thead>
<tr>
<th>Event</th>
<th>Action and Dose Modification</th>
</tr>
</thead>
</table>
| Grade 2-3 RPED (Symptomatic  | • Interrupt trametinib.  
| with mild to moderate decrease in visual acuity; limiting instrumental ADL) | • 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                                               |

6.24 Dose Modifications for Diarrhea

Episodes of diarrhea have occurred in patients receiving trametinib or GSK2141795 (Investigator’s Brochure, 2012a). Other frequent causes of diarrhea including concomitant medications (e.g., stool softeners, laxatives, antacids, etc.), infections by *Clostridium difficile* or other pathogens, or partial bowel obstruction should be excluded.

Guidelines regarding management and dose modification for diarrhea considered related to trametinib or trametinib plus GSK2141795 are provided in the table below.

<table>
<thead>
<tr>
<th>Management and Dose Modification Guidelines for Diarrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CTCAE Grade</strong></td>
</tr>
</tbody>
</table>
| Uncomplicated Diarrhea,\(^1\) Grade 1 or 2              | • Diet: Stop all lactose containing products; eat small meals, BRAT-diet (bananas, rice, apples, toast) recommended. | • Continue treatment.  
|                                                         | • Hydration: 8-10 large glasses of clear liquids per day (e.g., Gatorade or broth). | • If diarrhea is grade 2 for >48 h, interrupt GSK2141795 and trametinib until diarrhea resolves to grade ≤1.  
|                                                         | • Loperamide\(^2\): 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. | • Restart treatment at the same dose level.  
|                                                         | • Diarrhea >24 hours: Loperamide 2 mg every 2 hours; maximum 16 mg/day. Consider adding oral antibiotics. | • If treatment delay is > 21 days, discontinue both agents. (Resumption of trametinib or GSK2141795 alone may be considered based on toxicity-benefit consideration and after consultation with CTEP).  
|                                                         | • Diarrhea >48 hours: Loperamide 2 mg every 2 hours; maximum 16 mg/day. Add budesonide or other second-line therapies |                                                        |
Trametinib Dose Modification for Liver Chemistry Changes (05/12/14)

Uncomplicated Diarrhea, Grade 3 or 4

Any Complicated Diarrhea

- Clinical evaluation mandatory.
- Loperamide: Initially 4 mg, followed by 2 mg every 4 hours or after each 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.

Criteria for discontinuing study drug: When any of the liver stopping criteria are met any time, proceed as described below.

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 or trametinib and GSK2141795 to previous dose level(s) is allowed after consultation with the CTEP monitor and Study Chair and in the absence of another episode of complicated or severe diarrhea in the 4 weeks subsequent to dose reduction.

6.25 Trametinib Dose Modification for Liver Chemistry Changes
criteria below is met, discontinue trametinib

1. **ALT ≥ 3xULN and bilirubin ≥ 2xULN or >35% direct bilirubin**¹²
2. **ALT ≥ 3xULN and INR>1.5**, if INR measured² (INR threshold does not apply if subject is on anticoagulant)
3. **ALT ≥ 5xULn**
4. **ALT ≥ 3xULN persists for ≥4 weeks**
5. **ALT ≥ 3xULN and cannot be monitored weekly for 4 weeks**
6. **ALT ≥ 3xULN associated with symptoms³ (new or worsening) believed to be related to liver injury or hypersensitivity**

- Report as SAE if 1) CTEP-AERS reporting criteria are met or 2) patients meeting criteria 1-2
- Perform liver event **ASSESSMENT AND WORKUP** (see below)
- Monitor the subject until liver chemistries resolve, stabilize, or return to baseline (see **MONITORING** below)

### 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 hrs**
- 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 hrs**
- Monitor subjects weekly until LFTs return to normal/baseline or stabilize

### ASSESSMENT and WORKUP:

- Viral hepatitis serology⁴
- If possible, obtain blood sample for PK analysis⁵
- Serum CPK and LDH.
- Fractionate bilirubin, if total bilirubin≥2xULN
- 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 antibody⁶
- 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 ≥ 3xULN 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 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

If hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed) [Le Gal, 2005].

6.26 Trametinib Dose Modifications for Pneumonitis (07/28/14)

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

<table>
<thead>
<tr>
<th>Pneumonitis Guidelines for Trametinib Monotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CTCAE Grade</strong></td>
</tr>
</tbody>
</table>
| Grade 1 | • CT scan (high-resolution with lung windows) recommended.  
• Work-up for infection  
• Monitoring of oxygenation via pulse-oximetry recommended  
• Consultation with pulmonologist recommended | • Continue trametinib at current dose |
| Grade 2 | • CT scan (high-resolution with lung windows) recommended.  
• Work-up for infection  
• Consult pulmonologist  
• Pulmonary function tests – if < normal, repeat every 8 weeks until ≥ normal  
• Bronchoscopy with biopsy and/or BAL recommended  
• Symptomatic therapy including corticosteroids if clinically indicated | • Interrupt trametinib until recovery to grade ≤1  
• Restart treatment with trametinib reduced by one dose level  
• Escalation to previous dose level after 4 weeks may be considered after consultation with medical monitor  
• If no recovery to grade ≤1 within 4 weeks, permanently discontinue trametinib |
| Grade 3 | • Same as grade 2 | • Interrupt trametinib until recovery to grade ≤1  
• After consultation with medical monitor, trametinib may be restarted reduced by one dose level  
• If no recovery to grade ≤1 within 4 weeks, permanently discontinue trametinib |
| Grade 4 | • Same as grade 2 | • Permanently discontinue trametinib |

6.27 Trametinib Dose Modifications for Reduced Left Ventricular Ejection Fraction
Decreases of the left ventricular ejection fraction (LVEF) have been observed in patients receiving trametinib. GSK2141795 dose is to be modified the same as for trametinib. ECHOs must be performed in regular intervals outlined in the Study Calendar. The same procedure (either ECHO or MUGA, although ECHO is preferred) should be performed at baseline and at follow-up visit(s).

<table>
<thead>
<tr>
<th>Clinic</th>
<th>LVEF-drop (%) or CTCAE grade</th>
<th>Action and Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>Absolute decrease of &gt;10% in LVEF compared to baseline and ejection fraction below the institution’s LLN.</td>
<td>Follow the instructions for trametinib. When trametinib is on hold, GSK2141795 should be on hold.</td>
</tr>
<tr>
<td>Symptomatica</td>
<td>Grade 3: resting LVEF 39% or &gt;20% absolute reduction from baseline Grade 4: Resting LVEF ≤20%.</td>
<td>Permanently discontinue trametinib and GSK2141795 Report as SAE. Consult with cardiologist. Repeat ECHO after 2, 4, 8, 12, and 16 weeks or until resolution.</td>
</tr>
</tbody>
</table>

If ECHO does not show LVEF recovery after 2 weeks, repeat ECHO 2 weeks later. Symptoms may include: dyspnea, orthopnea, and other signs and symptoms of pulmonary congestion and edema.

6.271 Withholding Criteria for Reduced Left Ventricular Ejection Fraction (07/18/15)

LVEF should be assessed at baseline, at Week 4, and subsequently every 12 weeks or more frequently as clinically indicated.

- Subjects who have an asymptomatic, absolute decrease of >10% in LVEF compared to baseline and the ejection fraction is below the institution’s lower limit of normal (LLN) should have treatment with GSK1120212 interrupted and have a repeat evaluation of LVEF within 2 weeks.
If the LVEF recovers (defined as ≥LLN and absolute decrease ≤ 10% compared to baseline) at any time during the next 4 weeks, after consultation and approval of the GSK medical monitor, the subject may restart treatment with GSK1120212 at a reduced dose(s). For such subjects, monitoring of LVEF will then be performed 2 and 4 weeks after restarting treatment with GSK1120212, then every 4 weeks thereafter for 12 weeks and then per protocol.

If repeat LVEF does not recover within 4 weeks, then the subject should permanently discontinue treatment with GSK1120212. Evaluation by a cardiologist should be considered. Ejection fraction should continue to be monitored at 2 weeks, at 4 weeks, then every 4 weeks for 16 weeks or until resolution.

- Subjects with a CTCAE Grade 3 or 4 left ventricular cardiac dysfunction must permanently discontinue treatment with GSK1120212. Evaluation by a cardiologist should be considered. Ejection fraction should continue to be monitored at 2 weeks, at 4 weeks, then every 4 weeks for 16 weeks or until resolution.

6.28 Trametinib Dose Modification for QTc Prolongation (05/12/14)

<table>
<thead>
<tr>
<th>QTc Prolongation*</th>
<th>Action and Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>• QTcB ≥501 msec, or&lt;br&gt;• Uncorrected QT &gt;600 msec, or&lt;br&gt;• QTcB &gt;530 msec for subjects with bundle branch block</td>
<td>• Interrupt study treatment until QTcB prolongation resolves to grade 1 or baseline.&lt;br&gt;• Test serum potassium, calcium, phosphorus, and magnesium. If abnormal, correct per routine clinical practice to within normal limits.&lt;br&gt;• Review concomitant medication usage for a prolonged QTc.&lt;br&gt;• Restart at current dose level.b&lt;br&gt;• If the event does not resolve or recurs after restarting, permanently discontinue study treatment.</td>
</tr>
</tbody>
</table>

Abbreviations: msec = milliseconds; QTcB = QT interval on electrocardiogram corrected using Bazett’s formula

* Based on average QTc value of triplicate ECGs. For example, if an ECG demonstrates a prolonged QT interval, obtain two or more ECGs over a brief period, and then use the averaged QTc values of the three ECGs to determine if study treatments should be interrupted or discontinued.

b if the QTc prolongation resolves to grade 1 or baseline, the subject may resume study treatment if the investigator and the CTEP trametinib medical monitor agree that the subject will benefit from further treatment.

6.29 Trametinib Dose Modification for Hypertension (05/12/14)
Increases in blood pressure (BP) have been observed in patients receiving trametinib. Recommendations for BP monitoring and management are provided below.

**Monitoring:** All BP assessments should be performed under the following optimal conditions:

- The subject has been seated with back support, ensuring that legs are uncrossed and flat on the floor.
- The subject is relaxed comfortably for at least 5 minutes.
- Restrictive clothing has been removed from the cuff area, and the right cuff size has been selected.
- The subject’s arm is supported so that the middle of the cuff is at heart level.
- The subject remains quiet during the measurement.
- In subjects with an initial BP reading within the hypertensive range, a second reading should be taken at least 1 minute later, with the two readings averaged to obtain a final BP measurement. The averaged value should be recorded in the eCRF.
- Persistent hypertension is defined as an increase of systolic blood pressure (SBP) >140 mmHg and/or diastolic blood pressure (DBP) >90 mmHg in three consecutive visits with blood pressure assessments from two readings as described above. Visits to monitor increased blood pressure can be scheduled independently from the per-protocol visits outlined in the study calendar. Ideally, subsequent blood pressure assessments should be performed within 1 week.

