DF/HCC Protocol 13-334

A Single Arm, Single Stage Phase II Trial of GSK1120212 and GSK2141795 in Persistent or Recurrent Cervical Cancer

IND No.: 119567

Principal Investigator:

Ursula Matulonis, MD

Dana-Farber Cancer Institute
450 Brookline Avenue
Boston, MA 02215

Protocol Amendment 2
Date: July 11, 2017

Previous Protocol Version:
Original Protocol – August 23, 2013

SUMMARY OF CHANGES

DF/HCC Protocol # 13-334

Current Protocol Version Date: July 11, 2017

Previous Protocol Version Date: January 15, 2014

Section	Changes
Pages 1-2	Updates to participating sites and study team contact information.
Appendix C	Removal of Appendix C: DF/HCC Multi-Center Data and Safety Monitoring Plan. Removed because the trial never became a multi-center study.
Appendix G	OncoPanel information has been added to the protocol. APPENDIX G: Laboratory Correlative Studies <u>Mutational Analysis</u> ***OncoPanel*** **OncoPanel sequencing on archival specimens will be obtained from all patients where available. OncoPanel is a targeted next generation sequencing panel selected based on clinical actionability in cancer that is designed for the detection of single-nucleotide variants, insertions and deletions, copy number alterations, and structural variants. A validation study demonstrated that OncoPanel could successfully identify multiple types of genetic alterations, with a sensitivity of 98% for single-nucleotide variants, 84% for indels, 86% for copy number variants, and 74% for structural variants when compared to appropriate orthogonal detection methods, including single-gene assays, mass spectrometry-based genotyping, array comparative genomic hybridization, or fluorescence in situ hybridization (Garcia 2017). Where OncoPanel sequencing has already been performed on patient samples through DF/HCC protocol 11-104, we will plan to access these results to conserve primary patient samples for additional analyses.**
N/A	Administrative and editorial changes/updates throughout

PRINCIPAL INVESTIGATOR:
Ursula Matulonis, MD
Dana-Farber Cancer Institute
450 Brookline Ave, YC1421
Boston, MA 02215
Phone: 617-632-2334
Fax: 617-632-3479
Email: ursula_matulonis@dfci.harvard.edu

COORDINATING CENTER:
Dana-Farber Cancer Institute
450 Brookline Avenue
Boston, MA 02215

PARTICIPATING SITES:
Massachusetts General Hospital
55 Fruit Street
Boston, MA 02114

TRANSLATIONAL INVESTIGATOR:
Lewis Cantley, PhD
Cornell Weill Medical College
New York City, NY
Email: lewis_cantley@cornell.edu

STATISTICIAN:
William Barry, PhD
Dana-Farber Cancer Institute
11058 Center for Life Sciences, 11007
Boston, MA 02114
Phone: 617-632-5134
Email: bbarry@jimmy.harvard.edu

STUDY COORDINATOR:
Ariana Peralta
Dana-Farber Cancer Institute
450 Brookline Avenue, D117
Boston, MA 02215
Phone: 617-632-3743
Fax: 617-582-7921
Email: aperalta2@partners.org

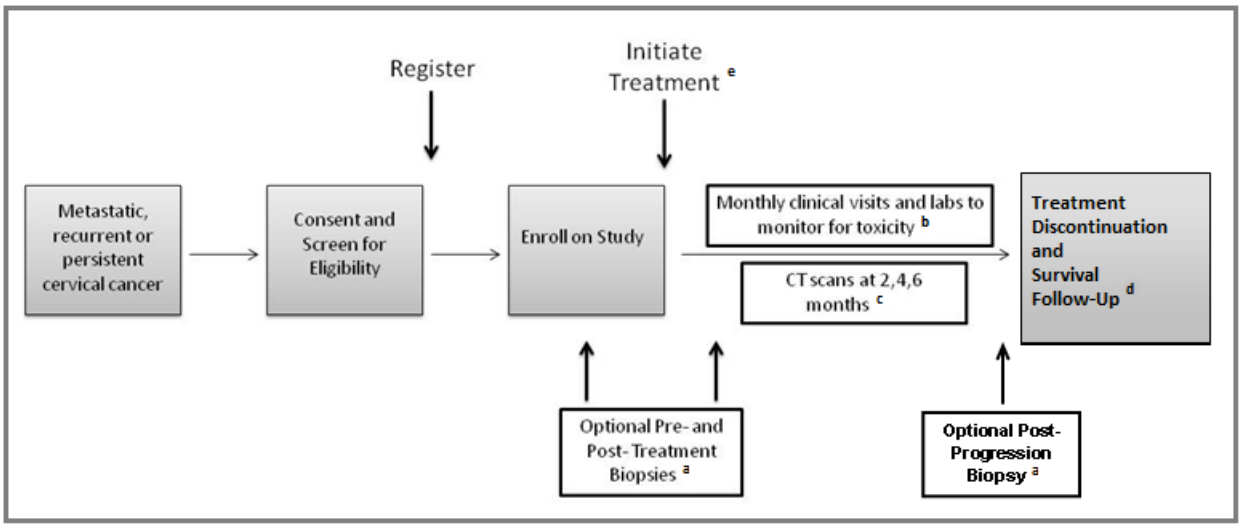
RESEARCH PROJECT MANAGER:
Jennifer Curtis
Dana-Farber Cancer Institute
450 Brookline Avenue, D117
Boston, MA 02215
Phone: 617-582-7183
Fax: 617-582-7921
Email: jdcurtis@partners.org

RESEARCH NURSE:
Christin Whalen, RN
Dana-Farber Cancer Institute
450 Brookline Ave, D117
Boston, MA 02215
Phone: 617-582-7738
Fax: 617-582-7921
Email: christin_whalen@dfci.harvard.edu

INVESTIGATIONAL AGENTS:
GSK1120212 (IND *#102,175*)
GSK2141795 (IND *#104,527*)

TABLE OF CONTENTS

SCHEMA



a: Pre- and post-treatment biopsies, as well as the post-progression biopsy, are *optional.* The pre-treatment biopsy will be performed prior to treatment. The post-treatment biopsy will be performed between 2-4 weeks after treatment initiation. The post-progression biopsy will be performed within 6 weeks of progression.

b: Participants will be monitored for toxicity as dictated by CTCAE v4.0.

c: From the CT results will be evaluated by RECIST 1.1 criteria. Scans will be performed every 2 cycles. Participants with progressive disease will discontinue the trial. Participants with stable disease, partial or complete responses will continue on study and as long as toxicities are acceptable.

d: Treatment will be discontinued as per Section 5.4, and patients will enter survival follow-up as per Section 5.5.

e: Treatment with GSK1120212 (trametinib) and GSK2141795 as per Section 5.

1. OBJECTIVES

1.1 Study Design

This is an open label, single-arm, single-stage, phase II multicenter trial.

1.2 Primary Objective

To assess the activity of GSK1120212 (trametinib) and GSK2141795 in combination in patients with recurrent or persistent cervical cancer. Activity will be ascertained by estimation of best objective tumor response per RECIST version 1.1.

1.3 Secondary Objectives

- To assess the duration of progression-free (PFS) and overall survival (OS) following initiation of therapy with GSK1120212 (trametinib) and GSK2141795
- To determine the nature and degree of toxicity of GSK1120212 (trametinib) and GSK2141795 as assessed by version 4.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) in this cohort of patients.
- To describe the mutation and co-mutation rates of genes in the PI3K and RAS-ERK signaling pathways in recurrent cervical cancer using high throughput targeted mutational analysis on participant tumor samples.
- To explore the association of mutational status with clinical benefit from GSK1120212 (trametinib) and GSK2141795.

2. BACKGROUND

2.1 Study Disease: Cervical Cancer

2.1.1 Epidemiology

In the United States, invasive cervical cancer will affect an estimated 12, 710 women this year with approximately 4290 resulting deaths [13]. While implementation of screening has greatly reduced the burden of this disease in the developed world, it remains a leading cause of cancer death globally [14]. Treatment options for persistent, recurrent or metastatic cervical cancer remain limited and prognosis is poor [15].

2.1.2 Treatment

From studies performed primarily by the Gynecology Oncology Group, pelvic radiation augmented with platinum based chemotherapy is first line therapy for bulky or advanced cervical cancer [16-19]. In the recurrent setting, cisplatin has emerged a favored agent for systemic treatment in combination with other cytotoxics with response rates around 25-40%

[20-24]. Sub-set analysis of these studies has demonstrated that patients with short intervals of disease control as well as those with disease that recurs within the irradiated pelvis have worse outcomes [25]. Two series within the GOG (127 and 227) have been developed to explore the chemotherapeutics and biologics for second line recurrence [26]. From over a dozen completed clinical studies in this population, bevacizumab has one of the higher levels of activity, resulting in a response rate of 11% and progression free survival rate of just 25% at 6 months [27]. There is a great need to identify more active agents in this population.

2.1.3 PI3K and RAS Signaling in Cervical Cancers

As compared to other women's cancers, there are limited comprehensive data on the rates of RAS-ERK and PI3K pathway alterations. PIK3CA and PTEN mutation have been characterized in one published study at a frequency of approximately 10% [9, 28]. However, molecular testing of phase I study participants from MD Anderson identified a PIK3CA mutation rate of 36% in squamous cervical cancer [29, 30]. At the Dana-Farber/Harvard Cancer Center (DF/HCC), patients' tumors are frequently genotyped for oncogenic mutations and our preliminary data support this higher rate of PIK3CA mutation [31]. K-RAS and H-RAS mutations have also each been reported at 10% and 22% [9, 29, 32]. In our own study at DFCI, in a group of 80 patients with both squamous cell or adenocarcinoma of the cervix, validated mutations were detected in 60.0% (48/80) of tumors examined. The highest mutation rates were *PIK3CA* (31.3%), *KRAS* (8.8%), and *EGFR* (3.8%). *PIK3CA* mutations were found at similar rates in both adenocarcinoma and squamous cell carcinomas (25.0% vs. 37.5%, p=0.33). In contrast, *K-RAS* mutations were identified only in adenocarcinoma (17.5% vs. 0%, p=0.01), and *EGFR* mutations were detected exclusively in patients with squamous cell carcinoma (0% vs. 7.5%). We did not see any co-mutations of both KRAS and PIK3CA in any samples [31 and submitted manuscript].

Both the RAS- ERK and PI3K pathways have been implicated in resistance to radiation, suggesting utility in previously irradiated patients. PI3K pathway activation, as measured by phosphorylated AKT has been shown to be associated with local recurrence after radiation [33]. Additionally, cervical patients with K-RAS mutations had poorer outcomes after treatment with radiation therapy [32].

PI3K and MEK inhibitors in Cervical Cancer

Multiple therapeutics that target the PI3K pathway are in clinical development including PI3K inhibitors, PI3K dual inhibitors (which target both PI3K and mTOR), AKT inhibitors, and mTOR inhibitors [34]. A recent report from MD Anderson evaluated clinical response to this large class of drugs in phase I trial in patients whose tumors had PIK3CA mutation or PTEN loss. Several patients with cervical cancer were among those to respond to drugs targeted to the PI3K pathway in these trials [30]. However, these responses were not durable suggesting the need for combination therapies. To date, MEK inhibition has not been explored for treatment of cervical cancer.

2.2 Investigational Agents: GSK1120212 and GSK2141795

2.2.1 GSK1120212 (trametinib)

Please see GSK1120212 Investigator's Brochure for additional information on this compound (1).

Nonclinical Pharmacology

GSK1120212 is a reversible, highly selective, allosteric inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2. MEK proteins are critical components of the extracellular signal-related kinase (ERK) pathway which is commonly hyperactivated in tumor cells. Oncogenic mutations in both BRAF and RAS signal through MEK1 and MEK2. GSK1120212 is non-competitive towards ATP and inhibits activation of MEK by RAF kinases as well as MEK kinase activity. The specificity of GSK1120212 to MEK1 and MEK2 was confirmed against a panel of 183 kinases, including MEK5, the closest kinase homolog to MEK1 and MEK2, and no significant inhibitory activity was measured [1]. In vitro, 80% of cell lines carrying activating mutations of B-Raf and 72% of Ras mutant cancer cell lines were sensitive to GSK1120212 in cell proliferation assays, and a majority (83%) of hematopoietic cancers from acute or chronic myeloid leukemia (AML or CML, respectively) origins were also very sensitive.

Anti-tumor Activity *in vitro*

Cancer cells expressing high constitutive levels of activated ERK (pERK) tend to be more sensitive to GSK1120212 than those with lower levels of pERK, suggesting that tumors with B-RAF or RAS mutations and/or high levels of pERK may respond to GSK1120212 treatment. In all cell lines, pERK was strongly inhibited following treatment with GSK1120212 and was independent of their proliferative response, suggesting that pERK inhibition is necessary but not sufficient to inhibit cell proliferation. In cell lines that were sensitive to the anti-proliferative activity of GSK1120212, the response was associated with arrest in G1 phase of the cell cycle, accumulation of p27, and reduction of cyclin D1 and phospho-retinoblastoma protein. Induction of apoptosis was demonstrated in some cell lines. Inhibition of pERK and inhibition of cancer cell proliferation were fully reversible following compound removal, suggesting that sustained exposure to GSK1120212, or potential combination with other drugs, may be required for full activity.

When GSK1120212 was combined with standard of care drugs against human cancer cell lines in vitro, an additive effect was observed for pancreatic cancer with gemcitabine or erlotinib and for colon cancer with 5-FU or irinotecan. The combination of GSK1120212 with rapamycin, ara-C, bexarotene or sorafanib produced an additive effect against most AML cell lines tested. In addition, combination of GSK1120212 with an investigational phosphoinositide 3-kinase (PI3K) inhibitor, as well as with a Centromer Protein-E (CENP-E) inhibitor, was synergistic on inhibition of cell growth in various cancer

(pancreas, colon, lung) cells. Additionally, the combination of GSK1120212 and a CENP-E inhibitor increased caspase activity, indicating enhanced apoptosis in colon cancer cell lines.
While many proliferating human cells are sensitive to GSK1120212 in vitro, GSK1120212 did not affect non-dividing normal cells and did not completely inhibit bone marrow progenitor cells at concentrations demonstrating anti-proliferative activity on very sensitive cancer cell lines.

Anti-tumor Activity *in vivo*

GSK1120212 was orally bioavailable in mice, and doses as low as 1 mg/kg reached blood concentrations that caused sustained reductions of pERK, an accumulation of p27, and a decrease of Ki67 in tumor xenografts; brain exposure levels were ~10% of those in blood, and no significant pERK inhibition was measured in brain tissue. In mice, exposure to GSK1120212 produced dose- and schedule-dependent anti-tumor responses correlating with blood levels. Typically, B-RAF--mutant xenografts responded with tumor regression while K-RAS-mutant xenografts responded with tumor growth inhibition. In vivo combination studies testing GSK1120212 together with various other anticancer drugs showed good potential for synergistic effects.

Safety Pharmacology

In a rat neurobehavioral screen, following a single oral dose of GSK1120212 at 650 mg/m2 to male rats, diarrhea, prone position, blepharoptosis, piloerection, reduced spontaneous locomotion and mydriasis were observed between 2 and 24 hours post dose. In a respiratory safety pharmacology study in rats, an oral dose of 1 mg/m2 produced a mild, transient decrease in body temperature (up to 0.8°C) at 1 hour post dose. There were no other effects on ventilatory function, airway resistance or body temperature. GSK1120212 inhibited hERG channel repolarization in HEK293 with an IC50 of1.54μM (950 ng/mL). In a rabbit left ventricular wedge assay, GSK1120212 had no significant effect on QT interval at concentrations up to 30 μM (18450 ng/mL; limit of solubility). However, significant decreases in isometric contractile force occurred at concentrations of 10 (6150 ng/mL) and 30 μM. GSK1120212 also decreased the Tp-e interval at a concentration of 30 μM. A single intravenous infusion of GSK1120212 in dogs at 20 mg/m2 over 10 minutes (Cmax of 2.5 μM or 1500 ng/mL) produced no changes in electrocardiogram (ECG) parameters, blood pressure or heart rate during the 30 minute measurement period. In addition, single oral doses up to 1.5 mg/m2 in dogs produced no changes in arterial blood pressure, heart rate, body temperature or ECG intervals, including QTc. While GSK1120212 affected cardiac electrophysiology in vitro, no effects were observed in vivo at doses that were maximally tolerated in dogs. This difference in responses is likely related to the very low Cmax (~10 ng/mL total drug) at tolerated doses in dogs and the high protein binding (97% in dogs) of GSK1120212. The concentrations at which effects were seen in these in vitro studies are significantly higher than the free fraction observed in nonclinical toxicology studies or the clinical dose (2 mg). These results suggest a low risk for cardiovascular effects in the clinic.

Pharmacokinetics and Product Metabolism in Animals

GSK1120212 exhibited low plasma clearance among nonclinical species (mouse, rat, dog and monkey) with varied but generally long half-lives. Oral bioavailability ranged between 42% and 100%. Since GSK1120212 is a low solubility, high permeability molecule, its absorption is likely limited by solubility and dissolution. Plasma protein binding was high in nonclinical species and human (>95%) and blood cell association was low. Consistent with high permeability, GSK1120212 had moderate to high volume of distribution among the nonclinical species studied and drug related material (DRM) was widely distributed into rat tissues. The low concentration of DRM observed in the brain up to 8 hours post dose was observed. Although studies showed protracted elimination of DRM (consistent with high volume and long half-life), DRM in tissues was not detectable by 35 days post dose.

In rats and dogs after repeat oral dosing up to 13 weeks, systemic exposure increased approximately dose-proportionally at higher doses or when steady state was reached at Week 3. Upon repeat dosing, increases in systemic exposure after Day 1 were observed up to Week 3; however, between Weeks 4 and 13, there was no marked increase in systemic exposure for either pre-clinical species. A tendency for higher exposure in females than in males was observed in some studies in both rats and dogs. No apparent human-specific metabolite was observed in the in vitro cross-species [14C] GSK1120212 metabolism study. [14C]GSK1120212 was also found to metabolize predominantly via a non-cytochrome P450 (CYP) mediated deacetylation with secondary oxidation or glucuronidation biotransformation pathways. CYP3A4 was implicated in the in-vitro formation of M7, a metabolite mediated by both non-CYP and CYP pathways. The relative contribution of CYP3A4 to the total metabolic clearance of GSK1120212 in human in vivo is not currently understood and, therefore, the possibility of a metabolic drug interaction cannot be eliminated. Elimination of DRM in rat and dog after oral administration occurred predominantly via the feces (>60% of dose), with urinary excretion (<7% of dose) representing a minor route.

Although GSK1120212 was found to be an in vitro inhibitor of CYP2C8, CYP2C9 and 2C19, inducer of CYP3A4 and inhibitor of the transporters (OATP1B1, OATP1B3, Pgp and BCRP), the low clinical GSK1120212 systemic exposure relative to these in vitro inhibition values suggests a low potential for GSK1120212 as a perpetrator in clinical drug-drug interaction (DDI). However, drugs with a narrow therapeutic index that are substrates of CYP2C8, the CYP with the lowest inhibition IC50, should be used with caution. There was no evidence of time-dependent inhibition with any of the CYP enzymes investigated. In addition, GSK1120212 was not found to be an in vitro substrate of the transporters Pgp and human breast cancer resistance protein (BCRP).

Toxicology

Systemic toxicity of GSK1120212 has been evaluated following oral dosing in rats and dogs for up to 13 weeks. In the most sensitive nonclinical species, rat, the principal adverse effects seen in oral toxicity studies of up to 13 weeks with daily dosing were skin

and stomach erosions, skin ulcerations, which were secondary to reduced proliferation, altered phosphate homeostasis that resulted in soft tissue mineralization, hepatocellular necrosis, bone marrow degeneration/necrosis and ovarian perturbations. The skin and stomach findings and phosphatemia demonstrated reversibility with 4 weeks of recovery. The maximum tolerated dose (MTD) in rats in the definitive 13 week study with daily dosing was 0.25 mg/m2/day (AUC0-t of 126 ng.h/mL, end of study). Reversible acute effects (diarrhea, decreased body weight gain, prone position, blepharoptosis, piloerection, reduced spontaneous locomotion and mydriasis) were observed following a single high dose of 650 mg/m2 to rats. In dogs, the principal dose-limiting toxicities seen oral toxicity studies of up to 13 weeks with daily dosing were related to gastrointestinal and hematopoietic perturbations. Inflammatory responses to gastrointestinal erosions were observed in dogs and were reversible following a recovery period. In the definitive 13 week daily oral dosing study in dogs, the No Observed Adverse Effect Level (NOAEL) was 0.45 mg/m2/day (AUC0-t of 139 ng.h/mL, end of study). Principal adverse effects were consistent with inhibition of cell proliferation and were monitorable and generally reversible. GSK1120212 was negative in both in vitro and in vivo genotoxicity assays.

Effects in Humans

The effect of GSK1120212 in subjects with a variety of refractory cancers is currently under evaluation in 14 clinical studies which are ongoing as of the IB cut-off date. GSK1120212 has been administered as monotherapy in 6 of these studies, and as combination therapy in the other 8 studies. As of 14 April 2011, 657 subjects with cancer have received at least one dose of GSK1120212 in the 13 ongoing Phase I/II/III clinical studies. This number does not include subjects from 2 randomized trials (MEK113487and MEK114267), from the blinded part of the combination trial (BRF113220), and from another combination trial (P3K113794). There are no completed clinical trials to date. Preliminary GSK1120212 pharmacokinetics were determined after single and repeat dose oral administration of GSK1120212 tablets in subjects with solid tumors. GSK1120212 is absorbed rapidly with median Tmax generally occurring within 1-3 hours after oral administration of GSK1120212 under fasting conditions. Following repeat-dosing the mean area under the curve (AUC0-τ) and maximum concentrations (Cmax) increased in an approximately dose proportional manner.

GSK1120212 accumulates with repeat dosing with a mean effective half life of approximately 5 days. Based on the adverse events (AEs) observed in the dose escalation phase of the first time in-human (FTIH) study MEK111054, the maximum tolerated dose was established at 3.0 mg once daily (QD), and the recommended Phase II dose (RP2D) of GSK1120212 was identified as 2.0 mg QD.

