SUMMARY OF CHANGES

For Protocol Amendment #15 to: A Randomized Two-Arm Phase II Study of Trametinib Alone and in Combination with GSK2141795 in Patients with Advanced Uveal Melanoma

NCI Protocol #: 9445
Local Protocol #: 13-144

NCI Version Date: 12/01/2016
Protocol Date: 12/01/2016

#	Section	Page(s)	Change
1.	N/A	N/A	Formatting and grammatical changes have been made throughout the protocol.
2.	N/A	N/A	NCI version date was updated to 12/01/2016 throughout the protocol document.
3.	N/A	N/A	Local IRB amendment number has been updated to A(15) throughout the protocol document.
4.	Protocol Type/Version Date	4	Amended/Version 1.13/Version date: 12/01/2016 was added to this section.
5.	Table of Contents	7-9	The table of contents was updated to reflect the body of the protocol.
6.	5.3	43	Upon discussion with Helen Chen, MD, we have revised the protocol to state that under special circumstance, continued therapy may be considered on a case-by-case basis if the patient is considered benefiting from the treatment.
7.	7.1.1	57-61	In response to NCI RRA, dated November 18, 2016 from Helen Chen, MD, the Trametinib CAEPR was updated to Version 2.4, October 7, 2016.

NCI Protocol #: 9445

Protocol Version Date: 12/01/2016

Local Protocol #: 13-144

TITLE: A Randomized Two-Arm Phase II Study of Trametinib Alone and in Combination with GSK2141795 in Patients with Advanced Uveal Melanoma

Coordinating Center:
Memorial Sloan Kettering Cancer Center
1275 York Ave
New York, NY 10065

***Principal Investigator:**
Alexander Shoushtari, MD*
Memorial Sloan Kettering Cancer Center
300 East 66th Street
New York, NY 10065
Telephone: 646-888-4161
Fax: 646-888-4253
E-mail: shoushta@mskcc.org

Co-Principal Investigator:
Paul Chapman, MD*

MSK Co-Investigators:
(* = Consenting Professionals)
Ping Chi, MD, PhD*
Sandra D'Angelo, MD*
Mark Dickson, MD*
Mary Louise Keohan, MD*
William Tap, MD*

IRBPB7592

Mrinal Gounder, MD*
Michael Postow, MD*
Margaret Callahan, MD, PhD*
Jedd Wolchok, MD, PhD*
Mark Bluth, MD
Joseph P. Erinjeri, MD, PhD
Mario E. Lacouture, MD
Katherine Panageas, DrPH
Mimma Errante, NP
Yelena Shames, NP
Nana Prempeh-Kete Ku, NP

***Consenting professionals**

Collaborating Site	Principal Investigator	Site's Role
M.D. Anderson Cancer Center	*Sapna Patel, MD MD Anderson Cancer Center 1515 Holcombe Blvd. Unit 430 Houston, TX 77030 Telephone: 713-792-4955 Email: SPPatel@mdanderson.org	Data Collection and Specimen Analysis
H. Lee Moffitt Cancer Center	*Geoffrey Gibney, MD H. Lee Moffitt Cancer Center 12902 Magnolia Drive, SRB-4 CUT-PROG Tampa, FL 33612 Telephone: 813-745-3437 Fax: 813-449-8584 Email: Geoffrey.Gibney@moffitt.org	Data Collection
Vanderbilt University Medical Center	*Kristin Kathleen Ancell, MD Vanderbilt University Medical Center 2220 Pierce Avenue 777 PRB Nashville, TN 37232 Phone: 615-322-4967 Email: Kristin.k.ancell@vanderbilt.edu	Data Collection
Emory University	*Ragini Kudchadkar, MD Emory University Winship Cancer Institute 1365-C Clifton Road Atlanta, GA 30322 Telephone: 404-778-1900 Email: rkudcha@emory.edu	Data Collection
New York Presbyterian Hospital/Columbia University, College of Physicians and Surgeons	*Richard D. Carvajal, MD New York Presbyterian Hospital/Columbia University, College of Physicians and Surgeons Milstein Hospital, Division of Hematology/Oncology 161 Ft. Washington Avenue New York, NY 10032 Telephone: 646-317-6041 E-mail: rdc2150@cumc.columbia.edu	Data Collection and Specimen Analysis Only

Institut Curie (EORTC)	*Sophie Piperno-Neuamnn, MD, PhD Institut Curie 26, rue d'Ulm 75231 Paris, France Telephone: 33 (0)1 44 32 46 72 Email: sophie.piperno-neumann@curie.net	Data Collection and Specimen Analysis
University of Liverpool	Sarah Coupland, MBBS, PhD, FRCPath University of Liverpool Department of Molecular and Clinical Cancer Medicine Institute of Translational Medicine 6th Floor Duncan Building Daulby Street Liverpool, L69 3GA Telephone: +44-151-706-5885 or 4494 Email: S.E.Coupland@liverpool.ac.uk	Specimen Analysis Only

Statistician:
Katherine Panageas, DrPH
Memorial Sloan Kettering Cancer Ctr
307 E 63rd St., 3rd Floor (Box 44), NY, NY 10065
Tel: 646-735-8119
panageak@mskcc.org

Study Coordinator:
Leigh Gaffney
Memorial Sloan Kettering Cancer Ctr
300 E 66th St., 12th Floor NY, NY 10065
Tel: 646-888-4375
Fax: 646-227-2426
frigugll@mskcc.org

Responsible Research Nurse:
Mimma Errante, NP
Memorial Sloan Kettering Cancer Ctr
160 E 53rd Street, NY, NY 10065
Tel: 646-888-4377
errantem@mskcc.org

Responsible Data Manager:
Roshani Shah
Memorial Sloan Kettering Cancer Ctr
300 E 66th St., 12th Floor NY, NY 10065
Tel: 646-888- 4375
Fax: 646-227-2426
shahr4@mskcc.org

Research Project Coordinator (for participating sites):
Talal Khawaja
Memorial Sloan Kettering Cancer Center
1114 First Avenue 7th Floor
New York, NY 10065
Tel: 646-888-1006
Fax: 646-227-2482
khawajat@mskcc.org

NCI Supplied Agents: Trametinib dimethyl sulfoxide (GSK1120212B) (NSC 763093)
GSK2141795 (NSC 767034)

IND Sponsor: NCI
IND 119432

Protocol Type / Version # / Version Date: Original / Version 1.0 / Version Date: 03/27/2013
Original / Version 1.1 / Version Date: 06/15/2013
Original / Version 1.2 / Version Date: 07/11/2013
Original / Version 1.3 / Version Date: 08/19/2013
Amended / Version 1.4 / Version Date: 09/17/2013
Amended / Version 1.5 / Version Date: 02/10/2014
Amended / Version 1.6 / Version Date: 04/28/2014
Amended / Version 1.7 / Version Date: 06/20/2014
Amended / Version 1.8 / Version Date: 10/20/2014
Amended / Version 1.9 / Version Date: 03/18/2015
Amended / Version 1.10 / Version Date: 08/10/2015
Amended/ Version 1.11/ Version Date: 11/06/2015
Amended/ Version 1.12/ Version Date: 04/20/2016
Amended/ Version 1.13/ Version Date: 12/01/2016

SCHEMA

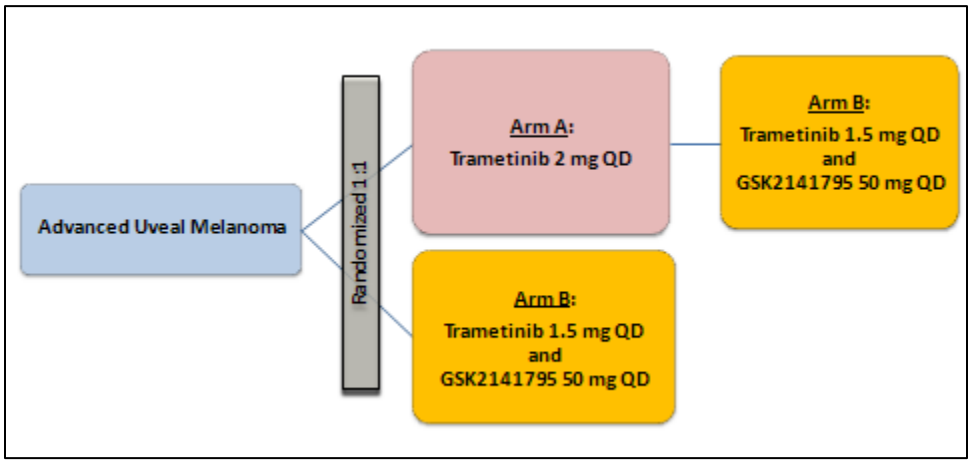
This trial is a randomized phase II study of trametinib alone or in combination with GSK2141795 in patients with advanced uveal melanoma. The primary endpoint (outcome measure) of this trial is progression-free survival (PFS). Secondary endpoints include overall survival (OS), RECIST response, and safety/toxicity. Exploratory endpoints include correlation of clinical outcome with Gnaq/11 mutational status.

All treatment will be performed in the outpatient setting. Eighty eligible and evaluable patients will be randomized on a 1:1 ratio, with randomization stratified by (i) the presence or absence of liver involvement and (ii) LDH (< 2 times ULN versus ≥ 2 times the upper limit of normal) to one of the two treatment arms:

1. Arm A (Trametinib): Experimental Arm A will explore the activity of MEK inhibition using trametinib in advanced UM. Patients randomized to this arm will receive trametinib 2 mg PO QD on a continual basis in 4 week cycles.

2. Arm B (Trametinib and GSK2141795): Experimental Arm B will explore the activity of combined MEK and AKT inhibition in advanced UM. Patients randomized to this arm will receive trametinib 1.5 mg PO QD in combination with GSK2141795 50 mg PO QD on a continual basis in 4 week cycles.

The study schema is as follows:



Tumor response will be measured radiographically at baseline, week 8, and every 8 weeks subsequently using standard RECIST 1.1 criteria. Although central radiology review will not be performed in real-time, all imaging studies will be collected to allow for the possibility of retrospective central review. Patients will remain on their initially assigned treatment arm until the sooner of (i) disease progression (primary outcome measure) or (ii) the development of unacceptable toxicity that is not manageable with dose reduction.

At that point, patients initially randomized to Arm A who develop disease progression and who remain eligible for trial therapy based upon the trial inclusion/exclusion criteria will be given the

option of receiving additional experimental therapy with trametinib and GSK2141795. This option will not be available to patients who are taken off treatment due to the development of unacceptable toxicity that is not manageable with dose reduction. This will provide, in an exploratory fashion, information about the ability of AKT inhibition with GSK2141795 to salvage progression to trametinib. Tumor response assessments and progression-free survival will be recorded, but these patients will not be included in analysis of the primary analysis of PFS after first randomization; however, clinical outcome will be followed and reported in a descriptive fashion.

Pre-treatment paraffin embedded tissue will be collected from all patients at baseline for Gnaq/11 molecular analysis, with additional tissue stored for the future conduct of additional correlative studies. All patients with safely accessible tumor will undergo pre- and post-treatment (day 14 +/- 3 days) tumor biopsies for biomarker and correlative analysis. The decision to not pursue these biopsies must be made in collaboration with the MSK Principal Investigator. An additional tumor biopsy will be requested from patients at the time of disease progression; however, this biopsy is optional. Blood samples will be collected from all patients at baseline and on a monthly basis for correlative analysis.

As of 11/06/2015, Arm B met the specified stopping rule for futility. The remaining patients will be accrued to Arm A, no patients will be enrolled to Arm B or Crossover therapy.

TABLE OF CONTENTS

1 OBJECTIVES

1.1 Primary Objectives

- To compare progression-free survival between those treated with trametinib alone and those treated with the combination of trametinib and GSK2141795

1.2 Secondary Objectives

- To compare overall survival between those treated with trametinib alone and those treated with the combination of trametinib and GSK2141795
- To compare the overall response rate between those treated with trametinib alone and those treated with the combination of trametinib and GSK2141795
- To compare the safety and toxicity between those treated with trametinib alone and those treated with the combination of trametinib and GSK2141795

1.3 Exploratory Objectives

- To assess clinical outcomes (response rate, progression-free and overall survival) with trametinib and GSK2141795 after progression on trametinib
- To assess toxicity with trametinib and GSK2141795 after progression on trametinib
- To correlate clinical outcome with Gnaq/11 mutational status
- To assess the pharmacodynamic effects of trametinib alone and with GSK2141795, and utilize whole-transcriptome and reverse phase protein array to identify markers of sensitivity and primary resistance to trametinib alone and with GSK2141795
- To assess for changes in circulating tumor DNA with therapy

2 BACKGROUND

2.1 Uveal Melanoma

Uveal melanoma is the most common primary intraocular malignancy in adults, and arises from melanocytes within the choroid plexus of the eye.[1] Melanomas of the ocular and adnexal structures comprise approximately 5% of all melanomas and are biologically and prognostically distinct from cutaneous melanoma.[2] In the United States, an estimated 2000 patients are diagnosed with this disease each year. Approximately 85% of ocular melanomas are uveal (iris, ciliary body, and choroid) in origin, with primary conjunctival and orbital melanomas being less common.[2,3] Cases are nearly equally distributed between male and female subjects, with a median age at diagnosis of 62 years.[4] The majority (97.8%) of cases of uveal melanoma occurs in the white population, with a white:black incidence ratio of 196:1.

The development of metastasis in this disease is common and occurs in approximately 50% of patients with posterior uveal melanoma within 15 years after the initial diagnosis and treatment.[5] Uveal melanoma is thought to be particularly resistant to systemic treatment, and no systemic therapy has yet been demonstrated to improve survival.[6] Drugs commonly used to treat

advanced cutaneous melanoma rarely achieve durable responses in patients with uveal melanoma. Nathan et al compared the outcome between 139 patients with non-uveal melanoma and 16 patients with uveal melanoma who were treated with DTIC, BCNU, cisplatin, and tamoxifen (Dartmouth regimen).[7] The response rates were 33% and 6% respectively. In a review of the MD Anderson Cancer Center experience of 143 treated patients with metastatic ocular melanoma, there was only a single objective response observed.[8] Retrospective reviews of the ECOG and SWOG experiences revealed similar findings.[9] Because of the lack of effective systemic treatment options, outcomes are poor once metastatic disease occurs, and the median survival from the time of the development of distant metastatic disease is 6 to 12 months.[10-12]

Although it is clear that novel effective therapies are desperately needed for this disease, the development of such therapies has been hampered by the rarity of uveal melanoma. Indeed, over the past decade, only 8 phase II trials in uveal melanoma have been published, with the largest of these trials accruing only 48 patients and none demonstrating significant efficacy in terms of response rate, overall survival or progression-free survival (see table below).

Published phase II trials in uveal melanoma.

Investigator	Study Treatment	n	Response Rate	Overall Survival	Progression-Free Survival
Homsi et al, 2010[13]	Docosahexaenoic acid-Paclitaxel	22	4%	9.8 mos	NR
Penel et al, 2008[14]	Imatinib	10	0%	10.8 mos	NR
Schmittel et al, 2006[15]	Gemcitabine/Treosulfan vs Treosulfan	48	2%	NR	2-3 mos
O'Neill et al, 2006[16]	DTIC/Treosulfan	15	0%	NR	3 mos
Schmittel et al, 2005[17]	Gemcitabine/Cisplatin/ Treosulfan	17	0%	NR	3 mos
Schmidt-Hieber et al, 2004[18]	Bendamustine	14	0%	NR	NR
Bedikian et al, 2004[19]	Temozolomide	14	0%	6.7 mos	1.8 mos
Kivelä et al, 2003[20]	Bleomycin/Vincristine/Lomustine/ DTIC + Interferon	22	0%	NR	1.9 mos

Despite our inability to identify effective therapies for this disease thus far, our increasing understanding of the underlying biology of uveal melanoma has led to the identification of a number of novel and promising therapeutic strategies that warrant investigation.

2.2 CTEP IND Agents

2.2.1 Trametinib Dimethyl Sulfoxide (GSK1120212B)

The RAF-MEK-ERK pathway plays a critical role in multiple cellular functions. Activation of the pathway can result from activation/mutations of the upstream receptor tyrosine kinases (RTKs) and RAS, or upregulation/mutations in RAF and MEK. Upon activation, RAF acts as the MAPK kinase and activates MAPKK (MEK1/2), which in turn catalyze activation of the effectors ERK1/ERK2. Once activated, ERK1/2 translocate into the nucleus and phosphorylate a number of effector proteins and transcriptional factors that regulate cell proliferation, motility, differentiation, and survival.

Trametinib is one of the several MEK inhibitors in clinical development. On May 29, 2013,

the U.S. Food and Drug Administration (FDA) approved trametinib for the treatment of patients with unresectable or metastatic melanoma with BRAFV600E or BRAFV600K mutations as detected by an FDA-approved test (U.S. Food and Drug Administration, 2013). On January 10, 2014, the Food and Drug Administration granted accelerated approval to trametinib and dabrafenib for use in combination to treat patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation as detected by an FDA-approved test (U.S. Food and Drug Administration, 2014).

Experience to date indicates that MEK is a valid target. In a phase III trial comparing trametinib with dacarbazine or paclitaxel in patients with BRAF V600E or V600K mutant metastatic melanoma, trametinib demonstrated a significantly better response rate, progression-free survival, and overall survival.[21] However, single agent activities are limited. Extensive research is underway to identify the patient selection markers and develop rational combination strategies. Preclinical studies have provided strong rationale and proof of principle for combination of MEK inhibitors with RTK inhibitors (EGFR or IGF-1R),[22,23] PI3K/AKT inhibitors,[24,25] and mTOR inhibitors. On the other hand, the optimal dose/schedule and patient selection criteria for combination regimens have not been defined. Phase 1 results for a number of combinations have been reported: Phase 1 selumetinib + MK2206,[26] phase 1 GDC-0973 + GDC-094 (MEK + PI3K inhibitor).[27]

The most up-to-date preclinical and clinical study information for trametinib can be found in the GSK1120212 (trametinib) Investigator's Brochure (2013).

2.2.1.1 Mechanisms of Action and Preclinical Data with Trametinib

Trametinib is a dimethyl sulfoxide (DMSO) solvate compound (ratio 1:1) with potent, allosteric and ATP non-competitive inhibition of MEK1/2 (IC_{50} of 0.7 and 0.9 nM against MEK1 and MEK2, respectively).[28] Trametinib inhibited MEK1/2 kinase activity and prevented RAF-dependent MEK phosphorylation (S217 for MEK1), producing prolonged pERK1/2 inhibition. Trametinib showed better potency against unphosphorylated MEK1/2 (u-MEK1/2) when compared with preactivated diphosphorylated MEK (pp-MEK), suggesting that u-MEK affords a higher affinity binding site for trametinib than does pp-MEK.