### Management and Trametinib Dose Modification for Hypertension

<table>
<thead>
<tr>
<th>Event</th>
<th>Management Guideline</th>
<th>Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definitions used in the table:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- <strong>Persistent hypertension:</strong> Hypertension detected in two separate readings during up to three subsequent visits.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- <strong>Well-controlled hypertension:</strong> Blood pressure of SBP ≤140 mmHg and DBP ≤90 mmHg in two separate readings during up to three subsequent visits.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- <strong>Symptomatic hypertension:</strong> 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.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- <strong>Asymptomatic hypertension:</strong> SBP &gt;140 mmHg and/or DBP &gt;90 mmHg in the absence of the above symptoms.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Scenario A**

- Asymptomatic and persistent SBP of ≥140 and <160 mmHg, or DBP ≥90 and <100 mmHg,
- 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.
### Management and Trametinib Dose Modification for Hypertension

<table>
<thead>
<tr>
<th>Event</th>
<th>Management Guideline</th>
<th>Dose Modification</th>
</tr>
</thead>
</table>
| **(Scenario B)** | • 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.² |
| Asymptomatic SBP ≥160 mmHg, or DBP ≥100 mmHg, or Failure to achieve well-controlled BP within 2 weeks in Scenario A. | | |
| **(Scenario C)** | • 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.² |
| Symptomatic hypertension or Persistent SBP ≥160 mmHg, or DBP ≥100 mmHg, despite antihypertensive medication and dose reduction of trametinib | | |
| **(Scenario D)** | Continue follow-up per protocol. | Permanently discontinue trametinib. |
| Refractory hypertension unresponsive to above interventions or hypertensive crisis. | | |

---

1. 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.

- These AEs are typically associated with trametinib.
- GSK2141795 may continue when trametinib is on hold if AEs are ≤ grade 2.
- If the above AEs are grade 3-4, GSK2141795 should be held when trametinib is held. Once the AEs have resolved to grade 1 or baseline, GSK2141795 may resume at the same dose.
- If GSK2141795 has been held for >21 days, a discussion with the CTEP drug monitor is required before resuming treatment with the agent.

### 6.30 GSK2141795 Dose Modifications for Hypo- or Hyperglycemia

Hyperglycemia has been associated with treatment with GSK2141795.

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Management Guidelines</th>
<th>Study Drug Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mild</strong></td>
<td>Monitor fasting and preprandial glucose.</td>
<td>Continue study drug</td>
</tr>
<tr>
<td>Fasting blood glucose &gt; 150mg/dL</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Management and Dose Modification Guidelines for Hypo- or Hyperglycemia

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Management Guidelines</th>
<th>Study Drug Modification</th>
</tr>
</thead>
</table>
| Moderate to Severe               | • If a blood glucose >250 mg/dL, monitor for ketoacidosis as clinically indicated.  
                                  | • When managing hyperglycemia associated with GSK2141795, be aware that the action of insulin or other antihyperglycemic agents (e.g., sulfonylureas, biguanides, etc.) may be substantially blocked by the study agent. However the action of antihyperglycemic agents would be restored as GSK2141795 is cleared. The patient should be observed closely for rebound hypoglycaemia as GSK2141795 is held/or discontinued.  
                                  | • Intravenous insulin treatment is recommended.  
                                  | Hold drug(s) and notify investigator immediately. The investigator should discuss intervention and possible resumption of study drug(s) with the CTEP monitor. |

- These AEs are typically associated with GSK2141795.
- Trametinib may continue when GSK2141795 is on hold if AEs are ≤ grade 2.
- If the above AEs are grade 3-4, trametinib should be held when GSK2141795 is held. Once the AEs have resolved to grade 1 or baseline, trametinib may resume at the same dose.
- If trametinib has been held for >21 days, a discussion with the CTEP drug monitor is required before resuming treatment with the agent.

### 6.31 Dose Modifications and Management of Mucositis (07/28/14)

Mucositis has been observed with GSK2141795.
Dose Modification Guidelines and Management for Mucositis

<table>
<thead>
<tr>
<th>Severity</th>
<th>Management Guideline</th>
<th>Dose Modification</th>
</tr>
</thead>
</table>
| Grade 1  | At the first sign of symptoms start treatment using regimens listed below. Reassess after 2 weeks. | • Continue treatment.  
• If mucositis does not recover to baseline within 2 weeks despite best supportive care, **reduce both agents by one dose level**.\(^1\) |
| Grade 2  | At the first sign of symptoms start treatment using regimens listed below. Reassess after 2 weeks | • **Reduce both agents by one dose level**.  
• If mucositis recovers to \(\leq\) grade 1 within 2 weeks, increase dose(s) to previous dose level.  
• If no recovery to \(\leq\) grade 1 within 2 weeks, interrupt treatment until recovery to \(\leq\) grade 1.  
• **Restart both agents at reduced dose level**. |
| Grade \(\geq\)3 | At the first sign of symptoms start treatment using regimens listed below. | • Interrupt both agents until mucositis recovers to \(\leq\) grade 1.  
• **Restart both agents with one dose level reduction**\(^1\).  
• If no recovery to \(\leq\) grade 2 within 3 weeks, **permanently discontinue both agents** |

---

\(^1\) Trametinib or GSK2141795 may be escalated to previous dose level if no mucositis is evident 4 weeks after restarting study treatment.

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At the very first sign of symptoms start treatment using the regimens as follows (Choice of regimen depends on the severity of the symptoms/signs, in increasing order):

a. Biotene (MW every 4 hours as needed) with first sign of symptoms

b. Xyloxylin (magic mouth wash) (1:1:1 ratio of diphenhydramine, Maalox, lidocaine; 10 mL swish/swallow QID)

c. Caphasol (sodium phosphate; 15 mL swish/spit every 4 hours as needed) and/or Carafate (1 gm/10 mL; 10 mL swish/swallow or spit QID)

If suspicious of herpes infection, start antiviral treatment
### 7.0 STUDY PARAMETERS

#### 7.1 Observations and Tests (12/23/13) (07/28/14)

The following observations and tests are to be performed and recorded on the appropriate form(s): See Sections 4.4, 7.2 and 10.3 for a description of the stained pathology slides that are required for central review by the GOG Pathology Committee to confirm eligibility and for instructions for shipping that material to the GOG Statistical and Data Center.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre-Therapy</th>
<th>Weekly during cycle one</th>
<th>Prior to Each cycle (Cycle length : 28 days)</th>
<th>Every 3 cycles</th>
<th>Every 8 weeks</th>
<th>Off of all study therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFPE tumor tissue for KRAS mutation testing</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History &amp; Physical</td>
<td>2</td>
<td>4</td>
<td>X</td>
<td></td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Vital status</td>
<td></td>
<td></td>
<td></td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>3</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vital Signs (blood pressure, heart rate and temperature)</td>
<td>3</td>
<td>4</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Performance status</td>
<td>2</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Toxicity Assessment</td>
<td>3</td>
<td>4</td>
<td>X</td>
<td></td>
<td>9</td>
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</tr>
<tr>
<td>CBC/Differential/Platelets</td>
<td>3</td>
<td>11</td>
<td>4,5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>3</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Electrolytes (Na, K, Cl, CO2), BUN, creatinine</td>
<td>3</td>
<td>11</td>
<td>4,5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin, AST, ALT, Albumin, Alkaline Phosphatase</td>
<td>3</td>
<td>11</td>
<td>4,5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT/INR and PTT</td>
<td>3</td>
<td></td>
<td></td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy test (for patients of child bearing potential)</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HgA1C</td>
<td>2, 12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSH</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Parameter</td>
<td>Pre-Therapy</td>
<td>Weekly during cycle one</td>
<td>Prior to Each cycle (Cycle length : 28 days)</td>
<td>Every 3 cycles</td>
<td>Every 8 weeks</td>
<td>Off of all study therapy</td>
</tr>
<tr>
<td>-----------------------------------------</td>
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<td>-----------------------------------------------</td>
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<td>-------------------------</td>
</tr>
<tr>
<td>X-ray or CT scan of the chest</td>
<td>2</td>
<td></td>
<td>6</td>
<td>6†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT or MRI of abdomen and pelvis</td>
<td>2</td>
<td></td>
<td>6</td>
<td>6†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Electrocardiogram (ECG)</td>
<td>2</td>
<td></td>
<td>7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF testing (ECHO or MUGA scan)*</td>
<td>2</td>
<td></td>
<td>7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ophthalmology exam*</td>
<td>2,13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

† Until disease progression or death. For patients that cross over from Regimen I to Regimen II at the time of disease progression continue until second disease progression or death or until patient is put on non-protocol therapy following the Regimen II treatment.
* Not standard of care, will be paid for by from study funds, email Nicole Lamack Nlamack@gog.org (05/12/14)

Notes:
1. FFPE tumor tissue must be submitted to BCM-Medical Genetics Laboratory for CLIA-certified KRAS mutation testing. See Appendix VII for details. Results must be reported on the eligibility checklist during registration in order to receive treatment assignment. Patients cannot initiate treatment until stratified and a treatment assignment provided by the SDC. Note: Testing turnaround time is one to two weeks. Note: If CLIA-certified KRAS mutation tumor testing is available from local or other source (e.g., Foundation Medicine) this report can be submitted to SDC to meet this requirement.
2. Must be obtained within 28 days prior to initiating protocol therapy.
3. Must be obtained within 14 days prior to initiating protocol therapy.
4. For the safety assessment, during the first cycle of therapy patients should be seen every week; thereafter the patient can be seen prior to each cycle. Cycle length is 28 days.
5. Laboratory tests must be obtained within 4 days of re-treatment with protocol therapy.
6. Perform every 8 weeks (+/- 7 days) (regardless of delays and/or changes in treatment schedule and including for patients off treatment prior to disease progression) for the first 8 months; then every 12 weeks (+/- 7 days) thereafter until disease progression is confirmed; also repeat at any other time if clinically indicated based on symptoms or physical signs suggestive of progressive disease. An Excel tool is provided to calculate dates of re-imaging (Appendix VIII).
7. ECG, Echocardiogram or MUGA and TSH should be performed within 7 days of the start of every 3 cycles (approximately every 12 weeks), i.e., prior to cycle 4, 7, 10, etc.
8. Follow-up every 3 months for 2 years and then every 6 months for 3 years. Follow-up Forms are collected for the 5 year follow-up period or until study termination.
9. Report all adverse events that occur within 30 days of last protocol treatment on the Follow-Up Adverse Event Reporting Forms for the last cycle of therapy administered. For reporting of delayed toxicity, see section 9.2.
10. PT/INR and PTT does not need to be repeated in absence of clinical need. Patients on prophylactic or therapeutic warfarin should have PT/INR monitored per usual practice: at a minimum prior to each cycle of therapy (laboratory tests must be obtained within 4 days of re-treatment with protocol therapy). Treatment should be held if INR is >3. Treatment can be held to achieve in range INR (less than or equal to 3) for a maximum of 21 days.

11. For the first 12 to 15 patients in the safety lead-in on Regimen II, blood work should be performed weekly during cycle 1 only. If grade 4 neutropenia is documented (ANC <500/mcl) obtain twice per week until grade 3 or less. If grade 3 or 4 AST, ALT, alkaline phosphatase, total bilirubin, or creatinine obtain twice per week until resolved to grade 1 or less. See section 6.25 for liver chemistry stopping criteria.

12. HgA1C should be checked prior to study enrollment for patients with a known diagnosis of diabetes mellitus. HgA1C does not need to be repeated in the absence of clinical need.

13. Patients are required to have a standard ophthalmic exam (visual acuity, visual field, and retinal evaluation) performed by an ophthalmologist at baseline and as clinically warranted during the course of the study. See section 6.23.