In the 3 monotherapy trials of GSK1120212 for which data are available (MEK111054, MEK111759, and MEK113583), 99% to 100% of all 356 subjects in any dose group experienced at least one AE, and 26% to 68% of all 356 subjects in any dose group experienced at least one SAE. Of the 356 subjects, 4% to 23% permanently discontinued study treatment due to AEs.

Of the 241 subjects in the 2.0 mg dose group in the 3 monotherapy trials (MEK111054, MEK111759, and MEK113583), 99% to 100% of subjects experienced at least one AE, and 26% to 71% of all subjects experienced SAEs. Of the 241 subjects, 4% to 23% permanently discontinued study treatment due to AEs.

In the 2.0 mg dose group across all 3 monotherapy trials, the most common AEs experienced were rash, diarrhea, nausea, fatigue, vomiting, anemia, peripheral edema, abdominal pain, constipation, dermatitis acneiform, decreased appetite, pruritus, dyspnea, pyrexia, pneumonia, febrile neutropenia, AST increased, ALT increased, and dry skin. In the 5 combination therapy trials of GSK1120212 for which data are available (MEK112110, MEK112111, MEK113486, open-label parts of BRF113220, andTAC113886), 89% to 100% of all 296 subjects in any dose group experienced at least one AE, and 21% to 45% of all 388 subjects in any dose group experienced at least one SAE. Of these 296 subjects, 4% to 10% permanently discontinued study treatment due to AEs.

In the 5 combination trials for which data are available, the most common AEs experienced were nausea, fatigue, diarrhea, vomiting, decreased appetite, pyrexia, rash, constipation, neutropenia, dry skin, dermatitis acneiform, anemia, mucosal inflammation, stomatitis, exfoliative rash, thrombocytopenia, peripheral edema, abdominal pain, cough, chills, and AST increased.

2.2.2 GSK2141795

Nonclinical Pharmacology

GSK2141795 is a novel member of the N-alkyl pyrazole class of orally available kinase inhibitors and has been shown to be a potent, pan AKT (a serine/threonine protein kinase with 3 isforms, AKT1, AKT2 and AKT3) inhibitor, with potency (Ki*) values for human AKT1, 2 and 3 kinases being 0.006, 1.4 and 1.5 nM, resp. GSK2141795 exhibited a time-dependent inhibition of AKT with a dissociation half-life of ≤ 20 mins. In vitro, GSK caused a concentration and time dependent reduction in phosphorylation of multiple proteins downstream of AKT such as glycogen synthase kinase 3 beta, an insulin-regulated inhibitor of the mammalian target of rapamycin complex 1 (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 cells from multiple histologies including breast, hematological, colon, ovarian and prostate (EC50 < 1 microM). 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.

In vivo studies conducted in immuno-compromised mice bearing human tumor cell line xenografts showed GSK2141795 can inhibit multiple AKT substrates

downstream of AKT in a dose- and time-dependent manner. The highest tolerated repeat dose in mice (30 mg/kg) caused a small elevation in blood glucose levels (~300 mg/dL). In mice, doses ≤10 mg/kg did not alter blood glucose levels, and repeat administration of GSK2141795 at 30 mg/kg elevated blood glucose levels without any evidence of a cumulative effect. Elevation in blood glucose was noted between 1 and 8 hours post dose with GSK2141795 and correlated with the pharmacodynamic effect of maximal inhibition of phospho-PRAS40. Additionally, studies have suggested that a combination of fasting and low carbohydrate diet in mice can minimize AKT inhibitor-induced glucose elevation. Further, co-administration of metformin with GSK2141795 appeared to reduce the magnitude of GSK2141795-induced glucose elevation in mice. Repeat oral administration of GSK2141795 for 3 weeks inhibited the growth of various tumor xenografts, including BT474 (breast), HCC1954 (breast), and SKOV3 (ovarian) in mice. Daily dosing with GSK2141795 was more efficacious at inhibiting the growth of tumor xenografts than less frequent dosing, suggesting the need for repeat administration for maximal anti-tumor effect.

GSK2141795 was further studied, in vitro and in vivo, in combination with other anti-cancer agents. In vitro, GSK2141795 was combined in a 3-day cell proliferation study with ofatumumab (an anti-CD20 antibody) against a panel of 10 lymphoma cell lines. In 3 lymphoma cell lines that were also sensitive to ofatumumab alone, the response after treatment with both GSK2141795 and ofatumumab was additive when compared to treatment of either alone. Similarly, GSK2141795 was combined in a 3-day cell proliferation study with GSK1120212 (a mitogen-activated protein kinase/ERK kinase [MEK] inhibitor) against a panel of 26 colon, 15 lung, and 6 pancreatic cancer cell lines. GSK2141795 and GSK1120212 were synergistic in cancer cell lines from colon (19 of 26), lung (4 of 15), and pancreatic (2 of 6).
In vivo, after daily oral combination treatment of GSK2141795 and lapatinib (a dual inhibitor of epidermal growth factor receptor [ErbB-1] and human epidermal growth factor receptor 2 [ErbB-2] tyrosine kinases) to mice, the anti-tumor effect on ErbB-2 overexpressing BT474 breast tumor xenografts (lapatinib sensitive) was additive, but the effect on non-ErbB-2 overexpressing MDA-MB-231 breast tumor xenografts (not very sensitive to lapatinib) was not improved over either agent alone. Similarly, no additive effect was seen with A2780 and SKOV-3 ovarian tumor xenografts after GSK2141795 was administered in combination with pazopanib, an angiogenesis inhibitor. Combination of GSK2141795 with pazopanib or GSK1363089 (a dual inhibitor of mesenchymal epithelial transition factor [MET] and vascular endothelial growth factor receptor-2 [VEGFR-2]) showed no advantage over GSK2141795 alone in a model of hepatocellular carcinoma using primary human tumor xenografts (LIX014).

Combination treatment of GSK2141795 and GSK1120212 (MEK inhibitor) resulted in an additive anti-tumor effect in HPAC pancreatic xenograft; however, there was no additive effect in Capan-2 pancreatic tumor xenograft.

GSK2141795 did not produce acute neurobehavioral or respiratory effects in rats at doses up to 20 mg/kg. In a dog cardiovascular study, there was a mild to moderate,

transient increase in mean arterial blood pressure (MAP; up to 20 mmHg) between 3 and 16 hours following a single oral 5 mg/kg dose (Cmax = 0.41 g/mL) of GSK2141795. There was a concurrent increase in pulse pressure (up to 13 mmHg), decrease in the QA interval (the time between the Q wave of the ECG and A point of the blood pressure waveform); up to 11 msec) and transient decrease in heart rate (up to 20 bpm) between 3 and 10 hours after treatment, likely reflecting a compensatory baroreflex response to the increased blood pressure. While GSK2141795 was an inhibitor of hERG repolarization (IC_{50} of 3.1 M; 1.36 g/mL) and inhibited cardiac sodium and calcium channel repolarization (IC_{50} of 7.2 M and 8.0 M [3.1 and 3.44 g/mL], respectively), there were no electrocardiogram (ECG) effects or meaningful prolongation of the QTc interval in an in vitro rabbit wedge assay. There were also no ECG effects or meaningful QTc prolongation in dogs in vivo. Given the high protein binding (>98% in dog and human plasma), the low Cmax concentrations at tolerated doses in animals and the absence of effects on the QT interval in dogs, there is a low risk for QTc prolongation in humans.

Pharmacokinetics and Product Metabolism in Animals

Nonclinical pharmacokinetic studies with GSK2141795 were conducted in the mouse, rat, dog, and monkey. In these species, oral bioavailability of GSK2141795 was moderate to high (≥40%), blood clearance was low to moderate (20% to 50% of liver blood flow) and volume of distribution was high (>6 times total body water). In toxicity studies in rats and dogs, systemic exposure generally increased dose-proportionally, with no consistent marked gender differences.

In vitro, GSK2141795 was moderately to highly bound (93% to >95%) to plasma proteins in nonclinical species and human, and had minimal to moderate association (0.99 to 1.64) with blood cells. GSK2141795 was a human P-glycoprotein (Pgp) and mouse breast cancer resistance protein (Bcrp 1) substrate and did not inhibit Pgp-mediated digoxin transport. GSK2141795 had moderate passive permeability (60 nm/sec) and low to moderate absorptive membrane permeabilities (3.0 to 11 nm/sec). GSK2141795 inhibited human organic anion transporting polypeptide (OATP) 1B1(IC50 of 16 μM) and 1B3 (IC50 of 21 μM) and BCRP-mediated transport of cimetidine (up to 50% of control at 3 μM). In a tissue distribution study following single oral administration of [14C] GSK2141795, consistent with its high volume of distribution, radioactivity was widely distributed into tissues, and most tissue concentrations were higher than those observed in blood. Concentrations of radioactivity generally declined over time, and by 7 days post dose, the levels of radioactivity were below the limit of quantification (BLQ) in most tissues. Radioactivity was still quantifiable at 35 days post dose in the uveal tract, suggesting the potential for the selective association of drug-related material with melanin.

In rats and dogs following single oral administration of [14C] GSK21417, the major route of elimination of drug-related material was via the feces, while urinary excretion constituted a minor route in both species.

In vitro intrinsic clearance for GSK2141795 was low in hepatocytes and microsomes from the mouse, rat, dog, monkey, and human. In rat and human hepatocytes, the metabolism of GSK2141795 occurred by mono-oxygenation, glucuronidation, oxidative deamination, and N-demethylation; there were no apparent human-specific metabolites, and cytochrome P450 (CYP) 3A4 was the primary enzyme responsible for the oxidative metabolism. No stereo-conversion to the R-enantiomer was observed in vitro, and no rearrangement to an acyl migrated isomer of parent was observed either in vitro or following oral administration to mice. In vitro, GSK2141795 demonstrated the potential for oxidative bioactivation. In vitro study results suggest that GSK2141795 has the potential to be a perpetrator in drug-drug interactions with substrates of CYP enzymes (notably CYP2C8 and CYP3A4) or the BCRP transporter, and to be a victim of drug-drug interactions upon co-administration with CYP3A4, Pgp, and BCRP inhibitors or potent inducers.

Toxicology

Systemic toxicity of GSK2141795 has been evaluated following oral dosing in rats and dogs for up to 4 weeks. The principal dose-limiting toxicities seen involved the gastrointestinal (GI) and hematopoietic systems. In rats, morbidity with marked clinical effects (severe body weight loss) was seen acutely following a single dose of 100 mg/kg or as early as 4 days of repeat daily dosing at .20 mg/kg/day. In dogs, morbidity was seen after a single dose of 150 mg/kg or repeat doses of .5 mg/kg/day for up to 7 days. Emesis, often frequent, frothy, mucoid, and blood tinged, together with loose watery feces, dominated the clinical picture. At lower doses administered for up to 4 weeks, GI effects and clinical signs were less severe but did contribute to a declining clinical condition. Microscopic lesions in the stomach, large intestine, and oral cavity were characterized by focal and multifocal erosions and ulcers with inflammation, hemorrhage, and submucosal edema. These findings likely resulted from a direct irritant effect at high doses along with a pharmacodynamic effect on the intestinal mucosa.

Hematopoietic toxicity manifested in rats as bone marrow hypocellularity with an accompanying lymphopenia. The GI and hematopoietic effects had reversed, or were improving, by the end of the 2 week recovery period. In one dog given a non-tolerated dose, a vascular lesion in the lung, consisting of focal medial degeneration and necrosis, was observed. Localized inflammation and reactive fibrosis of the splenic capsule was seen in rats. The relationship to treatment of either of these findings is unknown. Consistent with GSK2141795 inhibition of the AKT signaling pathway, mild to marked dose-dependent increases in plasma insulin were observed in rats and dogs. The insulin levels became persistently elevated following repeat dosing and reversed following cessation of treatment. There were no consistent changes in plasma glucose levels. Additional effects consistent with the pharmacologic action of GSK2141795 included decreased lymphoid cellularity in the thymus, peripheral lymph nodes and spleen with decreased circulating lymphocytes, particularly in rats. Lymph node involvement was more widespread in dogs where it persisted through the recovery period.

The maximum tolerated dose (MTD) of GSK2141795 in rats following daily dosing for 4 weeks was 10 mg/kg/day (AUC_{0-t} of 9.27 μg.h/mL and C_{max} of 0.644 μg/mL). The MTD in dogs was 2 mg/kg/day (AUC_{0-t} of 4.50 μg.h/mL and C_{max} of 0.298 μg/mL). A no observed adverse effect level (NOAEL) was not determined in rats or dogs, although effects at the low doses in these studies were generally mild, seen in individual animals and reversible. In addition, GSK2141795 is not likely to present a genotoxic hazard to humans.

Effects and pharmacokinetics in Humans

There are 3 clinical 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. Enrollment is complete as the primary objective was met and 2 subjects remain on study as of the data cut-off date. PCS113124 is an open-label, multiple-dose, dose-escalation study designed to explore the potential dose response relationship between the pharmacokinetics of GSK2141795 and [^{18}F] FDG PET pharmacodynamic markers of glucose metabolism in tumor tissue. The study enrolled a total of 12 subjects in order to meet the study's primary objective without necessitating enrolment of the estimated maximum number of subjects indicated in the protocol which allowed for replacement of any non-evaluable subjects. PCS113124 is clinically complete and the clinical study report is in progress. TAC113886 is an ongoing dose-escalation, open-label study to determine the recommended Phase II dose and regimen for the combination of the orally administered MEK inhibitor GSK1120212 and the orally administered AKT kinase inhibitor GSK2141795.

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 exposures 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_{max}) across doses was 3 hours and ranged from 0 to 4 hours. The mean value for the effective half-life of elimination ($t_{½}$, eff) across subjects was 3.0 days and ranged from approximately 1.3 to 5.5 days.

As of the safety cut-off date of 06-May-2012, a total of 151 subjects had enrolled and were administered at least 1 dose of GSK2141795 in these 3 studies combined. The most common adverse events (AEs) reported were primarily GI and metabolism and

nutritional disorders, (including nausea, vomiting, and diarrhea) and metabolism and nutritional disorders (primarily hypoglycemia and hyperglycemia). Dose limiting toxicities for the monotherapy are primarily related to glucose metabolism (hypoglycemia and hyperglycemia) and also include rash and mucositis. When administered in combination with the MEK inhibitor GSK1120212 (trametinib), the most common AEs are similar as in the case of GSK2141795 monotherapy, however the frequency and severity are increased. In particular, GI and dermatological toxicities are the most frequent overall and the most frequent serious adverse events in TAC113866 were reported in the GI disorders (e.g., nausea, vomiting, diarrhea, stomatitis) and Investigations system organ class (SOC). Preliminary responses have been seen for the combination of GSK2141795 and GSK1120212 (e.g., in highly pretreated triple negative breast cancer, endometrial cancer, ocular melanoma and a KRAS-mutant cancer of unknown primary origin). However, at this early stage in development, an assessment of clinical efficacy is premature. The effect of GSK2141795 in subjects with a variety of refractory cancers is currently under evaluation in 3 GSK-sponsored clinical studies as of 06 May 2012. In addition to this study, which explores GSK2141795 administered in combination with GSK1120212, two other studies administer GSK2141795 as monotherapy. As of the cut-off date, a total of 151 subjects with cancer have received at least one dose of GSK2141795.

The investigator should refer to the GSK2141795 Clinical Investigator's Brochure for detailed information regarding ongoing clinical studies, pharmacokinetics, as well as observed safety and efficacy findings.

Maximum Tolerated Dose (MTD) and Recommended Phase 2 Dose (RP2D) of Single Agent GSK2141795

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.

2.2.3 Data on Preclinical Combination and Preliminary Clinical Safety Data from TAC113886, Phase I of combined GSK1120212 with GSK2141795

Pre-clinical combination studies were performed *in vitro* on colon (n=25), pancreas (n=6), and lung (n=15) cell lines. A fixed ratio of GSK1120212 (0.25 μM) to GSK2141795 (10 μM) with 3-fold serial dilutions was used in a 3-day proliferation assay. The combination effect was determined by excess over highest single agent (EOHSA), BLISS, and Combination Index (CI) (<1). Results indicated synergy in 14 colon, 7 lung, and 2 pancreas cell lines; modest synergy in 7 each colon and lung, and 2 pancreas cell lines; additive in 3 colon, 1 lung, and 2 pancreas cell lines; and none in one colon cell line. Synergy was seen in one colon and one lung cell line at concentrations greater and equal to 0.003 μM (1.9 ng/mL) GSK1120212 and 0.124 μM (53 ng/mL) GSK2141795. Human steady-state plasma trough concentrations, not correcting for protein binding, similar to the *in vitro* values would be obtained at doses of 0.5 mg (GSK1120212) and 20 mg (GSK2141795). Different values were required for other tumor types.

Clinical Experience with the Combination of Trametinib and GSK2141795

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 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.

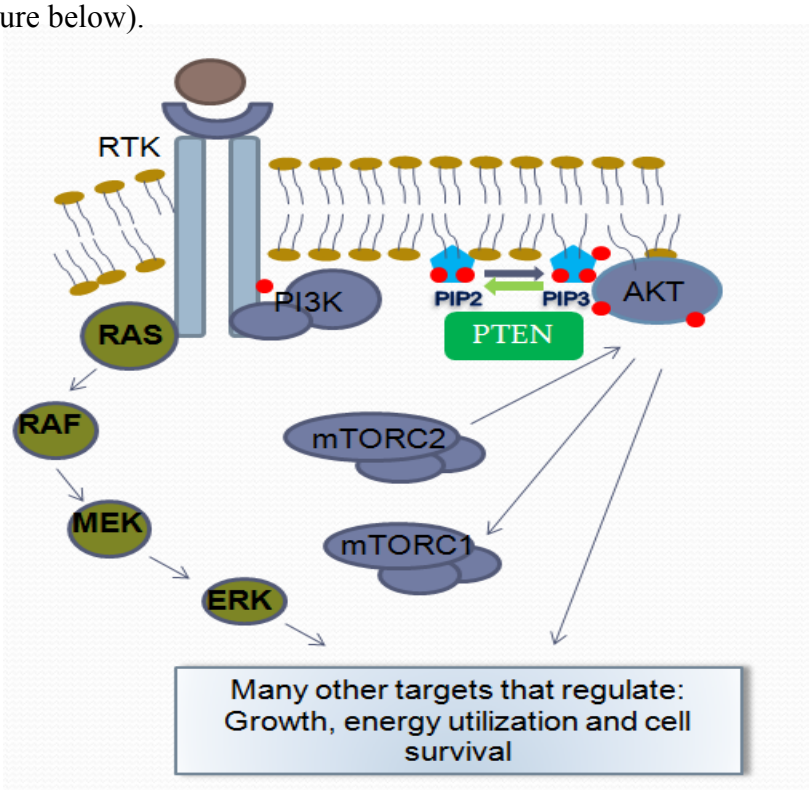
Rationale for the Selection of a Continuous Dosing Schedule

Combination studies were performed *in vitro* on colon (n=25), pancreas (n=6), and lung (n=15) cell lines. A fixed ratio of GSK1120212 (0.25 μM) to GSK2141795 (10 μM) with 3-fold serial dilutions was used in a 3-day proliferation assay. The combination effect was determined by excess over highest single agent (EOHSA), BLISS, and Combination Index (Cl) (<1). Results indicated synergy in 14 colon, 7 lung, and 2 pancreas cell lines; modest synergy in 7 each colon and lung, and 2 pancreas cell lines; additive in 3 colon, 1 lung, and 2 pancreas cell lines; and none in one colon cell line. Synergy was seen in one colon and one lung cell line at concentrations greater and equal to 0.003 μM (1.9 ng/mL) GSK1120212 and 0.124 μM (53 ng/mL) GSK2141795. Human steady-state plasma trough concentrations, not correcting for protein binding, similar to the *in vitro* values would be obtained at doses of 0.5 mg (GSK1120212) and 20 mg (GSK2141795). Different values were required for other tumor types.

2.2.4 AKT Inhibitors Dosed in Combination with MEK Inhibitors: Rationale for Treatment of Cervical Cancer

PI3K and RAS-ERK Signaling

Receptor Tyrosine Kinases (RTK) regulate cell growth, proliferation, and differentiation through downstream signals, including the PI3K and the RAS-RAF-MEK-ERK pathways [4] (see figure below).



PI3K enzymes are activated transfer phosphate groups to the inositol ring of phosphatidylinositol to produce the signaling molecule phosphatidylinositol 3,4,5tri-phosphate (PIP3)[5]. Alterations in the PI3K pathway are important in both the development and maintenance of cancer [6]. There are many underlying mechanisms for PI3K pathway activation in cancer, including receptor tyrosine kinase activation or amplification; mutation, deletion, or silencing of negative regulators of the PI3K pathway (such as PTEN) and activation or amplification of downstream kinase mediators [6]. RAS proteins are small GTPases and upon stimulation of an RTK initiates protein kinase cascade through RAF, MEK, and ERK protein kinases [7]. RAS proteins also interact with and signal through PI3K [8]. Specific oncogenic mutations in RAS (K-RAS, N-RAS and H-RAS) as well B-RAF are common some specific solid tumors [9]**.** Importantly, there is mounting evidence that the PI3K and RAS-ERK pathways have some redundant functions, that there are multiple negative feedback loops between theses pathways and that these interactions may be important for both primary and secondary resistance to inhibitors of either of these pathways in isolation [9].

Rationale for Dual Inhibition of PI3K and RAS- ERK Pathways

Pre-clinical and translational studies support the use of inhibitors of PI3kinase pathway and MEK inhibitors together given the redundancy of the pathways and negative feedback loops. Mouse models of K-RAS driven tumors do not response to either PI3K or MEK inhibition alone, but respond to the combination [10]. Interestingly the different isoforms of RAS (H-RAS, N-RAS) can have differential signaling through PI3K or RAF, suggesting the need for both inhibitors to cease all downstream signaling [8]. PI3K inhibition in patients can result in the activation of several RKTs that can signal through RAS-ERK. In a clinical study of breast cancer, ERK was activated after two weeks of treatment with a rapalog, RAD001 [11]. These data have resulted in the exploration of combination of PI3K and MEK inhibitors in patients. Importantly, Phase I studies of PI3K and MEK inhibitors in combination have shown activity in patients with gynecologic malignancies [12].