The specificity of trametinib was confirmed against a panel of 183 kinases, including MEK5 (the closet kinase homolog to MEK1/2), CRAF, BRAF, ERK1, and ERK2.[29] Trametinib demonstrated equal potency against activated MEK1- and MEK2-mediated phosphorylation of ERK (sequence identity of 85% across the whole protein and 100% in the active site for humans). Trametinib demonstrated preferential inhibition of RAF-mediated MEK1 activation (IC_{50} = 0.60 nM) over pMEK1 kinase activity (IC_{50} = 13 nM).[30]

BRAF-mutant Colo205, A375P F11s, and HT-29 human tumor xenograft mouse models showed the most significant mean tumor growth inhibition (TGI) (80% to 87%) at 3.0 mg/kg trametinib, with multiple complete and partial tumor regressions. In the Colo205 model, tumor regression was observed even at a dose of 0.3 mg/kg.[29] Two KRAS-

mutant xenograft models, HCT-116 and A549, also showed significant TGI (83% and 75%) but without significant tumor regressions.[28] As predicted by cell proliferation assays, tumor xenograft lines with wild-type (wt) RAF/RAS (PC3, BxPC3, and BT474) were much less sensitive, showing only modest TGI (44-46%) with no tumor regressions.

Pharmacodynamic studies were performed in mice treated with trametinib for 14 days.[28] In the A375P F11s xenograft model, the first dose of trametinib (3 mg/kg) significantly reduced pERK for more than 8 hours on Day 1. pERK inhibition was more sustained (over 24 hours) after the Day 7 dose, probably due to an increase in the steady-state levels of trametinib after repeated doses. The average C_{max} in blood was 1,410 nM on Day 7, with an estimated half-life ($t_{1/2}$) of 33 hours. In addition, immunohistochemistry (IHC) also confirmed inhibition of cell proliferation (reduced Ki67) and G1 cell cycle arrest (elevated p27Kip1/CDKN1B) following 4 days of treatment.

2.2.1.2 Clinical Pharmacokinetics (PK) and Activity of Trametinib

FTIH Phase 1 Trial of Trametinib Monotherapy (MEK111054): There were 3 parts in this study.

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

The MTD of trametinib was established as 3 mg QD, but the recommended phase 2 dose (RP2D) was chosen at 2 mg QD based on tolerability of repeated cycles.[31]

PK and Metabolism of Trametinib: PK measurements were conducted under fasting conditions. After a single dose (Day 1), AUC_{0-24} and C_{max} values were dose-proportional up to 6 mg, lower than dose proportional following 8 mg, and greater than dose proportional following the 10 mg dose. Median T_{max} was 1.5 hours.

After repeat doses (Day 15), trametinib accumulated with a mean accumulation ratio of 6.6 at the RP2D of 2 mg QD. Between-subject variability in exposure ranged from 27-50% for C_{max} and 20-41% for AUC_{0-24} across all dosing regimens. The effective $t_{1/2}$ was approximately 4.5 days, and steady state was reached by approximately Day 15. Trametinib had a small peak:trough ratio of ~2.[31] At 2 mg QD on Day 15, mean AUC_{0-24} was 376 ng•h/mL and C_{max} 23 ng/mL, and the mean trough concentrations ranged from 10.0 to18.9 ng/mL. The long half life and small peak:trough ratio of trametinib allowed constant target inhibition within a narrow range of exposure.

Drug-Drug Interactions: Trametinib is metabolized predominantly via deacetylation (non-cytochrome P450 [CYP450]-mediated) with secondary oxidation or in combination with glucuronidation biotransformation pathways.[30] The deacetylation is likely mediated by hydrolytic esterases, such as carboxylesterases, or amidases. Based on in vitro studies, trametinib is not an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2D6, and CYP3A4. Trametinib has an overall low potential for drug-drug interactions.

Pharmacodynamic effect and biomarkers: The relationship between dose and tumor biomarkers such as pERK, Ki67, and p27, were evaluated in patients with BRAF or NRAS mutation-positive metastatic melanoma (Investigator's Brochure, 2012a). In general, increasing exposures and/or doses provided greater pharmacodynamic effects. The median change observed at a dose of 2 mg QD was 62% inhibition of pERK, 83% inhibition of Ki67, and a 175% increase in p27.

Antitumor Activity of Trametinib Monotherapy: In the FTIH phase 1 trial, 14 patients with BRAF-mutant melanoma received trametinib at 2 mg QD (2 mg/day continuously, or 2 mg for 21 days followed by a 1 week break). The overall objective response rate (ORR) was 43% (6/14), including 2 complete responses (CRs).[30] In 9 patients with BRAF wt melanoma, 2 patients achieved a partial response (PR), and 3 stable disease (SD).[31] In 26 evaluable pancreatic cancer patients, there were 2 PRs (1 PR was KRAS mutation-positive) and 11 SD (2 achieved ≥20% tumor reduction).[32] Among the 27 CRC patients (without selection of RAS or RAF mutations), 8 SD were observed.

In a phase 3 trial, patients with unresectable stage IIIC or IV cutaneous melanoma with a BRAF V600E or V600K mutation were randomized (2:1) to trametinib (2 mg, PO, QD) or chemotherapy (dacarbazine or paclitaxel).[21] There were 322 patients in the intention-to-treat (ITT) population, of whom 273 (85%) were in the primary efficacy population (patients with $BRAF^{V600E}$-positive cancer who did not have brain metastases at baseline). In the ITT analyses, the ORR was 22% in the trametinib group and 8% in the chemotherapy group; the median duration of PFS was 4.8 months in the trametinib group as compared with 1.5 months in the chemotherapy group; and the 6-month OS rate was 81% in the trametinib group and 67% in the chemotherapy group.

Antitumor Activity of Trametinib in Cancer Other Than Melanoma: In a phase 1/2 monotherapy study, acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) patients were given trametinib at dose levels from 1-2 mg QD. Drug-related AEs in 45 patients were similar to that observed in patients with solid tumors, and 2 mg PO QD was selected for further investigation in this patient population. Twelve patients (23%) withdrew due to an AE, including cardiac failure (2) and infection (2). Efficacy was reported in 39 patients.[33] The best response in 13 patients with KRAS or NRAS mutations included 3 CRs (23%), 7 SD (54%), and 1 PD (progressive disease) (5%). In 26 patients with wild-type RAS or an unknown mutation, there were 2 PRs (8%).

Antitumor Activity of Trametinib in Uveal Melanoma: Although our initial trial of MEK inhibition in uveal melanoma utilized selumetinib, available clinical experience suggests

that trametinib is a clinically more effective agent than selumetinib in cutaneous melanoma harboring BRAF mutations. Indeed, while the RR of selumetinib in patients with BRAF mutant melanoma is 11.1%,[34] the phase II study of trametinib demonstrated a 25% RR in previously treated patients with BRAF mutant cutaneous melanoma who have not received a prior RAF inhibitor.[35]

Although no radiographic response was observed in 16 patients with advanced UM treated on the phase I study of trametinib,[36] 2 achieved 24% tumor reduction and 50% achieved stable disease, with 4 patients receiving treatment for 16 weeks or longer, and 2 receiving treatment for at least 40 weeks. Of these 16 patients, 7 had received 1-2 prior lines of therapy and 8 received 3 or more prior lines of therapy. As preliminary data from our selumetinib trial suggests that patients previously treated respond less well to MEK inhibition,[37] we do not believe that the published experience of trametinib in UM reflects the potential activity of this agent in an untreated patient population, and further evaluation of this agent is warranted.

2.2.1.3 Trametinib Safety Profile

A **Comprehensive Adverse Events and Potential Risks (CAEPR)** list using NCI Common Terminology Criteria for Adverse Events (CTCAE) terms is included in Section 7.1 of the protocol.

Due to limited experience in human subjects, there is currently incomplete information available about the relationship of AEs and administration of trametinib. Based on available AE data from clinical studies involving trametinib to date, the most common toxicities are rash and diarrhea. Rash and diarrhea are common, class-effect toxicities for MEK inhibitors. In addition, visual impairment and left ventricular ejection fraction (LVEF) reduction, although observed at lower frequencies, are also considered class-effect toxicities as they have been observed with trametinib as well as other MEK inhibitors.

AEs of special interest: Rash, diarrhea, visual disorders, hepatic disorders, cardiac-related AEs, and pneumonitis are considered AEs of special interest because they are either known class effects (i.e., have been observed with other MEK inhibitors) or are potentially life-threatening (Investigator's Brochure, 2013). The following sections provide integrated summaries for these AEs across different clinical trials, with emphasis on trials using trametinib as monotherapy, especially at the RP2D of 2 mg.

Refer to dose modification guidelines for the toxicities for which they are addressed in Section 6.

- Rash: Rash was a common AE observed across different dose levels and in different combinations (Investigator's Brochure, 2013). At the 2 mg dose, rash was seen in 27% to 78% of patients in different trials. Of the ~370 subjects with rash AEs at the 2 mg monotherapy dose (including crossover subjects) in five studies, the majority of rash AEs were grades 1 or 2 (24% to 73%); 0% to 9% of

patients experienced grade 3 rash AEs, and four patients had a grade 4 rash AE.

In a randomized phase 3 trial of trametinib vs. chemotherapy, the overall incidence of skin toxicity (including rash, dermatitis, acneiform rash, palmar-plantar erythrodysesthesia syndrome, and erythema) was 87% in patients treated with trametinib and 13% in chemotherapy-treated patients. Severe skin toxicity occurred in 12% of patients on the trametinib arm, most commonly for secondary infections of the skin The median time to onset of skin toxicity was 15 days (range: 1 to 221 days), and median time to resolution was 48 days (range: 1 to 282 days). Dose reduction was required in 12% for skin toxicities, and permanent discontinuation of trametinib was required in 1% of patients.

- Diarrhea: At the 2 mg monotherapy dose, 33% to 58% of patients in five trials had diarrhea (Investigator's Brochure, 2013). Of ~320 subjects (including crossover subjects) with diarrhea at this dose, the majority of diarrhea AEs were grade 1 or 2 in severity (33% to 56% of all study patients); 17 patients had grade 3 diarrhea, and none had grade 4 diarrhea.

- Visual disorders: At the 2 mg monotherapy dose, 4% to 21% of the patients in five trials experienced visual disorders (Investigator's Brochure, 2013). Of the 85 total subjects (including crossover subjects) experiencing visual disorders at this dose level, the majority of visual disorders were grades 1 or 2 (4% to 20% of all study patients); six patients experienced grade 3 visual disorders, and one patient experienced a grade 4 visual disorder.

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

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

conditions in another subject, at the time of the data cutoff. Three of these four cases were considered related to study treatment by the investigators.

- Hepatic disorders: Abnormalities of liver enzymes and bilirubin have been observed with administration of trametinib (Investigator's Brochure, 2013). However, assessment of these cases was often confounded by co-morbid conditions (such as biliary obstruction), concomitant use of other potentially hepatotoxic drugs, and liver metastases. At the 2 mg monotherapy dose, 8% to 34% of patients in five trials had LFT abnormalities. Of the 96 total patients (including crossovers) with LFT changes, the majority were grade 1 or 2 in severity (4% to 20% of all study patients); 26 had grade 3 events, and 6 patients had grade 4 events.

- Cardiac-related AEs: At the 2 mg monotherapy dose, 3% to 21% of the subjects in six studies had cardiac-related AEs (Investigator's Brochure, 2013). Of the 65 total subjects (including crossover subjects) experiencing cardiac-related AEs at the 2.0 mg monotherapy dose in five of the studies, the majority of cardiac-related AEs were grades 1 or 2 in severity (0% to 16% of all study subjects); 18 subjects had grade 3 cardiac-related AEs, and no subjects had Grade 4 cardiac-related AEs in any study. No subject in one study, which evaluated the effect of repeat oral dosing of trametinib 2 mg QD on cardiac repolarization in subjects with solid tumors, had cardiac-related AEs. One study subject receiving trametinib 2 mg QD had grade 5 (fatal) acute cardiac failure, with evidence of massive tumor invasion of the heart; this AE was considered not drug-related by the investigator.

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

- Pneumonitis: At the 2 mg monotherapy dose, 0% to 4% of the subjects in five studies had pneumonitis (Investigator's Brochure, 2013). Of the nine total subjects (including crossovers) experiencing pneumonitis AEs at this dose, three subjects had grade 1 or 2 pneumonitis and six subjects had grade 3 pneumonitis.

- Embryofetal toxicity: Based on its mechanism of action, trametinib can cause

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

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

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

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

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

	Trametinib (n=211)		**Chemotherapy (n=99)**	
Preferred term	**All Grades**	**Grades 3 and 4**	**All Grades**	**Grades 3 and 4**
Increased aspartate aminotransferase (AST)	60	2	16	1.1.1
Increased alanine aminotransferase (ALT)	39	3	20	3
Hypoalbuminemia	42	2	23	1
Anemia	38	2	26	3
Increased alkaline phosphatase	24	2	18	3

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

2.2.1.4 Clinical Experience with the Combination of Trametinib and Dabrafenib

Preliminary data on 45 patients participating in the phase 1/2 study of dabrafenib and trametinib, BRF113220, have been reported.[38]

PK: The plasma levels of dabrafenib were higher in combination with trametinib as compared to that with monotherapy. Geometric mean Day 15 AUC of dabrafenib in combination ranged from 3539 to 5187 ng•hr/mL, and the AUC observed in the monotherapy study was 2619 ng•hr/mL. Further data are required to understand this difference.

PK of trametinib did not appear to be affected by the addition of dabrafenib. Preliminary results showed that the geometric mean dose-normalized $AUC_{0-\tau}$ (CV%) for trametinib (dose normalized for the 2.0 mg QD dose) in combination with dabrafenib at 150 mg BID was 302 ng•hr/mL (n=17; 35%) on Day 15. Historical PK data from the trametinib FTIH study (MEK111054) indicated a mean Day 15 $AUC_{0-\tau}$ (CV%) of 360 ng•hr/mL (31%).

Safety and the RP2D for the combination of trametinib and dabrafenib: One DLT of a recurrent grade 2 neutrophilic panniculitis occurred, and pyrexia was common (51%). The RP2D was 150 mg BID dabrafenib plus 2 mg QD trametinib (both agents at the RP2D for single agent). Of the 137 patients enrolled, 32 patients were treated at the RP2D. SAEs experienced by more than one patient include: pyrexia (5%), hypotension (4%), nausea (3%), and 2% of patients had a constellation of AEs including vomiting, dehydration, or renal failure. The only grade 4 AE was a sepsis-like syndrome with fever/hypotension. Grade 3 AEs included generalized rash (n=2, 4%) and neutropenia (n=2, 4%). Skin toxicity (rash) occurred in 9 (20%) patients. Of note, the rate of SCC was 2% in this study. A single case of grade 5 hyponatremia was reported. Other common AEs are listed in the table below.

Selected AEs experienced by ≥5% of patients regardless of causality in BRF113220 (treated at the RP2D)

AE Term	Dose Escalation Cohort (150mg BID/2 mg QD) (n=31)
Any AE, n (%)	24 (77)
Pyrexia	10 (32)
Rash	4 (13)
Dermatitis acneiform	1 (3)
Hypotension	4 (13)

Activity: Among 77 evaluable patients with melanoma who had not received prior BRAF inhibitors, there were 43 responses (56%), including 4 CRs (5%) and 39 PRs (51%).[39] Twenty-nine patients experienced SD, and three patients experienced PD.

Patients were treated on four escalating dose levels of dabrafenib/trametinib (mg BID/mg QD): 75/1, 150/1, 150/1.5, 150/2. The confirmed RR for each dose level, respectively, was 67% (n=6), 64% (n=22), 48% (n=25), and 54% (n=24). Median PFS (months) for each of the first three dose levels, respectively, was 8.7, 8.3, and 5.5; PFS data are not mature for the fourth (150/2) dose level. Overall PFS was 7.4 months.

Currently, the randomized phase 2 portion (Part C) of the study of dabrafenib with or without trametinib has enrolled 162 patients as of September 1, 2011.[40]

2.2.1.5 Clinical Experience with the Combination of Trametinib + GSK2141795 (AKT inhibitor) (TAC113886)

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.[41] 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 (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.

2.2.2 GSK2141795

2.2.2.1 Mechanisms of Action and Preclinical Data with GSK2141795

GSK2141795 is a novel member of the N-alkyl pyrazole class of orally available kinase inhibitors and has been shown to be a potent, pan-AKT (a serine/threonine protein kinase with 3 isoforms, AKT1, AKT2 and AKT3) inhibitor, with potency (Ki*) values for human AKT1, 2, and 3 kinases being 0.066, 1.4, and 1.5 nM, respectively. GSK2141795 exhibited a time-dependent inhibition of AKT with a dissociation half-life of ≤20 minutes.

In vitro, GSK2141795 caused a concentration- and time-dependent reduction in phosphorylation of multiple proteins downstream of AKT such as glycogen synthase kinase 3 (GSK-3)β, 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 cell lines from multiple histologies including breast, hematological, colon, ovarian, and prostate (EC50 <1 μM). 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.

2.2.2.2 Clinical Pharmacokinetics (PK) and Activity of GSK2141795

Single-dose (Day 1) PK parameters of GSK2141795 were evaluated in the first-time-in-human (FTIH) study PCS112689 (GSK2141795 Investigator's Brochure, 2012). 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 (AUC0-24) and maximum plasma concentration (Cmax) values generally increased in a dose-proportional manner, although there was variability among subjects. Median time to reach peak concentration (Tmax) 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.

The MTD of single-agent GSK2141795 is 75 mg once-daily as determined by the FTIH study (GSK2141795 Investigator's Brochure, 2012). The RP2D of single-agent GSK2141795 has not been determined.

2.2.2.3 GSK2141795 Safety Profile

Common Terminology Criteria for Adverse Events (CTCAE) terms is included in Section 7.1 of the protocol.

Based on available adverse event (AE) data from 151 subjects dosed as of the data cut-off date of May 6, 2012, the most common toxicities of GSK2141795 monotherapy or in combination with trametinib are gastrointestinal (GI)-related (diarrhea, nausea, and vomiting) and fatigue.[40] Hyperglycemia, hypoglycemia, mucositis, and rash are also commonly observed. In addition, three cases of hypothyroidism have been noted.