7.2 Stained Pathology Slide Requirements For Central Review To Confirm Eligibility (07/28/14)

Stained pathology slides are required for central review by the GOG Pathology Committee to confirm eligibility for the protocol. At least one representative H&E stained slide (or slides) demonstrating primary site, histologic cell type, and grade, and one H&E stained slide showing the most advanced stage of disease will be required. If the most advanced stage of disease is not documented by histology, the method of stage documentation needs to be stated (e.g. CT, MRI, etc.). If this protocol allows patients with recurrent or persistent disease, slides from recurrence and/or persistent disease will be required only if recurrence/persistent disease is confirmed by histology or cytology.

When submitting pathology material to the GOG Statistical and Data Center individual slides must be labeled with GOG Patient ID, patient initials and the surgical / pathology accession number (e.g., S08-2355) and block identifier (e.g., A6). Do not label the slides with disease site (e.g., right ovary) or procedure date. Pack the labeled slides into plastic slide cassette(s). Tape plastic slide cassettes shut and wrap in bubble wrap or another type of padded material prior to shipping. Please include the GOG Patient ID, patient initials, and protocol number on all pages of the pathology report and black out the patient’s name. Ship pathology slides, three copies of both the Pathology Form F (if required for the protocol) and the official pathology report in your own shipping containing using postal mail at your own expense directly to the Pathology Materials Coordinator at the GOG Statistical and Data Center, Roswell Park Cancer Institute, Research Studies Center, Carlton and Elm Streets, Buffalo, New York, 14263; phone (716) 845-5702. The GOG Upload Application in SEDES is an alternative method for submitting pathology reports and Form F to the GOG Statistical and Data Center. Please see section 4.5 and 10.3 for additional requirements and instructions.

7.3 Translational Research
Note: Testing of banked samples will not occur until an amendment to this treatment protocol (or separate correlative science protocol) is reviewed and approved in accordance with National Clinical Trials Network (NCTN) policies.

7.31 Specimen Requirements (07/28/14)

If the patient gives permission for her specimens to be collected and used for this optional translational research component, participating institutions are required to submit the patient’s specimens as outlined below unless otherwise specified.

<table>
<thead>
<tr>
<th>Required Specimen (Specimen Code)</th>
<th>Collection Time Point</th>
<th>Ship To</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFPE Primary Tumor (FP01)*</td>
<td>Prior to all treatment</td>
<td></td>
</tr>
<tr>
<td>1st Choice: block</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd Choice: scroll (50-100µm in a cryovial)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FFPE Metastatic Tumor (FM01)*</td>
<td>Prior to study treatment</td>
<td>GOG Tissue Bank within 8 weeks of registration¹</td>
</tr>
<tr>
<td>1st Choice: block</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd Choice: scroll (50-100µm in a cryovial)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FFPE <strong>Recurrent Primary</strong> Tumor (FRP01)*</td>
<td>Prior to study treatment</td>
<td></td>
</tr>
<tr>
<td>1st Choice: block</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd Choice: scroll (50-100µm in a cryovial)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FFPE <strong>Recurrent Metastatic</strong> Tumor (FRM01)*</td>
<td>Prior to study treatment</td>
<td></td>
</tr>
<tr>
<td>1st Choice: block</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd Choice: scroll (50-100µm in a cryovial)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole Blood (WB01)</td>
<td>Prior to or after starting study treatment</td>
<td>GOG Tissue Bank the day the specimen is collected¹</td>
</tr>
<tr>
<td>7-10mL drawn into purple top (EDTA) tube(s)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* A copy of the corresponding pathology report must be shipped with all tissue specimens sent to the GOG Tissue Bank

¹ GOG Tissue Bank / Protocol GOG-0229O, Nationwide Children’s Hospital, 700 Children’s Drive, WA1340, Columbus, OH 43205, Phone: (614) 722-2865, FAX: (614) 722-2897, Email: GOGBank@nationwidechildrens.org

7.32 Laboratory Testing

7.321 KRAS/PTEN/PI3K Pathway Mutational Analysis

FFPE tumor will be used for mutational analyses to examine changes in KRAS/PTEN/PI3K pathway members (e.g., PIK3CA, PIK3R1, PIK3R2, PTEN, AKT1, RAS/RAF, JAK/STAT) with a focus on somatic changes present in tumor cells.
If mutations are observed, an aliquot of DNA extracted from whole blood will be tested to determine if the mutation is somatic or not.

7.322 Immunohistochemical Expression of PTEN

FFPE tumor will be used for PTEN IHC.

Complete absence of staining in tumor cells in the presence of internal positive control (stromal cells, lymphocytes) will be interpreted as PTEN loss. Cases will be scored as PTEN positive (or retained) if all or a majority of the tumor shows positive staining. Cases with “patchy” PTEN staining will be interpreted as showing heterogeneous staining.

7.33 Future Research

Details regarding the banking and use of specimens for future research can be found in Appendix V.

7.4 Quality of Life

This protocol does not include quality of life research.
8.0 EVALUATION CRITERIA

8.1 Antitumor Effect – Solid Tumors

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (Version 1.1). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

8.11 Disease Parameters

**Measurable disease:** Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥10 mm with CT scan, as ≥20 mm by chest x-ray, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in decimal fractions of centimeters.

Note: Tumor lesions that are situated in a previously irradiated area will not be considered measurable unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy.

**Malignant lymph nodes:** To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

**Non-measurable disease:** All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal/pelvic masses (identified by physical exam and not CT or MRI), are considered as non-measurable.

Notes:

**Bone lesions:** Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above. Blastic bone lesions are non-measurable.

**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. “Cystic lesions” thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

**Target lesions:** All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion which can be reproducibly measured should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

**Non-target lesions:** 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 and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

### 8.12 Methods for Evaluation of Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

**Clinical lesions:** Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans), but NOT lung.

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline, and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, subsequent image acquisitions should use the same type of scanner and follow the baseline imaging protocol as closely as possible. If possible, body scans should be performed with breath-hold scanning techniques.

PET-CT: At present, the low-dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. PET-CT scans are not always done with oral and IV contrast. In addition, the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed. For these reasons, the GOG will not allow PET-CT use for RECIST 1.1 response criteria.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible “new” disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

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

b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at
follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Note: A “positive” FDG-PET scan lesion means one that is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

**Ultrasound:** Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

**Endoscopy, Laparoscopy:** The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

**Cytology, Histology:** These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

It is mandatory to obtain cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when measureable disease has met criteria for response or stable disease. This confirmation is necessary to differentiate response or stable disease versus progressive disease, as an effusion may be a side effect of the treatment.

**8.13 Response Criteria**
Determination of response should take into consideration all target (See 8.131) and non-target lesions (See 8.132) and if appropriate, biomarkers (See 8.133).

**8.131 Evaluation of Target Lesions**
Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

Not evaluable (NE): When at least one target lesion is not evaluated at a particular time point.

8.132 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10 mm short axis)

Non-CR/Non-PD: Persistence of one or more non-target lesion(s)

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Not evaluable (NE): When at least one non-target lesion is not evaluated at a particular time point.

Although a clear progression of only “non-target” lesions is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).
8.133 Evaluation of Biomarkers
Biomarker measurements are not used to determine response or progression in this study.

8.134 Evaluation of Best Overall (unconfirmed) Response

The best overall response is the best time point response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest sum recorded since baseline). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria in some circumstances.

**Time Point Response for Patients with Measurable Disease at baseline (i.e., Target Disease)**

<table>
<thead>
<tr>
<th>Target Lesions</th>
<th>Non-Target Lesions</th>
<th>New Lesions*</th>
<th>Time Point Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>CR</td>
<td>No</td>
<td>CR</td>
</tr>
<tr>
<td>CR</td>
<td>Non-CR/Non-PD</td>
<td>No</td>
<td>PR</td>
</tr>
<tr>
<td>CR</td>
<td>Not evaluated</td>
<td>No</td>
<td>PR</td>
</tr>
<tr>
<td>PR</td>
<td>Non-PD or NE</td>
<td>No</td>
<td>PR</td>
</tr>
<tr>
<td>SD</td>
<td>Non-PD or NE</td>
<td>No</td>
<td>SD</td>
</tr>
<tr>
<td>NE</td>
<td>Non-PD</td>
<td>No</td>
<td>NE</td>
</tr>
<tr>
<td>PD</td>
<td>Any</td>
<td>Yes or No</td>
<td>PD</td>
</tr>
<tr>
<td>Any</td>
<td>PD**</td>
<td>Yes or No</td>
<td>PD</td>
</tr>
<tr>
<td>Any</td>
<td>Any</td>
<td>Yes</td>
<td>PD</td>
</tr>
</tbody>
</table>

*See RECIST 1.1 manuscript for further details on what is evidence of a new lesion
** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

**Time Point Response for Patients with only Non-Measurable Disease at baseline (i.e., Non-Target Disease)**

<table>
<thead>
<tr>
<th>Non-Target Lesions</th>
<th>New Lesions*</th>
<th>Time Point Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>No</td>
<td>CR</td>
</tr>
<tr>
<td>Non-CR/non-PD</td>
<td>No</td>
<td>Non-CR/non-PD**</td>
</tr>
<tr>
<td>NE</td>
<td>No</td>
<td>NE</td>
</tr>
<tr>
<td>Unequivocal PD*</td>
<td>Yes or No</td>
<td>PD</td>
</tr>
<tr>
<td>Any</td>
<td>Yes</td>
<td>PD</td>
</tr>
</tbody>
</table>

*See RECIST 1.1 manuscript for further details on what is evidence of a new lesion
** ‘Non-CR/non-PD’ is preferred over ‘stable disease’ for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

8.135 Best Overall Confirmed Response
Confirmation of CR and PR for determination of best overall response is required for studies with a primary endpoint that includes response.

Confirmed CR and PR for best overall confirmed response

<table>
<thead>
<tr>
<th>Time Point Response First time point</th>
<th>Time Point Response Subsequent time point</th>
<th>BEST overall confirmed response</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>CR</td>
<td>CR</td>
</tr>
<tr>
<td>CR</td>
<td>PR</td>
<td>SD, PD or PR*</td>
</tr>
<tr>
<td>CR</td>
<td>SD</td>
<td>SD provided minimum criteria for SD duration met, otherwise, PD</td>
</tr>
<tr>
<td>CR</td>
<td>PD</td>
<td>SD provided minimum criteria for SD duration met, otherwise, PD</td>
</tr>
<tr>
<td>CR</td>
<td>NE</td>
<td>SD provided minimum criteria for SD duration met, otherwise, NE</td>
</tr>
<tr>
<td>PR</td>
<td>CR</td>
<td>PR</td>
</tr>
<tr>
<td>PR</td>
<td>PR</td>
<td>PR</td>
</tr>
<tr>
<td>PR</td>
<td>SD</td>
<td>SD</td>
</tr>
<tr>
<td>PR</td>
<td>PD</td>
<td>SD provided minimum criteria for SD duration met, otherwise, PD</td>
</tr>
<tr>
<td>PR</td>
<td>NE</td>
<td>SD provided minimum criteria for SD duration met, otherwise, NE</td>
</tr>
<tr>
<td>NE</td>
<td>NE</td>
<td>NE</td>
</tr>
</tbody>
</table>

*If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). However, sometimes ‘CR’ may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR or SD, not CR at the first time point. Under these circumstances, the original CR should be changed to PR or SD and the best response is PR or SD.

In non-randomized trials where response is part of the primary endpoint, confirmation of CR or PR is needed to deem either one the “best overall response.” **Responses (CR and PR) require confirmation at greater than or equal to 4 weeks from initial documentation.**

For this study, the minimum criteria for SD duration is 6 weeks.