PI3K/AKT pathway interacts extensively with the RAF/MEK/ERK pathway. The PI3K/AKT pathway also influences the response of K-RAS mutant cancers to MEK inhibitors, as evidenced by the observation that B-RAF mutant cancers are highly sensitive to MEK inhibition whereas RAS mutant cancers have varied responses. Activating PIK3CA mutations and loss of PTEN function, both of which can lead to activation of AKT signaling, lead to resistance to MEK inhibitors. In tumors with coexisting KRAS and PI3KCA mutations, down-regulation of PI3KCA resensitizes tumors to MEK pathway inhibition. In addition, dual inhibition of the PI3K/AKT and RAF/MEK/ERK pathways also seems to be required for complete inhibition of downstream mTOR effector pathway.

2.3 Rationale for This Study

1. Pre-clinical and translational studies support the use of PI3K/AKT and MEK inhibitors together given the redundancy of the pathways and negative feedback loops. Mouse models of K-RAS driven tumors do not response to either PI3K or MEK inhibition alone, but respond to the combination [10]. Interestingly the different isoforms of RAS (H-RAS, N-RAS) can have differential signaling through PI3K or RAF, suggesting the need for both inhibitors to cease all downstream signaling [8]. PI3K pathway inhibition in patients can result in the activation of several RKTs that can signal through RAS-ERK.

2. Mutations in both RAS and PI3kinase have been found, with RAS mutations found only in adenocarcinomas and PI3kinase mutations found in both squamous cell and adenocarcinomas.

3. Phase I studies of PI3K and MEK inhibitors in combination have shown activity in patients with gynecologic malignancies [12].

4. Cervical cancer is the 2nd most common cause of cancer death in the world. Very few options exist for patients with recurrent cervical cancer, and chemotherapy has

little activity in this cancer at the time of recurrence. Newer options are needed for these patients.

2.4 Correlative Studies Background

The successful implementation of personalized medicine with targeted therapies continues to be fraught with unexpected pitfalls, decreasing the speed at which agents can be directed to patients that will benefit. The failure to understand the basic biology of therapeutic targets frequently results in the failure of targeted therapeutics to fulfill their promise. The key road block remains an inability to design and implement biomarker driven trials that match patients to targeted therapies most likely to inhibit their own tumor.

As compared to other women's cancers, there are limited comprehensive data on the rates of RAS-ERK and PI3K pathway alterations in cervical cancer. The translation component of this study is designed in part to help alleviate this knowledge deficit. PIK3CA and PTEN loss have been characterized in one published study at a frequency of approximately 10% [9, 28]. However, molecular testing of phase I study participants from MD Anderson identified a PIK3CA mutation rate of 36% in squamous cervical cancer [29, 30]. At the Dana-Farber/Harvard Cancer Center (DFHCC), patients' tumors are frequently genotyped for oncogenic mutations and our preliminary data support this higher rate of PIK3CA mutation [31]. K-RAS and H-RAS mutations have also each been reported at 10% and 22% [9, 29, 32].The co-mutation rates of PIK3CA and RAS are unknown but studies to explore this are ongoing at the DFHCC in archived samples.

To complete the translational research objectives listed above, primary tumor and blood will be collected from all women who consent to participate in the trial. Additionally patients with tumors that are accessible tumors for in-office biopsies (i.e. vaginal recurrences) will be given the *option* of undergoing pre-treatment and post-treatment biopsies. These tissues will be snap frozen tissue and amenable to phospho-protein analysis thereby allowing investigation of negative feedback loops within the RTK-RAS-ERK and PI3K pathways. The details of these procedures are noted in Appendix H.

3. PARTICIPANT SELECTION

3.1 Inclusion Criteria

Participants must meet the following criteria on screening examination to be eligible to participate in the study:

3.1.1 Participants must have histologically or cytologically confirmed cervical cancer which is now recurrent or metastatic and is refractory to curative therapy or established treatments. Histologic or cytologic confirmation of the original primary tumor is required. All histologic types of cervical origin are permitted.

3.1.2 All patients must have measurable disease as defined by RECIST 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 spiral CT, MRI or caliper measurement by clinical exam; or ≥ 20 mm with conventional techniques. Lymph nodes must be ≥ 15 mm in short axis when measured by CT or MRI.

3.1.3 Prior Therapy:

- Patients must have had one prior chemotherapeutic regimen for management of cervical carcinoma. Initial treatment may include chemotherapy, chemotherapy and radiation therapy, and/or chemotherapy as consolidation/maintenance therapy. Chemotherapy administered in conjunction with primary radiation as a radio-sensitizer will not be counted as a systemic chemotherapy regimen.

- Patients are allowed to receive, but are not required to receive, one additional prior treatment regimen (including a single chemotherapeutic, a combination of chemotherapeutics, or biologic drugs such as bevacizumab) for management of their recurrent or persistent disease.

- Patients must have NOT received any class of drugs targeted to the PI3K pathway (such has PI3K inhibitors or mTOR inhibitors) or RAS-ERK pathway for management of recurrent or persistent disease.

3.1.4 Age ≥ 18 years. Because no dosing or adverse event data are currently available on the use of GSK1120212 and GSK2141795 in participants < 18 years of age, children are excluded from this study. Cervical cancer is very rare in the pediatric population.

3.1.5 Life expectancy of greater than 3 months.

3.1.6 ECOG performance status ≤ 2 (see Appendix A).

3.1.7 Participants must have normal organ and marrow function as defined below:

- Absolute Neutrophil Count (ANC) ≥ 1,500/mcL

- Platelets ≥ 100,000/mcL
- Hemoglobin ≥ 9.0/dL
- PT/INR and PTT ≤ 1.5 × institutional ULN
- AST (SGOT) and ALT (SGPT) ≤ 2.5 × institutional ULN
- Total bilirubin within normal institutional limits (isolated bilirubin > 1.5 × institutional ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)
- Albumin ≥ 2.5 g/dL
- Creatinine ≤ institutional ULN or creatinine clearance ≥ 50 mL/min/1.73 m^2 for subjects with creatinine levels above institutional normal or ≥ 50 mL/min 24-hour creatinine clearance
- Left ventricular ejection fraction (LVEF) ≥ institutional LLN by ECHO or MUGA
- Fasting Blood Glucose within institutional normal limits (see Exclusion Criterion 3.26)

3.1.8 Availability of a formalin fixed paraffin embedded (FFPE) block of cancer tissue from the original or most recent biopsy for mutational analysis. Availability must be confirmed prior to enrollment.

3.1.9 Blood pressure well controlled and must have systolic < 140 mmHg and diastolic < 90 mmHg.

3.1.10 The effects of GSK1120212 (trametinib) and GSK2141795 on the developing human fetus at the recommended therapeutic dose are unknown. For this reason, women of childbearing potential must agree to use two forms of contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a patient become pregnant or suspect she is pregnant while she is participating in this study, she should inform the treating physician immediately.

3.1.11 Toxicities of prior therapy (excepting alopecia) should be resolved to ≤ grade 1 per the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0.

3.1.12 GSK1120212 (trametinib) and GSK2141795 are oral medications. Patients must be able to tolerate oral medications and not have gastrointestinal illnesses that would preclude absorption of GSK1120212 and GSK2141795.

3.1.13 Ability to understand and willingness to sign a written informed consent document.

3.2 Exclusion Criteria

Participants who exhibit any of the following conditions at screening will not be eligible for admission into the study.

3.2.1 Participants who have had chemotherapy within 3 weeks (6 weeks for nitrosoureas or mitomycin C,) or radiation therapy within 2 weeks prior to entering the study or those who have not recovered to ≤ grade 1 (except alopecia) from adverse events (as per the revised NCI CTCAE version 4) due to agents administered more than 3 weeks earlier.

3.2.2 Participants may not be receiving any other investigational agents nor have participated in an investigational trial within the past 4 weeks (or five half-lives whichever is shorter; with a minimum of 14 days from the last dose).

3.2.3 Presence of active GI disease or other condition that could affect gastrointestinal absorption (e.g. malabsorption syndrome) or predispose a subject to GI ulceration. Subjects with prior Whipple procedure are eligible.

3.2.4 Evidence of mucosal of internal bleeding

3.2.5 Any major surgery within the last 4 weeks

3.2.6 Participants with fasting blood glucose values that are > institutional ULN. 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 regular hemoglobin A1C (HbA1C) ≤8% at screening.

3.2.7 Participants with metastases are excluded if their brain metastases are:

- Symptomatic,
- Treated (e.g., surgery, radiation therapy) but not clinically and radiographically stable one month after therapy (as assessed by at least two distinct contrast enhanced MRI or CT scans over at least a one month period),

OR

- Asymptomatic and untreated but > 1 cm in the longest dimension

3.2.8 Symptomatic or untreated leptomeningeal or brain metastases or spinal cord compression. Should participants develop brain metastases while on trial and have clinical benefit from GSK1120212 and GSK2141795 otherwise, participants may continue on drug after clinical management of the brain metastases with the permission of the principal investigator. GSK1120212 and GSK2141795 should be restarted between 2 and 6 weeks after the last radiation treatment.

3.2.9 Pregnant women are excluded from this study because of the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk of adverse events in nursing infants secondary to treatment of the mother with GSK1120212 and GSK2141795

breastfeeding should be discontinued if the mother is treated with GSK1120212 and GSK2141795.

3.2.10 Individuals with a history of a different malignancy are ineligible except for the following circumstances:

- Individuals with a history of other malignancies are eligible if they have been disease-free for at least 3 years or are deemed by the investigator to be at low risk for recurrence of that malignancy.
- Individuals with the following cancers are eligible if diagnosed and treated within the past 3 years: breast cancer *in situ* and basal cell or squamous cell carcinoma of the skin, stage I colon carcinoma confined to a polyp.

3.2.11 Any serious and/or unstable pre-existing medical disorder (aside from malignancy exception above), psychiatric disorder, or other conditions that could interfere with subject's safety, obtaining informed consent or compliance to the study procedures, in the opinion of the Investigator.

3.2.12 Known Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), or Hepatitis C Virus (HCV) infection (with the exception of chronic or cleared HBV and HCV infection which will be allowed) as these individuals are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in participants receiving combination antiretroviral therapy when indicated.

3.2.13 *Required, chronic,* use of drugs that are *strong* inhibitors or inducers of p450 CYP3A4 (see Appendix E for a table of these agents).

3.2.14 Have a known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to GSK1120212 and GSK2141795, or excipients or to dimethyl sulfoxide (DMSO).

3.2.15 Participants may not use natural herbal products or remedies not approved by the FDA while participating in this study

3.2.16 History of interstitial lung disease or pneumonitis.

3.2.17 Presence of cardiac metastases

3.2.18 Subject with intra-cardiac defibrillators or pacemaker.

3.2.19 History of retinal vein occlusion (RVO).

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

- QTcF $\geq$ 480 msec ($\geq$ 500 msec for subject with bundle branch block)

- History or evidence of current clinically significant uncontrolled arrhythmias. *Exception:* Subjects with controlled atrial fibrillation for >30 days prior to randomization are eligible.
- History of acute coronary syndromes (including myocardial infarction and unstable angina), coronary angioplasty, or stenting within 6 months prior to randomization.
- History or evidence of current ≥ Class II congestive heart failure as defined by New York Heart Association (NYHA; Appendix B).

3.3 Inclusion of Women, Minorities and Other Underrepresented Populations

Only women will be included into this study because only women will develop cervical cancer.

Women of all racial and ethnic groups are eligible for this trial.

Accrual Targets			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	5		5
Not Hispanic or Latino	30		30
Ethnic Category: Total of all subjects	35	0	35
Racial Category			
American Indian or Alaskan Native	0		0
Asian	1		1
Black or African American	5		5
Native Hawaiian or other Pacific Islander	0		0
White	29		29
Racial Category: Total of all subjects	35	0	35

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC and DF/PCC Institutions

Institutions will register eligible participants with the DF/HCC Quality Assurance Office for Clinical Trials (QACT) central registration system. Registration must occur prior to the initiation of therapy. Any participant not registered to the protocol before treatment begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the QACT protocol-specific eligibility checklist.
Following registration, participants may begin protocol treatment. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study may be canceled. Notify the QACT Registrar of registration cancellations as soon as possible.

4.2 Registration Process for DF/HCC and DF/PCC Institutions

The QACT registration staff is accessible on Monday through Friday, from 8:00 AM to 5:00 PM Eastern Standard Time. In emergency situations when a participant must begin treatment during off-hours or holidays, call the QACT registration line at 617-632-3761 and follow the instructions for registering participants after hours.

The registration procedures are as follows:

1. Obtain written informed consent from the participant prior to the performance of any study related procedures or assessments.

2. Complete the QACT protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical record and/or research chart. **To be eligible for registration to the protocol, the participant must meet all inclusion and exclusion criterion as described in the protocol and reflected on the eligibility checklist.**

   Reminder: Confirm that a Formalin Fixed Paraffin Embedded (FFPE) tissue sample is available. Registration to both treatment and ancillary studies will not be completed if eligibility requirements are not met for all study aspects of the trial.

3. Fax the eligibility checklist and all pages of the consent form to the QACT at 617-632-2295.

4. Send FFPE block via overnight post to the following address:

   Ariana Peralta
   Dana-Farber Cancer Institute
   450 Brookline Avenue, D117

Boston, MA 02215
Telephone: 617-632-3743
Email: aperalta2@partners.org

5. The QACT Registrar will (a) review the eligibility checklist, (b) register the participant on the protocol, and (c) randomize the participant when applicable.

6. An email confirmation of the registration and will be sent to the Overall PI, study coordinator(s) from the Lead Site, treating investigator and registering person immediately following the registration.

5. TREATMENT PLAN

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks for GSK1120212 (trametinib) and GSK2126458 are described in Section 6 (Anticipated Toxicities and Dosing Delays/Dose Modification). No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy (see Section 5.3).

Each cycle will be 28 days. The starting doses of agents are: GSK1120212 (trametinib) 1.5 mg QD + GSK2141795 50 mg QD. Participants should plan to take GSK1120212 (trametinib) and GSK2141795 at the same time each day within a 1-2 hour window. GSK1120212 (trametinib) and GSK2141795 should be taken orally, with approximately 9 oz. of water. Participants must not eat grapefruit or drink grapefruit juice while taking study medications. Participants must not crush, chew or dissolve study medications. Participants will be expected to fast for 1 hour before and 2 hours after dosing of either study treatment. If a participant vomits after taking either study treatment, the subject should be instructed not to retake the dose and should take the next scheduled dose. Participants will have up to 2 hours from the scheduled dosing time to take study drugs. If it is beyond 2 hours, the dose will be skipped. The patient will be required to maintain a medication diary of each dose of each medication as included in Appendix D. Participants will be instructed in the use of the medication diary, and will return it to clinic staff at the end of each cycle. Participants should record doses as they are taken and not batch entries at a later time.

5.1 Pre-Treatment Criteria

5.1.1 Cycle 1, Day 1

- Participants must continue to meet all eligibility criteria listed in protocol sections 3.1 and 3.2. For clarity, **laboratory criteria are listed in the table below**
- Left Ventricular Ejection Fraction (LVEF) ≥ institutional lower limit of normal by ECHO or MUGA
- Toxicities of prior therapy (except alopecia) should be resolved to ≤ grade 1
- ECOG performance status ≤ 2
- No evidence of life-threatening medical problems

5.1.2 Subsequent Cycles, Day 1

- Participants must meet the **laboratory criteria listed in the table below**
- ECOG performance status ≤ 2
- All toxicities of previous cycles must have resolved to ≤ grade 2
- No evidence of life-threatening medical problems

Laboratory Pre-Treatment Criteria		
	Cycle 1, Day 1	**Subsequent Cycles, Day 1**
Absolute Neutrophil Count (ANC)	≥ 1,500 / mcL	≥ 1,000 / mcL
Platelets	≥ 100,000 / mcL	≥ 75,000 / mcL
Hemoglobin	> 9.0 mg/dL	
Total Bilirubin	Within normal institutional limits	N/A
ALT/SGPT and AST/SGOT	≤ 2.5 × institutional upper limit of normal	
Albumin	≥ 2.5 g/dL	N/A
Serum Creatinine	≤ institutional upper limits of normal or creatinine clearance ≥ 50 mL/min/1.73 m^2 for subjects with creatinine levels above institutional normal	
Fasting Glucose	Within normal institutional limits	

5.2 Agent Administration

5.2.1 GSK1120212 (Trametinib)

GSK1120212 will be given orally at 1.5 mg PO once per day in continuous 28 day cycle. Dose modification may be made for toxicities as noted in Section 6. Participants should plan to take GSK1120212 (trametinib) at the same time each day within a 1-2 hour window with 8 oz of water. Participants will be expected to fast for 1 hour before and 2 hours after dosing of either study treatment. If a participant vomits after taking either study treatment, the participant should be instructed not to retake the dose and should take the next scheduled dose. If a dose is forgotten, the participant should not "make up" a dose as per section 5. GSK1120212 (trametinib) will be dispensed at the start of each cycle. Participants will be provided with a pill diary (Appendix D), instructed in its use, and asked to bring it with them to each appointment.

5.2.2 GSK2141795

GSK2141795 will be given orally at 50 mg once PO daily continuously in 28 day cycles.

Based on nonclinical data and increasing clinical experience, it is possible that GSK2141795 may be a direct gastrointestinal mucosal irritant such that subjects with GI dysmotility or GERD may be predisposed to symptoms of dyspepsia. Therefore, in an effort to decrease this discomfort, we have the following recommendations:

- A small snack followed by a 1hr fast prior to taking GSK2141795. Water is allowed during this fasting period

- If possible; take each GSK2141795 capsule approximately 5 minutes apart with divided amounts of fluid (4-8 oz with each capsule for a total of at least 12 oz).
- Remain upright for 30min after taking the last capsule of GSK2141795
- Fast for 2hr after ingestion of the last capsule of GSK2141795. Water is allowed during this fasting period
- In more severe cases, consider sucralfate and/or Gaviscon as supportive care to be taken at least 2hr after ingestion of the last capsule of GSK2141795, so as to avoid any potential drug-drug interactions.

If the recommendations above are not sufficient to resolve the symptoms, the investigator should consider additional investigations such as upper endoscopy or barium radiography. When co-administration is scheduled, GSK1120212 (trametinib) and GSK2141795 should be administered at the same time.

Dose modification may be made for toxicities as noted in Section 6. Participants should plan to take GSK2141795 at the same time each day within a 1-2 hour window. Participants should plan to take GSK2141795 at the same time each day within a 1-2 hour window. Participants should take GSK2141795 with 8 oz of water. Participants will be expected to fast for 1 hour before and 2 hours after dosing of either study treatment. If a participant vomits after taking either study treatment, the participant should be instructed not to retake the dose and should take the next scheduled dose. If it is greater than 2 hours from the scheduled dosing, the participant will miss the dose and take the next scheduled dose of study drug. Missed doses will not be made up. GSK2141795 will be dispensed at the start of each cycle. Participants will be provided with a pill diary (Appendix D), instructed in its use, and asked to bring it with them to each appointment.

5.2.3 Other Procedures

Tumor Biopsies

Participants with tumor accessible for an in-office biopsy (e.g a skin or vaginal lesion) will be offered the option of undergoing paired tumor biopsies. The initial biopsy will be performed after the patient has signed consent and has been registered for the study prior to administration of any drug. The second biopsy will be planned for week 2 following initiation of treatment, although this may be delayed until week 3 or week 4 if necessary due to scheduling considerations.

Participants who derive clinical benefit from the drug will be offered a biopsy at the time of progression, should they have disease that is safely accessible. Participants will be consented for this procedure. This biopsy should be performed within 6 weeks after progression.

5.3 General Concomitant Medication and Supportive Care Guidelines

The following medications **are prohibited**:

1. Other anti-cancer therapy while on treatment in this study.
   NOTE: megestrol (Megace) if used as appetite stimulant is allowed and palliative radiation therapy can be permitted with the approval of the principal investigator.

2. Use of other investigational drugs within 28 days (or five half-lives whichever is shorter; with a minimum of 14 days from the last dose) preceding the first dose of GSK1120212 and GSK2141795during the study.

3. All medications in Appendix E are prohibited and those listed in Appendix F are to be used with caution.

4. Concurrent treatment with bisphosphonates is permitted; however, treatment must be initiated prior to the first dose of study therapy. Prophylactic use of bisphosphonates in subjects without bone disease is not permitted, except for the treatment of osteoporosis.

5. Subjects should abstain from taking any herbal and dietary supplements within 5 half lives (or 14 days if the drug is a potential enzyme inducer) prior to the first dose of either study drug until completion of the follow-up visit.

   Because the composition, pharmacokinetics 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).

   The investigator should contact the study PI before initiating treatment with any herbal preparation.

6. Growth factor support is allowed only with the permission of the principal investigator.

7. 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. Budenoside 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 his/her appropriate designee) will be expected to review concomitant medications with the subject at each clinical visit.

Drugs to be used with Caution with GSK1120212 and GSK2141795 are listed in Appendix F (the interactions with p450 for GSK2141795 in the in vitro studies are at much higher concentrations than with GSK1120212).

Drugs that Inhibit or Induce Cytochrome P450

In vitro studies suggest that the metabolism of GSK1120212 is mediated predominantly by non-CYP-mediated process and possibly by CYP3A4. Therefore, drugs that potently inhibit or induce CYP3A4 **should be administered with caution** as they may alter exposure to GSK1120212 and GSK2141795. Appendix F provides a list of possible medications including but not limited to those drug substances that may alter GSK1120212 elimination. Participants who require the chronic administration of strong CYP3A4 inhibitors or inducers should not be enrolled on study (see section 3.2) . Should a clinical situation arise in which a trial participant requires the intermittent use of strong inhibitor of inducer of the CYP3A4, alert the principal investigator.

GSK1120212 may be an inhibitor of CYP2C8 in vivo. **Caution** should be exercised when dosing GSK1120212 concurrently with medications with narrow therapeutic windows that are substrates of CYP2C8. Refer to Appendix F for list of medications which exposure may be increased by co-administration with GSK1120212.