2.3 Study Rationale

2.3.1 Uveal Melanoma is Characterized by Activation of the MAPK Pathway Via Functionally Activating Mutations in Gnaq/11.

Whereas cutaneous melanoma is characterized by the presence of activating mutations in BRAF or NRAS in 50% and 20% of cases, respectively,[42] leading to the constitutive activation of ERK1/2, such changes are rare in uveal melanoma (UM).[43,44] Indeed, no BRAF mutations were identified in a total of 276 primary or secondary uveal melanoma screened samples (although such mutations have been identified in occasional uveal melanoma cell lines).[45] Despite the absence of these mutations, activation of the mitogen-activated protein kinase (MAPK) pathway in UM remains important in the development and progression of this disease.

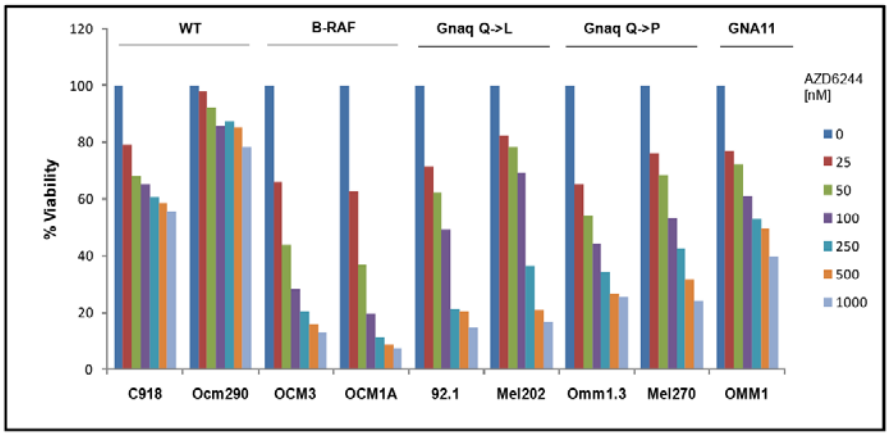
Work by William Harbour[46] and Boris Bastian[47] has demonstrated the presence of a functionally activating Q209L mutation in guanine nucleotide-binding protein Q polypeptide (Gnaq), a heterotrimeric protein that couples cell surface 7-transmembrane domain receptors to intracellular signaling pathways such as the MAP kinase pathway in 45% to 50% of primary UMs.[46,47] Of the primary UMs without a Gnaq mutation, greater than 50% carry a gain-of-function mutation in Gna11 that, like Gnaq, also encodes for a widely expressed G-protein alpha subunit.[48] These mutations are responsible for MAPK activation in the majority of primary UMs.

Harbour identified activating mutations of Gnaq in 33/67 (49%) primary UM samples.[46] Bastian sequenced the entire coding regions of Gnaq in a broad spectrum of melanocytic neoplasms and observed that 46% of UMs (n = 48) harbored mutations resulting in constitutive activation.[49] The somatic Gnaq exon 5 Q209L and Q209P mutations most commonly identified lead to a glutamine to lysine and glutamine to proline substitution, respectively, at position 209, which lies in the Ras-like domain of Gnaq. Mutations at this site cause loss of the intrinsic GTPase activity, similar to that seen in Ras family members, preventing hydrolysis of GTP and locking Gnaq in its active, GTP-bound state. These mutations lead to melanocyte proliferation in mice and can cooperate with other oncogenes to transform 3T3 cells and melanocytes.[47,50] Transfection of Q209L Gnaq into genetically modified melanocytes (transduced with telomerase and with inactivation of p53 and the p16/CDK4/RB pathways), as well as primary human melanocytes and 293T cells, results in increased levels of phospho-

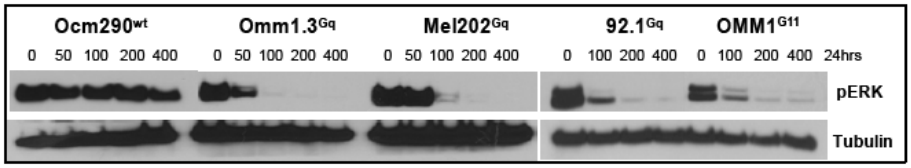
ERK when compared with control cells transfected with wild-type Gnaq or an empty vector. Transduction of Q209L Gnaq results in anchorage-independent growth not observed when unmodified melanocytes were transfected. Tumorgenicity studies in nude mice result in heavily pigmented tumors with injection of Q209L Gnaq transfected melanocytes, but not with injection of wild-type cells.[47] Furthermore, siRNA-mediated knockdown of Gnaq in UM cell lines characterized by a Gnaq mut result in decreased phospho-ERK, decrease in cell number, loss of anchorage-independent growth, and an increase in the sub-G0/G1 subpopulation when compared with control. Similar findings are observed when the UM cell line OMM1.3, which harbors the Q209L Gnaq mut, is treated with the MEK inhibitor UO126.[47] Gna11 mut most commonly results in a Q209L substitution and is analogous to the Q209L Gnaq mut. Gna11 has been validated as an oncogene that results in MAPK activation, comparable to that achieved with Gnaq.[48]

2.3.2 Gnaq/11 Mutant Uveal Melanoma Cell Lines Exhibit Dose Dependent Growth Inhibition and Inhibition of p-ERK by selumetinib

As U0126, a non-specific inhibitor of MEK at micromolar concentrations, has been shown to inhibit the growth of Gnaq mut melanoma cell lines in prior studies, we evaluated if a similar effect could be achieved with selumetinib, a clinically available MEK inhibitor.[51] We obtained and/or developed our own UM cell lines of differing genetic backgrounds. We treated cells with increasing concentrations of selumetinib and analyzed cell viability after 3 days of continuous drug exposure in the Dojindo cell based assay. Gnaq wild-type cells were resistant to increasing concentrations of selumetinib (see figure below) BRAF mutant cell lines tended to be more sensitive to the drug (IC50s <50nM), but Gnaq/11 mutant cell lines still exhibited a high degree of sensitivity, with IC50s between 100-250nM.

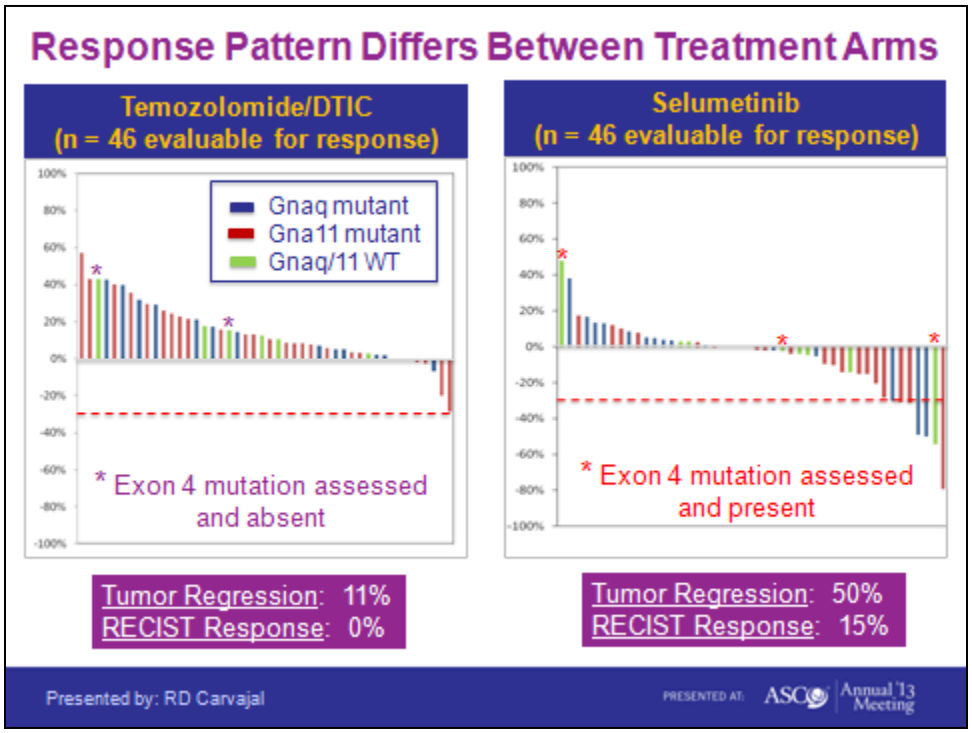


As shown by western blot (see figure below), this sensitivity correlated to the degree of p-ERK inhibition at 24 hours. Thus, the decrease in cell viability of Gnaq mut cell lines to selumetinib is dose dependent, associated with sustained inhibition of pERK at 24 hours, and comparable to that observed in BRAF mutant UM cell lines at clinically achievable drug concentrations.



2.3.3 Clinical Efficacy of Selumetinib in Patients with Advanced Uveal Melanoma.

Based upon this preclinical as well as preliminary clinical evidence of activity of selumetinib in advanced uveal melanoma,[52] we developed and are conducting a CTEP sponsored trial entitled, "A Randomized Phase II Trial of Temozolomide versus selumetinib in Patients with Metastatic Uveal Melanoma (NCI#8443)." As presented at the 2013 American Society of Clinical Oncology Annual Meeting (see figure below) , 7 of 46 patients initially randomized to selumetinib, achieved a RECIST partial response (15%), with half of the patients treated achieving radiographic shrinkage.[53] The response rate of those randomized to temozolomide/DTIC is 0%.



A total of 98 patients have been randomized to selumetinib (n=48) and temozolomide/DTIC (n=50). Randomization was balanced by age, gender, performance status, stage and prior therapies. Greater than 90% of patients on both arms had metastatic liver disease. The primary endpoint of this study was progression-free survival, with secondary endpoints including overall survival and safety/toxicity. As of April 22, 2013, 44 patients initially randomized to chemotherapy have experienced radiographic progression, with 3 patients having experienced clinical progression. Thirty-four patients initially randomized to selumetinib experienced radiographic progression, with 2 having clinical progression. The study met its primary endpoint of PFS, with a median PFS of 15.9 weeks (95% CI, 8.4 – 23.1) with selumetinib

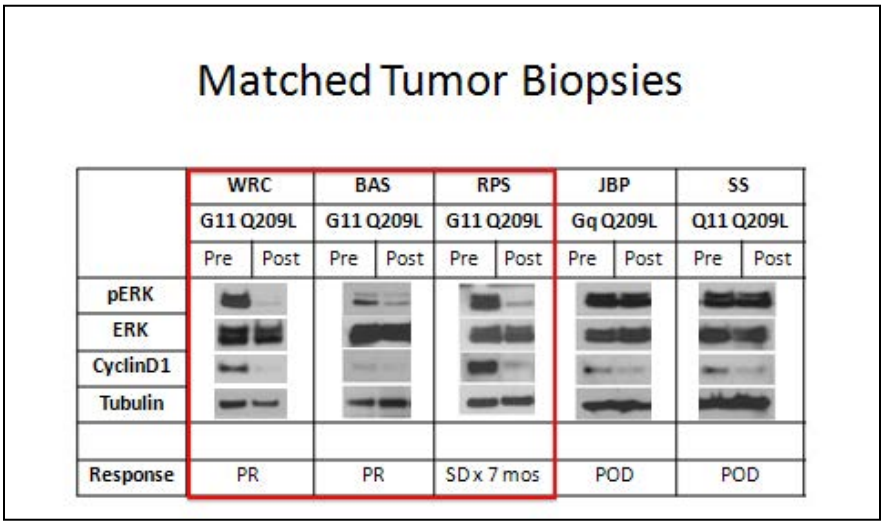
versus 7.0 weeks (95% CI, 4.3 – 8.4) with chemotherapy. The hazard ratio was 0.46 (95% CI, .30 - .71) with a p value of 0.0005). Despite the crossover design of the trial, with 80% of patients crossing over from chemotherapy to selumetinib, there was a trend towards improved survival with selumetinib (10.8 months versus 9.4 months; HR 0.79; p = 0.4).

2.3.4 Pharmacodynamic Activity of Selumetinib in Uveal Melanoma.

As part of this trial, we are collecting fresh tumor biopsies at baseline and after 14 days of treatment in patients treated at MSK with selumetinib. We have thus far successfully collected paired samples from 28 patients.

In our analysis of the first 18 patients treated with selumetinib from whom we have obtained paired tumor biopsies, we observed that the median pERK and cyclinD1 as measured by densitometry decreased by 48% (p=.03) and 76% (p=.03), respectively.[54] Radiographic regression correlated with suppression of pERK (p=0.04), but not cyclinD1 (p=0.38) in this sample set. Patients achieving clinical benefit as defined as having either a RECIST response or disease stability of 16 weeks or greater had a greater decline in median pERK (81.4%, interquartile range 58% to 96%) versus those not achieving clinical benefit (26.6%, interquartile range 11% to 60%), suggesting that more potent inhibition of the MAPK pathway may result in greater clinical benefit.

As shown in the figure below, effective target inhibition was observed as characterized by decreased phospho-ERK and cyclinD1; however, these pharmacodynamic effects were greatest in patients who achieved a clinical benefit. No suppression of phospho-ERK was observed in patients who experienced disease progression as their best response.

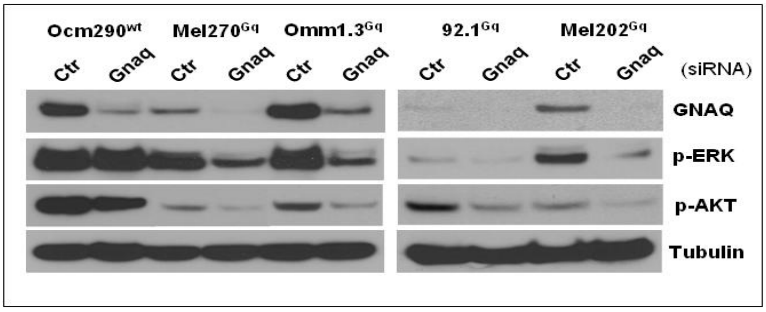


Despite the promising results observed thus far, not all patients treated with selumetinib have achieved a response and the responses observed are not indefinite. Using the matched tumor biopsies, we are working to assess mechanisms of primary and secondary resistance to MEK inhibition in uveal melanoma, and to identify potential methods to improve the efficacy of MEK inhibition in this disease. We thus analyzed the transcriptional profile of cell lines

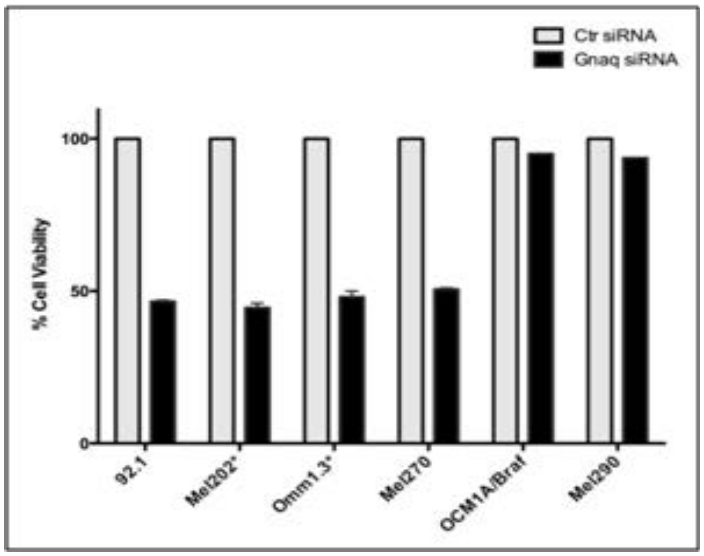
treated with selumetinib to identify gene targets of activated Gnaq and to evaluate the biologic importance of these genes in uveal melanoma.[55] We conducted microarray analysis of uveal melanoma cell lines with Gnaq mutations treated with selumetinib. For comparison, we used cells carrying BRAF (V600E) and cells without either mutation. Changes in the expression of selected genes were then confirmed by quantitative real-time PCR and immunoblotting. We found that Gnaq mutant cells have a MEK-dependent transcriptional output and identified a unique set of genes that are downregulated by MEK inhibition, including the RNA helicase DDX21 and the cyclin-dependent kinase regulator CDK5R1, whereas the transcription factor c-Jun was induced. These genes are involved in cell proliferation, tumor cell invasion, and drug resistance, respectively. We furthermore demonstrated that treatment with selumetinib regulates the expression of these genes in tumor tissues of patients with metastatic Gnaq/11 mutant uveal melanoma.

2.3.5 Concurrent Inhibition of MEK and AKT Results in Greater Antitumor Effects than Inhibition of Either Alone

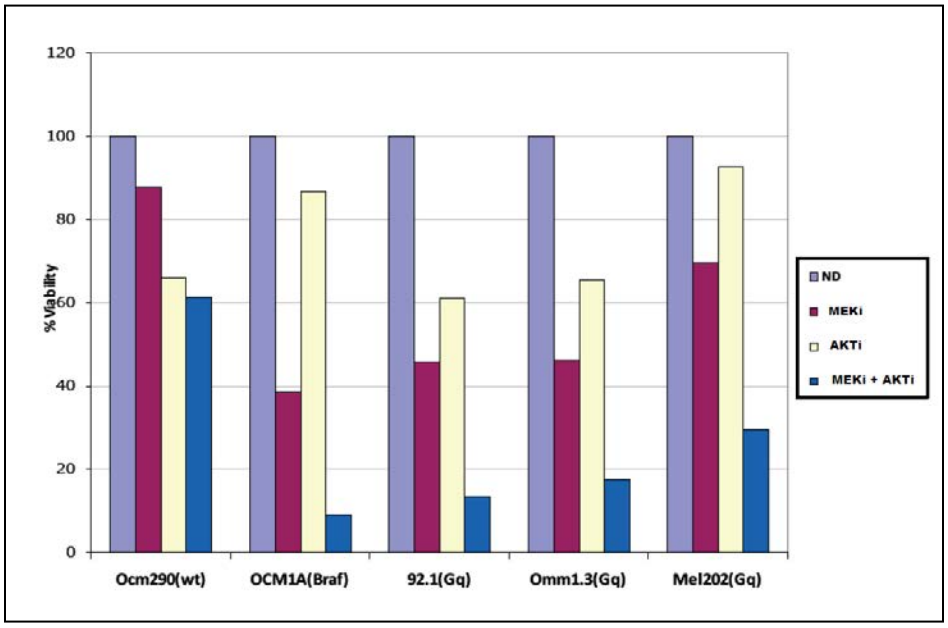
To examine other signaling pathways downstream of Gnaq, we transfected uveal melanoma cells with control siRNA (Ctr) and specific Gnaq siRNA (Gnaq). Forty-eight hours later, cell lysates were analyzed by Western blot. As shown in the figure below, knock-down of Gnaq by siRNA inhibits both p-ERK and p-AKT in the 4 Gnaq mut cell lines, while Gnaq wt cell line (OCM290, lanes 1 and 2) shows no inhibition of p-ERK and only a minimal effect on p-AKT.