Patients with a global deterioration of health status requiring discontinuation of treatment or die without objective evidence of disease progression at that time should be reported to be off study treatment due to “symptomatic deterioration.” Every effort should be made to document the objective progression even after discontinuation of treatment.
8.14 Duration of Response

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

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

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

8.15 Recurrence

Recurrence is defined as newly evident disease for patients who have no evidence of disease at baseline or progressive disease for patients who have strictly non-measurable disease at baseline.

8.16 Recurrence-Free Survival

Recurrence-Free Survival (RFS) is defined as the duration of time from study entry to time of recurrence or death, whichever occurs first.

8.17 Progression-Free Survival

Progression-Free Survival (PFS) is defined as the duration of time from study entry to time of progression or death, whichever occurs first.

8.18 Survival

Survival is defined as the duration of time from study entry to time of death or the date of last contact.
9.0 DURATION OF STUDY

9.1 Patients will receive therapy until disease progression or intolerable toxicity. The patient can refuse the study treatment at any time. Patients on Regimen I may cross-over to treatment with Regimen II at the time of disease progression.

9.2 All patients will be treated (with completion of all required case report forms) until disease progression (1st time on Regimen II and 2nd time for crossovers from Regimen I to II) or study therapy withdrawal. If a patient withdraws for reasons other than disease progression, then the patient should be followed for disease progression according to section 7.1. Patients will then be followed every three months for the first two years and then every six months for the next three years. Patients will be monitored for delayed toxicity and survival for this 5-year period with Follow-Up forms submitted to the GOG Statistical and Data Center, unless consent is withdrawn. Follow-Up forms will no longer be required if the study is terminated prior to the completion of the 5-year follow-up period.

9.3 A patient is considered off study therapy when the patient has progressed or died, a subsequent drug or therapy (directed at the disease) is initiated or all study therapy is discontinued. Report all treatment received on Cycle Drug Information Forms and adverse events on toxicity Report Forms until the patient qualifies as being off study therapy.
10.0 STUDY MONITORING & REPORTING PROCEDURES

10.1 Adverse Event Reporting For An Investigational Agent (CTEP IND) 
(05/12/14)

10.11 Definition of Adverse Events (AE)

Adverse event (21 CFR 312.32(a)): Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov). The CTCAE v4.0 Manual is also available on the GOG member web site (http://www.gog.org under MANUALS).

10.12 Reporting Expedited Adverse Events

Depending on the phase of the study, use of investigational agents, and role of the pharmaceutical sponsor, an expedited AE report may need to reach multiple destinations. For patients participating on a GOG trial, all expedited AE reports should be submitted by using the CTEP automated system for expedited reporting (CTEP-AERS). All CTEP-AERS submissions are reviewed by GOG before final submission to CTEP. Submitting a report through CTEP-AERS serves as notification to GOG, and satisfies the GOG requirements for expedited AE reporting. All CTEP-AERS reports will be immediately directed to the Study Chair for further action.

The requirement for timely reporting of AEs to the study sponsor is specified in the Statement of Investigator, Form FDA-1572. In signing the FDA-1572, the investigator assumes the responsibility for reporting AEs to the NCI. In compliance with FDA regulations, as contained in 21 CFR 312.64, AEs should be reported by the investigator.

10.13 Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under a CTEP IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention\(^1,2\)
Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under a CTEP IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention 1, 2

**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 $\geq 24$ 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>
<thead>
<tr>
<th>Hospitalization</th>
<th>Grade 1 and Grade 2 Timeframes</th>
<th>Grade 3-5 Timeframes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resulting in Hospitalization $\geq 24$ hrs</td>
<td>7 Calendar Days</td>
<td>24-Hour 3 Calendar Days</td>
</tr>
<tr>
<td>Not resulting in Hospitalization $\geq 24$ hrs</td>
<td>Not required</td>
<td></td>
</tr>
</tbody>
</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; 3 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 3 calendar days of the initial 24-hour report.
- “7 Calendar Days” - A complete expedited report on the AE must be submitted within 7 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 3 calendar days for:**

- All Grade 3, 4, and Grade 5 AEs

**Expedited 7 calendar day reports for:**

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

2 For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half lives, rounded up to the nearest whole day, after the agent/intervention was last administered. Footnote “1” above applies after this reporting period.
Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting:

There are no additional instructions or exceptions to CTEP-AERS expedited reporting requirements for this protocol.

10.14 Procedures for Expedited Adverse Event Reporting:

10.141 CTEP-AERS Expedited Reports: Expedited reports are to be submitted using CTEP-AERS available at http://ctep.cancer.gov. The CTEP, NCI Guidelines: Adverse Event Reporting Requirements for expedited adverse event reporting requirements are also available at this site.

AML/MDS events must be reported via CTEP-AERS (in addition to routine AE reporting mechanisms). In CTCAE v4.0, the event(s) may be reported as either: 1) Leukemia secondary to oncology chemotherapy, 2) Myelodysplastic syndrome, or 3) Treatment related secondary malignancy. Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via routine mechanisms outlined in each protocol.

For the purposes of expedited reporting of adverse events to CTEP, unexpected events are those not listed in the Agent Specific Adverse Event List (ASAEL). The ASAEL is a subset of AE’s within the Comprehensive Adverse Event and Potential Risks List (CAEPR). This list of events is based on CTEP’s clinical experience with this agent and defines “expected” Grade 2 and 3 AE’s not requiring hospitalization as exempt from expedited reporting. The CAEPR is a complete list of reported and/or potential AE’s associated with an agent under a CTEP IND. For questions or comments regarding the ASAEL or CAEPR, please contact the CTEP-AERS MD Help Desk at CTEP-AERSmd@tech-res.com.

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made to NCI by telephone at: 301-897-7497. An electronic report MUST be submitted immediately upon re-establishment of internet connection. Please note that all paper CTEP-AERS forms have been removed from the CTEP website and will NO LONGER be accepted. (07/28/14)
10.2 **Medidata Rave Data Submission and Reporting (05/12/14)**

*Note to LPO: You may add more detailed information regarding study specific data submission instructions and/or tailor the wording as needed.*

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, the site user 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 site 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/](http://www.ctsu.org/RAVE/) or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

10.3 **GOG Data Management Forms (12/23/13) (07/28/14)**

The following forms must be completed and submitted to the GOG Statistical and Data Center (SDC) in accordance with the schedule below. GOG electronic case report forms must be submitted through the Medidata Rave Electronic Data Entry System ([www.imedidata.com](http://www.imedidata.com)). All amendments to forms must also be submitted through Medidata Rave. The pathology reports can be sent to the GOG Statistical and Data Center via postal mail or uploaded in Medidata Rave. The upload option is an alternative method for submitting paper reports.
<table>
<thead>
<tr>
<th>Form</th>
<th>Comments</th>
</tr>
</thead>
</table>
| **Baseline Folder**  
 (*Forms due within 2 weeks of registration*) | |
| Baseline/History Forms:  
 - Visit Information – Baseline Form  
 - Registration Form  
 - History Information Form  
 - Primary Surgery Form  
 - Chemotherapy Information Form  
 - Pre-Treatment Summary Form  
 - Specimen Consent  
 - Vitals Form  
 - ECHO/MUGA Form | The appropriate forms will load in the Baseline Folder based on the answers reported on the corresponding Baseline Visit Information form. |
| Solid Tumor Evaluation Forms:  
 - Target Lesions Form  
 - Non-Target Lesions Form | |
| **Visit Folder**  
 (*Forms due within 2 weeks of the completion of each cycle*) | |
| Cycle Information and Treatment Forms:  
 - Visit Information Form  
 - Cycle Patient Information Form  
 - Cycle Drug Information Form  
 - Labs and Chemistries Form  
 - Vitals Form  
 - ECHO/MUGA Form  
 - ECG Information Form  
 - Ophthalmologic Exam Report Upload | The appropriate forms will load in the Visit Folder based on the answers reported on the corresponding Visit Information forms. |
| Toxicity Forms:  
 - Section 1 Form  
 - NADIRS Form  
 - Adverse Event Form  
 - Adverse Event Grades | For patients in the safety lead-in, the Vitals Forms, Toxicity Forms, and Labs and Chemistries Forms will be collected weekly for Cycle 1 and once per cycle thereafter. Additionally, for patients in the safety lead-in the Visit Folder (and all forms within the folder) are due within **72 hours** after completing each cycle. *Solid tumor forms will appear in this folder but will still be due within 14 days after completing each cycle and reflected as such in the SEDES form schedule. |
| Solid Tumor Evaluation Forms:  
 - Target Lesions Form  
 - Non-Target Form  
 - New Target Lesions Form  
 - Status and Response Form | ECHO/MUGA Form and ECG Information Form will be reported every 3 cycles (approximately every 12 weeks), i.e., prior to cycle 4, 7, 10, etc.  
 Upload the Ophthalmology Exam online via Rave as clinically warranted. |
### Pathology Folder

*Reports and slides due within 6 weeks of registration*

<table>
<thead>
<tr>
<th>Form</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary disease:</td>
<td>Submit stained slides with two copies of the pathology report to SDC via postal mail or upload the pathology report online via RAVE.</td>
</tr>
<tr>
<td>Pathology Report</td>
<td></td>
</tr>
<tr>
<td>Stained Slides</td>
<td></td>
</tr>
<tr>
<td>Recurrent or Persistent Disease:</td>
<td>Stained pathology slides are required for central review by the GOG Pathology Committee. See Section 7.2 for mailing instructions and Section 4.5 for Pathology eligibility. All stained slides MUST be submitted via postal mail.</td>
</tr>
<tr>
<td>Pathology Report</td>
<td></td>
</tr>
<tr>
<td>Stained Slides</td>
<td></td>
</tr>
<tr>
<td>KRAS Report</td>
<td>Upload the KRAS Report online via RAVE.</td>
</tr>
</tbody>
</table>

### Translational Research Folder

<table>
<thead>
<tr>
<th>TR Forms:</th>
<th>A completed copy of Form TR must accompany each specimen shipped to the GOG Tissue Bank (or alternate laboratory). Handwritten forms will not be accepted.</th>
</tr>
</thead>
<tbody>
<tr>
<td>- FFPE Primary Tumor (FP01)</td>
<td>FP01, FM01, FRP01, and FRM01 are due 8 weeks from registration.</td>
</tr>
<tr>
<td>- FFPE Metastatic Tumor (FM01)</td>
<td></td>
</tr>
<tr>
<td>optional</td>
<td></td>
</tr>
<tr>
<td>- FFPE Recurrent Primary Tumor (FRP01)</td>
<td>WB01 is due 26 weeks from registration.</td>
</tr>
<tr>
<td>optional</td>
<td></td>
</tr>
<tr>
<td>- FFPE Recurrent Metastatic Tumor (FRM01)</td>
<td></td>
</tr>
<tr>
<td>optional</td>
<td></td>
</tr>
<tr>
<td>- Whole Blood (WB01)</td>
<td></td>
</tr>
</tbody>
</table>

### Treatment Completion Folder

*Forms due within 2 weeks of treatment completion*

| Treatment Completion Form | |
|---------------------------| |

### Follow-up Visit Folder

*Forms due within 2 weeks of follow-up visits, disease progression or death*

| Visit Information Follow-Up Form | |
|----------------------------------| |
| Follow-Up Form | Follow-up visits should be scheduled quarterly for 2 years, semi-annually for 3 more years, and annually thereafter. |
| Follow-Up Period Adverse Event: | The appropriate forms will in the Follow-up Visit Folder based on the answers reported on the corresponding Follow-up Visit Information forms. |
| - Reporting Form – Part 1 | |
| - Reporting Form – Part 2 | |
| Solid Tumor Evaluation: | |
| - Target Lesions Form | |
| - Non-Target Form | |
| - New Target Lesions Form | |
| - Status and Response Form | |

This study will be monitored by the **Complete** Clinical Data Update System (CDUS) Version 3.0 CDUS data will be submitted quarterly to CTEP by electronic means.
11.0 STATISTICAL CONSIDERATIONS

This is phase II study with a safety assessment lead in phase. The purpose of the safety lead in phase is to assess the combination regimen (i.e. Regimen II: Trametinib 1.5 mg PO Daily and GSK2141795 50 mg PO Daily) for safety in approximately 12 patients.