GSK1120212 (as victim): *In vitro* studies suggest that the metabolism of GSK1120212 may be mediated by non-cytochrome P450 processes and potentially by CYP3A4. As there are currently no known marketed drugs that cause clinically relevant inhibition of non-CYP enzymes, low drug interaction risk from the non-CYP enzymes is expected. The contribution of the CYP3A4 pathway to the elimination of GSK1120212 in human *in vivo* is presently unknown. Drugs that potently inhibit or induce CYP3A4 should be administered with caution as they might increase or decrease exposure to GSK1120212.

GSK1120212 (as perpetrator): Although *in vitro* data indicate that GSK1120212 is a potential inhibitor of CYP2C8 (IC_{50} 0.34 μM), CYP2C9 (IC_{50} 4.1 μM) and CYP2C19 (IC_{50} 5 μM), the anticipated GSK1120212 clinical concentration C_{max} of 0.1 μM is below these *in vitro* IC_{50} values. The drug-drug interaction risk for substrates of CYP2C9 and CYP2C19 is, therefore, expected to be low. However, drugs with a narrow therapeutic index that are substrates of CYP2C8 should be used with caution. The CYP3A4 induction risk for GSK1120212 is also expected to be low for the same reason; the EC_{50} value of 1.7 μM is > 10-fold higher than the anticipated clinical Cmax values of both drugs.

GSK2141795 (as victim): *In vitro* data indicate that GSK2141795 is a CYP3A4 substrate. Drugs that potently inhibit CYP3A4 could lead to increased GSK2141795 exposure in subjects, and will either be prohibited or used with caution in the study. Drugs which are strong inducers of CYP3A and may result in lower exposures of GSK2141795 will also be prohibited.

GSK2141795 (as perpetrator) also appears to be a moderate *in vitro* inhibitor of CYP2C8 (IC_{50} 3 μM) and CYP3A4 (IC_{50} 11 μM). 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.

Transporter Liability

GSK1120212 (as victim) is neither a substrate for human P-gp nor human BCRP, and is, therefore, unlikely to pose a risk of being a victim of drug-drug interactions upon co-administration with P-gp or BCRP inhibitors.

GSK1120212 (as perpetrator) inhibited OATP1B1 (IC_{50} of 1.3 μM) and OATP1B3 (IC_{50} of 0.94 μM), and inhibited human BCRP mediated transport of cimetidine (IC_{50} of 1.1 μM). Since these IC_{50} values are higher than the anticipated GSK1120212 clinical concentration C_{max} of 0.1 μM, the risk is expected to be low. Co-administration of drugs that are sensitive to OATP1B1, OATP1B3, and BCRP substrates will be will be used with caution.

GSK2141795 (as victim) is a human p-glycoprotein (P-gp, ABCB1) and breast cancer resistant protein (BCRP, ABCG2) substrate. It has not been determined if GSK2141795 is a substrate for OATP.

GSK2141795 (as perpetrator) is also a potential inhibitor of BCRP (IC50 of ~1.9 μM). It is a weak inhibitor of OATP1B1 (IC50 of ~16 μM). Drugs that are inhibitors of P-gp and BCRP should be used with caution. Co-administration of drugs that are sensitive BCRP substrates, such as topotecan, will be prohibited.

Drug-Drug interactions of GSK2141795 and GSK1120212 Combination

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 [IC_{50}] 3 mcM) and CYP3A4 (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.

The following medications (including but not limited to) are prohibited during the study:

PROHIBITED – highly sensitive and/or low therapeutic index CYP3A/CYP2C8/BCRP/CYP3A4 substrates since concentrations of these drugs may be increased	
CYP3A Substrate	**Therapeutic Area**
Cisapride	Hypnotics and Sedatives
Pimozide	Antidepressant, Antipsychotics, Antianxiety agents
Astemizole	Antihistamine
BCRP Substrate	
rosuvastatin, sulfasalazine	HMG-CoA Reductase Inhibitors, gastrointestinal agents
PROHIBITED – strong inducers/inhibitors of CYP3A4	
Strong CYP3A4 Inhibitor/Inducer	**Therapeutic Area**
clarithromycin, telithromycin, rifamycin class agents (*e.g.*, rifampin, rifabutin, rifapentine), troleandomycin	Antibiotics
itraconazole, ketoconazole	Antifungals
Nefazodone	Antidepressants
atazanzvir, delaviridine, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, nevirapine	Antivirals
carbamazepine, phenobarbital, phenytoin	Anticonvulsants

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	
Drug	**Therapeutic Area**
quinidine, diltiazem, verapamil	Antiarrhythmics:
fluvoxamine, fluoxetine, paroxetine,nefazodone	Antidepressants:
aprepitant, cimetidine	Antiemetics
fluconazole, terbinafine, voriconazole	Antifungals
ciprofloxacin, erythromycin, isoniazid	Anti-infectives
mibefradil, diltiazem, verapamil	Calcium Channel Blockers
aprepitant, oxandrolone, tizanidine, gemfibrozil	Miscellaneous
USE WITH CAUTION – Drugs that may inhibit P-gp and BCRP	
Drug	**Therapeutic Area**
Valspoda	Miscellaneous
Atorvastatin	HMG-CoA Reductase Inhibitors
Carvedilol	Congestive Heart Failure
Methadone	Analgesic
Meperidine	Narcotic
Omeprazole	Proton Pump Inhibitor

USE WITH CAUTION – Drugs that may have their concentrations altered by trametinib or GSK2141795	
repaglinide, rosiglitazone, pioglitazone	Antidiabetics
alfentanil, fentanyl	Analgesics
Quinidine	Antiarrhythmics
Cilostazole	Anticoagulants and Antiplatelets
Astemizole	Antihistamines
diergotamine, ergotamine, eletriptan	Antimigraine agents
Pimozide	Antipsychotics
Buspirone	Anxiolytics
Felodipine	Calcium Channel Blockers
sildenafil, tadalafil, vardenafil	Erectile Dysfunction agents
cerivastatin,ovastatin, simvastatin, atorvastatin	HMG-CoA Reductase Inhibitors
alprazolam, diazepam, midazolam, triazolam	Hypnotics and Sedatives
cyclosporine, sirolimus, tacrolimus	Immunosuppressive agents
Cisapride	Prokinetic agents
cyclosporine, torsemide, chloroquine, zopiclone	Miscellaneous
Eperenone	Selective Aldosterone Blockers
chloroquine, zopiclone	Thiazolidinediones

The likelihood of drug-drug interactions between GSK1120212 and GSK2141795 is low because the *in vitro* IC_{50} values for inhibition and EC_{50} values for induction of CYP450 enzymes are 3- to 100-fold higher than the anticipated clinical C_{max} values for either drug. Further, pharmacokinetic analyses comparing steady state exposures with those following single doses will be assessed for both treatments to address this question.

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

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. Budenoside 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.

Subjects should abstain from taking any herbal and dietary supplements within 5 half lives (or 14 days if the drug is a potential enzyme inducer) prior to the first dose of either study drug until completion of the follow-up visit, unless in the opinion of the Investigator and sponsor there is little concern for a potential drug-drug interaction with the study drug(s). These herbal medications include, but are not limited to, St. John's wort, kava, ephedra (ma huang), ginkgo biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. The investigator should contact a Medical Monitor before initiating treatment with any herbal preparation.

5.4 Duration of Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse events, treatment may continue indefinitely or until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Participant decides to withdraw from the study,
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements
- Pregnancy, or
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the opinion of the treating investigator.

5.5 Duration of Follow Up

Participants will be followed for 3 years after removal from study or until death, whichever occurs first. Participants removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. Date and cause of death should be provided for participants who become deceased within the 3-year interval following removal from the study. Should a participant become pregnant while on trial, the patient will be withdrawn from the study. However, the outcome of the pregnancy and the newborn’s health, if the pregnancy is carried to term, will be monitored.

6. EXPECTED TOXICITIES AND DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made using the following recommendations. Toxicity assessments will be performed using the revised NCI CTCAE version 4. All appropriate treatment areas should have access to a copy of the CTCAE version 4, which can be downloaded at: http://ctep.cancer.gov.

If possible, symptoms should be managed symptomatically. In the case of toxicity, appropriate medical treatment should be used (including anti-emetics, anti-diarrheals, etc.).

All adverse events experienced by participants will be collected from the time of the first dose of study treatment, through the study and until the final study visit. Participants continuing to experience toxicity at the off study visit may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

Dose Level	Trametinib Dose	GSK2141795 Dose
0 → Starting Dose	1.5 mg PO every day	50 mg PO every day
-1	1.0 mg PO every day	25 mg PO every day

NOTE: AEs occurring in participants 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.

6.1 Anticipated Toxicities

A list of the adverse events and potential risks associated with the agents administered in this study appear below and will determine whether dose delays and modifications will be made or whether the event requires expedited reporting **in addition** to routine reporting.

Risk has been assessed based on nonclinical toxicological studies and clinical experience of in-class compounds, along with preliminary data from the ongoing single-agent FTIH studies with GSK1120212 and GSK2141795. Procedures to minimize or monitor potential risks are listed below.

6.1.1 Predicted Overlapping Toxicities

Gastrointestinal (GI) Toxicity: 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.

Rash: Subjects will be followed closely for signs and symptoms of rash and aggressive supportive care is recommended. Guidelines for rash prophylaxis and for rash treatment management have been provided in Section 6.3.1 (table titled "Dose Modification Guidelines and Management for Rash"). Treatment will be dose reduced or discontinued for clinically significant toxicity not adequately controlled by supportive care measures.

6.1.2 GSK2141795 Safety Profile and Management

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.

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 participants 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 of hydration with supplementary intravenous hydration as needed.

Rash: 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.

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

Hypoglycemia: Asymptomatic hypoglycemia occurred in participants 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 participants. 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.

6.1.3 Other Toxicities Based on Clinical Experience

Ocular Events (GSK1120212): To reduce the risk of ocular toxicity, subjects with a history of retinal vein occlusion (RVO) or central serous retinopathy (CSR), predisposing factors for RVO or CSR, or predisposing retinal pathology as described by ophthalmologic exams will be excluded. Ophthalmologic exams will be performed at baseline and as clinically warranted. Aggressive management and evaluation of all ocular symptoms, as well as specific ocular toxicity stopping criteria, will be implemented.

Metabolic Toxicity: To reduce the risk of hyperglycemia, subjects with abnormal fasting glucose values at screening will be excluded. In addition, subjects with Type 1 diabetes will also be excluded; however subjects with Type 2 diabetes will be permitted in Part 2 of the study only if they meet the specified entry criterion. If hyperglycemia is observed, supportive therapy will be provided according to standard medical practice. Treatment will be dose reduced or discontinued for clinically significant toxicity that cannot be adequately managed medically.

Cardiac toxicity (GSK1120212): To monitor cardiac function, echocardiogram (ECHO) exams and electrocardiograms (ECGs) will be performed at baseline, regular intervals, and as clinically warranted during study treatment. Specific cardiac toxicity stopping criteria will be implemented and treatment will be discontinued for clinically significant toxicity.

6.1.4 Other Potential Toxicities Based on Nonclinical Data

Hematologic Toxicity: Complete blood counts (CBC) will be measured frequently during therapy to monitor for hematologic toxicity. Supportive therapy will be provided according to standard medical practice and treatment will be discontinued for clinically significant toxicity.

Glandular Abnormalities: Frequent monitoring with medical history, physical examination and clinical laboratory assessments. If clinically significant toxicity is observed, supportive therapy will be provided according to standard medical practice and treatment will be discontinued if necessary.

Thyroid Abnormalities: Thyroid stimulating hormone (TSH) will be measured frequently during therapy to monitor for thyroid dysfunction. Supportive therapy will be provided according to standard medical practice and treatment will be discontinued for clinically significant toxicity.

6.1.5 Adverse Events List for GSK1120212

The most commonly reported AE's in Phase I studies of GSK1120212 are listed below. Other SAE's that attributed to GSK1120212 but less common include: hepatic encephalopathy, chorioterinopathy, pneumatosis intestinalis, retinal hemorrhage, myopathy and pulmonary hypertension.

Most Commonly Reported Adverse Events for trametinib (GSK1120212) in Phase I Studies	
rash	dyspnea
diarrhea	pyrexia
nausea	pneumonia
fatigue	febrile neutropenia
vomiting	AST increased
anemia	ALT increased
peripheral edema	dry skin
abdominal pain	thrombocytopenia
constipation	peripheral edema
dermatitis acneiform	cough
decreased appetite	chills
pruritus	

6.1.6 Adverse Events List for GSK 2141795

The most commonly reported adverse events in Phase I studies of GSK2141795 are listed below.

Most Commonly Reported Adverse Events for GSK2141795	
fatigue	pyrexia
nausea	back pain
diarrhea	mucositis
decreased appetite	hypoglycemia
blood glucose increased/hyperglycemia	hypertension
vomiting	liver enzyme elevation
dyspnea	dehydration
constipation	pruritus
rash	edema
cough	

6.2 Toxicity Management

The following section outlines specific management guidelines for the following toxicities: overdose (6.2.1), rash (6.2.2), diarrhea (6.2.3), hypertension (6.2.4), and other toxicities in 6.2.5 including QTc alterations, hypocalcemia and hypercalcemia,

pneumonitis, left ventricular changes, liver chemistry changes, visual changes, and all other toxicities.

6.2.1 Overdose

There is no specific guidance available regarding overdose due to the lack of clinical experience. In case of an acute overdose, it is recommended that activated charcoal be administered orally to reduce the absorption of GSK1120212 and GSK2141795.

6.3 Dose Modification and Dose Interruption

6.3.1 Dose Modification and Management Guidelines for Rash

Two types of rashes may be seen with the GSK1120212 (trametinib) + GSK2141795 combination:

1. ***Acneiform,*** typically associated with MEK inhibitor therapy (trametinib).

2. ***Maculopapular,*** 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 thinks 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 (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 maculopapular rash.

Rash prophylaxis is recommended for the first 6 weeks of study treatment.

Subjects should contact the investigator immediately upon onset of a rash. Full supportive care should be provided to subjects who experience a rash while on study.

The following information is a guideline. The investigator's best medical judgment should determine medical intervention for rash.

General Considerations in Rash Management

- Encourage subjects to avoid unnecessary exposure to sunlight.
- Employ a proactive approach (i.e., prophylactic treatment; see below for recommendations).
- If subject develops rash, verify treatment intervention and follow steps outlined below

Prophylactic Treatment (during the first 6 weeks of treatment)

The exact prophylactic regimen should be based on the investigator's experience; however, the following regimen is recommended:

- Broad-spectrum sunscreen (containing titanium dioxide or zinc oxide) with a skin protection factor (SPF) ≥15.
- Thick, alcohol-free emollient cream (e.g. glycerine and cetomacrogol cream) on dry areas of the body.

Reactive Rash Management

It is strongly recommended that subjects who develop rash or skin toxicities receive evaluations for management of the specific side effect.

- Upon the first signs of rash, mild strength topical steroid (e.g. hydrocortisone 1% cream) with escalation to higher strength and/or oral steroid as detailed below.
- Upon the first signs of papulopustular (acneiform) rash consider doxycycline (100 mg BID) or minocycline (100 mg BID).
- For pruritic lesions, the use of cool compresses and oral antihistamine agents may be helpful. Hypoallergenic moisturizers and emollients for dry skin (5% to10% urea in cetomacrogel cream or soft paraffin) may also provide symptomatic relief for pruritus.
- For **fissuring**, the use of Monsel's solution, silver nitrate, or zinc oxide cream is advised.
- For **desquamation**, thick emollients and mild soap are recommended.
- For **paronychia**, antiseptic bath and local potent corticosteroids in addition to oral antibiotics are recommended and, if no improvement is seen, a dermatology or surgery consultation is recommended.
- For **infected lesions**, bacterial and fungal culturing followed by the appropriate culture-driven systemic or topical antibiotics is indicated.
- For subjects who had study drug reduced because of rash, re-escalation may be considered if toxicity does not recur with a re-challenge at a lower dose.
- Consider the following algorithm (Table below) in a stepwise manner.

Rash Management Guidelines		
Rash Grading	**Management of Rash**	**Study Drug(s) Dose Adjustment**
Grade 1	Initiate Reactive Rash Management regimen Reassess after 2 weeks; if rash worsens or does not improve, proceed to step 2	Continue current dose.

Rash Management Guidelines		
Rash Grading	**Management of Rash**	**Study Drug(s) Dose Adjustment**
Grade 2	Initiate Reactive Rash Management regimen if not already started, but using moderate strength topical steroids.* Reassess after 2 weeks; if rash worsens or does not improve, proceed to step 3	Continue current dose.
≥Grade 3	Initiate Reactive Rash Management regimen if not already started, but using moderate strength topical steroids PLUS methyprednisolone dose pack. For papulopustular (acneiform) rash consider doxycycline 100 mg bid or minocycline 100 mg bid. Consider obtaining dermatology consultation. Manage rash per dermatologist's recommendation.	Hold study treatment until rash improves to < Grade 2 (or resolves), then reduce dose of study medications by at least 25% and monitor for change in rash severity*. Reassess after 2 weeks; if rash worsens or does not improve, discontinue treatment. *For first occurrence of Grade 3 rash: restarting at the original dose may be considered after instituting optimal rash management.

6.3.2 Dose Modification and Management Guidelines for Diarrhea

Episodes of diarrhea have occurred in patients receiving trametinib (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.

Management and Dose Modification Guidelines for Diarrhea		
CTCAE Grade	**Adverse Event Management**	**Action and Dose Modification**
Uncomplicated Diarrhea,[1] Grade 1 or 2	• Diet: Stop all lactose containing products; eat small meals, BRAT-diet (bananas, rice, apples, toast) recommended. • Hydration: 8-10 large glasses of clear liquids per day (*e.g.*, Gatorade or broth). • Loperamide[3]: Initially 4 mg, followed by 2 mg every 4 hours or after every unformed stool; maximum 16 mg/day. Continue until diarrhea-free for 12 hours. • Diarrhea >24 hours: Loperamide 2 mg every 2 hours; maximum 16 mg/day. Consider adding oral antibiotics.	• Continue treatment. • If diarrhea is grade 2 for > 48 h, interrupt GSK2141795 and trametinib (for up to 3 weeks) until diarrhea resolves to grade ≤1. • Restart treatment at the same dose level • 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 PI**).

Management and Dose Modification Guidelines for Diarrhea		
CTCAE Grade	**Adverse Event Management**	**Action and Dose Modification**
	• Diarrhea >48 hours: Loperamide 2 mg every 2 hours; maximum 16 mg/day. Add budesonide or other second-line therapies (octreotide, or tincture of opium) and oral antibiotics.	
Uncomplicated Diarrhea,[1] Grade 3 or 4 **and** **Any Complicated Diarrhea[2]**	• Clinical evaluation mandatory. • Loperamide[3]: Initially 4 mg, followed by 2 mg every 4 hours or after every unformed stool; maximum 16 mg/day. Continue until diarrhea-free for 12 hours. • Oral antibiotics and second-line therapies if clinically indicated • Hydration: Intravenous fluids if clinically indicated. • Antibiotics (oral or intravenous) if clinically indicated. • Intervention should be continued until the subject is diarrhea-free for ≥24 hours. • Intervention may require hospitalization for subjects at risk of life-threatening complications.	• Interrupt BOTH agents until diarrhea resolves to ≤ grade 1. • Restart with trametinib or GSK2141795 reduced by one dose level (for the combination, reduce both agents by one level).[4] • If more than one dose reduction of study treatment is clinically indicated, **permanently discontinue treatment**. • If treatment delay is >21 days, discontinue treatment. (resumption of trametinib or GSK2141795 alone may be considered based on toxicity-benefit consideration and after consultation with PI)

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

6.3.3 GSK2141795 Dose Modification and Management Guidelines for Hypo- or Hyperglycemia

Hyperglycemia has been associated with treatment with GSK2141795.

Management and Dose Modification Guidelines for Hypo- or Hyperglycemia		
Criteria	**Management Guidelines**	**Study Drug Modification**
(For management purposes, refer to mild, moderate and severe intensity criteria; however for eCRF reporting use NCI-CTCAE version 4.0 Grades 1-5)		
Mild Fasting blood glucose > 150mg/dL	Monitor fasting and preprandial glucose.	**Continue study drug**
Moderate to Severe Fasting blood glucose <70 mg/dL OR any blood glucose > 250mg/dL	• 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 hypoglycemia as GSK2141795 is held/or discontinued. • Intravenous insulin treatment is recommended.	Hold GSK2141795 and notify investigator immediately. The investigator should discuss intervention and possible resumption of GSK2141795 with the PI.

6.3.4 Dose Modification and Monitoring Guidelines for LVEF Decrease

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).

Dose Modification Guidelines and Stopping Criteria for LVEF Decrease		
Clinical Assessment	**LVEF-drop (%) or CTCAE grade**	**Action and Dose Modification**
Asymptomatic	Absolute decrease of >10% in LVEF compared to baseline **and** ejection fraction below the institution's LLN.	• Hold trametinib and GSK2141795. • Repeat ECHO in 2 weeks[a] • If the LVEF **recovers** within 4 weeks (defined as LVEF ≥ LLN and absolute decrease ≤10% compared to baseline) ○ Consult with the GSK medical monitor and request approval for restart ○ Restart treatment with trametinib reduced dose by one dose level[b] ○ Repeat ECHO/MUGA 2, 4, 8 and 12 weeks after re-start; continue in intervals of 12 weeks thereafter • If LVEF **does not recover** within 4 weeks ○ Consult with cardiologist ○ **Permanently discontinue trametinib** ○ Repeat ECHO/MUGA after 2, 4, 8, 12, and 16 weeks or until resolution ○ Consult with principal investigator and GSK medical monitor[c]
Symptomatic[c]	• Grade 3: resting LVEF 39-20% or >20% absolute reduction from baseline • Grade 4: Resting LVEF ≤ 20%.	• **Permanently discontinue trametinib and GSK2141795** • **Report as SAE** • **Consult with cardiologist** • Repeat ECHO after 2, 4, 8, 12 and 16 weeks or until resolution.
[a] If ECHO/MUGA does not show LVEF recovery after 2 weeks, repeat ECHO/MUGA 2 weeks later. [b] Escalation of trametinib to previous dose level can be considered if LVEF remains stable for 4 weeks after restarting of trametinib. Approval from GSK Medical Monitor is required. [c] Symptoms may include: dyspnea, orthopnea, and other signs and symptoms of pulmonary congestion and edema.		