This is consistent with the effect of Gnaq siRNA on cell proliferation (see figure below). Gnaq mutant siRNA transfected cells showed inhibition of cell proliferation by approximately 50%, whereas a B-RAF mutant (OCM1A) and Gnaq wt (Mel290) uveal melanoma cell lines were not affected. This data suggests that $Gnaq^{Q209L}$ is required for activation of both the MAPK and PI3K/AKT pathways.

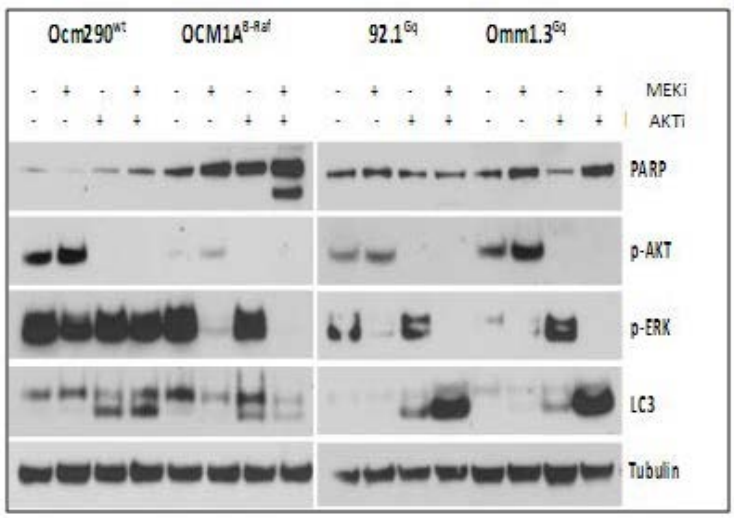


We therefore hypothesized that combined inhibition of these pathways will more comprehensively phenocopy the biologic effect of downregulating Gnaq mutations and result in enhanced anti-tumor effects. We thus treated UM cells with both MEK and AKT inhibition. We observed synergistic enhancement in the inhibition of cell proliferation in Gnaq mutant and BRAF mutant cells (see figure below) (combination Index <1 when analyzed with the Chou-Talalay method, data not shown), but not in the Gnaq wt cell line (far left in the panel).



Analysis of cell lysates confirmed inhibition of both p-ERK and p-AKT with the drug combination in the Gnaq mutant cell lines (see figure below). Interestingly, MEK inhibition alone activated p-AKT, but this was inhibited with combination therapy. Thus, it would appear that blocking both the MAPK and AKT pathways in Gnaq mutant UM cell lines will lead to an increased anti-tumor effect. As indicated, this combination resulted in apoptosis with PARP

cleavage in the BRAF mutant ocular melanoma, but induction of autophagy with increase in microtubule-associated protein 1 light chain 3 (LC3) a protein that localizes to autophagosomes as evidenced by western blot in the Gnaq mutant cells.



2.3.6 Concurrent Inhibition of MEK and AKT is a Strategy Worthy of Further Investigation in Uveal Melanoma.

Given the preliminary evidence of clinical activity with MEK inhibition in uveal melanoma and this preclinical data demonstrating improved antitumor effects with concurrent MEK and AKT inhibition, we believe that testing this combination is of significant priority to the uveal melanoma community.

2.4 Correlative Studies Background

2.4.1 Correlation of Treatment Response with Genetic Background

Whereas cutaneous melanoma is characterized by the presence of activating mutations in BRAF or NRAS in 60% and 20% of cases, respectively, leading to the constitutive activation of ERK1/2, such changes are rare in UM.[43,44] Despite the absence of BRAF or NRAS mutations,[45] the MAPK pathway remains of importance in the pathophysiology of UM, and constitutive activation of MEK and ERK have been observed.[45,56] Functionally activating mutations have been identified in codon 209 at Q209L of Gnaq in 45% to 50% of primary UMs which appears to account for MAPK activation in a significant proportion of tumors.[46,47] Of the primary UMs without a Gnaq mutation (mut), greater than 50% carry a gain-of-function mutation in Gna11 that, like Gnaq, also encodes for a widely expressed G-protein alpha subunit and also results in MAPK activation. Gna11 is a paralog of Gnaq that is 90% identical and shares overlapping functions in mouse melanocytes.[57,58] Gnaq/11 are genes that encode for q class G-protein α-subunits. G proteins are a family of heterotrimeric proteins (Gαβγ) coupled to cell surface, seven-transmembrane spanning receptors. Upon ligand binding to these receptors, the GDP bound to the Gα subunit of Gαβγ is exchanged for GTP, resulting in a conformational change and the subsequent dissociation of the Gα from the Gβγ subunits. These two subunits are then able to regulate various second messengers. Gα activation is terminated by a GTPase intrinsic to the Gα subunit. The q class Gα ($G_q\alpha$) mediates its activity

through stimulation of phospholipase Cβ, which cleaves phosphatidylinositol 4,5-bisphosphate (PIP2) to inosol triphosphate (IP3) and diacyl glycerol (DAG). DAG goes on to activate protein kinase C, which ultimately activates downstream pathways including the MAPK signaling pathway. These Gnaq/11 mutations are not associated with clinical, pathological, immunohistochemical, or genetic factors associated with advanced UM, and represent an early event in disease pathogenesis.[46]

We hypothesize that tumors that harbor a mutation in Gnaq/11 are more dependent upon MAPK and PI3K pathway signaling and will be more susceptible to MEK inhibition alone and in combination with AKT inhibition. To test this hypothesis, we will correlate clinical outcomes with mutation status. Tumor genotyping for Gnaq/11 will be performed for patients enrolled on this study at MSK or elsewhere. Genotyping can be performed retrospectively and will not delay patient enrollment. Analysis for Gnaq/11 will be performed using previously collected paraffin embedded tumor tissue; however, should previously collected tumor tissue be unavailable or insufficient for testing, a repeat biopsy will be requested but will not be mandatory for study participation.

2.4.2 Pharmacodynamic Analysis of MEK Inhibition with or without AKT Inhibition

We will continue the work we have initiated assessing the pharmacodynamic effects of MEK inhibition in uveal melanoma in this trial by performing pre- and post-treatment tumor biopsies. All patients with safely accessible tumor will undergo pre- and post-treatment (day 14 +/- 3 days) tumor biopsies for biomarker and correlative analysis. The decision to not pursue these biopsies must be made in collaboration with the MSK Principal Investigator. An additional tumor biopsy will be requested from patients at the time of disease progression; however, this biopsy is optional. These patients will undergo several core biopsies (or one excisional biopsy) at each time point, with a portion of the sample flash frozen and a portion reserved for paraffin. Analysis will include, but is not limited to, reverse phase protein array and gene expression analysis.

2.4.3 Assessment of Circulating Tumor DNA and Correlation with Treatment Response

It is now well established that human tumor cells, through a variety of physiologic events such as apoptosis, necrosis and secretion, release single and double stranded fragments of DNA into the circulation.[59,60] These oligonucleotides, which can range in size from 70 to 21,000 base pairs, have been detected in plasma samples as circulating, cell-free, tumor-derived DNA (ctdDNA) in a variety of human cancers.[59] Interesting, ctdDNA share the specific genetic and epigenetic abnormalities as their tumor cell of origin, and thus, are readily distinguished from cell-free DNA derived from normal cells. Point mutations, methylation patterns, and microsatellite alterations have all been indentified in ctdDNA and have the potential to function as biomarkers for both tumor burden and even treatment response.

As discussed above, 80% of uveal melanomas harbor mutations in GNAQ and GNA11.[49] These genetic alterations are found predominately at nucleotide position 626 on codon 209 and are the product of a missence mutation (i.e. $GNAQ^{626A>T}$, $GNAQ^{626A>C}$, and $GNA11^{626A>T}$), which results ultimately in glutamine being replaced by leucine or proline (i.e. GNAQ

Glu209Leu, GNA11 Glu209Leu, and GNAQ Glu209Pro). Recently, Madic and colleagues developed and validated a method using real-time PCR using bi-directional pyrophosphorolysis-activated polymerization (PAP) that detects and quantifies tumor specific GNAQ/GNA11 mutations in ctdDNA in patients with uveal melanoma.[61] Activating mutations in GNAQ/GNA11 were detected in the plasma samples of 20 of 21 (95%) patients with metastatic uveal melanoma, while such ctdDNA was absent in 20 healthy donors. Interesting, the level of ctdDNA strongly and significantly correlated with tumor burden as assessed by cross sectional imaging. This indicates that tumor volume is a major determinate of ctdDNA.

In collaboration with investigators at the Institut Curie, Paris France, MSK, and/or Columbia, we propose to prospectively measure ctdDNA in patients with metastatic uveal melanoma. The primary objective is to describe the evolution of ctdDNA levels measured by PAP in plasma of patients under treatment for metastatic uveal melanoma. Additionally, we will evaluate the early changes of circulating tumor DNA levels as early indicator of efficiency or non-efficiency of treatment and correlate circulating DNA levels with tumor imaging of metastases. Patients on this study at MSK will be required to submit peripheral blood samples prior to treatment, at various time points on treatment, and at progression.

All patients will undergo blood collection on a monthly basis for analysis of circulating tumor DNA levels. Using a real-time PCR developed based on bi-directional pyrophosphorolysis-activated polymerization (bi-PAP) for the quantification of ctDNA using 3'blocked primer pairs specific for the 3 recurrent mutually exclusive mutations of Gα subunits Gnaq and Gna11, Madic et. al. have been able to detect and quantify circulating tumor DNA in metastatic UM patients.[61] We will utilize this assay to measure circulating tumor DNA and correlate changes in DNA levels with response to treatment.

3 PATIENT SELECTION

The below eligbility sections contain eligbility requirements for Randomization and Crossover registrations. Additional Crossover-specific instructions and exceptions are listed in Section 3.3.

3.1 Inclusion Criteria

3.1.1 Patients must have metastatic histologically or cytologically confirmed uveal melanoma. If histologic or cytologic confirmation of the primary is not available, confirmation of the primary diagnosis of uveal melanoma by the treating investigator can be clinically obtained, as per standard practice for uveal melanoma. Pathologic confirmation of metastatic disease will be performed at MSK or at a participating site.

3.1.2 Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as $\geq$ 20 mm with conventional techniques or as $\geq$10 mm with spiral CT scan. See Section 11.0 for the evaluation of measurable disease.

3.1.3 Patients may not have received prior systemic or hepatic directed infusional/embolization therapies for advanced uveal melanoma. Local therapies such as radiofrequency ablation or cryotherapy for metastatic disease are permitted but must have been performed at least 21 days prior to initiation of study therapy. Lesions treated with local modalities such as radiofrequency ablation or cryotherapy may not be used as target lesions unless they demonstrate growth over a minimum of 3 months on subsequent imaging studies.

3.1.4 Age ≥18 years. Because no dosing or adverse event data are currently available on the use of trametinib and GSK2141795 in patients <18 years of age, children are excluded from this study but will be eligible for future pediatric single-agent trials, if applicable.

3.1.5 ECOG performance status ≤ 1 (Karnofsky ≥ 70%, see Appendix A).

3.1.6 Life expectancy of greater than 3 months.

3.1.7 Able to swallow and retain orally-administered medication and does not have any clinically significant gastrointestinal abnormalities that may alter absorption such as malabsorption syndrome or major resection of the stomach or bowels.

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

3.1.9 Patients must have normal organ and marrow function as defined below:

Leukocytes	≥ 3,000/mcL
Absolute neutrophil count	≥ 1,500/mcL
Platelets	≥ 100,000/mcL
Hemoglobin	≥ 9.0 g/dL (not requiring transfusions within the past 2 weeks)
Total bilirubin*	≤ 1.5 X institutional upper limit of normal
AST (SGOT)/ALT(SGPT)	≤ 1.5 X institutional upper limit of normal for patients with no concurrent liver metastases, OR ≤ 2.5 X institutional upper limit of normal for patients with concurrent liver metastases
Creatinine	≤ 1.5 mg/dL OR Calculated creatinine clearance (Cockroft-Gault formula) ≥50 mL/min OR 24-hour urine creatinine clearance ≥50 mL/min

Left ventricular ejection fraction ≥ institutional lower limit of normal (LLN) by ECHO

or MUGA

***Note:** Patients with hyperbilirubinemia clinically consistent with an inherited disorder of bilirubin metabolism (e.g., Gilbert syndrome) will be eligible at the discretion of the treating physician and/or the principal investigator.

3.1.10 The effects of trametinib and GSK2141795 on the developing human fetus are unknown. For this reason, and because MEK inhibitors as well as other therapeutic agents used in this trial are known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Women of child-bearing potential must have a negative blood pregnancy test within 14 days prior to start of protocol treatment. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 4 months after completion of trametinib administration.

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

3.1.12 Patients must agree to provide all imaging studies for central radiology review. This central radiology review may be performed retrospectively and will not be utilized for decision making for patients on study.

3.2 Exclusion Criteria

3.2.1 History of another malignancy except for those who have been disease-free for 3 years, or patients with a history of completely resected non-melanoma skin cancer and/or patients with indolent secondary malignancies not requiring active therapy, are eligible. Consult the study MSKPrincipal Investigator or the CTEP Medical Monitor if unsure whether second malignancies meet the requirements specified above.

3.2.2 History of interstitial lung disease or pneumonitis.

3.2.3 Any major surgery or extensive radiotherapy within 21 days prior to randomization and crossover.

3.2.4 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 trametinib alone or with GSK2141795 and during the study.

3.2.5 Symptomatic or untreated leptomeningeal or brain metastases or spinal cord compression. Treated brain metastases must have been stable for at least 1 month.

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

3.2.7 Current use of a prohibited medication. See Appendix B for a list of prohibited medications or non-drug therapies.

3.2.8 History or current evidence/risk of retinal vein occlusion (RVO) or retinal pigment epithelial detachment (RPED) in the eye unaffected by uveal melanoma.

3.2.9 Patients with abnormal fasting glucose values (values > ULN or < LLN) at screening will be excluded. In addition, patients with Type 1 diabetes will also be excluded; however, patients with Type 2 diabetes will be allowed if diagnosed ≥6 months prior to enrollment, and if presenting with a normal fasting glucose value and a hemoglobin A1C (HbA1C) ≤8% at screening.

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

- LVEF < LLN
- A QT interval corrected for heart rate using the Bazett's formula QTcB ≥ 480 msec.
- History or evidence of current clinically significant uncontrolled arrhythmias (exception: patients with controlled atrial fibrillation for >30 days prior to 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 the New York Heart Association (NYHA) functional classification system (see Appendix C).
- Treatment-refractory hypertension defined as a blood pressure of systolic >140 mmHg and/or diastolic >90 mmHg which cannot be controlled by anti-hypertensive therapy.
- Patients with intra-cardiac defibrillators.
- Known cardiac metastases.

3.2.11 Known Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV) infection (patients with chronic or cleared HBV and HCV infection are eligible). Patients with Human Immunodeficiency Virus (HIV) are not eligible if on anti-retroviral medications.

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

3.2.13 Animal reproductive studies have not been conducted with trametinib or GSK2141795. Therefore, the study drug must not be administered to pregnant women or nursing mothers. Women of childbearing potential should be advised to avoid pregnancy and use effective methods of contraception. Men with a female partner of childbearing potential must have either had a prior vasectomy or agree to use effective contraception. If a female patient or a female partner of a patient becomes pregnant while the patient receives trametinib, the potential hazard to the fetus should be explained to the patient and partner (as applicable).

3.3 Eligibility Criteria for Crossover Registrations

3.3.1 Previously treated with Trametinib on Arm A and experienced objective disease progression by RECIST 1.1.

3.3.2 Not removed from trametinib treatment due to the development of unacceptable toxicity that is not manageable with dose reduction.

3.3.3 No other drug treatment for malignant melanoma administrered after completing study treatment with trametinib.

3.3.4 Meet all eligibility criteria as outlined in Sections 3.1 Inclusion Criteria and 3.2 Exclusion Criteria with the exception of:

- 3.1.3: Prior therapy with trametinib will be permitted.
- 3.1.9: All laboratory parameters must be met as outlined in Section 3.1.9 except for ALT and total bilirubin, which must meet criteria for continued therapy as outlined in Section 6.2.4.
- 3.2.4: Prior therapy with trametinib is permitted.
- 3.2.8: Patients who are eligible for cross-over will not need to undergo another ophthalmologic examination.

3.4 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

The accrual estimates for this trial are as follows:

Accrual Targets					
Ethnic Category	**Sex/Gender**				
	Females		**Males**		**Total**
Hispanic or Latino	2	+	2	=	4
Not Hispanic or Latino	38	+	38	=	76
Ethnic Category: Total of all subjects	40	+	40	=	80
Racial Category					
American Indian or Alaskan Native	1	+	1	=	2
Asian	1	+	1	=	2
Black or African American	1	+	1	=	2

Native Hawaiian or other Pacific Islander	1	+	1	=	2
White	36	+	36	=	72
Racial Category: Total of all subjects	40	+	40	=	80

4 REGISTRATION PROCEDURES

4.1 Investigator Registration

All investigators who participate on the clinical trial and will be responsible for patient care and patient enrollment to the trial must have an active investigator registration status with the NCI. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Date Form (IDF), and Financial Disclosure Form (FDF). Annual renewal is required.

MSK, as the coordinator site, will be responsible for verifying the investigator registration status when registering patients from EU/UK sites.

4.2 MSK Research Participant Registration Procedures

Confirm eligibility as defined in the section entitled Patient Selection.

Obtain informed consent by following procedures defined in section entitled Informed Consent Procedures.

During the registration process, registering individuals will be required to complete a protocol specific Eligibility Checklist.

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

4.3 Participating Sites Research Participant Registration Process

To complete registration and enroll a participant from another institution within North America, the study staff at that site must contact the designated research staff at MSK to notify him/her of the participant registration. The site staff then needs to submit registration/eligibility documents to the Multi-Center Trial Core Representative at MSK (email to: medmctcore@mskcc.org).

The following documents must be sent for each enrollment **within 24 hours** of the informed consent form being signed:

- The completed or partially completed MSK eligibility checklist
- The signed informed consent and signed HIPAA Authorization form (Research Authorization)
- Supporting source documentation for eligibility questions (laboratory results, pathology report, radiology reports, MD notes, physical exam sheets, medical history, prior treatment records, EKG report, ECHO or MUGA report and ophthalmology report).