Once safety is assured, the trial will open group wide for accrual to a randomized phase II study to compare the activity of Regimen II (Trametinib 1.5 mg PO Daily and GSK2141795 50 mg PO Daily) against Regimen I (Trametinib 2.0 mg PO Daily) through progression-free survival (log-rank statistic) as a superiority study. The combination regimen should demonstrate a reduction in the hazard rate before it can be deemed interesting and worthy of further investigation. A reduction in the hazard rate by 40% is considered important to detect. This will require a total of 106 events with an interim futility analysis and utility evaluation conducted after 53 events are observed. A maximum sample size of 133 patients will be recruited to observe these events (total number in entire study with the safety assessment is about 148).

Patients will be prospectively randomized by KRAS mutational status (KRAS mutant versus KRAS wild type), performance status (PF=0 versus PF=1), and histology (serous versus not). Patients need to submit tumor tissue to determine their KRAS status before entering the study.

Regimen I: Trametinib 2.0 mg PO Daily (1 cycle = 28 days)

Regimen II: Trametinib 1.5 mg PO Daily and GSK2141795 50 mg PO Daily (1 cycle = 28 days).

Patients on Regimen I may cross over to Regimen II at progression.

11.1 Parameters employed to evaluate treatment efficacy and toxicity are:

11.11 Primary Endpoints

11.111 Phase II: Progression-free survival (PFS) by regimen administered (Intent to Treat Analysis, ITT).

11.112 Safety assessment and Phase II: The frequency and severity of adverse events.

11.113 Safety assessment: Dose-limiting toxicity (DLT) in cycle 1. (07/28/14)

11.12 Secondary Endpoints

11.121 KRAS status (mutant or wild type), tumor response, and PFS by regimen.
11.12 Overall survival (OS) by regimen.

11.123 Response duration as determined from the first date of response until disease progression or death (by KRAS mutation and regimen).

11.124 Proportion responding (and with 6-month PFS) on this study and a potential historical control.

11.13 Exploratory Endpoints

11.131 Baseline genomic biomarkers assessed against tumor response, PFS, OS (excluding crossovers) by regimen and KRAS status.

11.2 The anticipated annual accrual is approximately 50 patients.

11.21 The anticipated period of active accrual is about 4 to 7 months for the safety assessment lead in phase (depending on the time for IRB approval). The anticipated period of active accrual is about 32 months for the phase II study.

11.3 Study Plan (05/12/14) (07/28/14)

Safety Assessment Lead In

The first safety assessment lead-in concluded that the proposed regimen was too toxic for further evaluation in a phase II study. Another regimen will now be proposed. It will be assessed in a 2-stage design with 6 evaluable patients in each stage. The decision rules are outlined below:

Accrue 6 patients in Stage 1. If 0 patients (i.e. no patients) experience a DLT in cycle 1 (including significant delays in cycle 2 administration), then the study can conclude that the regimen is safe and proceed to the randomized phase II. If 3 or more patients experience DLTs, then this part of the study will terminate early and conclude that the regimen is too toxic for further study. If the number of DLTs is either 1 or 2, then the study will proceed to a second stage to accrue 6 additional patients. If the total number of DLTs is 3 or less in 12 (25% or less), then with medical judgment indicating, the regimen will be considered safe for further investigation in the randomized phase II study. Otherwise, the study should be amended to examine another regimen.

The operating characteristics of the design marginalized over two stages are listed in the table below:
The probability of correctly declaring a safe regimen as being safe after the first stage is 26.2%. The probability of correctly declaring an unsafe regimen as being unsafe after Stage 1 is 45.6%.

**Randomized Phase II**
Patients will be prospectively randomized by KRAS mutational status (KRAS mutant versus KRAS wild type), performance status (PF=0 versus PF=1), and histology (serous versus not). They will be randomized to Regimen I and II in a 1:1 fashion. The maximum number of patients accrued to this study (phase II part) will be 133 patients.

The primary endpoint used in this study will be progression-free survival. The null hypothesis is that the addition of GSK2141795 to Trametinib (Regimen II) does not prolong the duration of PFS relative to treatment with Trametinib alone (Regimen I). This equivalency of PFS can be expressed as a hazard ratio of Regimen II to Regimen I for progression or death (PFS endpoint) being equal to one. That is to say:

Ho: HR ≥ 1.00  
Ha: HR ≤ 0.60

Where HR > (≤) 1 indicate that Regimen II has a greater (lesser) hazard than Regimen I. Ha is the alternative hypothesis where hazard ratios 0.60 or less are considered to be clinically interesting. The null hypothesis will be tested against the alternative with a stratified log-rank test using strata as defined above. As a first approximation to the required number of events in order to detect the alternative hypothesis with 90% power at the 10% level of significance, Schoenfeld’s equation indicates: D = (Z_α + Z_β)^2 x (R + 1)^2 / (R x ln {Δ}^2)=100.7 when Z_α = 1.2816, Z_β = 1.2816, and R = 1. Z_α = 1.28 since the alternative hypothesis is one-sided. R is the ratio of patients assigned to the experimental therapy to the control therapy which equals one since patients will be assigned to the arms with equal probability. Δ is the minimally clinically significant hazard ratio (in this case, Δ=0.60). Therefore, we need to observe at least 101 patients (in total) with times of disease progression or death. With an interim analysis, this number will increase slightly. With an interim analysis, beta spending requires the observation of 106 events in order to guarantee 90% power under the alternative (see below).

**Interim Futility Analysis**
The trial will suspend accrual after 67 patients have entered.
At approximately the 53\textsuperscript{rd} event (taking events from both treatment arms), an interim futility analysis will be conducted using the method provided by Weiand’s et al.\cite{42} futility rule. More specifically, the interim decision rule will consider alternative designs if the combination regimen is not performing at least as well as the Regimen I (such as recruiting patients who are KRAS mutant only, rejection of the combination arm, or termination of the study). In this case, after consultation with the GOG DMC, a discussion will be held with investigators and CTEP officials about the subsequent course of action. For the sake of simplicity, we will consider the case where the combination therapy would be rejected. The combination therapy would be deemed uninteresting in the current study population if the stratified log-rank statistic (before squaring) is greater than 0. This decision rule will stop the study early 50\% of the time when the hazard ratio is truly one. On the other hand, there could be a non-trivial probability of falsely declaring active regimens not interesting. To correct this problem, group sequential methods will be utilized that incorporate the futility rule as outlined by Jennison and Turnbull \cite{43} (p49, eq. 3.1). The standardized test statistics, related to the log-rank statistic at the interim and final analyses will be designated by $Z_1$ and $Z_2$, respectively. Specifically, $Z_i = (L_i - 0)/\sigma_i$ where $i = 1, 2$ according the stage of the study and $L_i$ is the log-rank statistic at stage $i$. According to Jennison and Turnbull, these statistics will be distributed as a multivariate normal distribution with the following parameters:

$$
\begin{pmatrix} Z_1 \\ Z_2 \end{pmatrix} \sim MVN \left( \begin{pmatrix} \theta \sqrt{I_1} \\ \theta \sqrt{I_2} \end{pmatrix}, \Sigma = \begin{bmatrix} 1 & \sqrt{I_1/I_2} \\ \sqrt{I_1/I_2} & 1 \end{bmatrix} \right)
$$

where $I_k$ is the information obtained at the $k$\textsuperscript{th} stage of the design with $I_k = d_k/4$ and $d_k$ being the total number of observed events at that time. $\theta$ is the logarithm of the hazard ratio. Since the use of Weiand et al. plans on observing $Z_1$ at 50\% information time, the covariance between $Z_1$ and $Z_2$ is about 0.707. The cumulative distribution function of $Z_1$ and $Z_2$ is provided below by $F(.)$:

$$
P(Z_1 \leq z_1, Z_2 \leq z_2) = F(z_1, z_2 | \theta, I_1, I_2)
$$

The design will reject the regimen if $Z_1 > 0$ in the first stage or $Z_1 < 0$ in the first stage, but $Z_2 > c_2$ in the second stage where $c_2$ is a critical value for rejecting $H_0$. This is expressed mathematically as:

$$
P(Z_1 > 0 \cup \{Z_1 < 0 \cap Z_2 > c_2\}) = P(Z_1 > 0) + P(Z_1 < 0, Z_2 > c_2)
$$

$$
= [1 - P(Z_1 < 0)] + [P(Z_1 < 0) - P(Z_1 < 0, Z_2 < c_2)]
$$

$$
= 1 - F(0, \infty | \theta, I_1, I_2) + F(0, \infty | \theta, I_1, I_2) - F(0, c_2 | \theta, I_1, I_2)
$$

$$
= 1 - F(0, c_2)
$$

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Under H₀, the desired probability of rejecting the regimen is 90% (when the null hypothesis is true, alpha = 1 – 90% = 10%). Searching algorithms can quickly find the value of \( c = -1.25 \) which deviates slightly from the usual value of -1.28 obtained with a single stage test.

The required total number of events to obtain 90% power is 106 when a study is conducted with an interim analysis after observing 53 events. That is to say:

\[
F(0, -1.25 | \theta = -0.51, I_1 = 13.25, I_2 = 26.5) = 0.904
\]

The total number of patients that should be recruited is \[106 \times 1.25\] + 1 = 133.

Study enrollment will be suspended during the futility analysis. The study may continue with Regimen I if Regimen II is dropped for futility. Comparisons with a possible historical control can be utilized in order to help guide a decision.

11.4 Secondary and Exploratory Analyses

It is unknown whether trametinib in Regimen I has activity. Unfortunately, there is no known historical control to assess for a comparison. However, GOG 0129 and 0229 may serve as a potential historical control. Patients in this study will be compared to patients on these studies through response and 6-month PFS.

The impact of KRAS mutation on response and PFS will be assessed according to the regimens administered. Given the possibility that KRAS+ patients may be small in number (20%), these comparisons may be informal (e.g. Kaplan-Meier survival estimates). If KRAS+ patients appear to be responding more fully after the interim analysis or after the study is complete, the study may be amended so that eligibility is restricted to these patients. In this case, additional patients should contribute to a separate analysis in order to avoid problems with potential bias. Overall survival will be compared by regimen with log-rank tests and Cox modeling. If patients crossover to Regimen II, they will be dropped from the analysis. However, since the OS comparison between the regimens is no longer strictly randomized, there are potential problems with bias. Tests for associations between prognostic factors and whether a patient decides to crossover from Regimen I to Regimen II will be assessed. Response duration will be assessed with Kaplan-Meier curves. Baseline genomic biomarkers will be assessed against response, PFS, OS (excluding crossovers) by regimen and KRAS status through odds ratios and proportional hazards estimates where possible.