If LVEF recovers (defined as greater than or equal to LLN AND absolute decrease is less than or equal to 10% compared to baseline) at any time during the next 4 weeks, **after consultation with the PI,** both trametinib and GSK141795 can be restarted at a reduced dose. Monitoring LVEF will be performed 2 and 4 weeks after re-challenge, and every 4 weeks thereafter for 12 weeks and then by protocol

Copies of all cardiology consultations performed on subjects who experience a > 10% decrease in LVEF from baseline and whose cardiac ejection fraction is below the institution's LLN may also be required by GSK for review.

6.3.5 Dose Modification and Monitoring Guidelines for Liver Chemistry Changes

Liver chemistry stopping criteria are defined as follows:

When any of the liver chemistry stopping criteria are met, immediately discontinue trametinib and GSK2141795, perform liver event follow-up assessments, and monitor the patient until liver chemistries resolve, stabilize, or return to baseline values.

- ALT ≥ 3 × institutional ULN **and** bilirubin ≥2x institutional ULN (>35% direct bilirubin) (or ALT ≥3x institutional ULN and international normalized ratio [INR] >1.5x institutional ULN, if INR measured). **NOTE:** If serum bilirubin fractionation is not immediately available, treatment should be discontinued if ALT ≥ 3 × institutional ULN **and** bilirubin ≥2x institutional ULN. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
- ALT ≥ 5 × institutional ULN.
- ALT ≥ 3 × institutional ULN if associated with the appearance or worsening of symptoms of hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia.
- ALT ≥ 3 × institutional ULN persisting for ≥4 weeks.
- ALT ≥ 3 × institutional ULN and cannot be monitored weekly for 4 weeks.

Liver chemistry threshold stopping criteria have been designed to assure subject safety and to evaluate liver event etiology during administration of investigational product and the follow-up period, and are in alignment with the FDA premarketing clinical liver safety guidance (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf). These procedures do not apply if subjects develop liver chemistry abnormalities as a result of progressive disease:

- Immediately withdraw the subject from study treatments.

- Notify NCCN within 24 hours of learning of the abnormality to confirm the subject's study treatment cessation and follow-up.

- Complete the "Safety Follow-Up Procedures" listed below.

- Complete the liver event case report forms. If the event also meets the criteria of an SAE (see Section 11.1.2), the SAE data collection tool will be completed separately with the relevant details.

- Upon completion of the safety follow-up, investigator to decide whether to permanently withdraw the subject from the study. Approval by the study PI for restarting IP can be considered where the subject is receiving compelling benefit and no effective alternative therapy is available OR liver chemistries have a clear underlying cause (*e.g*. biliary obstruction, hypotension) and liver chemistries have improved to normal or within 1.5x baseline and ALT < 3x institutional ULN). Subjects **approved by the study PI** for restarting IP must return twice a week for liver chemistries until stable, and then resume routine lab monitoring as per protocol.

Restarting IP: If requested by the investigator, drug restart /rechallenge following liver events that are possibly related to investigational product may be considered only for subjects who are already receiving compelling benefit from a critical or life-saving drug for whom there is no alternative treatment. In these cases, approval by the study PI for restart may be approved when the following conditions are satisfied:

- Ethics Committee or Institutional Review Board approval of drug restart/rechallenge must be obtained before IP can be administered.
- If the restart/rechallenge is approved by the study PI in writing, the subject must be provided with a clear description of the possible benefits and risks of drug administration, including the possibility of recurrent, more severe liver injury or death.
- The subject must also provide signed informed consent specifically for the IP restart/rechallenge. Documentation of informed consent must be recorded in the study chart.
- Study drug must be administered at the dose specified by the study PI.

Safety Follow-Up Procedures for subjects with ALT ≥ 3x institutional **ULN and ≥ 2 × value at Screening:**

- Make every reasonable attempt to have subjects return to the clinic within 24 to 72 hours for repeat liver chemistries, additional testing.
- Monitor subjects at least weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.

Safety Follow-Up Procedures for subjects with ALT ≥ 3 × institutional **ULN and bilirubin ≥ 2 ×** institutional **ULN (or ALT ≥ 3 ×** institutional **ULN and INR1 > 1.5):**

- This event is considered an SAE (see Section 11.1.2). Serum bilirubin fractionation should be performed if testing is available. If fractionation is unavailable, urinary

bilirubin is to be measured via dipstick (a measurement of direct bilirubin, which would suggest liver injury).
- Make every reasonable attempt to have subjects return to the clinic within 24 hours for repeat liver chemistries, additional testing, and close monitoring (with specialist or hepatology consultation recommended).
- Monitor subjects twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.

In addition, for all subjects with no evidence of malignant involvement of the liver and ALT ≥ 3 × institutional **ULN, every attempt must be made to also obtain the following:**
- Obtain viral hepatitis serology testing including:
  - 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
- Blood sample for analysis of serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
- Fractionate bilirubin, if total bilirubin ≥2x institutional ULN.
- Assess eosinophilia.
- Record the appearance or worsening of clinical symptoms of hepatitis, or hypersensitivity, fatigue, decreased appetite, nausea, vomiting, abdominal pain, jaundice, fever, or rash as relevant on the AE eCRF.
- Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins on the Concomitant Medications eCRF.
- Record alcohol use on the Liver Events eCRF.

The following are required for subjects with ALT ≥3x institutional ULN and total bilirubin ≥ 2x institutional ULN (>35% direct bilirubin; bilirubin fractionation required) or INR > 1.5x institutional ULN, without evidence of biliary obstruction or progressive disease, but are optional for other abnormal liver chemistries:

- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies.
- Serum acetaminophen adduct assay (quantifies potential acetaminophen contribution to liver injury, detectable by HPLC assay more than 1 week following acetaminophen use) [41]
- Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen): quantitative hepatitis B DNA and hepatitis delta antibody.

- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease.
- The Liver Imaging and/or Liver Biopsy eCRFs are also to be completed if these tests are performed.

6.3.6 Dose Modification, Monitoring, and Management of Hypertension

Increases in blood pressure have been observed in subjects receiving trametinib. Recommendations for blood pressure monitoring and management are provided below.

Monitoring of Hypertension

All blood pressure assessments should be performed under optimal conditions i.e. after (i) subject has been seated with back support, ensuring that legs are uncrossed and flat on the floor, (ii) subject is relaxed comfortably for at least 5 minutes, (ii) preparatory steps including removal of any restrictive clothing over the cuff area and selection of the right cuff size have been ensured, (iii) the arm is supported so that the middle of the cuff is at the heart level, and (iv) the subject remains quiet during the measurement. In subjects with an initial blood pressure reading within the hypertensive range, a second reading should be taken at least 1 minute later, with the 2 readings averaged to obtain a final blood pressure measurement.

Persistent hypertension is defined as an increase of systolic blood pressure (SBP) > 140 mm Hg and/or diastolic blood pressure (DBP) > 90 mm Hg in up to three subsequent visits with blood pressure assessments from two readings under the optimal conditions described above. Visits to monitor increased blood pressure should be scheduled independently from the per-protocol visits outlined in the time-and-events schedule; ideally, subsequent blood pressure assessments should be performed within one week.

Asymptomatic hypertension is defined as an increase of SBP > 140 mm Hg and/or DBP > 90 mm Hg in the absence of headache, light-headedness, vertigo, tinnitus, episodes of fainting, or other symptoms indicative of hypertension which would disappear after the blood pressure is controlled within the normal range.

Dose Modification and Management of Hypertension

- Hypertension is typically associated with trametinib. Please follow guidelines for trametinib.
- GSK2141795 may continue when trametinib is on hold if AEs are ≤ grade 2.
- If hypertension is grade 3-4, GSK2141795 should be held when trametinib is held. Once hypertension has resolved to grade 1 or baseline, GSK2141795 may resume at the same dose.
- If GSK2141795795 has been held for >21 days, a discussion with the PI is required before resuming treatment with the agent.

For subjects experiencing an increase in systolic and/or diastolic blood pressure that is persistent and may be associated with the study treatment, recommendations for the clinical management of hypertension are described in the table below:

Management of Hypertension	
Scenario A: • Asymptomatic and persistent[a] SBP of ≥ 140 and < 160 mm Hg, or DBP ≥ 90 and <100 mm Hg **or** • Clinically significant increase in DBP of 20 mm Hg (but still below 100 mmHg)	**Step 1:** Continue GSK1120212 (trametinib) at the current dose. **Step 2:** Adjust current or initiate new antihypertensive medication(s). **Step 3:** Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled[b] blood pressure (BP). If BP is not well-controlled within 2 weeks, consider referral to a specialist and go to scenario B.
Scenario B: • Asymptomatic SBP ≥160 mmHg, or DBP ≥100 mmHg **or** • Failure to achieve well-controlled BP within 2 weeks in scenario A	**Step 1:** Interrupt GSK1120212 (trametinib), if clinically indicated. **Step 2:** Adjust current or initiate new antihypertensive medication(s). **Step 3:** Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled BP. **Step 4:** Once BP is well-controlled[b], restart GSK1120212 reduced by one dose level[c]
Scenario C. • Symptomatic[d] hypertension **or** • Persistent SBP ≥ 160 mm Hg, or DBP ≥ 100 mm Hg, despite modification of antihypertensive medication(s) and dose reduction of trametinib	**Step 1:** Interrupt GSK1120212(trametinib) **Step 2:** Adjust current or initiate new antihypertensive medication(s). **Step 3:** Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled BP. Referral to a specialist for further evaluation and follow-up is also recommended. **Step 4:** Once BP is well-controlled, restart GSK1120212 (trametinib) reduced by one dose level[c]
Scenario D: Refractory hypertension unresponsive to above interventions.	Permanently discontinue GSK1120212 (trametinib) and continue follow-up per protocol.
a. hypertension detected in two separate readings during up to three subsequent visits **b.** Well-controlled blood pressure defined as SBP ≤ 140 mmHg and DBP ≤ 90 mmHg in two separate readings during up to three subsequent visits **c.** Escalation of trametinib to previous dose level can be considered if BPs remain well-controlled for 4 weeks after restarting of trametinib. Approval from GSK Medical Monitor is required. **d.** Symptomatic hypertension defined as hypertension aggravated by symptoms (e.g., headache, light-headedness, vertigo, tinnitus, episodes of fainting) that resolve after the blood pressure is controlled within the normal range.	

6.3.7 Dose Modification and Monitoring for QTc Prolongation

Guidelines for dose modification and stopping criteria due to QTC-prolongation are provided in the table below. Refer to Appendix I for QTcB prolongation correction guidance.

Dose Modification and Monitoring for QTc Prolongation	
QTc Prolongation[a] Criteria	**Management Guidelines**
• QTcF ≥ 501 msec (Grade 3 or 4 QTc prolongation) **or** • uncorrected QT > 600 msec **or** • QTcF > 530 msec for subjects with bundle branch block	• Hold study drug(s) until QTcB prolongation resolves to Grade 1 or baseline • Recommend testing of serum potassium, calcium, phosphorus, and magnesium. If abnormal, correct per routine clinical practice to within normal limits • Review concomitant medication usage for a prolonged QTc • Restart study drug(s) at the current dose level[b] • If the event recurs, permanently discontinue study treatment
a. Based on average QTc value of triplicate ECGs. For example, if an ECG demonstrates a prolonged QT interval, obtain two or more ECGs over a brief period, and then use the averaged QTc values of the three ECGs to determine if study treatments should be interrupted or discontinued. **b.** If the QTc prolongation resolves to Grade 1 or baseline, the subject may resume study treatment if the investigator and GSK medical monitor agree that the subject will benefit from further treatment.	

6.3.8 Dose Modification and Monitoring for Pneumonitis

- Pneumonitis is typically associated with trametinib. Please follow guidelines for trametinib.
- GSK2141795 may continue when trametinib is on hold if AEs are ≤ grade 2.
- If pneumonitis is grade 3-4, GSK2141795 should be held when trametinib is held. Once pneumonitis has resolved to grade 1 or baseline, GSK2141795 may resume at the same dose.
- If GSK2141795795 has been held for >21 days, a discussion with the PI is required before resuming treatment with the agent.

Dose Modification and Monitoring for Pneumonitis	
Criteria	**Management Guidelines**
For all grades, **obtain high resolution chest CT** if possible.	
Grade 1	Consider evaluation by pulmonologist. Consider room air O_2 saturation at rest via pulse oximetry reading (x2, 5 mins apart). Repeat evaluations every 8-12 weeks until return to within normal limits (WNL). Continue study drug(s) at current dose(s).
Grade 2	For Grade 2 or higher respiratory symptoms (i.e cough, dyspnea, hypoxia, etc.) consider evaluation by pulmonologist. Consider pulmonary function tests including: spirometry, DL_{CO}, and room air O_2 saturation at rest via pulse oximetry reading (x2, 5 mins apart). Repeat evaluations every 8-12 weeks until return to WNL. Consider a bronchoscopy with biopsy and/or bronchoalveolar lavage (BAL). Treat only if symptomatic. Consider corticosteroids if symptoms are troublesome and infective origin is ruled out. Taper as medically indicated. Hold study drug(s) until recovery to ≤ Grade 1, then reduce dose by at least 25%. Discontinue study drug(s) if no recovery to ≤ Grade 1 within 4 weeks. May consider escalation to pre-event dose(s).
Grade 3 or 4	Evaluation by pulmonologist. Required pulmonary function tests including: spirometry, DL_{CO}, and room air O_2 saturation at rest via pulse oximetry reading (x 2, 5 mins apart). Repeat evaluations at least every 8 weeks until return to WNL. Bronchoscopy with biopsy and/or BAL is recommended. Consider corticosteroids if infective origin is ruled out. Taper as medically indicated. **(Grade 3)** Hold study drug(s) until recovery to ≤ Grade 1. Discontinue study drug(s) if no recovery to ≤ Grade 1 within 4 weeks. May consider restarting study drug(s) at a reduced dose(s). Monitor if there is clinical benefit. **(Grade 4)** Discontinue study drug(s)

6.3.9 Dose Modification and Monitoring for Mucositis

Dose Modification and Monitoring for Mucositis	
Criteria	**Management Guidelines**
Grade 1 or 2	Encourage oral hygiene. Offer topical supportive anesthetics. Encourage adequate hydration.
Grade 3 or 4	As above, plus systemic opiate administration as needed. Consider IV hydration and hospital admission as appropriate. Temporarily discontinue study drug(s).

6.3.10 Dose Modifications, Monitoring, and Stopping Rules for Visual Disturbance

Episodes of visual changes have been observed in subjects receiving trametinib, and ocular adverse events are known to be related to trametinib. 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), monitor closely but ophthalmic examination can be deferred. Special attention should be given to retinal findings (e.g. retinal pigment epithelial detachment (RPED), retinal vein abnormalities (e.g. branch or central retinal vein occlusions (RVO)), or optic nerve swelling.

Guidelines regarding management and dose reduction for visual changes and/or ophthalmic examination findings considered to be related to study treatment are provided in the tables below:

Table 6.3.10 A: Management and Dose Modification Guidelines for Visual Changes and/or Ophthalmic Examination Findings
Table 6.3.10 B: NCI-CTCAE v 4.0: "Eye Disorders - Other, specify"
Table 6.3.10 C: Recommended dose modifications for trametinib for retinal pigment epithelial detachments (RPED)
Table 6.3.10 D: NCI-CTCAE v 4.0: "Retinopathy"

Ophthalmologic Exam

At certain time points in the trial and if visual changes develop, an eye exam is indicated. (Refer to Table 6.3.10 A for visual changes stopping criteria). The exam will include best corrected visual acuity, visual field examination, tonometry, slit lamp biomicroscopic examination, and indirect fundoscopy, with special attention to retinal abnormalities. 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.

Table 6.3.10 A: Management and Dose Modification Guidelines for Visual Changes and/or Ophthalmic Examination Findings		
CTCAE Grade[a]	**Adverse Event Management**	**Action and Dose Modification**
Grade 1[b]	• Consult ophthalmologist within 7 days of onset	• If dilated fundus examination cannot be performed within 7 days of onset, interrupt trametinib until RPED, and RVO can be excluded by retina specialist/ophthalmologist. • If RPED and RVO excluded, continue (or restart) trametinib at same dose level • If RPED suspected or confirmed: see RPED dose modification table below; **report as SAE.** • If RVO diagnosed: **Permanently discontinue trametinib and report as SAE.**
Grade 2 and Grade 3	• Consult ophthalmologist immediately • Interrupt trametinib	• If RPED and RVO excluded and ophthalmic findings are consistent with an alternative suspected trametinib-related ocular adverse event (e.g., optic neuropathy), and signs and symptoms resolve to baseline, **resume trametinib at a lower dose (reduced by 0.5 mg) or discontinue trametinib in patients taking 1 mg daily**. • If RPED and RVO excluded and ophthalmic findings are NOT consistent with an alternative suspected trametinib-related ocular adverse event (e.g., optic neuropathy), restart trametinib at same dose level • If RPED diagnosed, see RPED dose modification table below; **report as SAE.** • If RVO diagnosed: **Permanently discontinue trametinib and report as SAE**
Grade 4	• Consult ophthalmologist immediately	• **If RVO or RPED then permanently discontinue trametinib and report as SAE** • If RPED and RVO excluded and ophthalmic findings are consistent with an alternative suspected trametinib-related ocular adverse event (e.g. optic neuropathy), then **permanently discontinue trametinib and report as SAE** • If RPED and RVO excluded, and ophthalmic findings are NOT consistent with an alternative suspected trametinib-related ocular adverse event, interrupt treatment with trametinib and report as an SAE. If signs and symptoms resolve to baseline, may consider restarting trametinib at same or reduced dose

a. Refers to **CTCAE Version 4.0 'Eye disorders – Other, specify,'** as detailed in **Table 6.3.10 B, below**
b. If visual changes are clearly unrelated to study treatment (e.g., allergic conjunctivitis), monitor closely but ophthalmic examination is not required.

Table 6.3.10 B: NCI-CTCAE v 4.0: 'Eye Disorders - Other, specify'	
Grade	**Description**
1	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)
3	Severe or medically significant but not immediately sight-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL
4	Sight-threatening consequences; urgent intervention indicated; blindness (20/200 or worse) in the affected eye

Table 6.3.10 C: Recommended dose modifications for trametinib for retinal pigment epithelial detachments (RPED)[a]	
Grade 1 RPED (Asymptomatic; clinical or diagnostic observations only)	• Continue treatment with retinal evaluation monthly until resolution. If RPED worsens follow instructions below and withhold trametinib for up to 3 weeks
Grade 2-3 RPED (Symptomatic with Mild to moderate decrease in visual acuity; limiting instrumental ADL	• Withhold trametinib for up to 3 weeks
Grade 2-3 RPED that improves to Grade 0-1 within 3 weeks	• If improved within 3 weeks, resume trametinib at a lower dose (reduced by 0.5 mg) or discontinue trametinib in patients taking trametinib 1 mg daily
Grade 2-3 RPED that does not improve to at least Grade 1 within 3 weeks	• Permanently discontinue trametinib

a. Refers to **CTCAE Version 4.0 'Retinopathy,'** as detailed in **Table 6.3.10 D, below**

Table 6.3.10 D: NCI-CTCAE v 4.0: 'Retinopathy'	
Grade	**Description**
1	Asymptomatic; clinical or diagnostic observations only
2	Symptomatic with moderate decrease in visual acuity (20/40 or better); limiting instrumental ADL
3	Symptomatic with marked decrease in visual acuity (worse than 20/40); disabling; limiting self care ADL
4	Blindness (20/200 or worse) in the affected eye

6.4 Dose Adjustment/Stopping Safety Criteria for Other Clinically Significant Toxicities

Dose modification guidelines are outlined in the table below for clinically significant toxicities, including hematologic toxicities, that are deemed related to study medication(s) but are not addressed above. If a given toxicity is considered by the

investigator to be related to a single investigational drug and not both, then dose modification may occur only with the drug associated with a specific toxicity or event of clinical concern.

Dose Modification Guidelines for GSK1120212 (trametinib) and/or GSK2141795	
Toxicity Grade[a]	**Dose Modification of GSK1120212 (trametinib) and/or GSK2141795**
Grade 1	Continue at current dose level. Consider supportive care recommendations.
Grade 2	Consider withholding dose until toxicity resolves to Grade 1 or baseline. Upon resolution, then restart at current dose level. Consider supportive care recommendations.
Grade 3	Withhold dose until toxicity resolves to Grade 1 or baseline. Upon resolution, then consider dose reducing by next lower dose level. Consider supportive care recommendations.
Grade 4	Permanently discontinue study medications.

a. Considered related to study drug.

6.4.1 Management of Fever and Neutropenia

Participants who develop fever and neutropenia will be managed via standard medical practice and American Society of Clinical Oncology and NCCN guidelines. Participants will need to recover from fever and active infectious issues prior to resuming therapy. Use of growth factors may be considered after discussion with the primary investigator.

6.4.2 Additional Toxicities

Other toxicities are possible on this trial. Participants developing drug-associated grade 3 or 4 non-hematological toxicities or grade 4 hematological toxicities that do not resolve or improve to grade 1 within 21 days will be removed from protocol. Participants whose toxicity has resolved to baseline or Grade 1 and whose therapy has been discontinued for fewer than 21 days may resume therapy with 1 level of dose reduction.

7. DRUG FORMULATION AND ADMINISTRATION

7.1 GSK1120212 (Trametinib)

Please refer to the Investigator's Brochure for GSK1120212 information in addition to the information below.