Upon receipt, the research staff at MSK will conduct an interim review of all documents. If the eligibility checklist is not complete, the patient will be registered PENDING and the site is responsible for sending a completed form within 30 days of the consent.

If the eligibility checklist is complete, participant meets all criteria, all source documentation is received, the participating site IRB has granted approval for the protocol, and the site is in good standing with MSK, the MSK research staff will send the completed registration documents to the MSK Protocol Participant Registration (PPR) Office to be enrolled as stated in section 4.2. The participant will be registered. The Study Coordinator should be notified of cancellations as soon as possible.

Once eligibility has been established and the participant is registered, the participant will be assigned an MSK Clinical Research Database (CRDB) number (protocol participant number). This number is unique to the participant and must be written on all data and correspondence for the participant. This protocol participant number will be relayed back to study staff at the registering site via e-mail and will serve as the enrollment confirmation.

Except in very unusual circumstances, each participating institution will order DCTD-supplied agents directly from CTEP. Agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO (PIO@ctep.nci.nih.gov) except for Group studies.

4.4 Randomization

All patients will be randomized to trametinib alone or in combination with GSK2141795. After eligibility is established and immediately after consent is obtained, patients will be registered in the Protocol Participant Registration (PPR) system and randomized using the Clinical Research Database (CRDB), between the hours of 8:30am and 5:30pm (ET), Monday - Friday. Randomization will be accomplished by the method of random permuted block, and patients will be stratified by (i) the presence or absence of liver involvement and (ii) LDH (< 2 times ULN versus two times above (≥2 x) the upper limit of normal) (see section 5.1).

As of 11/06/2015, Arm B met the specified stopping rule for futility. The remaining patients will be accrued to Arm A, no patients will be enrolled to Arm B or Crossover therapy.

4.5 Crossover

Patients initially randomized to Arm A and eligible for crossover will be registered using the crossover eligibility checklist.

To complete a crossover registration from another institution within North America, the study staff at that site must contact the designated research staff at MSK to notify him/her of the participant registration. The site staff then needs to submit registration/eligibility documents to the Multi-Center Trial Core Representative at MSK (email to: medmctcore@mskcc.org).

The following documents must be sent for each registration:

- MSK *Crossover* eligibility checklist
- Supporting source documentation for eligibility questions (radiology reports, MD notes, physical exam sheets).

If the eligibility checklist is complete, participant meets all criteria, all source documentation is received, the participating site IRB has granted approval for the protocol, and the site is in good standing with MSK, the MSK research staff will send the completed registration documents to the MSK Protocol Participant Registration (PPR) Office to be enrolled to the crossover arm. Once the participant is registered to crossover, MSK research staff will send confirmation via e-mail to the site study staff.

Patients will be registered for crossover by MSK staff in the Protocol Participant Registration (PPR) system. PPR is available Monday through Friday from 8:30am – 5:30pm (ET) at 646-735-8000. Registrations must be submitted via the PPR Electronic Registration System (http://ppr/). The completed Eligibility Checklist and other relevant documents must be uploaded via the PPR Electronic Registration System.

As of 11/06/2015, Arm B met the specified stopping rule for futility. The remaining patients will be accrued to Arm A, no patients will be enrolled to Arm B or Crossover therapy.

5 TREATMENT PLAN

5.1 Agent Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Eligible patients will be randomized on a 1:1 ratio, with randomization stratified by presence or absence of liver involvement and LDH (<2 times ULN vs ≥2 times the upper limit of normal), to one of the two treatment arms:

1. Arm A (Trametinib): Experimental Arm A will explore the activity of MEK inhibition

using trametinib in advanced UM. Patients randomized to this arm will receive trametinib 2 mg PO QD in 4 week cycles.

2. Arm B (Trametinib + GSK2141795): Experimental Arm B will explore the activity of combined MEK + AKT inhibition in advanced UM. Patients randomized to this arm will receive trametinib 1.5 mg PO QD in combination with GSK2141795 50 mg PO QD in 4 week cycles.

Patients will remain on their initially assigned treatment arm until the sooner of (i) disease progression (primary outcome measure) or (ii) the development of unacceptable toxicity that is not manageable with dose reduction. At that point, patients initially randomized to Arm A that experienced objective disease progression will be given the option of receiving additional experimental therapy with trametinib 1.5 mg QD and GSK2141795 50 mg QD.

The option of crossover will not be available to patients who are taken off treatment due to the development of unacceptable toxicity that is not manageable with dose reduction. Tumor response assessments and progression-free survival following cross-over will be recorded, but, for the purposes of the primary endpoint of progression-free survival after first randomization, these patients will be counted as a progression-event. Clinical outcome following cross-over will be followed and reported in a descriptive fashion.

Patients randomized to Arm A will be eligible for crossover if they meet the eligibility criteria outlined in Section 3.0.

Patients will be followed in an identical manner to those initially randomized as outlined in the Study Calendar below; however, no tumor biopsies will be performed on this cohort of patients. Results from these assessments will be collected in electronic CRFs up to the time of progression on trametinib in the same manner as during the randomized phase of the study (i.e., target and non-target lesions recorded in the same order). Patients may continue to receive trametinib and GSK2141795 until disease progression. Patients may receive any subsequent therapy for their disease at the discretion of the investigator.

All patients will be requested to maintain a medication diary of each dose of medication (see Appendix F). The medication diary will be returned to the research staff at the end of each treatment cycle. Missed doses should be recorded on the Medication Diary but will not be considered violations of the protocol.

Patients on the study may continue treatment, however, supply of GSK2141795 will end on March 31, 2017, and there will be no additional drug available for clinical use after that date. Therefore, all patients must be off treatment by March 31, 2017.

As of 11/06/2015, Arm B met the specified stopping rule for futility. The remaining patients will be accrued to Arm A, no patients will be enrolled to Arm B or Crossover therapy.

5.1.1 Effect of Food

The effect of food on trametinib and GSK2141795 absorption is unknown.

The effect of a high-fat, high-calorie meal on the single-dose PK of trametinib was evaluated in a Phase I, open-label, randomized, 2-treatment, 2 period crossover study with an incomplete 7-day wash-out in subjects with solid tumors. Administration of a single dose of trametinib with a high-fat, high-calorie meal decreased AUC by 24%, Cmax by 70%, and delayed Tmax by approximately 4 hours as compared to fasted conditions

A food effect study with GSK2141795 has not been completed; however its physiochemical properties suggest that a high fat meal may affect plasma concentrations.

Therefore, both trametinib and GSK2141795 are recommended to be administered under fasting conditions, both 1 hour before or 2 hours after a meal. These agents can be administered either (1) together at the same time of the day or (2) with one agent taken in the morning and the other taken in the evening, at the discretion at the treating investigator.

5.1.2 Management of Toxicities due to Trametinib

Guidelines regarding the management of toxicities due to trametinib are below. Please also refer to Section 6.1 regarding requirements for dose modification due to toxicity.

Cutaneous AEs: Rash is a frequent AE observed in patients receiving trametinib.[30] Recommendations for supportive care and guidelines for dose modifications for rash are based on experience with other MEK inhibitors and EGFR inhibitors.[62,63] The institutional standards for the management of skin-related AEs can differ from these guidelines. In this case, best clinical judgment should be applied and a consultation with the study chair or the CTEP Medical Monitor may be required.

Guidelines for Supportive Care of Rash	
Type of Care	**Action**
Prevention/Prophylaxis[a]	• Avoid unnecessary exposure to sunlight. • Apply broad-spectrum sunscreen (containing titanium dioxide or zinc oxide) with a skin protection factor (SPF) ≥15 at least twice daily. • Use thick, alcohol-free emollient cream (*e.g.*, glycerine and cetomacrogol cream) on dry areas of the body at least twice daily. • Topical steroids and antibiotics should be applied at least twice daily, starting on Day 1 of study treatment, to body areas such as face, chest, and upper back. • Use mild-strength topical steroid (hydrocortisone 1% cream) or topical antibiotic (*e.g.*, clindamycin) or oral antibiotics (*e.g.*, doxycycline 100 mg BID, minocycline 100 mg BID).

Guidelines for Supportive Care of Rash	
Type of Care	**Action**
Symptomatic Care[b]	• Pruritic lesions: Cool compresses and oral antihistamine therapies. • Fissuring lesions: Monsel's solution, silver nitrate, or zinc oxide cream. • Desquamation: Thick emollients and mild soap. • Paronychia: Antiseptic bath, local potent corticosteroids in addition to antibiotics; if no improvement, consult dermatologist or surgeon. • Infected lesions: Appropriate bacterial/fungal culture-driven systemic or topical antibiotics.
[a] Rash prophylaxis is recommended for the first 6 weeks of study treatment. [b] Patients who develop rash/skin toxicities should be seen by a qualified physician and should receive evaluation for symptomatic/supportive care management.	

Visual AEs: Episodes of visual changes have been observed in subjects receiving trametinib, and ocular adverse events are known to be related to trametinib. An ophthalmologist or other qualified investigator (e.g., optometrist) should be consulted if changes in vision develop. However, if the visual changes are clearly unrelated to study treatment (e.g., allergic conjunctivitis), then close monitor closely as it may be reasonable to defer ophthalmic examination. Special attention should be given to retinal findings (e.g., retinal pigment epithelial detachment (RPED) or retinovascular abnormalities (i.e., branch or central retinal vein occlusions (RVO)).

Diarrhea: Episodes of diarrhea have occurred in patients receiving trametinib or GSK2141795.[30] Other frequent causes of diarrhea may include concomitant medications (*e.g.*, stool softeners, laxatives, antacids, *etc.*), infections by *C. difficile* or other pathogens, or partial bowel obstruction. Those conditions should be excluded.

Cardiac AEs:

- Decrease in LVEF - Decreases of the left ventricular ejection fraction (LVEF) have been observed in patients receiving trametinib. Therefore, ECHOs must be performed in regular intervals as 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).

- Hypertension - Increases in blood pressure (BP) have been observed in patients receiving trametinib. All BP assessments should be performed under the following optimal conditions:

    - The subject has been seated with back support, ensuring that legs are uncrossed and flat on the floor.
    - The subject is relaxed comfortably for at least 5 minutes.
    - Restrictive clothing has been removed from the cuff area, and the correct cuff has been selected.
    - The subject's arm is supported so that the middle of the cuff is at heart level.

- The subject remains quiet during the measurement.
- In subjects with an initial BP reading within the hypertensive range, a second reading should be taken at least 1 minute later.
- Visits to monitor increased blood pressure can be scheduled independently from the per-protocol visits outlined in the Study calendar. Ideally, subsequent blood pressure assessments should be performed within 1 week.

5.1.3 Management of Toxicities due to GSK2141795

Based on available adverse event (AE) data from 151 patients 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.

Guidelines regarding the management of toxicities due to GSK2141795 are below. Please also refer to Section 6.4 regarding requirements for dose modification due to toxicity.

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

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

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

Cutaneous AEs: Two types of rashes may be seen with the trametinib + GSK2141795 combination:

1. Acneiform rash, typically associated with MEK inhibitor therapy (trametinib).
2. Maculopapular rash, often associated with pruritus (GSK2141795).

If the diagnosis is unclear, a biopsy and photographs should be obtained as well as a dermatology consult. In addition, if the investigator feels the rash is not consistent with a MEK inhibitor-associated acneiform rash and is Grade 2 or greater, 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 may or may not be associated with pruritus. Preliminary data suggest that drug interruption and dose reduction upon re-challenge ameliorate the symptoms. Rash management should focus on symptom relief and maintenance of an intact integument. Dermatology consult is recommended when clinically appropriate. Topical steroid creams have been found to provide some relief from symptoms. Treatment will be dose reduced or discontinued for clinically significant toxicity not adequately controlled by supportive care measures.

Glucose Abnormalities:

- Hyperglycemia - Hyperglycemia occurred in patients receiving GSK2141795 ≥75 mg/day, with the majority of events occurring at doses exceeding the maximum tolerated dose (MTD) of 75 mg/day. Treatment-related grade 3 or grade 4 events were observed at 75 mg, 100 mg, and 150 mg daily doses. The frequency and severity of hyperglycemia AEs is reduced at the 75mg/day dose as compared with higher doses. It is not clear if oral anti-hyperglycemic drugs are useful to ameliorate the hyperglycemia, although both intravenous and sliding scale insulin have been helpful.

  To reduce the risk of hyperglycemia, patients with abnormal fasting glucose values at screening will be excluded. In addition, patients with Type 1 diabetes will also be excluded; however, patients with Type 2 diabetes will be allowed if diagnosed ≥6 months prior to enrollment, and if presenting with a normal fasting glucose value and a hemoglobin A1C (HbA1C) ≤8% at screening. Patients will have glucose and insulin monitored during the study. If hyperglycemia is observed, supportive therapy will be provided according 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 patients receiving GSK2141795 ≥75 mg/day. Treatment-related grade 3 or grade 4 events were observed at 75 mg and 100 mg daily doses. The mechanism of hypoglycemia is currently unknown. Careful monitoring of glucose levels and encouragement of adequate oral intake are recommended.

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

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

5.2 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of trametinib and GSK2141795 with other concomitantly administered drugs through the cytochrome P450 system, the electronic case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The local Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes. Appendix D is a patient information sheet that can be used for this specific protocol and presented to the patient.

5.3 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression, unless the patient is experiencing clinical benefit from therapy as determined by the study PI. Continued treatment in these situations will be approved once the study PI and CTEP medical monitor have reviewed the case,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

5.4 Duration of Follow Up

Patients will be followed for 4 weeks after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

Patients will be contacted or evaluated approximately every 12 weeks (+/- 1 week) until death for survival assessment. Follow-up for overall survival will continue until all patients have completed study therapy and sufficient data is available to analyze the primary endpoint; however, survival follow-up may continue beyond this time point at the discretion of the MSK principal investigator and CTEP.

5.5 Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed in Section 5.3 applies. The reason for study removal and the date the patient was removed must be documented in the electronic Case Report Form.

6 DOSING DELAYS/DOSE MODIFICATIONS

AEs occurring in patients treated with GSK2141795 and 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. If a patient experiences several adverse events and there are conflicting recommendations, the investigator should use the recommended dose adjustment that reduces the dose to the lowest level. General guidelines are provided below. CTEP drug monitors should be consulted if there are questions about the attribution of AEs and how the doses should be modified. Although dose alterations and modifications are described below by specific CTCAE grade, in general any intolerable toxicity, regardless of severity, may necessitate transient breaks in drug therapy after discussion with the CTEP drug monitor.

Hypertension, pneumonitis, and visual disturbances are AEs typically associated with trametinib. Please follow guidelines for trametinib outlined below. In general, dosing for GSK2141795 may continue when trametinib is on hold if AEs are $\leq$ grade 2; however:

- If the above AEs are grade 3-4, GSK2141795 should be held when trametinib is held. Once the AEs have resolved to grade 1 or baseline, GSK2141795 may resume at the same dose.
- If GSK2141795795 has been held for >21 days, a discussion with the CTEP drug monitor is required before resuming treatment with the agent.

6.1 Trametinib and GSK2141795 Dose Modifications

6.1.1 Trametinib Dose Modifications

The table below outlines the dose levels to be used for any necessary trametinib dose modifications. Please note that the trametinib starting doses are different depending upon treatment arm.

Dose Level	Trametinib Dose/Schedule
0	2 mg QD
-1	1.5 mg QD
-2	1 mg QD

If trametinib 1 mg QD is not tolerated, then treatment will be permanently discontinued.

6.1.2 Trametinib Dose Modification for Toxicities Not Specified in Subsequent Sections

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

6.1.3 GSK2141795 Dose Modification

The table below outlines the dose levels to be used for any necessary GSK2141795 dose modifications:

Dose Level	GSK2141795 Dose/Schedule
0	50 mg QD
-1	25 mg QD

A maximum of one GSK2141795 dose level reduction is allowed. If a second dose level reduction is required, treatment will be permanently discontinued.

6.1.4 GSK2141795 Dose Modification for Toxicities Not Specified in Subsequent Sections

Toxicity Grade[a]	**Dose Modification of 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, resume at the next lower dose level. Consider supportive care recommendations.
Grade 4	Permanently discontinue GSK2141795.
a: The guidelines are for AEs thought to be related to GSK2141795. However, temporary interruption of the agent should be considered if the patient is critically ill due to AEs of any attribution	

6.2 Dose Modifications for Toxicities Attributable to Both Trametinib and GSK2141795

6.2.1 Dose Modification for Rash

Guidelines regarding event management and dose reduction for rash considered to be related to study treatment are provided in the table below. Of note, the treating physician can at his or her discretion hold protocol therapy for rash sooner than listed below if they document that, in their opinion, it will mitigate the severity of a rash that would have otherwise compromised dose intensity.

Dose Modification Guidelines and Management for Rash		
Rash Severity	Management Guideline	Dose Modification
Grade 1	• Initiate prophylactic and symptomatic treatment measures.[1] • Use moderate strength topical steroid.[2] • Reassess after 2 weeks.	• Continue treatment. • If rash does not recover to baseline within 2 weeks despite best supportive care, **reduce trametinib or both agents by one dose level**.[3]

Dose Modification Guidelines and Management for Rash		
Rash Severity	Management Guideline	Dose Modification
Grade 2	• Initiate prophylactic and symptomatic treatment measures.[1] • Use moderate strength topical steroid.[2] • Reassess after 2 weeks.	• Continue treatment • **Reduce trametinib or both agents by one dose level.** • If rash recovers to ≤ grade 1 within 2 weeks, increase dose(s) to previous dose level. • If no recovery to ≤ grade 1 within 2 weeks, interrupt treatment until recovery to ≤ grade 1. • **Restart trametinib or both agents at reduced dose level.**
Grade ≥3	• Use moderate strength topical steroids PLUS oral methyl-prednisolone dose pack.[2] • Consult dermatologist.	• Interrupt trametinib or both agents until rash recovers to ≤ grade 1. • **Restart with trametinib or both agents with one dose level reduction**[3,] • If no recovery to ≤ grade 2 within 3 weeks, **permanently discontinue both agents** (resumption of trametinib or GSK2141795 alone may be considered based on toxicity-benefit consideration and after consultation with CTEP).
1. Rash prophylaxis is recommended for the first 6 weeks of study treatment (refer to guidelines for trametinib). 2. Moderate-strength topical steroids: Hydrocortisone 2.5% cream or fluticasone propionate 0.5% cream. 3. Trametinib or GSK2141795 may be escalated to previous dose level if no rash is evident 4 weeks after restarting study treatment.		