The PFS times may be discretized to 2 and 4 months in a similar manner as in GOG-0186K to assess the robustness of the study conclusions against biased CT scans by the regimen randomized.
11.5 PTEN assessment (12/26/2017)

Protein expression of PTEN will be assessed by IHC. The level of expression will be dichotomized into 2 groups: high and low. It is anticipated that there will be 30 to 50% of the patients who are expected to express high levels of PTEN. The clinical trial enrolled 26 patients. Of these 25 have progressed and 19 have died. Figure 1 below provides a power curve of a log-rank test for equivalent PFS on high versus low expressers of PTEN; the null hypothesis Ho: HR=1 is tested against Ha: HR ≠ 1 at the 5% level of significance.

The higher (blue) curve is obtained when the proportion of PTEN expressers is 50% (versus 30% of expressers shown in the lower (purple) curve). When the proportion of PTEN expressers is 50%, the study obtains 41% power when the HR=0.5 or 2.0. When the proportion of PTEN expressers is 30%, the study obtains 36% power when the HR=0.5 or 2.0.

With 19 deaths, the ability of the study to detect changes in the HR is not as great for a specific value of the HR, but frequently the impact of the biomarkers can be more pronounced with OS (i.e. the HR can be further from the null value of 1.0). The Figure 2 below provides the power curves for when the proportion of expressers is 30 and 50% like that presented above.
Figure 2

These curves span a greater range of values (HR from 1/3 to 3). The higher (blue) curve is obtained when the proportion of PTEN expressers is 50% (versus the 30% of expressers for the lower curve). When the proportion of PTEN expressers is 50%, the study obtains 67% power when the HR=0.33 or 3.0. When the proportion of PTEN expressers is 30%, the study obtains 59% power when the HR=0.33 or 3.0. For comparison purposes to PFS, when the proportion of PTEN expressers is 50%, the study obtains 33% power for HR=0.5 or 2.0. When the proportion of PTEN expressers is 30%, the study obtains 28% power when the HR of death is 0.5 or 2.0.

If the number of events is less than 10 in either group, then the asymptotic methods may become questionable. In these cases, permutation methods may be considered.

11.6 Analysis of Genes (12/26/2017)

There will be about 200 genes assessed for mutations. These genes will be dichotomized as being mutant or wild type. The association between gene mutational status and a positive outcome such as tumor response or surviving progression free for 6 months will be explored. If we let \( r \) be the total number of patients with responses, \( r_m \) be the observed number of patients who have responses and are mutant, \( M \) be the number of patients with mutations, and \( n \) be the number in the trial that are examined, then Fisher’s Exact Test can be used to determine the significance of a positive association through p-values as follows:

\[
p - \text{value} = \sum_{i=r_m}^{\min(r,M)} \frac{\binom{M}{i} \binom{n-M}{r-i}}{\binom{n}{r}}
\]

The number of patients who responded to therapy was one person. The number of patients with mutations for any particular gene is expected to be relatively small (1 or 2 patients). Given that there will be about 26 patients analyzed for mutations, we have \( n = 26 \). Therefore, we anticipate only one circumstance involving tumor response that would be interesting, and that circumstance is when
$M = 1$ and $r_m = 1$. The probability that the mutated person is the person with the tumor response by mere chance is $1/26$ or about 0.0385. Under the null hypothesis of no association between mutation and response, we expect to see $g_{M1} \times 0.0385$ cases highlighted as being potentially interesting where $g_{M1}$ are the number of genes with only 1 mutation among the sample of 26 patients. If $g_{M1} = 200$ (i.e. all genes truly have no association with response), then we expect to see about 8 cases listed as being suggestive (i.e. have a p-value<0.05). Ninety-five percent of the time, the total number of false positive cases will be 12 or less when $g_{M1} = 200$.

Another important question deals with the chances of classifying a particular mutation as being suggestive when an actual association exists between the mutation and response. In general, the relationship of statistical power when using Fisher’s Exact Test is provided by the following expression where $\Delta$ is the odds ratio of having a response among mutated patients to having a response among wild type patients:

$$\text{Power} = \frac{\sum_{i=r_C}^{\min(r,M)} \binom{M}{i} \binom{n-M}{r-i} \Delta^i}{\sum_{i=\max(0,r-n+M)}^{\min(r,M)} \binom{M}{i} \binom{n-M}{r-i} \Delta^i}$$

For the specific case examined previously where $M = 1$ and $r_C = 1$, power can be evaluated simply as:

$$\text{Power} = \frac{\Delta}{25 + \Delta}$$

A plot of statistical power as a function of the true odds ratio is provided below.

We can see from the plot that a strong association between response and mutation is required before the chances of classifying a relationship as being suggestive is reasonably high (e.g. a $\Delta > 25$ yields 50% or more in statistical power). However, when a true association exists, it is not unreasonable to expect a very strong association to hold (e.g. see Schilder et al.).

When analyzing the associations between mutations and 6-month PFS, the problem is more complex because the number of patients who have 6-month PFS is 5. If we have a gene where 5 patients have mutations, we need to see at least 3
mutant patients who have 6-month PFS before the association is deemed suggestive \((p=0.033536)\). If we have 4 patients with mutations, we need to see at least 3 mutant patients who have 6-month PFS before the association is deemed suggestive \((p=0.014381)\). If we have 3 patients with mutations, we need to see all 3 mutant patients with 6-month PFS before the association is deemed suggestive \((p=0.003846)\). If we have 2 patients with mutations, we need to see all mutant patients with 6-month PFS before the association is deemed suggestive \((p=0.030769)\). If there is only 1 patient with a mutation, then the data cannot be deemed suggestive. Since we do not expect to see many examples where the number of patients with mutations is greater than 3, we will restrict our attention to the case where we have \(M = 3\) and \(r_m = 3\) where “response” is now the outcome of having 6-month PFS. Then statistical power can be found with the formula above and applied specifically to this example:

\[
\text{Power} = \frac{253\Delta^3}{33649 + 26565\Delta + 5313\Delta^2 + 253\Delta^3}
\]

A plot of statistical power as a function of the true odds ratio is provided below.

The power to detect an association between mutation and 6-month PFS in this setting is about the same as the power to detect an association between mutation and response.

### 11.7 Minority Accrual

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<th>Ethnic Category</th>
<th>Sex/Gender</th>
<th>Total</th>
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<tbody>
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<td></td>
<td>Females</td>
<td>Males</td>
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<tr>
<td>Not Hispanic or Latino</td>
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<td>+ 0</td>
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<td>Ethnic Category: Total of all subjects</td>
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<td>+ 0</td>
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<table>
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<th>Racial Category</th>
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<td>Racial Category</td>
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<td>Native Hawaiian or other Pacific Islander</td>
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<tr>
<td>White</td>
<td>131</td>
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<tr>
<td>Racial Category: Total of all subjects</td>
<td>148</td>
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</table>
12.0 BIBLIOGRAPHY


Appendix I - General Chemotherapy Guidelines:

- For 21 or 28 day cycles, a patient will be permitted to have a new cycle of chemotherapy delayed up to 7 days (without this being considered to be a protocol violation) for major life events (e.g., serious illness in a family member, major holiday, vacation which is unable to be re-scheduled). Documentation to justify this decision should be provided.

- It will be acceptable for individual chemotherapy doses to be delivered within a “24-hour window before and after the protocol-defined date” for “Day 1” treatment of 21 or 28 day cycles. If the treatment due date is a Friday, and the patient cannot be treated on that Friday, then the window for treatment would include the Thursday (1 day earlier than due) through the Monday (day 3 past due).

- For weekly regimens, it will be acceptable for individual chemotherapy doses to be delivered within a “24-hour window,” for example; “Day 8 chemotherapy” can be delivered on Day 7, Day 8, or Day 9 and “Day 15 chemotherapy” can be given on Day 14, Day 15, or Day 16.

- Chemotherapy doses can be “rounded” according to institutional standards without being considered a protocol violation (most institutions use a rule of approximately +/- 5% of the calculated dose).

- Chemotherapy doses will be based on the subject’s weight at baseline and will remain the same throughout the study. However, the doses will be recalculated if the patient has a weight change of greater than or equal to 10% from baseline.

- Maximum body surface area used for chemotherapy dose calculations will be 2.0 m². For chemotherapy dose calculations that use mg/kg, there will be no maximum kilogram amount used (doses will be calculated on actual weight in kg).
Appendix II - Congestive Heart Failure – New York Heart Association Criteria

<table>
<thead>
<tr>
<th>Class</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>No limitation: Ordinary physical activity does not cause undue fatigue, dyspnea, or palpitation</td>
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<tr>
<td>II</td>
<td>Slight limitation of physical activity: Such patients are comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnea, or angina.</td>
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<td>III</td>
<td>Marked limitation of physical activity: Although patients are comfortable at rest, less than ordinary physical activity will lead to symptoms.</td>
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<tr>
<td>IV</td>
<td>Inability to carry on physical activity without discomfort: Symptoms of congestive heart failure are present even with rest. With any physical activity, increased discomfort is experienced.</td>
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</table>

Appendix III - PATIENT PILL CALENDAR: REGIMEN I

Patient Name: ___________________________  Month/Date of first dose on calendar: _______________________
Patient Study ID: _________________________  Cycle #: ____________________________

1. Complete one form for each cycle of treatment.
2. Trametinib can be stored at room temperature.
3. You will take trametinib once a day. Take the medicine on an empty stomach, either one hour before or two hours after a meal. **Morning dose: take trametinib tablets**
4. Record the date, the number of trametinib tablets you swallowed in the morning and when you swallowed the medicine.
5. If you vomit or miss a dose of trametinib do not take the missed dose or double the next. Continue with the assigned dosing schedule.
6. If you have any comments or notice any side effects, please record them in the Comments column.
7. Please bring this form and your bottles of trametinib each time you return for an appointment.

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<th>Dose taken</th>
<th># of tablets taken</th>
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PATIENT PILL CALENDAR: REGIMEN I

Patient’s Signature:


Physician’s Office will complete this section:
1. Date patient started protocol treatment: ________________________________
2. Date patient was removed from study: ________________________________
3. Patient’s planned total daily dose: ________________________________
4. Total number of tablets taken this month: ________________________________
5. Physician/Nurse/Data Manager’s Signature: ________________________________
Appendix IV - PATIENT PILL CALENDAR: REGIMEN II

Patient Name: ___________________________  Month/Date of first dose on calendar: ____________
Patient Study ID: ________________________  Cycle #: ________________________________

1. Complete one form for each cycle of treatment.
2. Trametinib should be kept at room temperature. GSK2141795 should be refrigerated.
3. You will take GSK2141795 and trametinib once a day.
   - Take trametinib tablets on an empty stomach (at least 2 hours after any food).
   - One hour later, eat a meal followed by 60 minutes of fasting prior to taking GSK2141795 capsules. Water is allowed during this fasting period.
   - Remain upright for 30 minutes after taking the last capsule of GSK2141795 to avoid stomach irritation.
   - Fast for 2 hours after ingestion of the last capsule of GSK2141795. Water is allowed during this fasting period.
4. Record the date, the number of trametinib tablets and GSK2141795 capsules you swallowed in the morning and when you swallowed the medicine.
5. If you vomit or miss a dose of trametinib and/or GSK2141795 do not take the missed dose or double the next. Continue with the assigned dosing schedule.
6. If you have any comments or notice any side effects, please record them in the Comments column.
7. Please bring this form and your bottles of trametinib and GSK2141795 each time you return for an appointment.