7.1.1 Description

Chemical Structure:	GSK1120212 polycyclic, nitrogen containing heterocycle also possessing aromatic halide and amide functionality, and is a dimethyl sulfoxide solvate. The biochemical structure has been unambiguously identified.
Other Names:	GSK1120212B, trametinib
Classification:	MEK 1/2 inhibitor
Approximate Solubility:	Almost insoluble in water (<0.0001 mg/mL at 25°C). Aqueous solubility is not affected by pH in the range 2-10.
Mode of Action:	The RAS-ERK pathway is downstream of EGFR, HER2, IGF1R, and cMet, and is a suspected driver of tumor progression in many cancers. GSK 1120212 inhibits MEK, a kinase within the RAS-ERK cascade.
Description:	MEK 1/2 inhibitor

7.1.2 Form

How Supplied: GSK1120212B Tablets are supplied as 0.5 mg and 2 mg (as free base) tablets for oral administration. GSK1120212B Tablets, 0.5 mg (as free base) are white or yellow, modified oval, biconvex, film-coated tablets. GSK1120212B Tablets, 2 mg (as free base) are pink, round, biconvex, film-coated tablets.

GSK1120212B Tablets are packaged into a high density polyethylene (HDPE) bottle that contains desiccant with a child-resistant closure that includes an induction seal liner. The HDPE bottle may be enclosed in a paperboard carton. The carton is required for white 0.25 mg, 0.5 mg, and 1 mg tablets and optional for yellow 0.5 mg tablets and pink 2 mg tablets.

List of Excipients

Tablet Core:	Mannitol, Microcrystalline cellulose, Hypromellose, Croscarmellose sodium, Magnesium stearate (non-animal), Colloidal silicon dioxide, Sodium lauryl sulfate

Aqueous Film Coating: Opadry White OY-S-28876 (all strengths except 2 mg) containing hypromellose, titanium dioxide, polyethylene glycol; Opadry Pink YS-1-14762-A (2 mg only) containing hypromellose, titanium dioxide, polyethylene glycol, polysorbate 80, iron oxide red; Opadry Yellow 03B120006 (0.5 mg only) containing hypromellose, titanium dioxide, polyethylene glycol, iron oxide yellow

7.1.3 Storage and Stability

The recommended storage conditions, and expiry date where required, are stated on the product label. Under normal conditions of handling and administration, GSK1120212 is not expected to pose significant safety risks to site staff. A Material Safety Data Sheet (MSDS) describing the occupational hazards and recommended handling precautions will be provided to site staff if required by local laws or will otherwise be available from GSK upon request.

7.1.4 Compatibility

Potential Drug Interactions: No clinical drug interaction studies have been performed with GSK1120212. GSK1120212 may induce of inhibitor of major P450 enzymes CYP34A and 2C9.

7.1.5 Availability

GSK1120212 is an investigational agent and will be supplied to investigators by the GSK.

7.1.6 Administration

Route of Administration: Oral

Method of Administration: Take GSK1120212 with 8 oz of water.

7.1.7 Patient Care Implications

In acute overdose, use activated charcoal to reduce the absorption of GSK1120212. If additional measures are needed, consider emptying the stomach. Administer specific medical therapy as clinically appropriate.

7.1.8 Ordering

GSK1120212 may be requested by the Principal Investigators (or their authorized designee) at each participating institution from GlaxoSmithKline.

7.1.9 Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the agent (investigational or free of charge) using the NCI Drug Accountability Record or another comparable drug accountability form. (See the CTEP website at http://ctep.cancer.gov/protocolDevelopment for the "Policy and Guidelines for Accountability and Storage of Investigational Agents" or to obtain a copy of the drug accountability form.)

7.1.10 Destruction and Return

At the end of the study, unused supplies of GSK1120212 should be destroyed according to institutional policies. Destruction will be documented in the Drug Accountability Record Form.

7.2 GSK2141795

Please refer to the Investigator's Brochure for GSK2141795 information in addition to the information below.

7.2.1 Description

Chemical Structure:	GSK2141795
Other Names:	GSK2141795
Classification:	AKT inhibitor
Approximate Solubility:	GSK2141795 is very slightly soluble in water (0.18 mg/ml) at room temperature. > 11 mg/mL in Simulated Gastric Fluid at 37^0C. Solubility decreases as pH increases.
Mode of Action:	The PI3K pathway is downstream of EGFR, HER2, IGF1R, and cMet, and is a suspected driver of tumor progression in many cancers. GSK2141795 inhibits AKT.
Description:	AKT inhibitor

7.2.2 Form

How Supplied: Four strengths of GSK2141795C are supplied as capsules for oral administration equivalent to 1 mg (orange/white, opaque size 4 gelatin capsules with thick and thin bars printed in black ink), 5 mg (blue/white, opaque size 3 gelatin capsules with thick and thin bars printed in black ink), 5 mg (white opaque body and cap, size 3 gelatin capsules), 25 mg (Swedish orange, opaque size 2 gelatin capsules), 100 mg (purple/white, opaque size 1 gelatin capsules with thick and thin bars printed in black ink) or 100 mg

(white opaque body and cap, size 1 gelatin capsules).

The capsules are packaged in white high density polyethylene bottles with white plastic, induction-seal, child-resistant caps.

7.2.3 Storage and Stability

The recommended storage conditions, and expiry date where required, are stated on the product label. Patients can have the drug at room temperature during travel from the clinic to home. The drug should be kept refrigerated once the patient arrives at home. Advise the subjects to notify the study staff if the drug is left at room temperature for long periods of time.

7.2.4 Compatibility

Potential Drug Interactions: No clinical drug interaction studies have been performed with GSK2141795.

7.2.5 Availability

GSK2141795 is an investigational agent and will be supplied to investigators by GlaxoSmithKline.

7.2.6 Administration

Route of Administration: Oral

Method of Administration**:** GSK2121795 should be taken orally, with approximately 200 mL of water. Participants will be expected to fast for 1 hour before and 2 hours after dosing of either study treatment. If a participant vomits after taking either study treatment, the participant should be instructed not to retake the dose and should take the next scheduled dose.

7.2.7 Patient Care Implications

In acute overdose, use activated charcoal to reduce the absorption of GSK2141795. If additional measures are needed, consider emptying the stomach. Administer specific medical therapy as clinically appropriate.

7.2.8 Ordering

GSK2121795 may be requested by the Principal Investigators (or their authorized designee) at each participating institution from GlaxoSmithKline.

7.2.9 Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the agent (investigational or free of charge) using the NCI Drug Accountability Record or another comparable drug accountability form. (See the CTEP website at http://ctep.cancer.gov/protocolDevelopment for the "Policy and Guidelines for Accountability and Storage of Investigational Agents" or to obtain a copy of the drug accountability form.)

7.2.10 Destruction and Return

At the end of the study, unused supplies of GSK2141795 should be destroyed according to institutional policies. Destruction will be documented in the Drug Accountability Record Form.

8. CORRELATIVE/SPECIAL STUDIES

8.1 Hypothesis

The further development and study of molecular targeted therapy has revealed that in many cases, the genetic makeup of the tumor can be used to predict response or resistance to treatment with a given therapeutic. The pre-clinical studies of PI3K pathway and MEK inhibitors, suggest that these drugs will have differential effects on tumors harboring different genetic aberrations [35, 36]. The hypothesis of these studies is that cervical cancers harbor high rates of mutations in both PI3K and RAS pathways and that these mutations may make them more susceptible to agents that target these pathways.

8.2 Preliminary Data

Isolated mutational analyses of PIK3CA, K-RAS and H-RAS genes from cervical cancers from different clinical cohorts have identified mutational rates of 10-33%, 10% and 9-22% respectively [9, 29, 32]. Parallel mutational analysis of these genes has not been reported and, as such, it is unknown if co-mutation occurs (as it does commonly in endometrial cancer) [37]. These studies are underway at the DF/HCC.

8.3 Study Design

Tumor specimens from archived specimens will be required for all participants in the clinical study. Tissue will be requested from either the original hysterectomy specimen or from biopsies at recurrence. A single vial of whole blood will also be collected for isolation of control germline DNA. Dependent upon the amount of DNA available, targeted mutation detection, targeted gene sequencing or targeting SNP analysis will be performed (see methodology below). Correlative studies of RAS isoform mutation and PIK3CA mutation to clinical benefit will be performed (see Appendix H for details). Optional pre and post- treatment biopsies will be requested from participants whose tumors are amenable to an in-office biopsy (e.g. vaginal recurrence or cervical recurrence). Participants who derive benefit from GSK1120212 and GSK2126458 and whose tumors are amenable to an in-office biopsy will be offered optional biopsies at the time of progression. These samples will be amenable to more detailed protein evaluation including pharmacodynamic studies and exploration of mechanisms of resistance. These studies will be exploratory in nature (see analytic plan).

8.4 Study Population

Tumors tissue will be sought from all participants in the clinical study.

8.5 Methodology

Unlike other gynecologic malignancies, surgery is not necessarily performed on all patients and hysterectomy tissues, which can be ample, will not be available for all participants. As such, correlative studies will need to be designed with the presumption

that material will be available from biopsies at recurrence, which have limited tissue. Technology advances now allow for parallel sequencing of multiple targets, from small amounts of DNA (50-500ng) For this study, we propose to evaluate the PI3K and RAS-ERK pathway in detail with the use of either next generation targeted sequencing, mutation detection with sequenome technology, or SNP hybridization analysis for mutation and copy number analysis (all described in Appendix H). The decision of which assay to use will depend upon amount of DNA available as well as proven validity of each assay at the time of sample processing as these technologies are being rapidly improved. For example, targeted DNA sequencing could offer the discovery of new gene mutations as well as some information about copy number. However, it may be more susceptible to false positives. It is expected that there will be advanced in the precision and experience with all of these assays by the time these samples are studied (approximately 2 years from now). Pre-and post- treatment as well as progression samples will be collected both in formalin as well as flash frozen. Formalin samples will be paraffin embedded. These samples will be H and E stained for histological evaluation. IHC or RPPA will performed on frozen samples.

8.6 Analytic Plan

Molecular correlative analyses will be conducted and all patient outcomes: response, PFS, OS and toxicity will be compared between the PIK3CA and RAS-isoform mutated and WT groups using the statistical methodologies specified above; estimating the proportion of participants harboring mutations in both genes is also of interest, as is comparing their outcomes to those in the remainder of the cohort. These analyses are considered exploratory and will not be adjusted for multiple comparisons.

8.7 Specimen Requirements

Participation in the laboratory correlative study component of this study is mandatory for all participants. Additional details regarding correlative studies are outlined in Appendix H and the lab manual. The participating institution will collect and submit the patient's specimens as outlined below:

Required Specimen	Collection Time Point	Specific Instructions
Archival Formalin-Fixed Paraffin-Embedded (FFPE) Tumor **Required for Study Eligibility**	Collected prior to initiating study treatment	1st choice: block 2nd choice: 25 unstained sections (10- 5 µm and 15- 10 µm)
Pre-treatment Whole Blood	Collected prior to initiating study treatment	Blood drawn into **two (2)** EDTA tubes, 7-10 mL blood into each tube

Required Specimen	Collection Time Point	Specific Instructions
Pre-treatment Plasma	Collected prior to initiating study treatment	7-10 mL drawn into appropriate plasma separator tube
Snap Frozen Primary Tumor[1]	Collected prior to initiating study treatment	N/A
Pre-treatment Biopsy[2]	Collected after screening and prior to initiating study treatment	Minimum 3 cores: 1 FFPE 2 snap frozen
Post-treatment Biopsy[3]	Collected at Cycle 1 between Days 8-15[4], after initiation of study treatment	Minimum 3 cores: 1 FFPE 2 snap frozen
Post-progression Biopsy[5]	Collected within 6 weeks of progression	Minimum 3 cores: 1 FFPE 2 snap frozen

[1] If available from the participating institution's tissue banks
[2] Optional in participants with accessible, biopsiable lesions
[3] Only in participants who had an initial pre-treatment biopsy. Post-treatment biopsy will not be required in participants who have had a complete response or whose tumor has responded such that lesions are no longer biopsiable.
[4] Can be collected at any point during Cycle 1 between Days 8-15, preferred. If unable to collect during Days 8-15 for scheduling reasons, it will be acceptable to perform the biopsy between Days 15-28 of Cycle 1.
[5] Optional in participants with accessible, biopsiable lesions

Shipping instructions for frozen samples will be clarified at a later time point.

Sites should send ambient FFPE biopsy samples directly to the Clinical Research Coordinator at the following address:

Ariana Peralta
Dana-Farber Cancer Institute
450 Brookline Avenue, D117
Boston, MA 02215
Telephone: 617-632-3743
Email: aperalta2@partners.org

9. STUDY CALENDAR

Baseline evaluations should be conducted within **14 days** prior to start of protocol therapy. **Scans must be done ≤ 28 days** prior to the start of therapy. All assessments must be performed **prior to administration** of any study medication. All study assessments should be administered within **+/- 3 days** of the protocol-specified date, unless otherwise noted. Study assessments not required after an indicated timepoint should be performed **as clinically indicated** in the future. In the event that the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy. **One treatment cycle is 28 days** in duration.

Study Assessments [a]	**Screen** [b]	**Cycle 1**				**Cycle 2**	**Cycle 3**	**Cycle 4**	**Subsequent Cycles** [c]	**Even Cycles**	**Off-Treatment Visit** [d]
		Day 1	**Day 8**	**Day 15**	**Day 22**	**Day 1**	**Day 1**	**Day 1**	**Day 1**	**Between Days 22 - 28**	
Informed Consent	X										
Demographics	X										
Medical History / Interim History	X	X	X [e]	X	X [e]	X	X	X	X		X
Physical Exam [f]	X	X		X		X	X	X	X		X
ECOG Performance Status	X	X [g]		X		X	X	X	X		X
Vital Signs [w]	X	X		X		X	X	X	X		X
Height and Weight [v]	X	X [g]				X	X	X	X		X
Hematology [h]	X	X [g]	X [e]	X	X [e]	X	X	X	X		X
Clinical Chemistry [i]	X	X [g]	X [e]	X	X [e]	X	X	X	X		X
Fasting Blood Glucose [y]	X	X	X	X	X	X	X	X	X		X
Coagulation [j]	X	X [g]									
Creatinine Clearance	X										
Pregnancy Test [k]	X							X [v]			X
Fasting Lipid Panel	X							X [v]			X
Hemoglobin A1C	X							X [v]			X
TSH	X							X [v]			X
1,5-anhydroglucitol (1,5-AG) [l]	X			X		X [l]	X [l]	X [l]			
12-Lead ECG [m]	X	X		X					X		X
ECHO or MUGA [n]	X					X [u]					X

Study Assessments [a]	Screen [b]	Cycle 1				Cycle 2	Cycle 3	Cycle 4	Subsequent Cycles [c]	Even Cycles	Off-Treatment Visit [d]
		Day 1	Day 8	Day 15	Day 22	Day 1	Day 1	Day 1	Day 1	Between Days 22 - 28	
Ophthalmic Exam [o]	X										
Disease Assessment [r]	X									X	X
Brain Imaging [s]	X									X	
Chest Imaging (X-ray or CT) [t]	X									X	X
Trametinib and GSK2141795 Dosing		X (Continuous daily dosing) ---------- X									
Circulating Free Tumor DNA [p]		X [g]									X
Archival Tumor Tissue [p]	X										
Biopsies [q]	X		X								X
Concomitant Medications	X	X (Continuous) ---------- X									
Adverse Events		X (Continuous) ---------- X									

a. Assessments should be done prior to administration of study drug(s), unless otherwise specified.

b. Within 14 days before first dose with the following exceptions:
- LVEF assessment can occur within 45 days of first dose
- disease assessment can occur within 28 days of first dose

c. If clinically indicated, assessments during subsequent cycles can occur more frequently.

d. Final study visit should occur 21 days (±7 days) after last dose of study drug.

e. Medical history and interim history for Cycle 1 Day 8 and Day 22 can be obtained through a phone call to the participant. Hematology and clinical chemistry can be obtained locally.

f. Physical exams should be completed as follows:
- Screening physical exam should include: the evaluation of the head, eyes, ears, nose, and throat, cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal and neurological systems.
- After screening, targeted physical examinations should be limited to systems of primary relevance and those systems associated with symptoms.

g. If completed within 72 hours prior to dosing, this assessment does not need to be repeated.

h. Hematology should include: red blood cell count, total white blood cell count, hemoglobin, hematocrit, platelet count, WBC differential (absolute)

i. Clinical chemistry should include: sodium, BUN, creatinine, bicarbonate, chloride, calcium, LDH, phosphorus, GGT, magnesium, potassium, total protein, albumin, SGOT (AST), SGPT (ALT), alkaline phosphatase, total bilirubin

j. Coagulation should include: prothrombin time (PT)/international normalized ratio (INR) and activated partial thromboplastin time (aPTT).

k. Perform only in women of child-bearing potential. A serum pregnancy test should be performed at screening; subsequent pregnancy tests may be either

serum or urine.

l. Should be collected pre-dose while the participant is on treatment. If 1,5-AG test is not available in a given country, the analyte is not required to be performed in that country.

m. A single 12-lead ECG should be performed at screening, prior to dosing on Day 1 and Day 15 of Cycle 1, and prior to dosing on Day 1 of each subsequent cycle.

n. Either an ECHO or MUGA should be performed to assess LVEF at screening, Cycle 2 Day 1, then every 12 weeks, at the final study visit, and as symptomatically warranted

o. Ophthalmic exam will include indirect and direct fundoscopy, visual acuity (corrected), visual field examination, tonometry, and color fundus photos. Additional ophthalmic exams will be performed if symptomatically warranted.

p. Refer to the Lab Manual and Section 8.7 of the protocol.

q. Pre-treatment biopsy to be collected after screening and prior to initiation of study treatment. Post-treatment biopsy to be collected at Cycle 1 at any point during Days 8 – 14 (preferred); collected during Days 15-28 are also acceptable. Post-progression biopsy to be collected within 6 weeks of progression. Refer to Section 8.7.

r. CT or MRI in between Days 22-28 of every even cycle. The same radiographic procedure used for screening should be used throughout the study. A confirmatory disease assessment should be performed no fewer than 4 weeks (28 days) after the criteria for response (PR or CR) are first met. If subject was withdrawn due to radiographic progression of disease (PD), disease assessments do not need to be repeated at the final study visit.

s. Head CT with contrast or brain MRI imaging required only for subjects with brain metastases present at screening.

t. Chest imaging required only for subjects with chest metastases present at screening. If a patient develops pneumonitis while on study, a high-resolution chest CT should be obtained, if feasible.

u. Repeat every 12 weeks from the time point marked with footnote "u."

v. Height to be measured at baseline only.

w. Vital signs should include: BP, HR, Temperature.

y. Fasting blood glucose levels should be obtained weekly during Cycle 1 (locally, along with Clinical Chemistry). If $\geq$ grade 2 hyperglycemia occurs, initiate **daily home glucose monitoring**, until FBS resolves to $\leq$ grade 1. Daily glucose monitoring should be recorded by the participant in the Home Glucose Monitoring Diary (Appendix K). Please refer to Section 6.3.3.

10. MEASUREMENT OF EFFECT

For the purposes of this study, participants should be reevaluated at the end of every 2 cycles (+/- 1 week) and should be completed prior to the participant initiating the next cycle. In addition to a baseline scan, confirmatory scans should also be obtained at least 4 weeks following initial documentation of an objective response.

10.1 Antitumor Effect– Solid Tumors

For the purposes of this study, participants should be re-evaluated for response every 2 cycles (+/- 1 week), which should be completed prior to the participant initiating the next cycle. In addition to a baseline scan, confirmatory scans should also be obtained at least 4 weeks following initial documentation of objective response. The next scheduled restaging scan may be used as the confirmatory scan.

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) (Eisenhauer et al, 2009) guideline version 1.1. Changes in the diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria.

10.1.1 Definitions

Evaluable for toxicity. All participants who receive at least one dose of study treatment will be evaluable for toxicity from the time of their first treatment.

Evaluable for objective response. Only those participants who have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression or die due to disease progression prior to the end of cycle 1 will also be considered evaluable.)

10.1.2 Disease Parameters

Measurable Disease
Measurable disease is the presence of at least one (1) lesion that can be accurately measured in at least one dimension with longest diameter > 20 millimeters (mm) using conventional techniques (CT, MRI, x-ray) or $\geq$ 10 mm with spiral CT scan. Measurable lesions must be at least 2 times the slice thickness in mm. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Lesions situated in a previously irradiated area will be considered measurable if there is objective evidence of progression of the lesion prior to study enrollment. Lesions in previously irradiated areas must be clearly identified as such.

Malignant lymph Nodes
To be considered pathologically enlarged and measurable, a lymph node must be $\geq$ 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 < 15mm short axis, are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques, and cystic lesions are all considered non-measurable.

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. Lesions must be accurately measured in 1 dimension with a minimum size of 10 mm by CT or MRI (slice thickness no greater than 5 mm), 20 mm by *chest* x-ray. Nodes must have a short axis ≥ 15 mm. The short axis should be included in the sum of the lesions in the calculation of response. Nodes that shrink to < 10 mm are considered normal. Target lesions should be selected on the basis of their size, be representative of all the involved organs, and should be lesions that can be followed with reproducible repeated measurements.

Lytic bone lesions or mixed lytic-blastic lesions, *with identifiable soft tissue components*, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered target lesions if the *soft tissue component* meets the definition of measurability as defined above. Cystic lesions thought to represent cystic metastases can be considered as target lesions. However, if non-cystic lesions are present, these are preferred for selection as target lesions. Lesions in previously irradiated areas or areas subject to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression of that lesion.

Non-target Lesions
All other lesions, including small lesions < 10 mm or pathological lymph nodes measuring ≥ 10 mm to < 15 mm in short axis, as well as truly non-measurable lesions, which include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques.

10.2 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation, using a ruler, calipers, or digital measurement tool. 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 when both methods have been used to assess the anti-tumor effect of a treatment.

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
These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols. MRI is also acceptable in certain situations (e.g. for body scans).

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 version 1.1 guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

10.3 Response Criteria

10.3.1 Evaluation of Target Lesions

Complete Response (CR):
Disappearance of all target lesions. Any pathological lymph node 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 with at least a 5 mm absolute increase in the sum of all lesions. The appearance of one or more new lesions* denotes disease progression.

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.

Unknown (UN):
Assessment of target lesions cannot be made due to insufficient or unevaluable data. In this case, a concise explanation must be given.