6.2.2 Dose Modification for Diarrhea

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

Management and Dose Modification Guidelines for Diarrhea		
CTCAE Grade	**Adverse Event Management**	**Action and Dose Modification**

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. • 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.	• Continue treatment. • If diarrhea is grade 2 for >48 h, interrupt GSK2141795 and trametinib 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 CTEP).
Uncomplicated Diarrhea,[1] Grade 3 or 4 **Any Complicated Diarrhea[2]**	• Clinical evaluation mandatory. • Loperamide[3]: Initially 4 mg, followed by 2 mg every 4 hours or after every unformed stool; maximum 16 mg/day. Continue until diarrhea-free for 12 hours. • Oral antibiotics and second-line therapies if clinically indicated. • Hydration: Intravenous fluids if clinically indicated. • Antibiotics (oral or intravenous) if clinically indicated. • Intervention should be continued until the subject is diarrhea-free for ≥24 hours. • Intervention may require hospitalization for subjects at risk of life-threatening complications.	• Interrupt protocol therapy until diarrhea resolves to ≤ grade 1. • Restart with trametinib or trametinib and 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 CTEP).

1. **Uncomplicated diarrhea** defined by the absence of symptoms such as cramping, nausea/vomiting, ≥ grade 2, decreased performance status, pyrexia, sepsis, neutropenia ≥ grade 3, frank bleeding, and/or dehydration requiring intravenous fluid substitution.
2. **Complicated diarrhea** defined by the presence of symptoms such as cramping, nausea/vomiting, ≥ grade 2, decreased performance status, pyrexia, sepsis, neutropenia ≥ grade 3, frank bleeding, and/or dehydration requiring intravenous fluid substitution.
3. Loperamide should be made available prior to start of study treatment so loperamide administration can begin at the first signs of diarrhea.
4. Escalation of trametinib or trametinib and GSK2141795 to previous dose level(s) is allowed after consultation with the CTEP monitor and Study Chair and in the absence of another episode of complicated or severe diarrhea in the 4 weeks subsequent to dose reduction.

6.2.3 Dose Modification for Reduced Left Ventricular Ejection Fraction

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

Guidelines regarding event management and dose reduction for reduced left ventricular ejection fraction considered to be related to study treatment are provided in the table below.

Dose Modification Guidelines and Stopping Criteria for LVEF Decrease		
Clinic	**LVEF-drop (%) or CTCAE grade**	**Action and Dose Modification**
Asymptomatic	Absolute decrease of >10% in LVEF compared to baseline and ejection fraction below the institution's LLN.	• Interrupt trametinib and repeat ECHO/MUGA within 2 weeks[a] If the LVEF **recovers** within 4 weeks (defined as LVEF ≥ LLN and absolute decrease ≤ 10% compared to baseline), then: o Consult with the CTEP medical monitor and request approval to restart o Restart treatment with trametinib and GSK2141795 reduced dose by one dose level[b] o 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: o Consult with cardiologist o **Permanently discontinue trametinib and GSK2141795** o **Report as SAE** o Repeat ECHO/MUGA after 2, 4, 8, 12, and 16 weeks or until resolution
Symptomatic[c]	• Grade 3: resting LVEF 39% 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.

Dose Modification Guidelines and Stopping Criteria for LVEF Decrease		
Clinic	**LVEF-drop (%) or CTCAE grade**	**Action and Dose Modification**
Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; ECHO = echocardiogram; GSK = GlaxoSmithKline; LLN = lower limit of normal; LVEF = left ventricular ejection fraction; If ECHO/MUGA does not show LVEF recovery after 2 weeks, repeat ECHO/MUGA 2 weeks later. 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. Symptoms may include: dyspnea, orthopenea, and other signs and symptoms of pulmonary congestion and edema.		

6.2.4 Dose Modification for Liver Chemistry Changes

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

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

Trametinib Dose Modification for Liver Function Test Abnormalities	
Event	**Treatment modifications and assessment/monitoring**
	ASSESSMENT and WORKUP: • Viral hepatitis.[4] • If possible, obtain blood sample for PK analysis.[5] • CPK and LDH. • Fractionate bilirubin, if total bilirubin ≥ 2x ULN. • CBC with differential to assess eosinophilia. • Record clinical symptoms of liver injury, or hypersensitivity on AE CRF. • Record concomitant medications (including acetaminophen, herbal remedies, other over the counter medications). • Record alcohol use. *Additional work up for patient stopping for criteria 1-2 (with abnormal TB and INR, indicating potentially more significant liver toxicities)*: • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Acetaminophen adduct HPLC assay (in subjects with likely preceeding acetaminophen use). • If there is underlying chronic hepatitis B (e.g. positive hepatitis B surface antigen): quantitative hepatitis B DNA and hepatitis delta antibody.[6] • Liver imaging (ultrasound, MRI, CT) and /or liver biopsy.
Footnotes: 1. Bilirubin fractionation should be performed if testing is available. If bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, which indicates direct bilirubin elevations and suggesting liver injury. 2. All events of ALT ≥3xULN **and** bilirubin ≥2xULN (>35% direct bilirubin) or ALT ≥3x ULN **and** INR >1.5 (if INR measured) may indicate severe liver injury (possible "Hy's Law"). INR measurement is not required, and the threshold value stated will not apply to subjects receiving anticoagulants. 3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia) 4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody 5. PK sample is desired if feasible. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. 6. If hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed) (Le Gal *et al.*, 2005).	

6.3 Dose Modifications for Toxicities Attributable to Trametinib

6.3.1 Trametinib Dose Modifications for Visual Changes

Visual changes have been observed in patients receiving trametinib, and can be caused by retinal pigment epithelial detachments (RPED), or retinal vein abnormalities (e.g., branch or central Retinal Vein Occlusion [RVO]) or optic nerve swelling. Patients are required to have a

standard ophthalmic exam performed by an ophthalmologist or other qualified investigator (e.g., optometrist) at baseline and at any time patients report visual disturbance.

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

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

<table>
<tr><th colspan="3">Management and Trametinib Dose Modification for Visual Changes</th></tr>
<tr><th>Event
CTCAE Grade</th><th>Management Guideline</th><th>Dose Modification</th></tr>
<tr><td colspan="3">Any grade of RPED, or RVO should be reported as SAEs to CTEP-AERS</td></tr>
<tr><td>Grade 1
Asymptomatic or symptomatic but not limiting ADL; intervention not indicated.</td><td rowspan="2">• Consult ophthalmologist or other qualified investigator (e.g., optometrist) any time when patient reports visual disturbance. This should be done within 7 days for grade 1 events, and should be done immediately for grade 2-3 events.
• Workup to rule out, RPED or RVO. Consult retinal specialist if available.
• Continue follow up examination(s) for RPED, and RVO.
• Report RVO or RPED as SAE regardless of grade</td><td>• Continue therapy. Obtain ophthalmologic exam*
• If ophthalmologic examination cannot be performed within 7 days of onset, hold trametinib until RPED and RVO are excluded and symptoms resolve.
• If RPED and RVO excluded, restart trametinib at same dose level.
• <u>If RPED (regardless of symptoms)</u>: Interrupt trametinib until symptoms resolve and ophthalmology exam shows resolution. May restart trametinib with one dose level reduction*. If no resolution within 3 weeks, permanently discontinue trametinib.
• <u>If RVO</u>: Permanently discontinue trametinib.</td></tr>
<tr><td>Grade 2 and 3
Grade 2defined as: Symptomatic with moderate decrease in visual acuity (20/40 or better; limiting instrumental ADL; local or non-invasive intervention indicated).

Grade 3 defined as: Symptomatic with marked decrease in visual acuity or marked visual field defect (worse than 20/40 but better than 20/200); severe pain or medically significant; operative intervention indicated.</td><td>•Interrupt trametinib until signs/ symptoms resolve to baseline*.
•If not RPED/RVO but related to other trametinib-related ocular AE (e.g., optic neuropathy), restart trametinib with one dose level reduction AFTER symptoms resolved.
•If not related to trametinib, resume trametinib at the same dose, AFTER symptoms resolved.
• <u>If RPED</u>: Hold trametinib until symptoms resolve and exam (by retinal specialist if available) shows resolution. Restart trametinib with one dose level reduction.
• If no resolution within 3 weeks, permanently discontinue trametinib.
• <u>If RVO</u>: Permanently discontinue trametinib.</td></tr>
</table>

Grade 4 Sight-threatening consequences; urgent intervention indicated; blindness (20/200 or worse).		**Permanently discontinue trametinib**.
Abbreviations: RPED = retinal pigment epithelial detachments; RVO = retinal vein occlusion; SAE = serious adverse event *If ocular toxicities do not resolve within 21 days, permanently discontinue trametinib.		

6.3.2 Trametinib Dose Modification for Pneumonitis

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

Pneumonitis Guidelines for Trametinib Monotherapy		
CTCAE Grade	**Adverse Event Management**	**Action and Dose Modification**
Grade 1	• CT scan (high-resolution with lung windows) recommended. • Work-up for infection. • Monitoring of oxygenation via pulse-oximetry recommended. • Consultation with pulmonologist recommended.	Continue trametinib at current dose.
Grade 2	• CT scan (high-resolution with lung windows). • Work-up for infection. • Consult pulmonologist. • Pulmonary function tests: If < normal, repeat every 8 weeks until ≥ normal. • Bronchoscopy with biopsy and/or BAL recommended. • Symptomatic therapy including corticosteroids if clinically indicated.	• Interrupt trametinib until recovery to grade ≤1. • If AE resolved to grade ≤1 and relationship to trametinib is equivocal, restarting trametinib with one dose reduction may be considered, after discussion with the medical monitor. • If treatment delay is > 4 weeks, **permanently discontinue trametinib**.
Grade 3	• CT scan (high-resolution with lung windows). • Work-up for infection. • Consult pulmonologist. • Pulmonary function tests-if < normal, repeat every 8 weeks until ≥ normal. • Bronchoscopy with biopsy and/or BAL if possible. • Symptomatic therapy including corticosteroids as clinically indicated.	• Interrupt trametinib until recovery to grade ≤1. • If AE resolved to grade ≤1 and relationship to trametinib is equivocal, restarting trametinib with one dose reduction may be considered, after discussion with the medical monitor. • If treatment delay is >4 weeks, **permanently discontinue trametinib**.
Grade 4	Same as grade 3.	**Permanently discontinue trametinib.**
Abbreviations: BAL = bronchoalveolar lavage; CT = computed tomography.		

6.3.3 Trametinib Dose Modification for QTc Prolongation

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

QTc-Prolongation[a]	Action and Dose Modification
• QTcB ≥501 msec or • uncorrected QT>600 msec or • QTcB>530 msec for subjects with bundle branch block	• Interrupt study treatment until QTcB prolongation resolves to Grade 1 or baseline • Test potassium, calcium, phosphorus and magnesium. If abnormal, correct per routine clinical practice to within normal limits. • Review concomitant medication usage for a prolonged QTc. • Restart at current dose level[b] • **If event recurs, permanently discontinue study treatment**
Abbreviations: msec = milliseconds; QTcB = QT interval on electrocardiogram corrected using the Bazett's formula a. Based on average QTc value of triplicate ECGs. For example, if an ECG demonstrates a prolonged QT interval, obtain two or more ECGs over a brief period, and then use the averaged QTc values of the three ECGs to determine if study treatments should be interrupted or discontinued. b. If the QTc prolongation resolves to Grade 1 or baseline, the subject may resume study treatment if the investigator and GSK medical monitor agree that the subject will benefit from further treatment.	

6.3.4 Trametinib Dose Modification for Hypertension

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

Management and Trametinib Dose Modification for Hypertension		
Event	**Management Guideline**	**Dose Modification**
Definitions used in the table: - Persistent hypertension: Hypertension detected in two separate readings during up to three subsequent visits. - Well-controlled hypertension: Blood pressure of SBP ≤140 mmHg and DBP ≤90 mmHg in two separate readings during up to three subsequent visits. - Symptomatic hypertension: Hypertension associated with symptoms (*e.g.*, headache, light-headedness, vertigo, tinnitus, episodes of fainting or other symptoms indicative of hypertension) that resolve after the blood pressure is controlled within the normal range. - Asymptomatic hypertension: SBP >140 mmHg and/or DBP >90 mmHg in the absence of the above symptoms.		

(Scenario A) • Asymptomatic and persistent SBP of ≥140 and <160 mmHg, or DBP ≥90 and <100 mmHg, or Clinically significant increase in DBP of 20 mmHg (but still below 100 mmHg).	• Adjust current or initiate new antihypertensive medication(s). • Titrate antihypertensive medication(s) during the next 2 weeks to achieve well-controlled BP. If BP is not well-controlled within 2 weeks, consider referral to a specialist and go to scenario (B).	Continue trametinib at the current dose.
(Scenario B) • Asymptomatic SBP ≥160 mmHg, or DBP ≥100 mmHg, or Failure to achieve well-controlled BP within 2 weeks in Scenario A.	• Adjust current or initiate new antihypertensive medication(s). • Titrate antihypertensive medication(s) during the next 2 weeks to achieve well-controlled BP.	• Interrupt trametinib if clinically indicated. • Once BP is well-controlled, restart trametinib **reduced by one dose level**.[a]
(Scenario C) • Symptomatic hypertension or Persistent SBP ≥160 mmHg, or DBP ≥100 mmHg, despite antihypertensive medication and dose reduction of trametinib	• Adjust current or initiate new antihypertensive medication(s). • Titrate antihypertensive medication(s) during the next 2 weeks to achieve well-controlled BP. • Referral to a specialist for further evaluation and follow-up is recommended.	• Interrupt trametinib. • Once BP is well-controlled, restart trametinib **reduced by one dose level**.[a]
(Scenario D) Refractory hypertension unresponsive to above interventions or hypertensive crisis.	Continue follow-up per protocol.	**Permanently discontinue trametinib**.
a. Escalation of trametinib to previous dose level can be considered if BPs remain well controlled for 4 weeks after restarting of trametinib. Approval from Medical Monitor is required.		

6.4 Dose Modifications for Toxicities Attributable to GSK2141795

6.4.1 GSK2141795 Dose Modification for Hypo- or Hyperglycemia

Guidelines regarding event management and dose reduction for hypo- or hyperglycemia considered to be related to study treatment are provided in the table below.

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**

Management and Dose Modification Guidelines for Hypo- or Hyperglycemia		
Criteria	**Management Guidelines**	**Study Drug Modification**
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 hypoglycaemia as GSK2141795 is held/or discontinued. • Intravenous insulin treatment is recommended.	Hold drug(s) and notify investigator immediately. The investigator should discuss intervention and possible resumption of study drug(s) with the CTEP monitor.

6.4.2 GSK2141795 Dose Modification for Nausea/Vomiting

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

Event Name	Nausea	
Grade of Event	**Management/Next Dose for GSK2141795**	**Management/Next Dose for GSK2141795**
≤ Grade 1	No change in dose	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy.		
Recommended management: antiemetics.		

7 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting (via CTEP-AERS) **in addition** to routine reporting.

7.1 Comprehensive Adverse Events and Potential Risks Lists (CAEPRs)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation

of events by body system. In addition to the comprehensive list, a subset of AEs, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with ***bold*** and ***italicized*** text. The SPEER is a list of events that are protocol-specific exceptions to expedited reporting to NCI via CTEP-AERS (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification.

NOTE: The highest grade currently reported is noted in parentheses next to the AE in the SPEER. Report **ONLY** AEs higher than this grade expeditiously via CTEP-AERS. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

7.1.1 CAEPRs for CTEP IND Agents

7.1.1.1 CAEPR for Trametinib

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

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

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

Version 2.4, October 7, 2016[1]

Adverse Events with Possible Relationship to Trametinib dimethyl sulfoxide (GSK1120212B) (CTCAE 4.0 Term) [n= 1111]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 2)***
CARDIAC DISORDERS			
		Heart failure	

Adverse Events with Possible Relationship to Trametinib dimethyl sulfoxide (GSK1120212B) (CTCAE 4.0 Term) [n= 1111]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Left ventricular systolic dysfunction	
	Sinus bradycardia		
EYE DISORDERS			
	Blurred vision		
	Dry eye		
		Eye disorders - Other (chorioretinopathy also known as retinal pigment epithelial detachment)	
		Eye disorders - Other (retinal vein occlusion)	
	Eye disorders - Other (visual disorders)[2]		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
		Colitis	
		Colonic perforation	
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 3)***
	Dry mouth		***Dry mouth (Gr 2)***
	Dyspepsia		***Dyspepsia (Gr 2)***
	Mucositis oral		***Mucositis oral (Gr 2)***
Nausea			***Nausea (Gr 3)***
	Vomiting		***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		***Chills (Gr 2)***
	Edema face		
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
IMMUNE SYSTEM DISORDERS			
	Allergic reaction[3]		
INFECTIONS AND INFESTATIONS			
	Lung infection		
	Paronychia		***Paronychia (Gr 2)***
	Skin infection		***Skin infection (Gr 2)***
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 2)***
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr 2)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 2)***
	CPK increased		
	Ejection fraction decreased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
	Dehydration		***Dehydration (Gr 3)***
	Hypoalbuminemia		

Adverse Events with Possible Relationship to Trametinib dimethyl sulfoxide (GSK1120212B) (CTCAE 4.0 Term) [n= 1111]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Hypomagnesemia		***Hypomagnesemia (Gr 2)***
	Hyponatremia		***Hyponatremia (Gr 3)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Back pain		***Back pain (Gr 2)***
		Musculoskeletal and connective tissue disorder - Other (rhabdomyolysis)	
	Pain in extremity		***Pain in extremity (Gr 2)***
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Headache		***Headache (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 2)***
		Pneumonitis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		***Alopecia (Gr 2)***
	Dry skin		***Dry skin (Gr 2)***
		Palmar-plantar erythrodysesthesia syndrome	
	Periorbital edema		
	Pruritus		***Pruritus (Gr 2)***
	Skin and subcutaneous tissue disorders - Other (folliculitis)		***Skin and subcutaneous tissue disorders - Other (folliculitis) (Gr 2)***
Skin and subcutaneous tissue disorders - Other (rash)[4]			***Skin and subcutaneous tissue disorders - Other (rash)[4] (Gr 3)***
VASCULAR DISORDERS			
	Hypertension		***Hypertension (Gr 2)***
Vascular disorders - Other (edema)[5]			***Vascular disorders - Other (edema)[5] (Gr 2)***
	Vascular disorders - Other (hemorrhage)[6]		

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

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

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

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

[5]Edema includes edema, lymphedema, and edema limbs.