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<th>Day</th>
<th>Date</th>
<th>Time of GSK2141795 dose</th>
<th>Dose taken</th>
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<th>Comments</th>
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</table>
PATIENT PILL CALENDAR: REGIMEN II

Patient’s Signature:

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physician’s Office will complete this section:</strong></td>
<td></td>
</tr>
<tr>
<td>1. Date patient started protocol treatment:</td>
<td></td>
</tr>
<tr>
<td>2. Date patient was removed from study:</td>
<td></td>
</tr>
<tr>
<td>3. Patient’s planned total daily dose:</td>
<td></td>
</tr>
<tr>
<td>4. Total number of capsules/tablets taken this month:</td>
<td></td>
</tr>
<tr>
<td>5. Physician/Nurse/Data Manager’s Signature:</td>
<td></td>
</tr>
</tbody>
</table>

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Appendix V - Translational Research Specimen Procedures (12/23/13)(07/28/14)

I. Summary of Translational Research Specimen Requirements

If the patient gives permission for her specimens to be collected and used for this optional translational research component, then participating institutions are required to submit the patient’s specimens as outlined below (unless otherwise specified).

<table>
<thead>
<tr>
<th>Required Specimen (Specimen Code)</th>
<th>Collection Time Point</th>
<th>Ship To</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFPE Primary Tumor (FP01)*</td>
<td>Prior to all treatment</td>
<td></td>
</tr>
<tr>
<td>1st Choice: block</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd Choice: scroll (50-100µm in a cryovial)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FFPE Metastatic Tumor (FM01)*</td>
<td>Prior to all treatment</td>
<td></td>
</tr>
<tr>
<td>1st Choice: block</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd Choice: scroll (50-100µm in a cryovial)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FFPE Recurrent Primary Tumor (FRP01)*</td>
<td>Prior to study treatment</td>
<td>GOG Tissue Bank within 8 weeks of registration¹</td>
</tr>
<tr>
<td>1st Choice: block</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd Choice: scroll (50-100µm in a cryovial)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FFPE Recurrent Metastatic Tumor (FRM01)*</td>
<td>Prior to study treatment</td>
<td>GOG Tissue Bank within 8 weeks of registration¹</td>
</tr>
<tr>
<td>1st Choice: block</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd Choice: scroll (50-100µm in a cryovial)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole Blood (WB01)</td>
<td>Prior to or after starting study treatment</td>
<td>GOG Tissue Bank the day the specimen is collected¹</td>
</tr>
<tr>
<td>7-10mL drawn into purple top (EDTA) tube(s)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* A copy of the corresponding pathology report must be shipped with all tissue specimens sent to the GOG Tissue Bank

¹ GOG Tissue Bank / Protocol GOG-0229O, Nationwide Children’s Hospital, 700 Children’s Drive, WA1340, Columbus, OH 43205, Phone: (614) 722-2865, FAX: (614) 722-2897, Email: GOGBank@nationwidechildrens.org

II. Obtaining a GOG Bank ID for Translational Research Specimens

Only one GOG Bank ID (###-#-G###) is assigned per patient. All translational research specimens and accompanying paperwork must be labeled with this coded patient number. A GOG Bank ID can be obtained online via the Tissue Bank Portal on the GOG website (under Tools on the Web Menu page).

Obtain the patient’s study ID (GOG #) for all protocols with translational research specimen requirements before requesting a Bank ID from the Tissue Bank Portal. **Be sure to indicate if the patient has a previous GOG # when registering.** This will ensure that the patient is only assigned one Bank ID. The GOG ID – Bank ID Lookup on the Tissue Bank Portal can be used to search for an existing Bank ID.

Please contact GOG User Support if you need assistance or have assigned more than one Bank ID to a patient (Email: support@gogstats.org; Phone: 716-845-7767).
III. Requesting Translational Research Specimen Kits

Kits are not provided for this protocol.

IV. Labeling Translational Research Specimens

A waterproof permanent marker or printed label should be used to label each translational research specimen with:

- GOG Bank ID (# # # - # - G # # #)
- GOG protocol number (GOG- # # # #)
- specimen code (see section I)
- collection date (mm/dd/yyyy)
- surgical pathology accession number (tissue specimens only)
- block number (tissue specimens only)

V. Submitting Formalin-Fixed, Paraffin-Embedded Tissue

Formalin-fixed, paraffin embedded (FFPE) tissue should be the most representative of the specimen type (primary, metastatic, recurrent). Primary and metastatic tumor should be collected prior to all treatment. Recurrent tumor should be collected prior to the study treatment. Only one block may be submitted per tissue type.

Every attempt should be made to provide a FFPE block; however, if a block cannot be provided on a permanent basis, then an FFPE “scroll” (50-100µm in a cryovial) should be submitted.

Note: Unstained slides for eligibility (i.e., KRAS testing) and stained slides to confirm patient eligibility by central pathology review are required for this protocol, but are NOT sent to the GOG Tissue Bank (see protocol for details). If these slides will be cut from the same block that will be submitted for translational research, your pathology department should cut these slides prior to submitting the block for translational research.

The type of specimen (block or scroll) should be specified on Form TR. If submitting scrolls, the thickness should also be specified.

All FFPE tissue should be submitted with the corresponding pathology report.

VI. Submitting Whole Blood

1. Label the lavender/purple top (EDTA) collection tube(s) as described above. Multiple tubes may be used to collect the required amount.

2. Draw 7-10mL of blood into the labeled lavender/purple top tube(s). A minimum of 3mL is needed for processing.
3. Immediately after collection, gently invert the tube 5-10 times to mix the blood and EDTA.

4. Whole blood specimens should be refrigerated (4°C) until the specimens can be shipped. Ship whole blood to the GOG Tissue Bank the day the specimen is collected. If the whole blood absolutely cannot be shipped the day it is collected, the tube(s) should be refrigerated (4°C) until the specimen can be shipped.

VII. Submitting Form TR

A completed copy of Form TR must accompany each specimen shipped to the GOG Tissue Bank (or alternate laboratory). Handwritten forms will not be accepted.

Note: A copy does not need to be sent to the GOG Tissue Bank (or alternate laboratory) if specimens are not collected.

Retain a printout of the completed form for your records.

Please contact User Support at the GOG Statistical and Data Center if you need assistance (Email: support@gogstats.org; Phone: 716-845-7767).

VIII. Shipping Translational Research Specimens

A completed copy of Form TR must be included for each translational research specimen.

A. FFPE Tissue

FFPE tissue and a copy of the corresponding pathology report should be shipped using your own container at your own expense to:

GOG Tissue Bank / Protocol GOG-0229O
Nationwide Children’s Hospital
700 Children’s Dr, WA1340
Columbus, OH 43205
Phone: (614) 722-2865
FAX: (614) 722-2897
Email: GOGBank@nationwidechildrens.org

Do not ship FFPE tissue for Saturday delivery.

B. Whole Blood

All whole blood specimens should be shipped to the GOG Tissue Bank (address above).

Whole blood specimens can be shipped to the GOG Tissue Bank Monday through Friday for Tuesday through Saturday delivery. Please do not ship whole blood the day
before a holiday. Use your own shipping container to ship specimens via **FedEx priority overnight**.

When shipping whole blood specimens, **please be aware that your Institution must comply with IATA standards** ([www.iata.org](http://www.iata.org)). If you have questions regarding your shipment, contact the GOG Tissue Bank at GOGBank@nationwidechildrens.org or by phoning 866-GOG-BANC (866-464-2262).

To ship whole blood specimens you will need (1) a sturdy shipping container (e.g., a cardboard or styrofoam box), (2) a leak proof biohazard envelope with absorbent material*, (3) a puncture and pressure resistant envelope (e.g. Tyvek envelope), (4) an Exempt Human Specimen Sticker, and (5) a pre-paid FedEx air bill.

*If you will be shipping whole blood specimens from more than one patient, please put each specimen in a separate plastic zip-lock bag before placing the specimens in the shipping bag. You may include up to four different blood specimens in one biohazard envelope.

If you do not have these materials available at your institution, you may order them from any supplier (e.g., Saf-T-Pak; Phone: 800-814-7484; Website: [www.saftpak.com](http://www.saftpak.com)).

**Shipping Whole Blood Using Your Own Shipping Container**

1. Place the whole blood specimen in a biohazard envelope containing absorbent material. Expel as much air as possible before sealing the bag.

2. Wrap the biohazard envelope in bubble wrap or another padded material.

3. Place the padded tube(s) into a Tyvek envelope. Expel as much air as possible before sealing the envelope.

4. Place the Tyvek envelope in a sturdy shipping contained (e.g., cardboard FedEx box).

5. Insert a copy of Form TR for each specimen.

6. Attach an Exempt Human Specimen Sticker to the outside of the shipping container.

7. Print a pre-paid FedEx air bill using the Kit Management application (found under Data Entry on the Web Menu page). Attach the air bill.

8. Make arrangements for FedEx pick-up through your usual institutional procedure or by calling 800-238-5355.

IX. **Distributing Specimens for Translational Research**
Note: Testing of banked samples will not occur until an amendment to this treatment protocol (or separate correlative science protocol) is reviewed and approved in accordance with National Clinical Trials Network (NCTN) policies.

The GOG Statistical and Data Center and Tissue Bank (or alternate laboratory) will coordinate the distribution of specimens to approved investigators for translational research.

Investigators will not be given access to any personal identifiers.

Investigators will be responsible for the direct supervision and oversight of translational research and for keeping accurate records.

Investigators will ensure the results are linked to the appropriate specimen-specific identifiers and are responsible for transferring relevant laboratory data to the GOG Statistical and Data Center.

At the discretion of the Chair of the Committee on Experimental Medicine and the Director of the GOG Tissue Bank, investigators may be required to ship any specimens (or by-products) remaining after the completion of the translational research to the GOG Tissue Bank.

A. **FFPE**

   FFPE will be batch shipped upon trial completion to:

   Dr. Gordon Mills  
   c/o Yiling Lu  
   Dept of Systems Biology  
   Rm 2SCR2.2209  
   7435 Fannin St  
   Houston, TX 77054  
   Phone: 713-563-4218  
   FAX: 713-563-4230  
   Email: YilingLu@mdanderson.org

B. **Whole Blood**

   The GOG Tissue Bank will extract DNA from whole blood. DNA will be batch shipped upon trial completion to Dr. Gordon Mills (address above).

X. **Banking Translational Research Specimens for Future Research**

   Specimens will remain banked in the GOG Tissue Bank and made available for approved research projects if the patient has provided permission for the use of her specimens for future health research. The patient’s choices will be recorded on the signed informed consent
document and electronically via the online Specimen Consent form. At the time of specimen selection for project distribution, the most recent consent information will be used.

**Institutions can amend a patient’s choices regarding the future use of her specimens at any time if the patient changes her mind.**

If the patient revokes permission to use her specimens, the GOG Tissue Bank will destroy or return any remaining specimens. The patient’s specimens will not be used for any further research; however, any specimens distributed for research prior to revoking of consent cannot be returned or destroyed. In addition, the patient cannot be removed from any research that has been done with her specimens prior to revoking consent.