Note: If tumor response data is missing for target lesions, the overall assessment must be UN unless there is new disease that would result in an overall assessment of PD. However, if there is missing or unevaluable data for non-target lesions, but data is available for all target lesions, the overall response for that time point will be assigned based on the sum LD of all target lesions. Additionally, the assessment of CR cannot be made if there is missing or unevaluable data for non-target lesions. In this case, the overall assessment would be PR.

***Definition of New Lesion**: The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality or findings thought to represent something other than tumor (ex: new bone lesions may be healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size, etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

10.3.2 Evaluation of Non-Target Lesions

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

Note: If tumor markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response.

Incomplete Response/Stable Disease (SD):
Persistence of one or more non-target lesions and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD):
Appearance of one or more new lesions* (new lesions must be > slice thickness) and/or unequivocal progression of existing non-target lesions.

Overall level of substantial worsening that merits discontinuation of therapy. A useful test that can be applied when assessing non-targets for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease.

Unknown (UN):
Assessment of non-target lesions cannot be made due to insufficient or unevaluable data. In this case, a concise explanation must be given.

***Definition of New Lesion**: The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (ex: new bone lesions may be healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size, etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

10.3.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The participant's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Participants with Measurable Disease (i.e., Target Disease)				
Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**	**Best Overall Response for when Confirmation is Required:**
CR	CR	No	CR	≥ 4 wks confirmation
CR	Non-CR/Non-PD	No	PR	≥ 4 wks confirmation
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/Not evaluated	No	PR	
SD	Non-CR/Non-PD/Not evaluated	No	SD	Documented at least once ≥ 4 wks from baseline
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as *"symptomatic deterioration"*. Every effort should be made to document the objective progression even after discontinuation of treatment.

10.3.4 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 recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

Duration of overall complete response: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

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

10.3.5 Progression-Free Survival

Progression-Free Survival (PFS) is defined as the duration of time from start of treatment to time of objective disease progression.

10.3.6 Response Review

Radiology assessments for DF/HCC sites will be provided by the DF/HCC tumormetrics core. Assessment for other participating sites should be performed per local protocols. All complete or partial responses should be confirmed by the DF/HCC tumormetrics core. Please see Appendix I for procedures for submission of materials for DF/HCC tumormetrics review from non-DF/HCC participating institutions.

11. ADVERSE EVENT REPORTING REQUIREMENTS

11.1 Definitions

11.1.1 Adverse Event (AE)

An adverse event (AE) is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study.

Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

Please see Section 6.1, "Anticipated Toxicities" for specific information about expected toxicities for both study agents.

11.1.2 Serious Adverse Event (SAE)

A serious adverse event (SAE) is any adverse event, occurring at any dose and regardless of causality that:

- **Results in death.**
- **Is life-threatening.** Life-threatening means that the person was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- **Requires or prolongs inpatient hospitalization** (i.e., the event required at least a 24-hour hospitalization or prolonged a hospitalization beyond the expected length of stay). Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered SAEs if the illness or disease existed before the person was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).
- **Results in persistent or significant disability/incapacity.** Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- **Is a congenital anomaly or birth defect.**
- **Is an important medical event** when, based upon appropriate medical judgment, it may jeopardize the participant and require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
- **Newly diagnosed cancer** (not the cancer under treatment).
- **Overdose.**

Events **not** considered to be serious adverse events are hospitalizations for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- elective or pre-planned treatment for a pre-existing condition that did not worsen
- emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- respite care

11.1.3 Expectedness

Adverse events can be 'Expected' or 'Unexpected.'

Expected Adverse Event

Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.

Refer to Section 6.1 for a listing of expected adverse events associated with the study agents.

Unexpected Adverse Event

For the purposes of this study, an adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list, the Investigator's Brochure, the package insert or when it is not included in the informed consent document as a potential risk.

11.1.4 Attribution

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

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

11.2 Procedures for AE and SAE Recording and Reporting

Participating investigators will assess the occurrence of AEs and SAEs at all participant evaluation time points during the study.

All AEs and SAEs whether reported by the participant, discovered during questioning, directly observed, or detected by physical examination, laboratory test or other means,

will be recorded in the participant's medical record and on the appropriate study-specific case report forms.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4. The CTCAE version 4 can be downloaded from the CTEP website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

11.3 Reporting Requirements

For multi-site trials where a DF/HCC investigator is serving as the principal investigator, each participating investigator is required to abide by the reporting requirements set by the DF/HCC. The study must be conducted in compliance with FDA regulations, local safety reporting requirements, and reporting requirements of the principal investigator.

Each investigative site will be responsible to report SAEs that occur at that institution to their respective IRB. It is the responsibility of each participating investigator to report serious adverse events to the study sponsor and/or others as described below.

11.4 Reporting to the Study Sponsor

11.4.1 Serious Adverse Event Reporting

All serious adverse events that occur after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment must be reported to the DF/HCC Overall Principal Investigator on the local institutional SAE form. This includes events meeting the criteria outlined in Section 11.1.2, as well as the following:

- Grade 2 (moderate) and Grade 3 (severe) events that are unexpected and at least possibly related/associated with the intervention.
- All Grade 4 (life-threatening or disabling) events that are unexpected or not specifically listed in the protocol as not requiring reporting.
- All Grade 5 (fatal) events while the participant is enrolled and actively participating in the trial OR when the event occurs within 30 days of the last study intervention.

Note: If the participant is in long term follow up, report the death at the time of continuing review.

Participating investigators must report each serious adverse event to the DF/HCC Overall Principal Investigator within 1 business day of learning of the occurrence. In the event that the participating investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 1 business day after learning of it and document the time of

his or her first awareness of the adverse event. Report serious adverse events by facsimile (preferred), email, or telephone to:

Ursula Matulonis, MD
Phone: 617 632-2334
Fax: 617-582-7921
Pager: 617-632-3352
Email: umatulonis@partners.org

Within the following 24-48 hours, the participating investigator must provide follow-up information on the serious adverse event. Follow-up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation.

For multi-institution studies where a DF/HCC investigator is serving as the Overall Principal Investigator, each participating institution must abide by the reporting requirements set by the DF/HCC. This applies to any medical event equivalent to an unexpected grade 2 or 3 with a possible, probable or definite attribution, unexpected grade 4 toxicities, and grade 5 (death) regardless of study phase or attribution.

11.4.2 Non-Serious Adverse Event Reporting

Non-serious adverse events will be reported to the DF/HCC Overall Principal Investigator on the toxicity Case Report Forms.

11.5 Reporting to NCCN and GSK

In addition to complying with all applicable regulatory reporting laws and regulations, the DF/HCC Overall Principal Investigator will report the following information to NCCN and Grantor in writing via fax **within one business day of the occurrence**, referencing the applicable Protocol number that is assigned by Grantor upon approval of the Study. Such reports shall be directed to the following contacts at NCCN and GSK:

NCCN:
Email: **ORPReports@nccn.org**

GSK:
Michael Arbushites and Jeremey Levin
Fax: 610-200-1767 or
Email: Michael.2.arbushites@gsk.com
and Jeremey.2.levin@gsk.com

Reports include:

(a) All SAEs;
(b) Reports of pregnancy exposure (pregnancy encompasses the entire course of pregnancy and delivery, perinatal and neonatal outcomes, even if there were no abnormal findings; both maternal and paternal exposure is collected);
(c) Reports of lactation exposure;
(d) Overdose (with or without an SAE);
(e) Abuse (use for non-clinical reasons with or without an SAE);
(f) Inadvertent or accidental exposure; and
(g) Follow-up information regarding any of the above.

The Investigator should include his or her assessment of the causal relationship between each SAE and the Grantor product in the form faxed to Grantor and NCCN.

11.6 Reporting to the Institutional Review Board (IRB)

Investigative sites within DF/HCC will report all serious adverse events directly to the DFCI Office for Human Research Studies (OHRS).

Other investigative at external sites will report SAEs to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. A copy of the submitted institutional SAE form should be forwarded to the Overall PI within the timeframes detailed in the table below.

DF/HCC Reportable AEs					
Attribution	**Gr. 2 & 3 AE Expected**	**Gr. 2 & 3 AE Unexpected**	**Gr. 4 AE Expected**	**Gr. 4 AE Unexpected**	**Gr. 5 AE Expected or Unexpected**
Unrelated Unlikely	Not required	Not required	5 calendar days[#]	5 calendar days	24 hours*
Possible Probable Definite	Not required	5 calendar days	5 calendar days[#]	5 calendar days	24 hours*
# If listed in protocol as expected and not requiring expedited reporting, event does not need to be reported.					
* For participants enrolled and actively participating in the study ***or*** for AEs occurring within 30 days of the last intervention, the AE should be reported within 24 business hours of learning of the event.					

Other investigators must submit SAE reports to the Overall PI via this contact information:

Ursula Matulonis, MD
Phone: 617 632-2334
Fax: 617-582-7921
Pager: 617-632-3352
Email: umatulonis@partners.org

The Overall PI will submit SAE reports from outside institutions to the DFCI OHRS according to DFCI IRB policies and procedures in reporting adverse events.

11.7 Reporting to the Food and Drug Administration (FDA)

The DF/HCC Overall Principal Investigator, as holder of the IND, will be responsible for all communication with the FDA. The DF/HCC Overall Principal Investigator will report to the FDA, regardless of the site of occurrence, any adverse event that is serious, unexpected and reasonably related (i.e., possible, probable, definite) to the investigational agents.

Unexpected fatal or life-threatening experiences associated with the use of the investigational agents will be reported to FDA as soon as possible but in no event later than 7 calendar days after initial receipt of the information.

All other serious unexpected experiences associated with the use of the investigational agents will be reported to FDA as soon as possible but in no event later than 15 calendar days after initial receipt of the information.

Events will be reported to the FDA using Form FDA 3500A (Mandatory Reporting Form for investigational agents) by sending the paper report via overnight, traceable delivery service. Forms are available at http://www.fda.gov/medwatch/getforms.htm

11.8 Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any subject safety reports or sentinel events that require reporting according to institutional policy.

11.9 Monitoring of Adverse Events and Period of Observation

All adverse events, both serious and non-serious, and deaths that are encountered from initiation of study intervention, throughout the study, and within 30 days of the last study intervention should be followed to their resolution, or until the participating investigator assesses them as stable, or the participating investigator determines the event to be irreversible, or the participant is lost to follow-up. The presence and resolution of AEs and SAEs (with dates) should be documented on the appropriate case report form and recorded in the participant's medical record to facilitate source data verification.

For some SAEs, the study sponsor or designee may follow-up by telephone, fax, and/or monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. Participating investigators should notify the DF/HCC Overall Principal Investigator and their respective IRB of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

12. DATA AND SAFETY MONITORING

12.1 Data Reporting

12.1.1 Method

The QACT will collect, manage, and monitor data for this study.

12.1.2 Data Submission

The schedule for completion and submission of case report forms (paper or electronic) to the QACT is as follows:

Form	Submission Timeline
Eligibility Checklist	Complete prior to registration with QACT
On Study Form	Within 14 days of registration
Baseline Assessment Form	Within 14 days of registration
Treatment Form	Within 10 days of the last day of the cycle
Adverse Event Report Form	Within 10 days of the last day of the cycle
Response Assessment Form	Within 10 days of the completion of the cycle required for response evaluation
Off Treatment/Off Study Form	Within 14 days of completing treatment or being taken off study for any reason
Follow up/Survival Form	Within 14 days of the protocol defined follow up visit date or call

12.2 Safety Meetings

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this trial. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Principal Investigator and study team.

The DSMC will meet quarterly and/or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days for Phase I or II protocols; for gene transfer protocols, summary of all deaths while being treated and during active follow-up; any response information;

audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3 Monitoring

Involvement in this study as a participating investigator implies acceptance of potential audits or inspections, including source data verification, by representatives designated by the DF/HCC Overall Principal Investigator (or Protocol Chair) or DF/HCC. The purpose of these audits or inspections is to examine study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported in accordance with the protocol, institutional policy, and any applicable regulatory requirements.

All data will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. Monitoring will begin at the time of participant registration and will continue during protocol performance and completion. Please see Section 5.0 of the Data and Safety Monitoring Plan (Appendix C) for monitoring details.

13. REGULATORY CONSIDERATIONS

13.1 Protocol Review and Amendments

This protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other necessary documents must be submitted, reviewed and approved by a properly constituted IRB governing each study location.

Any changes made to the protocol must be submitted as amendments and must be approved by the IRB prior to implementation. Any changes in study conduct must be reported to the IRB. The DF/HCC Overall Principal Investigator (or Protocol Chair) will disseminate protocol amendment information to all participating investigators.

All decisions of the IRB concerning the conduct of the study must be made in writing.

13.2 Informed Consent

All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant's legally authorized representative, and by the person obtaining the consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

13.3 Ethics

This study is to be conducted according to the following considerations, which represent good and sound research practice:

- US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki
  - Title 21 Part 50 – Protection of Human Subjects www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html
  - Title 21 Part 54 – Financial Disclosure by Clinical Investigators www.access.gpo.gov/nara/cfr/waisidx_02/21cfr54_02.html
  - Title 21 Part 56 – Institutional Review Boards www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html
  - Title 21 Part 312 – Investigational New Drug Application www.access.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html
- State laws
- DF/HCC research policies and procedures http://www.dfhcc.harvard.edu/clinical-research-support/clinical-research-unit-cru/policies-and-procedures/

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. In such case, the deviation must be reported to the IRB according to the local reporting policy.

13.4 Study Documentation

The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified.

Original source documents supporting entries in the case report forms include but are not limited to hospital records, clinical charts, laboratory and pharmacy records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays.

13.5 Records Retention

All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

13.6 Multi-center Guidelines

This protocol will adhere to the policies and requirements of the Dana-Farber/Harvard Cancer Center. The specific responsibilities of the DF/HCC Overall Principal Investigator (or Protocol Chair), Coordinating Center, and Participating Institutions are presented in the Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (see Appendix C)

- The DF/HCC Overall Principal Investigator/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports to all participating institutions for submission to their individual IRBs for action as required.
- Mechanisms will be in place to ensure quality assurance, protocol compliance, and adverse event reporting at each site.
- Except in very unusual circumstances, each participating institution will order the agents directly from the supplier. A participating site may order the agents only after the initial IRB approval for the site has been forwarded to the Coordinating Center.

14. STATISTICAL CONSIDERATIONS

14.1 Study Design/Endpoints

14.1.1 Study Design

This is an open label single-arm single-stage phase II multicenter trial.

14.1.2 Primary Objective

To assess the activity of GSK1120212 and GSK2141795 in combination in patients with recurrent or persistent cervical cancer. Activity will be ascertained by estimation of best objective tumor response per RECIST version 1.1.

14.1.3 Secondary Objectives

- To assess the duration of progression-free and overall survival following initiation of therapy with GSK1120212 and GSK2141795

- To determine the nature and degree of toxicity of GSK1120212 and GSK2141795 as assessed by version 4 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) in this cohort of patients.

- To describe the mutation and co-mutation rates of genes in the PI3K and RAS-ERK signaling pathways in recurrent cervical cancer using high throughput targeted mutational analysis on participant tumor samples.

- To explore the association of mutational status with clinical benefit from GSK1120212 and GSK2141795.

14.2 Statistical Analysis

The primary objective of this study is estimation of the best objective response rate (CR + PR) per RECIST 1.1. With the planned accrual of 35 participants to this single-arm trial, there is 91% power to detect an improvement in response rate from 0.07 to 0.22 using a one-sided 0.09-level exact binomial test. Therefore, the null hypothesis will be rejected if 5 or more participants respond to combination therapy with GSK1120212 and GSK2141795. The null hypothesis of 0.07 is based on a weighted average of the observed response rates from the 11 cohorts enrolled to GOG 127 and 227 series.

Secondary objectives include progression-free and overall survival, both of which will be estimated by the Kaplan-Meier method. PFS is defined as the time from registration to the study until documented disease progression or death without progression, whichever occurs first. Participants not experiencing a PFS event will be censored at the last date of documented disease evaluation. Overall survival is defined as the time from study registration to the time of death from any cause, with follow-up censored at the last date

known to be alive. Cox's proportional hazards models will be fitted to explore significant predictors of event-time endpoints.

Toxicity data will be tabulated and compared between any groups of interest using Fisher's exact tests, and will be routinely monitored, analyzed and reviewed by the DF/HCC DSMC.

Molecular correlative analyses will be conducted and all patient outcomes: response, PFS, OS and toxicity will be compared between the PIK3CA and RAS-isoform mutated and WT groups using the statistical methodologies specified above; estimating the proportion of participants harboring mutations in both genes is also of interest, as is comparing their outcomes to those in the remainder of the cohort. These analyses are considered exploratory and will not be adjusted for multiple comparisons.

14.3 Sample Size/Accrual Rate

The planned sample size is a maximum of 35 participants. The estimated monthly accrual rate is 2 participants. Participants will be followed for a maximum of 3 years.

14.4 Reporting and Exclusions

14.4.1 Evaluation of Toxicity

All participants will be evaluable for toxicity from the time of their first treatment.

14.4.2 Evaluation of Response

All participants included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each participant should be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.

All participants who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. Participants in response categories 5-9 will not be considered evaluable but will remain within the intention to treat analysis.
Participants who develop brain metastasis on study, but continue on study after definitive treatment of their cranial disease, will be considered to have had progressive disease at the point of the diagnosis of the initial brain metastasis.

All conclusions should be based on all evaluable participants. Subanalyses may then be performed on the basis of a subset of participants, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the

reasons for excluding participants from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

15. PUBLICATION PLAN

Publication guidelines exist within the DF/HCC Gynecologic Oncology Program. The study principal investigator will be responsible for collection of data, interpretation of data, monitoring of toxicities, and publication of abstracts and final manuscripts. The principal investigator chooses the different authorship slots per the DF/HCC gynecologic oncology program guidelines.

The results should be made public within 24 months of the end of data collection. The NCCN research agreement stipulates that the initial publication will be submitted to a peer-reviewed journal six months after the Trial's conclusion as defined by data lock or termination of the study.

16. REFERENCES

1. GSK1120212 Investigator's Brochure

2. Yamaguchi T, Kakefuda R, Tajima N, Sowa Y, Sakai T. Antitumor activities of JTP-74057 (GSK1120212), a novel MEK1/2 inhibitor, on colorectal cancer cell lines in vitro and in vivo.Int J Oncol. 2011 Jul;39(1):23-31.

3. GSK2141795 Investigator's Brochure

4. Mendoza MC, Er EE, Blenis J. The Ras-ERK and PI3K-mTOR pathways: cross-talk and compensation. Trends Biochem Sci. 2011 Jun;36(6):320-8.

5. Engelman, J.A., J. Luo, and L.C. Cantley, The evolution of phosphatidylinositol 3-kinases as regulators of growth and metabolism. Nat Rev Genet, 2006. 7(8): p. 606-19.

6. Yuan, T.L. and L.C. Cantley, PI3K pathway alterations in cancer: variations on a theme. Oncogene, 2008. 27(41): p. 5497-510.

7. Downward, J., Targeting RAS signalling pathways in cancer therapy. Nat Rev Cancer, 2003. 3(1): p. 11-22.

8. Yan, J., et al., Ras isoforms vary in their ability to activate Raf-1 and phosphoinositide 3-kinase. J Biol Chem, 1998. 273(37): p. 24052-6.

9. Forbes, S.A., et al., COSMIC (the Catalogue of Somatic Mutations in Cancer): a resource to investigate acquired mutations in human cancer. Nucleic Acids Res, 2010. 38(Database issue): p. D652-7.

10. Engelman, J.A., et al., Effective use of PI3K and MEK inhibitors to treat mutant Kras G12D and PIK3CA H1047R murine lung cancers. Nat Med, 2008. 14(12): p. 1351-6.

11. Carracedo, A., et al., Inhibition of mTORC1 leads to MAPK pathway activation through a PI3K-dependent feedback loop in human cancer. J Clin Invest, 2008. 118(9): p. 3065-74.

12. G. Shapiro, P.L., E. L. Kwak, J. M. Cleary, L. Musib, C. Jones, A. de Crespigny, M. Belvin, M. McKenzie, M. R. Gates, I. T. Chan, J. C. Bendell. Clinical combination of the MEK inhibitor GDC-0973 and the PI3K inhibitor GDC-0941: A first-in-human phase Ib study testing daily and intermittent dosing schedules in patients with advanced solid tumors. in ASCO. 2011. Chicago: J Clin Oncol.

13. Siegel, R., et al., Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. CA Cancer J Clin, 2011. 61(4): p. 212-36.

14. Jemal, A., et al., Global cancer statistics. CA Cancer J Clin, 2011. 61(2): p. 69-90.

15. Long, H.J., 3rd, Management of metastatic cervical cancer: review of the literature. J Clin Oncol, 2007. 25(20): p. 2966-74.

16. Keys, H.M., et al., Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. N Engl J Med, 1999. 340(15): p. 1154-61.

17. Morris, M., et al., Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. N Engl J Med, 1999. 340(15): p. 1137-43

18. Rose, P.G., et al., Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. N Engl J Med, 1999. 340(15): p. 1144-53.

19. Peters, W.A., 3rd, et al., Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. J Clin Oncol, 2000. 18(8): p. 1606-13.

20. Omura, G.A., et al., Randomized trial of cisplatin versus cisplatin plus mitolactol versus cisplatin plus ifosfamide in advanced squamous carcinoma of the cervix: a Gynecologic Oncology Group study. J Clin Oncol, 1997. 15(1): p. 165-71.

21. Brewer, C.A., et al., Cisplatin plus gemcitabine in previously treated squamous cell carcinoma of the cervix: a phase II study of the Gynecologic Oncology Group. Gynecol Oncol 2006. 100(2): p. 385-8.

22. Moore, D.H., et al., Phase III study of cisplatin with or without paclitaxel in stage IVB, recurrent, or persistent squamous cell carcinoma of the cervix: a gynecologic oncology group study. J Clin Oncol, 2004. 22(15): p. 3113-9.