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

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

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Disseminated intravascular coagulation; Febrile neutropenia; Leukocytosis
CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Myocardial infarction; Restrictive cardiomyopathy; Sinus tachycardia
EYE DISORDERS - Corneal ulcer; Eyelid function disorder; Flashing lights; Floaters; Glaucoma; Papilledema; Photophobia; Retinal detachment
GASTROINTESTINAL DISORDERS - Anal hemorrhage; Ascites; Duodenal ulcer; Enterocolitis; Esophageal necrosis; Esophageal ulcer; Esophagitis; Gastric hemorrhage; Gastric ulcer; Gastritis; Gastrointestinal disorders - Other (intestinal obstruction); Gastrointestinal disorders - Other (oropharyngeal pain); Gastrointestinal disorders - Other (pneumatosis intestinalis); Gastrointestinal fistula; Gingival pain; Hemorrhoidal hemorrhage; Ileus; Lower gastrointestinal hemorrhage; Obstruction gastric; Pancreatitis; Rectal hemorrhage; Small intestinal obstruction; Upper gastrointestinal hemorrhage
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Flu like symptoms; General disorders and administration site conditions - Other (axillary pain); Localized edema; Malaise; Non-cardiac chest pain; Pain
HEPATOBILIARY DISORDERS - Cholecystitis; Hepatic failure; Hepatic pain; Hepatobiliary disorders - Other (hepatic encephalopathy)
INFECTIONS AND INFESTATIONS - Biliary tract infection; Catheter related infection; Device related infection; Endocarditis infective; Enterocolitis infectious; Hepatitis viral; Infections and infestations - Other (abscess limb); Infections and infestations - Other (necrotizing fasciitis); Infections and infestations - Other (oral infection); Pharyngitis; Rash pustular; Sepsis; Upper respiratory infection; Urinary tract infection
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising
INVESTIGATIONS - Blood bilirubin increased; Creatinine increased; Electrocardiogram QT corrected interval prolonged; GGT increased; Investigations - Other (blood lactate dehydrogenase increased); Lipase increased; Lymphocyte count decreased; Platelet count decreased; Serum amylase increased; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Hyperglycemia; Hyperkalemia; Hyperuricemia; Hypocalcemia; Hypoglycemia; Hypokalemia; Metabolism and nutrition disorders -

Other (hyperphosphatemia)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Generalized muscle weakness; Musculoskeletal and connective tissue disorder - Other (compression fracture); Musculoskeletal and connective tissue disorder - Other (muscle spasm); Myalgia; Neck pain
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (tumor hemorrhage); Tumor pain
NERVOUS SYSTEM DISORDERS - Dysgeusia; Encephalopathy; Intracranial hemorrhage; Lethargy; Nervous system disorders - Other (diplopia); Seizure; Somnolence; Stroke; Syncope; Transient ischemic attacks
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Delirium; Depression; Hallucinations; Insomnia; Personality change
RENAL AND URINARY DISORDERS - Acute kidney injury; Cystitis noninfective; Hematuria; Proteinuria; Renal and urinary disorders - Other (dysuria); Urinary incontinence
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Vaginal fistula; Vaginal hemorrhage
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Epistaxis; Hypoxia; Laryngeal edema; Pleural effusion; Pneumothorax; Productive cough; Pulmonary hypertension; Respiratory failure; Sinus disorder
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Bullous dermatitis; Photosensitivity; Purpura; Skin and subcutaneous tissue disorders - Other (erythema nodosum); Skin and subcutaneous tissue disorders - Other (nail disorder); Skin and subcutaneous tissue disorders - Other (skin fissures); Skin ulceration; Urticaria
VASCULAR DISORDERS - Hematoma; Hot flashes; Hypotension; Thromboembolic event (venous)

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

7.1.1.2 CAEPR for GSK2141795

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
GSK2141795 (NSC 767034)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI via CTEP-AERS (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 150 patients.* Below is the CAEPR for GSK2141795.

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE

listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.1, July 26, 2013[1]

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

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

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

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

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

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

RENAL AND URINARY DISORDERS - Acute kidney injury
VASCULAR DISORDERS - Thromboembolic event

Note: GSK2141795 in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- For expedited reporting purposes only:
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section 7.1.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.
  - Other AEs for the protocol that do not require expedited reporting are outlined in Section 7.3.4 .

- **Attribution** of the AE:
  - 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.

7.3 Expedited Adverse Event Reporting

7.3.1 Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP Web site (http://ctep.cancer.gov). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP Web site (http://ctep.cancer.gov). These requirements are briefly outlined in the tables below (Section 7.3.3).

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

7.3.2 CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Study Coordinator of the Lead Organization, Principal Investigator, and the local treating physician. CTEP-AERS provides a copy feature for other e-mail recipients.

In addition to reporting to CTEP-AERS:

- Participating sites are responsible for submitting all reportable SAEs to their local IRB per institutional guidelines
- Participating sites are responsible for reporting all reportable SAEs to the MSK PI via e-mail within 3 calendar days of learning of the event. Participating sites should use the SAE Report Form found in MSK's internet-based Clinical Research Database, CRDBi-Multicenter, to report SAEs to MSK.
- Participating sites should notify the MSK PI of any grade 5 event immediately.

SAE contact information for the Coordinating Center is listed below:

Alexander Shoushtari, MD
Memorial Sloan Kettering Cancer Center
300 East 66th Street
New York, NY 10065
Telephone: 646-888-4161
Fax: 646-888-4253
Email: shoushta@mskcc.org

Multicenter Research Team
Memorial Sloan Kettering Cancer Center
Email: medmctcore@mskcc.org

The MSK Research Staff is responsible for submitting all SAEs to the MSK IRB/PB within 5 days of learning of the event.

Safety Reports:

- MSK will distribute outside safety reports to the participating sites immediately upon receipt.
- MSK must submit safety reports to the MSK IRB/PB according to institutional guidelines.
- Participating sites must submit safety reports to their institution's IRBs within 90 days of the date of the report, per CTEP guidelines**.**

7.3.3 Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be

provided.

Death due to progressive disease should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (Progressive Disease)"** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

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

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

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

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

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

Expedited AE reporting timelines are defined as:

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

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

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

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

7.3.4 Additional Protocol-Specific Expedited Adverse Event Reporting Exclusions

Not applicable.

7.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported through CTEP-AERS must <u>also</u> be reported in routine study data submissions.**

7.5 Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.
CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

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

7.6 Second Malignancy

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

7.7 Serious Adverse Event (SAE) Reporting for MSK Patients Only

Any SAE must be reported to the IRB/PB as soon as possible but no later than 5 calendar days. The IRB/PB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to

the SAE Office at sae@mskcc.org. The report should contain the following information:

Fields populated from CRDB:
- Subject's name (generate the report with only initials if it will be sent outside of MSK)
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:
- The date the adverse event occurred
- The adverse event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
  - An explanation of how the AE was handled
  - A description of the subject's condition
  - Indication if the subject remains on the study
  - If an amendment will need to be made to the protocol and/or consent form.

The PI's signature and the date it was signed are required on the completed report.

8 PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agents administered in this study can be found in Section 7.1.

8.1 CTEP IND Agent(s)

8.1.1 Trametinib dimethyl sulfoxide (GSK1120212B) (NSC 763093) Investigationally labeled

Chemical Name (IUPAC): equimolecular combination of N-(3-{3-cyclopropyl-5-[(2-fluoro-4-iodophenyl)amino]-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydropyrido[4,3-d]pyrimidin-1(2H)-yl}phenyl)acetamide with (methylsulfinyl)methane

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

CAS Registry Number: 1187431-43-1

Classification: MEK inhibitor

Molecular Formula: $C_{26}H_{23}FIN_5O_4 \cdot C_2H_6OS$ **M.W.:** 693.54 (dimethyl sulfoxide solvate) 615.41 (anhydrous parent)

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

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

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

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

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

- 0.5 mg tablets are yellow, modified oval, biconvex and film-coated. Aqueous film coating consists of Opadry Yellow 03B120006 (hypromellose, titanium dioxide, polyethylene glycol, iron oxide yellow).
- 2 mg tablets are pink, round, biconvex and film-coated. Aqueous film coating consists of Opadry Pink YS-1-14762-A (hypromellose, titanium dioxide, polyethylene glycol, polysorbate 80, iron oxide red).

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

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

Route of Administration: Oral. Take by mouth on an empty stomach, either 1 hour before or 2 hours after a meal.

Potential Drug Interactions: *In vitro* studies suggest that trametinib dimethyl sulfoxide is not a substrate of CYP enzymes or of human Pgp, BCRP, OATP1B1 or OATP1B3 transporters.

Trametinib dimethyl sulfoxide is a weak CYP2C8 inhibitor and weak CYP3A4 inducer. Drug-drug interactions with sensitive substrates of 2C8 and 3A4 are not anticipated

Availability: Trametinib dimethyl sulfoxide (GSK1120212B) is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

Trametinib dimethyl sulfoxide (GSK1120212B) is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 12.3).

8.1.2 Trametinib dimethyl sulfoxide (GSK1120212B) (NSC 763093) Commercially labeled.

Chemical Name (IUPAC): equimolecular combination of acetamide, N-[3-[3-cyclopropyl-5-[(2-fluoro-4-iodophenyl)amino]-3,4,6,7-tetrahydro6,8-dimethyl- 2,4,7-trioxopyrido[4,3-d]pyrimidin-1(2H)-yl]phenyl] with 1,1'-sulfinylbis[methane]

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

CAS Registry Number: 1187431-43-1

Classification: MEK inhibitor

Molecular Formula: $C_{26}H_{23}FIN_5O_4 \cdot C_2H_6OS$ **M.W.:** 693.53

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

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

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

How Supplied: Novartis supplies and CTEP, NCI, DCTD distributes 0.5 mg and 2 mg (as free base) tablets. Each commercially-labeled bottle contains 30 tablets with a desiccant.

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

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

Storage: Store tablets at 2°C -8°C in the original bottle. Do not repackage tablets or remove desiccant.

Bottles should be protected from light and moisture.

If a storage temperature excursion is identified, promptly return trametinib to 2°C -8°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability: Refer to the package label for expiration.

Route of Administration: Oral. Take by mouth on an empty stomach, either 1 hour before or 2 hours after a meal. If a dose of trametinib is missed, the dose can be taken if it is more than 12 hours until the next scheduled dose.

Potential Drug Interactions: *In vitro* studies suggest that trametinib dimethyl sulfoxide is not a substrate of CYP enzymes or of human BCRP, MRP2, OATP1B1, OATP1B3, OATP2B1, OCT1 or MATE1 transporters. Trametinib elimination by deacetylation to metabolite M5 is dependent on carboxylesterases (CES1b, CES1c and CES2). M5 is eliminated by CYP3A4 and other pathways, presenting the clinically relevant, albeit low, potential for drug-drug interaction. Trametinib is a substrate for P-gp and BSEP, but this is not expected to be clinically relevant due to trametinib's high permeability.

Trametinib dimethyl sulfoxide is an *in vitro* inhibitor of CYP 2C8, and is anticipated to have overall low potential for drug interactions as a perpetrator. It is also a weak CYP3A4 inducer and expected to have little clinical effect on sensitive substrates. Trametinib is not an inhibitor of CYP 1A2, 2A6, 2B6, 2C9, 2C19, 2D6 and 3A4 and not an inhibitor of P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT2 MRP2 and MATE1.

Patient Care Implications: Advise women study participants of reproductive potential to use effective contraception while receiving study treatment and for 4 months after the last dose of trametinib. Refer to the protocol document for specific guidance.

8.1.3 GSK2141795 (NSC 767034)

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

Other Names: GSK2141795C

Classification: pan-AKT inhibitor

CAS Registry Number: 1047634-65-0

Molecular Formula: $C_{18}H_{16}Cl_2F_2N_4O_2$ **M.W.:** 429.25 g/mol

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

mg/mL.

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

Description: white to off-white powder

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

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

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

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

Route of Administration: Oral administration. Capsules must be taken fasting 1 hour before or 2 hours after a meal.

Potential Drug Interactions: *In vitro* data suggest GSK2141795 is a substrate of CYP450 3A4. Potent inhibitors and inducers of 3A4 are prohibited. GSK2141795 appears to be a moderate inhibitor of CYP 2C8 and 3A4 by *in vitro* testing. Drugs that are substrates of these isoenzymes should be used with caution and ones with a narrow therapeutic index should be avoided.

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

Availability: GSK2141795 is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

GSK2141795 is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 12.3).

8.1.4 Agent Ordering and Agent Accountability

Agent ordering and agent accountability will occur for other centers as outlined in this

section.

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

Agent may be requested electronically to PMB. Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account https://eapps-ctep.nci.nih.gov/iam/ and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

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

9 BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Biomarker Study Overview

Tumor GNAQ and GNA11 status will be determined for all patients treated on this study using archived or newly acquired tumor material. All patients with safely accessible tumor will undergo pre- and post-treatment (day 14 +/- 3 days) tumor biopsies for biomarker and correlative analysis. The decision to not pursue these biopsies must be made in collaboration with the MSK Principal Investigator. An additional tumor biopsy will be requested from patients at the time of disease progression; however, this biopsy is optional. Blood samples will be collected from all patients at baseline and on a monthly basis for correlative analysis.

In addition to GNAQ and GNA11 analysis which will be performed in all cases, we will conduct next-generation DNA sequencing, whole-transcriptome sequencing (RNAseq), and reverse phase protein array (RPPA), among other assays, using the fresh tumor material acquired as part of this study. Results from these analyses will be stored in the cBioPortal for Cancer Genomics

(http://www.cbioportal.org/public-portal/), an open access web-based database developed and maintained by the Computational Biology Center at Memorial Sloan Kettering Cancer Center that provides visualization, analysis and download of large-scale cancer genomics data sets. The web-based database also provides access to analysis tools in the areas of signaling pathways, mutations, and copy number alterations.

The analysis of specific correlative assays is planned as below; however, due to cost considerations or material scarcity, the tasks may be consolidated and performed in one or more of the centers below:

- **Whole-Transcriptome Sequencing**
  Raya Kanin, PhD
  Memorial Sloan Kettering Cancer Center
  Bioinformatics Core
  Zuckerman Research Center 415-417 East 68th Street
  New York, NY 10065
  Telephone: 646-888-2603
  Email: khaninr@mskcc.org

- **Reverse Phase Protein Array**
  Scott E. Woodman, MD, PhD
  M. D. Anderson Cancer Center
  South Campus Research Building
  SCR 2.3022
  7455 Fanning St.
  Houston, TX 77054
  Telephone: 713-792-2921
  Email: swoodman@mdanderson.org

- **Targeted Pharmacodynamic Analysis**
  Gary K. Schwartz, MD
  New York Presbyterian/Columbia University
  Milstein Hospital
  Division of Hematology/Oncology
  177 Ft. Washington Avenue, Suite 6-435
  New York, NY 10032
  Telephone: 212-305-2055
  Email: schwartzg@columbia.edu

- **Circulating Tumor DNA Analysis**
  Marc-Henri Stern, MD PhD
  Institut Curie
  Immunologie 4ème étage
  26 rue d'Ulm
  75005 Paris cedex 05 France

Telephone: +33 (0)1 56 24 66 46
Email: Marc-Henri.Stern@curie.fr

- **Exosomal/Proteomic Analyses of Plasma**
  Professor Sarah Coupland
  Department of Molecular and Clinical Cancer Medicine
  Institute of Translational Medicine
  University of Liverpool
  6th Floor Duncan Building
  Daulby Street
  Liverpool
  L69 3GA
  Telephone: +44-151-706-5885 or 4494
  Email: S.E.Coupland@liverpool.ac.uk

Utilization of the available tumor biopsy material will be prioritized as outlined below. In the case of excisional biopsies (as opposed to core needle biopsies), material will be divided and utilized based upon prioritization. Banked tumor material may be utilized for future correlative studies, as determined by a steering committee made up of the MSK Principal Investigator, and a representative from the UK.

Prioritization for Baseline, Day 14 and Progression Tumor Biopsies

1. Core 1 will be placed in buffered formalin and embedded in paraffin.
2. Core 2 will be flash frozen.
3. Core 3 will be flash frozen.
4. Core 4 will be flash frozen.
5. Core 5 will be placed in buffered formalin and embedded in paraffin.
6. Core 6 will be flash frozen.
7. Core 7 will be flash frozen.
8. Any additional cores will be banked for future as-yet undefined correlative studies.

9.2 Laboratory Correlative Studies

9.2.1 Tumor Biopsies

Patients will undergo tumor biopsies at baseline and 14 days (+/- 3 days) following initiation of therapy, with an optional tumor biopsy conducted at the time of disease progression. The pre-treatment biopsy will be obtained within 28 days of starting therapy. Issues that would cause treatment delays should be discussed with the MSK PI who may grant permission on a case-by-case basis to analyze tissue from a protocol pre-treatment biopsy that has occurred greater than 28 days prior to study treatment. The post-treatment biopsy will be performed at day 14 ± 3 days prior to the morning dose of the study medications. An optional third tumor biopsy will be requested of these patients at the time of tumor progression, with particular efforts made at

obtaining such biopsies in patients who have developed progression after achieving a radiographic response to treatment or after prolonged disease control (i.e., greater than 4 months). Up to eight core samples will be obtained with each biopsy, providing sufficient tissue for the correlative studies.

Tissue will be divided such that a portion (one core in the case of core needle biopsy procedures) is placed in buffered formalin and embedded in paraffin. From this, an H&E section will be cut for confirmation and diagnostic purposes. It will be designated for immunohistochemistry (IHC) and any remainder flash frozen in liquid nitrogen.

Fresh tumor biopsy samples should be snap-frozen using liquid nitrogen or a dry ice slurry as outlined below. The tissue must be frozen as soon as possible after biopsy to minimize any form of degradation and to avoid risking the viability of the tissue.

Snap-Freezing in Liquid Nitrogen:

1. Label cryogenic vial(s) with the subject's study identification number (ie. Accession number for MSK patients), the date of collection, time point (baseline, day 14, or progression) and the study center performing the biopsy. Ensure that the label adheres to the vial and does not come off when placed in liquid nitrogen. Labels cannot be adequately affixed to the vials after freezing.

2. Immediately place the freshly obtained tissue into the labelled cryogenic vial. Place the vial with tissue in liquid nitrogen for 2 minutes or longer to snap-freeze the tissue. Tumor cores should be frozen individually in separate cryovials as collected in order to minimize the time between removal and freezing.