Note: If return of specimens is requested, shipping will be at the institution’s expense.
Appendix VI – Collaborative Agreement

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(s) in this study:

1. Agent(s) may not be used for any purpose 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 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 prior 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 that 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 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 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 Collaborator(s) for Phase 3 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 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:

Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator’s confidential/ proprietary information.
Appendix VII – KRAS Test Requisition and Shipping Instructions (12/23/13)(07/28/14)

<table>
<thead>
<tr>
<th>TUMOR INDICATION</th>
<th>SAMPLE INFORMATION</th>
<th>TELING INFORMATION</th>
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<td>ENDOMETRAL CANCER</td>
<td>DATE OF COLLECTION:</td>
<td>INSTITUTION: MDACC GOG-02290</td>
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<tr>
<td></td>
<td>/ /</td>
<td>INSTITUTION CODE: UTSC</td>
</tr>
<tr>
<td></td>
<td>TIME OF COLLECTION:</td>
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</table>

- FFPE - Slides* & :
  - Ten unstained 5 micron slides and one H&E stained slide
  - DE-IDENTIFIED SURGICAL PATHOLOGY REPORT MUST BE ATTACHED FOR ALL TUMOR SAMPLES

- TEST REQUESTED
  - #126  KRAS Codon 12, 13, 61 Mutation Analysis

- RETURN OF FFPE SPECIMENS
  - CHECk IF H&E STAINED SLIDES SHOULD BE RETURNED, PLEASE FILL OUT THE RETURN ADDRESS INFORMATION BELOW, OR AFFIX PREPRINTED LABEL
  - THIS SECTION WILL BE USED AS THE RETURN ADDRESS LABEL

<table>
<thead>
<tr>
<th>INSTITUTION:</th>
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<tbody>
<tr>
<td>ATT:</td>
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<tr>
<td>ADDRESS:</td>
<td></td>
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<tr>
<td>CITY, STATE, ZIP:</td>
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### Appendix VIII – CT Scan Date Calculator (12/23/13)

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<td>Week 140</td>
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<td>Week 152</td>
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</tr>
</tbody>
</table>

**Instructions:**

Enter Patient Number in Cell B1  
Enter Patient Initials in Cell B2  
Enter Date of Cycle 1, Day 1 (first dose) in Cell B3  

Projected CT Scan dates will appear in cells B4 through B17. Please use these dates to schedule CT scans for this patient. You may print this sheet for your reference.
APPENDIX IX – TRANSLATIONAL RESEARCH LABORATORY TESTING PROCEDURES (12/26/2017)

Original Translational Objective
To estimate the association between baseline genomic biomarkers in the PI3K/AKT pathway and clinical activity (e.g. response and PFS) in two subgroups of patients defined above with recurrent or persistent endometrial cancer who are treated with trametinib alone or in combination with GSK2141795.

Revised Translational Objective
To estimate the association between baseline genomic biomarkers in a deep sequencing panel of 200 genes and clinical activity (e.g. response and PFS) in patients with recurrent or persistent endometrial cancer who are treated with trametinib and GSK2141795.

I. KRAS/PTEN/PI3K Pathway Mutational Analysis

A. Overview

The overarching goal of the translational objective is to identify and validate biomarkers able to predict benefit of combination therapy with PI3K and RAS/RAF pathway inhibitors in recurrent/metastatic EC. The clinical trial was based on our observation of a high frequency of PI3K and RAS/RAF pathway aberrations combined with modest activity of mTOR inhibitors in EC(1-3). The negative predictive value of RAS mutation and S6 phosphorylation for response to mTOR inhibitors(4) argued that coordinate inhibition of the PI3K and RAS/RAF pathways would be required for optimal patient benefit.
EC can be divided into 5 proteomic groups with prognostic and therapeutic relevance (Figure). The largest group (light blue) has high ER, PI3K and RAS/MAPK pathway activation with a high frequency of PI3K pathway, KRAS and ARID1A mutations and a relatively low frequency of p53 mutations and myc amplification. The second group (light green) is also ER high but with low PI3K and RAS/MAPK pathway activity and fewer mutations in the PI3K and RAS pathways, and particularly in ARID1A. Serous and serous-like tumors encompass a distinct group (dark blue) with fewer PI3K pathway mutations and frequent p53 (92%) mutations as well as frequent copy number aberrations (CNA) including myc and HER2 amplification (27%) with concomitant increased protein levels. Serous and serous-like tumors demonstrate EMT, cell cycle progression, and DNA damage response with decreased PI3K and hormonal signaling (5). While the high rate of p53 mutations and CNA are similar to high-grade serous ovarian cancers, the other characteristics are unique to serous and serous-like EC. The “reactive” (5) (dark green) group identifies an endometrioid subset with a poor outcome similar to serous EC (Figure 2B). The final group (mid blue) demonstrated EMT, with myc but not HER2 amplification.

Our findings that the PI3K and RAS pathways were highly activated (Figure 2) (5) and mutated in EC, with concurrent mutations in multiple pathway members and in both pathways (6, 7), were confirmed by TCGA (8). The pattern of PI3K pathway aberrations in EC is unique, with co-mutation of PI3K pathway members being common compared to mutual exclusivity in most other lineages. Distinct mutational events in EC include a skew towards hinge region and R88Q PIK3CA mutations, a gain of function hotspot mutation at R130 in PTEN (manuscript in preparation), a hotspot termination mutation at R348* in PIK3R1, and the highest frequency of PIK3R1 mutations in any tumor lineage (6-9). Through integrated genomic and proteomic analysis, we demonstrated that PI3K loss or PIK3CA or PIK3R1 mutation can drive pathway activation (Figure) (6). We have shown mutations in PIK3R1 to regulate PTEN stability (6) and that a recurrent mutation in PIK3R1 is a novel neomorph unexpectedly activating and driving tumor growth through the MAPK pathway (9).

Given the high proportion of PI3K/AKT and RAS/RAF/MEK pathway aberrations found in endometrial cancer, targeting these pathways holds great promise for improving outcomes for this aggressive disease. Our group and others have found that the presence of mutations in the PI3K/AKT pathway incur sensitivity to the antitumor effects of PI3K pathway directed agents. In addition, the presence of KRAS mutations are dominant predictors of resistance to targeted therapies (erlotinib, cetuximab) in colorectal and lung cancers (10, 11). Emerging data in endometrial cancer and other solid tumors suggest that combination therapy with PI3K pathway and RAS/RAF pathway inhibitors may be necessary for improved outcomes (12). The majority of current clinical trials of targeted therapy in gynecologic malignancies include all patients, regardless of molecular profile. In order to avoid incorrect classification of an agent as inactive, it is essential that patients who are likely to benefit from a given therapy are identified at initial assessment in clinical trials. We hypothesize that a comprehensive assessment of PI3K/AKT and

**Figure A. Heat map Header:** White indicates missing data. **Subtype:** Orange serous, yellow mixed and pink endometrioid. **Stage:** High orange/green and low pink. **Genomic aberrations:** are indicated in red. **MSI:** High pink, low green and stable orange. **TCGA clusters:** PolE blue, MSI orange, CN low green, and CN high purple. **PPPA clusters:** demarcated by the red line, described in the text. **Heat map:** 404 endometrial cancer samples were analyzed by RPPA with 205 antibodies. Red increased and blue decreased protein levels. Targets of interest are indicated to the right. **B. Outcomes** Serous and serous-like and reactive clusters have poor outcomes. ER with either signaling high or low have the best outcomes.
RAS/RAF/MEK pathway aberrations, as well as additional pathways of interest, will provide potential markers for response to therapy with trametinib and GSK2141795.

**B. Laboratory Testing Procedures**

We will perform the high depth targeted sequencing platform (T200) to identify actionable DNA mutation in FFPE tumor samples targeting KRAS/PTEN/PI3K signal pathway members including PIK3CA, PIK3R1, PIK3R2, PTEN, AKT1, RAS/RAF and JAK/STAT genes, and will focus on somatic changes present in tumor cells. This T200 platform has been established in the Mills laboratory with a very low level of failure and high level of accuracy and sensitivity(13).

Formalin-fixed, paraffin-embedded (FFPE) slides (2-4 per samples) with 5µM thickness each will be cut from FFPE tumor samples, and will be assessed by pathologist for cellularity on Hematoxylin and eosin (HE) staining slides. Genomic DNA will be extracted from FFPE samples using QIAamp DNA FFPE Micro Kit (QIAGEN) following manufacture’s protocol, and then will be quantified by Qubit (Invitrogen) and quality will be accessed using Genomic DNA Tape for the 2200 Tapestation (Agilent).

DNA will be fragmented and libraries will be made by ligating indexed adaptors that allows for sample pooling. Hybridization with T200 probes will be performed. In brief, T200 platform is input on about 200 cancer related genes on the basis of mutation al data and the Catalogue of Somatic Mutations in Cancer (COSMIC)(14) and The Cancer Genome Atlas (TCGA). Captured DNA will be washed and amplified and proceeded to DNA sequencing, and then captured DNA will be sequenced in a 100-bp paired-end mode using HiSeq 2000(Illumina Inc) on a version 3 TruSeq paired end flowcell according to manufacturer’s instruction at a cluster density between 700-1000K clusters/mm2.

Sequencing will be performed on a HiSeq2000 for 2 x 100 paired end reads with a 7 nt read for indexes using Cycle Sequencing v3 reagents (Illumina). After sequencing samples are demultiplexed and the raw data will be submitted to data analysis for mutations and copy number variations identification. If mutations are observed, an aliquot of genomic DNA extracted from whole blood will be examined to determine if the mutation is somatic or not.

**C. References**


II. Immunohistochemical Expression of PTEN
A. Overview
Given the high proportion of PI3K/AKT and RAS/RAF/MEK pathway aberrations found in endometrial cancer, targeting these pathways holds great promise for improving outcomes for
this aggressive disease. Our group and others have found that the presence of mutations in the PI3K/AKT pathway incur sensitivity to the antitumor effects of PI3K pathway directed agents. In addition, the presence of KRAS mutations are dominant predictors of resistance to targeted therapies (erlotinib, cetuximab) in colorectal and lung cancers (10, 11). Emerging data in endometrial cancer and other solid tumors suggest that combination therapy with PI3K pathway and RAS/RAF pathway inhibitors may be necessary for improved outcomes (12). We hypothesize that a comprehensive assessment of PI3K/AKT and RAS/RAF/MEK pathway aberrations will predict response to therapy with the AKT inhibitor, GSK2141795, in combination with the MEK inhibitor TRAMETINIB.

The majority of current clinical trials of targeted therapy in gynecologic malignancies include all patients, regardless of molecular profile. In order to avoid incorrect classification of an agent as inactive, it is essential that patients who are likely to benefit from a given therapy are identified at initial assessment in clinical trials. The proposed trial will stratify subjects based on key molecular alterations that have the potential to predict response and resistance to agents targeting the PI3K/AKT and RAS/RAF/MEK pathways. The use of multiple platforms will allow analysis of interaction of biomarkers of importance.

B. Laboratory Testing Procedures
FFPE tumor will be used for PTEN IHC. We will perform IHC utilizing methods which have been published previously (13, 14).

Complete absence of staining in tumor cells in the presence of internal positive control (stromal cells, lymphocytes) will be interpreted as PTEN loss. Cases will be scored as PTEN positive (or retained) if all or a majority of the tumor shows positive staining. Cases with “patchy” PTEN staining will be interpreted as showing heterogeneous staining.

C. References