23. Long, H.J., 3rd, et al., Randomized phase III trial of cisplatin with or without topotecan in carcinoma of the uterine cervix: a Gynecologic Oncology Group Study. J Clin Oncol, 2005. 23(21): p. 4626-33.

24. Thigpen, T., et al., Cis-platinum in treatment of advanced or recurrent squamous cell carcinoma of the cervix: a phase II study of the Gynecologic Oncology Group. Cancer, 1981. 48(4): p. 899-903.

25. Moore, D.H., et al., Prognostic factors for response to cisplatin-based chemotherapy in advanced cervical carcinoma: a Gynecologic Oncology Group Study. Gynecol Oncol, 2010. 116(1): p. 44-9.

26. Tewari, K.S. and B.J. Monk, Recent achievements and future developments in advanced and recurrent cervical cancer: trials of the Gynecologic Oncology Group. Semin Oncol, 2009. 36(2): p. 170-80.

27. Monk, B.J., et al., Phase II trial of bevacizumab in the treatment of persistent or recurrent squamous cell carcinoma of the cervix: a gynecologic oncology group study. J Clin Oncol, 2009. 27(7): p. 1069-74.

28. Bertelsen, B.I., et al., Molecular analysis of the PI3K-AKT pathway in uterine cervical neoplasia: frequent PIK3CA amplification and AKT phosphorylation. Int J Cancer, 2006. 118(8): p. 1877-83.

29. Janku, F., et al., PIK3CA mutations frequently coexist with RAS and BRAF mutations in patients with advanced cancers. PLoS One, 2011. 6(7): p. e22769.

30. Janku, F., et al., PIK3CA mutations in patients with advanced cancers treated with PI3K/AKT/mTOR axis inhibitors. Mol Cancer Ther, 2011. 10(3): p. 558-65.

31. Wright AA, MS Hirsch, N Wagle, BE Howitt, E Palescandolo, LE MacConaill, P Van Hummelen, M Shoni, WC Hahn, UA Matulonis. *KRAS* and *EGFR* mutations to distinguish adenocarcinomas and squamous cell carcinomas *of t*he c*ervix*. J Clin Oncol 30, 2012 (suppl; abstr) 5011.

32. Wegman, P., C. *Ahlin*, an*d B.* Sorbe, Genetic alterations in the K-Ras gene influence the prognosis in patient*s wit*h ce*rvica*l cancer treated by radiotherapy. Int J Gynecol Cancer, 2011. 21(1): p. 86-91.

33. Kim, T.J., et al., Increased expression of pAKT is associated with radiation resistance in cervical cancer. Br J Cancer, 2006. 94(11): p. 1678-82.

34. Courtney, K.D., R.B. Corcoran, and J.A. Engelman, The PI3K pathway as drug target in human cancer. J Clin Oncol, 2010. 28(6): p. 1075-83.

35. Bollag, G., et al., Clinical efficacy of a RAF inhibitor needs broad target blockade in BRAF-mutant melanoma. Nature, 2010. 467(7315): p. 596-9.

36. She, Q.B., et al., Breast tumor cells with PI3K mutation or HER2 amplification are selectively addicted to Akt signaling. PLoS One, 2008. 3(8): p. e3065.

37. Cheung, L.W., et al., High Frequency of PIK3R1 and PIK3R2 Mutations in Endometrial Cancer Elucidates a Novel Mechanism for Regulation of PTEN Protein Stability. Cancer Discov, 2011. 1(2): p. 170-185.

38. Wagle, N., et al., Dissecting therapeutic resistance to RAF inhibition in melanoma by tumor genomic profiling. J Clin Oncol, 2011. 29(22): p. 3085-96.

39. Thomas, R.K., et al., High-throughput oncogene mutation profiling in human cancer. Nat Genet, 2007. 39(3): p. 347-51.

40. Wang, Y., et al., High quality copy number and genotype data from FFPE samples using Molecular Inversion Probe (MIP) microarrays. BMC Med Genomics, 2009. 2: p. 8.

41. Davern TJ 2nd, James LP, Hinson JA, Polson J, Larson AM, Fontana RJ, Lalani E, Munoz S, Shakil AO, Lee WM; Acute Liver Failure Study Group. Measurement of serum acetaminophen-protein adducts in patients with acute liver failure. Gastroenterology. 2006 Mar;130 (3):687-94.

17. APPENDICES

APPENDIX A: Performance Status Criteria

ECOG Performance Status Scale	
Grade	**Description**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX B: New York Heart Association Classification of Heart Failure

Class	Patient symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased

APPENDIX C: Participant Drug Diaries for GSK1120212 (trametinib) and GSK2141795

PATIENT'S MEDICATION DIARY: GSK1120212 (trametinib)

Protocol # 13-334

Instructions:

1. Complete one form for each cycle of treatment.
2. Take _____ (number) _____mg (dosage) tablet(s) of **GSK1120212 (trametinib)** daily within 1-2 hours. You must fast for 1 hour before and 2 hours after taking study medication. If a dose is forgotten or vomited, **do not** make up the dose. Take with 9 oz of water. **Do not** eat grapefruit, drink grapefruit juice while taking medications. **Do not** crush, chew, or dissolve study medications.
3. Record the date, the number 0.5 mg tablets that you took, and when you took them. **Do not** batch entries at a later time. You have up to 2 hours from your scheduled dosing time to take the study medications. If it is beyond 2 hours, you must skip the dose.
4. If you have any comments or notice any side effects please record them in the comments column.
5. Please bring this form and the bottles of trametinib tablets when you return for each appointment.

Today's Date: _____ **Agents: GSK1120212 (trametinib)**

Patient Name: _____ (*initials acceptable)* **Patient Study ID:** _____

Date	Day	Time	# of 0.5 mg tablets taken of trametinib	Comments
	1			
	2			
	3			
	4			
	5			
	6			
	7			
	8			
	9			
	10			
	11			
	12			
	13			
	14			
	15			
	16			
	17			
	18			
	19			
	20			
	21			
	22			
	23			
	24			
	25			
	26			
	27			
	28			

Patient's Signature: _____ **Date:** _____ **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 or Research Nurse Signature:	

PATIENT'S MEDICATION DIARY: GSK2141795

Protocol # 13-334

Instructions:

1. Complete one form for each cycle of treatment. GSK2141795 must be **stored in your refrigerator.**
2. Take _____ (number) _____mg (dosage) capsule(s) of **GSK2141795** daily within 1-2 hours. You must fast for 1 hour before and 2 hours after taking study medication. If a dose is forgotten or vomited, **do not** make up the dose. Take with 9 oz of water. **Do not** eat grapefruit, drink grapefruit juice while taking medications. **Do not** crush, chew or dissolve study medications.
3. Record the date, the number of 25 mg capsules you took, and when you took them. Do not batch entries at a later time. You have up to 2 hours from your scheduled dosing time to take the study medications. If it is beyond 2 hours, you must skip the dose.
4. If you have any comments or notice any side effects please record them in the comments column.
5. Please bring this form and the bottles of GSK2141795 capsules when you return for each appointment.

Today's Date: _____ **Agents: GSK2141795**

Patient Name: _____ *(initials acceptable)* **Patient Study ID:** _____

Date	Day	Time	# of 25 mg capsules taken of GSK2141795	Comments
	1			
	2			
	3			
	4			
	5			
	6			
	7			
	8			
	9			
	10			
	11			
	12			
	13			
	14			
	15			
	16			
	17			
	18			
	19			
	20			
	21			
	22			
	23			
	24			
	25			
	26			
	27			
	28			

Patient's Signature: _____ **Date:** _____

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 capsules taken this month:	
5. Physician or Research Nurse Signature:	

APPENDIX D: List of Prohibited Medications

The following medications, including but not limited to, are **prohibited during the study**:

PROHIBITED – highly sensitive and/or low therapeutic index CYP3A/CYP2C8/BCRP/ CYP3A4 substrates since concentrations of these drugs may be increased	
CYP3A Substrate	**Therapeutic Area**
Cisapride	Hypnotics and Sedatives
Pimozide	Antidepressant, Antipsychotics, Antianxiety agents
Astemizole	Antihistamine
BCRP Substrate	
rosuvastatin, sulfasalazine	HMG-CoA Reductase Inhibitors, gastrointestinal agents
PROHIBITED – strong inducers/inhibitors of CYP3A4	
Strong CYP3A4 Inhibitor/Inducer	**Therapeutic Area**
clarithromycin, telithromycin, rifamycin class agents (e.g., rifampin, rifabutin, rifapentine), troleandomycin	Antibiotics
itraconazole, ketoconazole	Antifungals
Nefazodone	Antidepressants
atazanzvir, delaviridine, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, nevirapine	Antivirals
carbamazepine, phenobarbital, phenytoin	Anticonvulsants

APPENDIX E: List of Cautionary Medications

Medications, including but not limited to the following, that may alter the concentrations of GSK1120212 or GSK2141795 or have their elimination altered by GSK1120212 or GSK2141795 **should be administered WITH CAUTION**.

USE WITH CAUTION – Drugs Potentially Affecting GSK1120212 or GSK2141795 concentrations	
Drug	**Therapeutic Area**
quinidine, diltiazem, verapamil	Antiarrhythmics:
fluvoxamine, fluoxetine,	Antidepressants:
aprepitant, cimetidine	Antiemetics
fluconazole, terbinafine, voriconazole	Antifungals
ciprofloxacin, erythromycin, isoniazid	Anti-infectives
mibefradil, diltiazem, verapamil	Calcium Channel Blockers
aprepitant,oxandrolone, tizanidine,	Miscellaneous
USE WITH CAUTION – Drugs that may inhibit P-gp and BCRP	
Drug	**Therapeutic Area**
valspoda	Miscellaneous
atorvastatin,	HMG-CoA Reductase Inhibitors
carvedilol	Congestive Heart Failure
methadone	Analgesic
meperidine	Narcotic
omeprazole	Proton Pump Inhibitor
USE WITH CAUTION – Drugs that may have their concentrations altered by GSK1120212 or GSK2141795	
repaglinide, rosiglitazone, pioglitazone	Antidiabetics
alfentanil, fentanyl	Analgesics
quinidine	Antiarrhythmics
cilostazole	Anticoagulants and Antiplatelets
astemizole	Antihistamines
diergotamine, ergotamine, eletriptan	Antimigraine agents
pimozide	Antipsychotics
buspirone	Anxiolytics
felodipine	Calcium Channel Blockers
sildenafil, tadalafil, vardenafil	Erectile Dysfunction agents
cerivastatin,ovastatin, simvastatin,	HMG-CoA Reductase Inhibitors

alprazolam, diazepam, midazolam, triazolam	Hypnotics and Sedatives
cyclosporine, sirolimus, tacrolimus	Immunosuppressive agents
cisapride	Prokinetic agents
cyclosporine, torsemide, chloroquine,	Miscellaneous
eperenone	Selective Aldosterone Blockers
chloroquine, zopiclone	Thiazolidnediones

Use of repaglinide, rosiglitazone and/or pioglitazone is permitted only after approval of the study PI.

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. Budenoside 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 his/her appropriate designee) will be expected to review concomitant medications with the subject at each clinical visit.

APPENDIX F: CTCAE v 4.0 Grading of Visual Changes

Visual Changes - Grading Based on NCI-CTCAE v 4.0

Grade	Description
1	Asymptomatic or symptomatic but not limiting ADL; clinical or diagnostic observations only; intervention not indicated
2	Symptomatic with moderate decrease in visual acuity (20/40 or better); limiting instrumental ADL; local or noninvasive intervention indicated (e.g., topical or oral agents)
3	Symptomatic with marked decrease in visual acuity or marked visual field defect (worse than 20/40 but better than 20/200 in the affected eye); Severe pain or medically significant but not immediately sight-threatening; operative intervention indicated; disabling; limiting self care ADL
4	Sight-threatening consequences; urgent intervention indicated; blindness (20/200 or worse) in the affected eye

Ophthalmologic Exam

Subjects are required to have a standard ophthalmic exam performed by an ophthalmologist at baseline and as clinically warranted per protocol's guidance (Refer to Section 6.3.9 for visual changes stopping criteria). The exam will include indirect fundoscopic examination, visual acuity (corrected), visual field examination, tonometry, and direct fundoscopy, with special attention to retinal abnormality that are predisposing factors for RVO or CSR.

For participants with clinical suspicion of RVO or CSR, fluorescein angiography and/or optical coherence tomography are highly recommended.

APPENDIX G: Laboratory Correlative Studies

Mutational Analysis

OncoPanel

OncoPanel sequencing on archival specimens will be obtained from all patients where available. OncoPanel is a targeted next generation sequencing panel selected based on clinical actionability in cancer that is designed for the detection of single-nucleotide variants, insertions and deletions, copy number alterations, and structural variants. A validation study demonstrated that OncoPanel could successfully identify multiple types of genetic alterations, with a sensitivity of 98% for single-nucleotide variants, 84% for indels, 86% for copy number variants, and 74% for structural variants when compared to appropriate orthogonal detection methods, including single-gene assays, mass spectrometry-based genotyping, array comparative genomic hybridization, or fluorescence in situ hybridization (Garcia 2017). Where OncoPanel sequencing has already been performed on patient samples through DF/HCC protocol 11-104, we will plan to access these results to conserve primary patient samples for additional analyses.

Targeted Sequencing [38]

Samples will be analyzed by next generation sequencing on a 2.1Mb subset of the genome with relevance in cancer development. 300ng genomic DNA will be randomly sheared to 250bp average fragments and ligated to sequence adaptors that contain sequencing primers and sample specific barcodes. Using Agilent's Sureselect hybrid capture technology the exonic sequences of 646 genes will be enriched for each samples and up to 12 samples with unique barcodes are pooled and subsequently sequenced on a Hiseq2000 sequencer from Illumina. We will sequence 2x 100bp of each sample in a pair-end mode until an average coverage of around 300x. After sequencing, variant sequences will be determined using cancer-specific variant discovery tools (GATK), including MuTect for Somatic base substitutions and Somatic Indel Detector for insertions and deletions.

Mutation Detection

OncoMap is a high throughput sequencing assay using Sequenom technology that has been developed by investigators at Dana-Farber Cancer Institute and the Broad Institute, with the goal of being able to interrogate for known cancer mutations from formalin-fixed paraffin-embedded (FFPE) tissues as well as from fresh tissue [36] this assay, a series of primers have been designed that enable mutation detection (e.g., point mutations and small deletions or insertions) in a multiplexed fashion. Using publicly available resources such as COSMIC (www.sanger.ac.uk), as well as internal sequencing databases generated at the Broad Institute, an expanded cancer gene mutation assay collection has been generated. In total, an expanded iPLEX assay collection has been compiled that includes approximately 1138 functioning, non-redundant mutations in 114 oncogenes and selected tumor suppressor genes. Whole genome amplification (WGA) will be performed using the phi-29 DNA polymerase strand-displacement method using the GenomePlex Complete Whole Genome Amplification kit (Sigma). For each sample, a PCR reaction is performed to assess DNA quality. Specifically, we amplify three fragments of 100 bp, 150 bp, and 200 bp respectively derived from chromosomes 14, 17 and 21. Two of the three

fragments must be amplified to pass this quality assurance step.

Samples will be run on the mass spectrometry based genotyping platform and analyzed according to current standardized protocols [39]. Control samples with known oncogenic mutations will be included in each plate. In addition, induction of experimental artifacts by WGA will be assessed by examining the status of 24 SNPs using a 100K SNP array (Affymetrix). If we identify ≥3 SNP discrepancies between the SNPs found in pre- and post-WGA samples, then this sample is not used for further analysis. Typer Analyzer v3.4 (Sequenom), which identifies mutations based on an algorithm that was initially developed to detect germline SNPs, will be used to identify oncogenic mutations.

Each mutation identified by this approach will be validated using two methods. First, confirmatory evaluations will be performed using a different platform (homogeneous Mass EXTEND®, hem). Next, direct sequencing will be performed from the genomic DNA. Based on prior experience, the amount and quality of DNA isolated for this analysis is sufficient to perform these validation studies.

SNP Hybridization for Copy Number Analysis or Somatic Mutation [40]

This assay tagged nucleotide probes designed to target the candidate region within genomic DNA. Hybridized probes are then selected for in an exonuclease reaction, amplified and hybridized to an array with the tagged sequences, supplying both qualitative and quantitative data on point mutations and, when applied to contiguous probes, genomic copy number. This assay uses as little as 50 ng of DNA per reaction and is successful with the use of DNA derived from FFPE samples. In collaboration with Affymetrix, the SU2C Dream Team Studying "PI3K signaling in Women's Cancers" has designed a chip specifically for detecting mutations and copy number alterations in 200 genes that are commonly molecularly altered in breast, ovarian, and endometrial cancers. Given the focus on specific genes within the whole genome, the density of coverage can be increased, allowing for a more sensitive copy number analysis. This chip has 300, 000 probes to identify mutation and copy number alteration in these 200 genes.

Protein Expression Analysis

IHC

Pre-treatment snap frozen core biopsy, post-treatment snap frozen core biopsy, and post-progression snap frozen core biopsy specimens will be directly shipped to pathology core, where specimens will be freshly sectioned for IHC expression analyses. IHC staining will be conducted for pAKT, pS6K, pPRAS40, and pERK. For pAKT and pS6K, nuclear and cytoplasmic staining will be assessed and if both are present the specimen will be scored as positive; otherwise the specimen will be scored as negative. If there is not sufficient material to perform all assays, the order of priority will be pAKT, pERK, pPRAS40.

RPPA

RPPA is high-throughput antibody-based technique used to compare protein levels in different samples. Using standard methods protein will be extracted from the collected tissues described above. They will be processed by the core proteomic facility at MD Anderson. In brief, lysates

will be serially diluted, denatured, printed on nitrocellulose-coated slides and probed with validated antibodies that recognize signaling molecules or their activated forms. Signals will be captured by tyramide dye deposition (CSA System, DAKO). Data will be collected and analyzed using quantification software specifically developed for this approach The RPPA platform contains 127 protein antibodies involved in cancer growth (26). To identify protein changes associated with drug resistance, data will be analyzed by K-means analysis and principle component analysis.

Copy Number Analysis

Should there be ample material DNA will be extracted from FFPE primary tumor sections for copy number analysis. Copy number alterations will be determined in aliquots of tumor DNA by array comparative genome hybridization (aCGH) using one of several platforms. The platforms currently available to us are the Agilent 1M CGH microarray, the Affymetrix MIP chip, and a custom Agilent CGH array. These platforms vary in breadth of coverage and sample requirements. At the time of research testing, contemporary metrics will be compared and based on sample availability, one of these or similar platforms will be employed. A minimum of 50ng of DNA is required for the MIP chips, 500ng of DNA is required for the custom Agilent array, and at least 1ug of DNA is required for the 1M Agilent array.

PTEN Assay

Unstained sections of formalin-fixed, paraffin-embedded primary tumor and biopsies will be collected for analysis of PTEN by immunohistochemistry. Five micrometer thick unstained slides of archival FFPE tumor will be used for IHC expression analyses. Tumor expression of PTEN will be assessed by immunohistochemistry at the BWH. Loss of PTEN will be evaluated in a CLIA certified laboratory at the BWH by immunostaining for PTEN in a validated immunohistochemistry assay with the rabbit monoclonal antibody 138G6 (Cell Signaling, Cat No 9559). Results scored as follows. Complete absence of or minimal (<10% of tumor cells) staining in the tumor cells in the presence of internal positive control (stromal cells, lymphocytes) will be interpreted as PTEN loss. Cases will be scored as being PTEN positive or retained if all or majority of the tumor shows positive staining. Cases with patchy PTEN staining will be interpreted as showing mixed staining.

APPENDIX H: DF/HCC Tumor Imaging Metrics Core (TIMC) Submission Procedures for non-DF/HCC Sites

All participants with measurable disease with partial or complete responses on trial should have their responses confirmed by the DF/HCC Tumor Imaging Metrics Core (TIMC). For participants with responses, the following materials should be submitted to the Dana-Farber Cancer Institute:

- Baseline CT/MRI study on CD
- CT/MRI documenting response on CD
- CT/MRI confirming response on CD
- Radiology reports from baseline CT/MRI and CT/MRIs in which response was documented and confirmed.

All materials should be sent to the Clinical Research Coordinator at the following address:

Ariana Peralta
Dana-Farber Cancer Institute
450 Brookline Ave, D117
Dana-Farber Cancer Institute
Boston, MA 02215
Telephone: 617-632-3743
Email: aperalta2@partners.org

APPENDIX I: Data Collection Forms

Data collection will occur through the use of the Electronic Data Capture (EDC) system through Phase Forward Inform.

Sites should identify the appropriate data management personnel. An EDC team member from DFCI will contact each site to provide information regarding training on the EDC as well as EDC site access to identified personnel. Site members at each site will need to complete online training prior to obtaining access to the electronic system.

APPENDIX J: PATIENT'S HOME GLUCOSE MONITORING DIARY

Protocol # 13-334

Instructions:

1. Take home glucose readings as instructed by your study doctor or study nurse.
2. Record date, time, and value of glucose reading below.

Patient Name_____ (*initials acceptable)* **Patient Study ID** _____

		AM Reading		PM Reading				AM Reading		PM Reading	
Date	**Day**	**Time**	**Glucose Value**	**Time**	**Glucose Value**	**Date**	**Day**	**Time**	**Glucose Value**	**Time**	**Glucose Value**
	1						15				
	2						16				
	3						17				
	4						18				
	5						19				
	6						20				
	7						21				
	8						22				
	9						23				
	10						24				
	11						25				
	12						26				
	13						27				
	14						28				

Patient's Signature: _____ **Date:** _____

Physician's Office will complete this section:
Physician or Research Nurse Signature: _____ Date: _____

Appendix K: QT interval on ECG corrected using the Bazett's formula (QTcB)

Bazett's formula used to correct QT interval for heart rate is:

$$QTcB = \frac{QT}{\sqrt{RR}}$$

Where QTcB is the QT interval corrected for heart rate, RR is the interval from the onset of one QRS complex to the onset of the next QRS complex, measured in seconds, often derived from the heart rate (HR) as 60/HR, and QT is the QT interval measured in milliseconds.

Reference

Bazett HC. An analysis of the time-relations of electrocardiograms. Heart 1920; 7: 353-370.