3. Remove the crygenic vial from the liquid nitrogen.

4. Store the sample in a -80°C freezer (-65°C to -80°C is acceptable) until ready for shipping.

Freezing Procedure with Dry Ice Slurry

1. Materials required include: 5 lbs dry ice, alcohol (ethanol or comparable), basin, long forceps

2. Place at least 5 lbs of dry ice into a basin and pour one liter of alcohol over the ice.

3. Label cryogenic vial(s) with the subject's study identification number (ie. Accession number for MSK patients), the date of collection, and the study center performing the biopsy. Ensure that the label adheres to the vial and does not come off when placed in liquid nitrogen. Labels cannot be adequately affixed to the vials after freezing.

4. Immediately place the freshly obtained tissue into the labelled cryogenic vial. Place the vial with tissue in liquid nitrogen for 2 minutes or longer to snap-freeze the tissue.

Tumor cores should be frozen individually in separate cryovials as collected in order to minimize the time between removal and freezing.

5. Pace the lower half of the sealed cryotube containing tissue into the solution for at least 2 minutes until frozen solid.

6. Store the sample in a -80°C freezer (-65°C to -80°C is acceptable) until ready for shipping.

9.2.2 Research Blood Collection

Two 10 ml sodium heparin tubes will be collected from patients prior to treatment, at the beginning of each cycle, and at the off-study visit. Samples will be subsequently stored for future correlative studies. The samples drawn prior to treatment can be drawn on C1W1 prior to initiation of study drug.

Processing instructions for the use of either green sodium heparin tubes or CPT tubes with sodium heparin are as follows:

Green Sodium Heparin

1. Collect two 10 mL Sodium heparin tubes

2. Prepare Accuspin tubes by adding 15.5 ml of Ficoll (or Lymphoprep) to tube

3. Spin 30 seconds at 1000 g at room temperature (RT)

4. Use one Accuspin with Ficoll or LSM per 3 green top tubes of blood

5. Pour blood from 3 green top tubes into Accuspin tubes making sure to wipe each cap with EtOH before opening

6. Spin loaded tubes 20 min at 2000 RPM (Room Temperature) (brakes off)

7. Collect plasma and place into 15 mL tubes. The plasma may be discarded.

8. Collect cells from Accuspin tubes and place into separate 15ml tubes

9. Fill the 15 mL conical tubes with the cells (from Accuspin) with PBS. Invert several times to mix.

10. Cap tubes and centrifuge at 300 *g* for 10 minutes at room temperature. Pour off PBS and repeat this step twice (wash).

11. After the third wash, carefully pour off the PBS one last time and freeze the cell pellet at -80°C until shipment to the respective biorepository. No freezing media is necessary.

12. Label tubes with the subject's study identification number, initials, date of collection, time point and protocol NCI #9445. MSK patients will be identified by accession number.

CPT with sodium heparin

1. Collect two 8 mL CPT with sodium heparin tubes

2. Mix the blood with the anticoagulant by gently inverting the tube 8 to 10 times

3. Centrifuge sample within 2 hours of collection at room temperature for 20 minutes at 1500 to 1800 g with the brake off

4. Transfer the plasma layer (leaving the mononuclear layer undisturbed at the interface) to 15 mL tubes. The plasma may be discarded.

5. Transfer the mononuclear cell layer to a 15 mL conical centrifuge tube

6. Add phosphate buffered saline (PBS) to the centrifuge tube bringing the volume to 15 mL

7. Cap and mix the cells by gently inverting the tube 5 times

8. Centrifuge for 15 minutes at 300 g at room temperature

9. Discard the supernatant gently using the transfer pipettes provided, without disturbing the cell pellet

10. Resuspend the cell pellet by gently vortexing or tapping the tube with your index finger.

11. Add PBS to the tube bringing the volume to 10 mL

12. Cap and invert 5 times to mix the cells

13. Centrifuge for 10 minutes at 300 g at room temperature. Discard the supernatant Repeat the wash one more time.

14. After the third wash, carefully pour off the PBS one last time and freeze the cell pellet at -80°C until shipment to the respective biorepository. No freezing media is needed.

15. Label tubes with the subject's study identification number, initials, the date of collection, time point and protocol NCI #9445. MSK patients will be identified by accession number.

9.2.3 Circulating Tumor DNA Plasma Collection

Two 10 cc lavender top tube (EDTA) will be collected prior to treatment, at the beginning of each cycle, and at the End of Treatment visit. The samples drawn prior to treatment can be drawn on C1W1 prior to initiation of study drug.

Plasma samples should be prepared as described by Diehl et. al. and as summarized below:[65]

1. Within 1 hour of collection, blood is centrifuged at 820 g for 10 minutes.

2. Supernatant is transferred to 1.5 mL sterile tubes in 1 mL aliquots and centrifuged at 16,000g for 10 minutes at 4°C to pellet any remaining cellular debris. Discard the pellet.

3. Label tubes with the subject's study identification number, the date of collection, time point (baseline, cycle number, or end of study) and the study center. MSK patients will be identified by accession number.

4. The supernatant should subsequently be stored at -80°C.

5. The overall process from blood collection to plasma storage should not exceed 3 hours.

6. The supernatent will be shipped from each investigational site directly to the Institut Curie.

DNA extraction will be performed at the Institut Curie as follows:

1. DNA extraction from plasma of patients should be accomplished using the Qiagen QIAamp circulating nucleic acid kits or an acceptable alternative. Extraction should be performed according to the manufacturer instructions.

2. Nucleic acids should be stored at -20°C.

9.2.4 Blood Collection and Processing for Exosomal/Proteomic Analyses

Two 10ml EDTA tubes will be collected prior to treatment, at the beginning of each cycle, and at the end of treatment visit. Standardization of sample site, needle gauge (wider may be better) and other variables is recommended. The first few millimeters of drawn blood should be discarded.

Collected blood should be handled gently and processed rapidly (within 30 minutes – 1 hour of drawing).

Plasma samples should be prepared as follows:

1. Centrifuge for 15 minutes at 2,000 g at 4°C.

2. Immediately transfer the supernatant (plasma) into a clean polypropylene tube as 0.5ml aliquots and store at -80°C prior to shipping.

3. Label tubes with the subject's study identification number, the date of collection, time point (baseline, cycle number, or end of study) and the study center. MSK patients will be identified by accession number.

9.3 Specimen Shipment Procedures

Two region-specific biospecimen repositories will be utilized for this trial, with one repository for the North American trial centers.The Institute Curie will collect circulating tumor DNA for all regions. The University of Liverpool will collect plasma for exosomal/proteomic analysis for all regions.

Trial Center Region	**Biospecimen Repository**	**Shipping Address**
North America	**MSK** (Tumor and Blood)	Taha Merghoub, MD 415 East 68th Street Room# Z-1525 New York, NY 11065 646-888-2580 merghout@mskcc.org shoushta@mskcc.org CTO_MSO_MCT@mskcc.org
*Of note, MD Anderson Cancer Center can keep on site the core for reverse phase protein array (Core #3) as long as the collection of the sample is communicated to the MSK PI, Research Project Coordinator, and Research Study Assistant.		
All Regions	**Institut Curie** (Circulating Tumor DNA)	Marc-Henri Stern, MD PhD Institut Curie Immunologie 4ème étage 26 rue d'Ulm 75005 Paris cedex 05 France maud.milder@curie.net aurore.rampanou@curie.fr delphine.louis@curie.net isabelle.peguillet@curie.net
All Regions	**University of Liverpool** (Exosomal/Preoteomic Analysis)	Professor Sarah Coupland Department of Molecular and Clinical Cancer Medicine Institute of Translational Medicine University of Liverpool 6th Floor Duncan Building

		Daulby Street Liverpool L69 3GA S.E.Coupland@liverpool.ac.uk

Shipments will be sent from participating centers to the appropriate biospecimen repository in batches whenever possible. The biospecimen repository research team will be notified by email the day that the samples are sent. This email will contain the following information:

- Site Name
- Subject ID
- Subject initials
- Shipment date
- Contents of shipment

All shipments should be directed to the address listed on the tissue sample shipment form. Samples should be shipped by courier so that the package can be tracked appropriately (specifically, Federal Express or UPS). Study materials for sample collection, processing and shipping should be obtained by the site.

Each repository will be responsible for coordinating with the MSK Principal Investigator the shipment of biospecimens from the repository to the analysis centers.

9.3.1 Paraffin-Embedded Tumor Specimens

Up to 20 unstained slides from paraffin embedded tumor or the tumor block will be sent via messenger or shipped via overnight carrier, as applicable, to the appropriate repository. All shipments should be directed to the address listed on the study tissue sample shipment form.

Necessary slides will be cut from paraffin embedded pre-treatment tumor. This material will be packaged in a way to ensure they do not break. All slides (and/or blocks) must be shipped with appropriate identifiers including a pathology report from the collaborating institution and the tumor tissue shipment form.

9.3.2 Fresh-Frozen Tumor Specimens

Specimens will be packaged with dry ice in a way to ensure they remain frozen during shipment and do not break. All specimens must be shipped with appropriate identifiers including the study tumor tissue shipment form.

9.3.3 Research Blood Specimens

Specimens will be packaged with dry ice in a way to ensure they remain frozen during shipment and do not break. All specimens must be shipped with appropriate identifiers including the study tumor tissue shipment form.

9.3.4 Circulating Tumor DNA Plasma Specimens

Samples will be shipped in bulk to the Institut Curie throughout the study.

9.3.5 Specimens will be packaged with dry ice in a way to ensure they remain frozen during shipment and do not break. All specimens must be shipped with appropriate identifiers including the study tumor tissue shipment form.

9.3.6 Exosomal and Proteomic Plasma Specimens

Samples will be shipped in bulk to the GCLP Facility at the University of Liverpool, UK throughout the study.
9.3.7
9.3.8 Specimens will be packaged with dry ice in a way to ensure they remain frozen during shipment and do not break. All specimens must be shipped with appropriate identifiers including the study tumor tissue shipment form.

9.4 Laboratory Correlative Studies

9.4.1 Correlation of Clinical Outcome with Gnaq/11 Mutational Status

Tumor Gnaq and Gna11 status will be determined for all patients treated on this study. Five unstained slides obtained from paraffin-embedded tumor tissue will be required for this testing. DNA will be extracted from paraffin embedded tissue sections. DNA will be extracted from the tumor area contained in at least 10x5µm-thick sections placed on uncharged glass slides. A hematoxylin-eosin stained slide will be used to distinguish tumor cells. Genomic DNA will be prepared using the Wizard Genomic DNA purification kit (Promega). Exon 5 of GNAQ will be sequenced by routine methods following polymerase chain reaction amplification of exon 5 with primers: GNAQE5L: 5'-TTCCCTAAGTTTGTAAGTAGTGC and GNAQE5R:5'-AGAAGTAAGTTCACTCCATTCC. This will generate a product of 317 bp that includes codon 209. Sequences will be analyzed with Sequencer 4.5 software (GeneCodes, Madison, WI, USA). Tumor samples not harboring the more common exon 5 mutations may be tested for the presence of exon 4 Gnaq or Gna11 mutations should sufficient material be available.

DNA from normal tissue, if available, will be analyzed to demonstrate the somatic nature of identified mutations and novel polymorphisms.

9.4.2 Assessment of Pharmacodynamic Effects of Therapy

Patients with accessible tumor will undergo pre- and post-treatment (day 14 +/- 3 days) tumor biopsies for pharmacodynamic analysis. Studies which may include, but are not limited to, reverse phase protein array and Western blotting may be performed on serial tumor samples obtained from patients treated with trametinib alone and with the combination of trametinib and GSK2141795 for pERK, pAKT, cyclin D1, and others. Changes in protein levels will be semi-quantified by densitometry. We anticipate inhibition of pERK and cyclin D1 and

induction of pAKT with trametinib alone, and inhibition of pERK, cyclin D1, and pAKT with combination therapy.

RNA-seq will be performed using pre- and post-treatment material obtained from 5 patients achieving clinical benefit and 5 patients not achieving clinical benefit on each treatment arm. Clinical benefit is defined as a RECIST response or progression-free survival greater than 16 weeks. From our computations,[64] in order to identify 90% of differentially expressed genes between two conditions (with fold-changes=2 and FDR=0.05), 4 replicates per condition would be required. However, taking in account the inherit variability of biological samples, our power calculations suggest that 5 biological replicates per condition will be sufficient to identify 85-90% of differentially expressed (DE) genes. Our interim analysis of patients treated with selumetinib on NCI Protocol #8443 demonstrated a 40% clinical benefit rate. Assuming a similar clinical benefit rate for patients treated with trametinib alone and a clinical benefit rate of 60% for patients treated with trametinib and GSK2141795, we would predict that for every 13 patients, there will be at least 5 who achieve clinical benefit and 5 who do not. As the true clinical benefit rate for each arm is not known, we will perform paired biopsies on the first 15 patients treated on each arm.

10 STUDY CALENDAR

Baseline evaluations are to be conducted within 14 days prior to start of protocol therapy. Imaging studies and cardiac evaluation (e.g., echocardiogram, MUGA, EKG) must be done ≤4 weeks prior to the start of therapy. The pre-treatment biopsy for patients with safely accessible tumor will be obtained within 28 days of starting therapy (see Section 9.2.1 for more information). In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of therapy. All blood work, examinations and procedures may be performed +/- 3 days from the scheduled date. Imaging studies may be performed +/- 1 week from the scheduled date.

		Cycle 1				Cycle 2				Cycle 3[m]				
	Pre-Study	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	End of Treatment[n]
Trametinib (Arms A or B)		X----------X												
GSK2141795 (Arm B Only)		X----------X												
Informed consent	X													
Demographics	X													
Medical history	X													
Concurrent meds	X	X----------X												
Physical exam	X	X		X		X				X				X
Ophthalmology Exam[a]	X[a]													
Vital signs[b]	X[b]	X		X		X				X				X
Height	X													
Weight	X	X		X		X				X				X
Performance status	X	X		X		X				X				X
CBC w/diff, plts	X	X	X[o]	X	X[o]	X				X				X
Chemistries[c]	X	X	X[o]	X	X[o]	X				X				X
PT/PTT	X													
Fasting Lipid Panel[d]	X									X				X
Fasting Glucose	X													
Hemoglobin A1c[d]	X									X				X
TSH[d]	X									X				X
EKG[e]	X			X		X				X				X
Echocardiogram or MUGA[f]	X					X								X
Adverse event evaluation		X----------X												X

CAP CT or Chest CT and AP MRI[g]	X	Tumor measurements are repeated every 8 weeks.												X
B-HCG[h]	X													
Archived Tumor Tissue[i]	X													
Tumor Biopsy[j]	X			X										(X)
Research Blood Collection[k]		X				X				X				X
ctDNA Blood Collection[l]		X				X				X				X

a: Ophthalmic exam will include indirect fundoscopy, slit lamp exam, visual acuity, visual field examination, tonometry and color fundus photos. Additional ophthalmic exams will be performed if symptomatically warranted. Note that patients with the presence at baseline of a risk factor for RVO or REPD such as evidence of new optic disc cupping, evidence of new visual field defects, and intraocular pressure >21 mm Hg are excluded from this trial.

b: Patients with treatment-refractory hypertension defined as a blood pressure of systolic >140 mmHg and/or diastolic >90 mmHg which cannot be controlled by anti-hypertensive therapy are excluded from this trial.

c: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.

d: Repeat test every 8 weeks.

e: A single 12-lead ECG should be performed at Screening, Day 15, and prior to dosing at the start of every 4 weeks. The baseline EKG may be conducted within 28 days of treatment start date. Additional EKGs will be performed as clinically indicated. Patients with a baseline QT interval corrected for heart rate using the Bazett's formula QTcB ≥ 480 msec are excluded from this trial.

f: Echocardiogram or MUGA should be performed at screening, Week 5 Day 1, then every 12 weeks, at final study visit, and as clinically indicated. The same methodology should be used throughout the study.

g: CT of the chest, abdomen and pelvis with contrast OR CT of the chest (with or without contrast) and MRI of the abdomen and pelvis at baseline and again every subsequent 8 weeks (+/- 1 week). Other imaging modalities can be used in addition to these at the discretion of the treating physician. If the patient is taken off treatment for any reason other than disease progression, End of Treatment imaging is not required at that visit; however, the patient should undergo restaging scans 8 weeks (+/- 1 week) from the time of the first dose and continue having scans every 8 weeks (+/- 1 week) until progression is documented, the start of new anticancer therapy, or death.

h: Perform only in women of child-bearing potential. A blood pregnancy test should be performed at Screening, and subsequent pregnancy tests may be either blood or urine.

i: Up to twenty unstained slides from archived or newly acquired paraffin embedded tumor or the tumor block will be collected from all patients enrolled on this study.

j: Tumor biopsies will be performed at baseline and after 14 +/- 3 days of therapy. A third optional tumor biopsy may be performed on these patients at the time of disease progression.

k: Serum will be collected from patients as outlined in Section 9 prior to treatment, at the beginning of each cycle, and at the off-study visit and subsequently stored for future correlative studies. The samples drawn prior to treatment can be drawn on C1W1 prior to initiation of study drug.

l: Two 10 cc lavender top tube (EDTA) will be collected prior to treatment, at the beginning of each cycle, and at the End of Treatment visit. The samples drawn prior to treatment can be drawn on C1W1 prior to initiation of study drug.

m: Cycle 4+ will be conducted as indicated for cycle 3.

n: End of Treatment Visit performed 4 weeks from last treatment. Patients will be contacted or evaluated every 12 weeks (+/- 1 week) for survival assessment after End of Treatment visit or last date of follow up. In the event that the patient's health deteriorates such that the follow-up visit is not feasible, a note will be placed in the subject's medical record documenting the situation. This will not be considered a protocol violation. In addition, the last treatment visit can be considered the End of Treatment visit if the patient is unable to return, a note will be placed in the subject's medical record documenting this situation.

o: Test can be performed locally.

11 MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every *8* weeks. As per RECIST 1.1, confirmatory scans obtained 4 weeks following initial documentation of objective response is not necessary in this study where the primary endpoint is PFS. Patients will be re-evaluated for response until progression is documented, the start of new anticancer therapy, or death.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1).[66] Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with trametinib alone or with GSK2141795.

Evaluable for objective response. Only those patients 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. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.1.2 Disease Parameters

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

> Note: Lesions that are previously irradiated must show clear evidence of progression over a minimum of 3 months to include as measurable. This period of time is used to discount tumor edema in an irradiated field as a false sign of disease progression.

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

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

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

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

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

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

11.1.3 Methods for Evaluation of Measurable Disease

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

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is

preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

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

PET-CT At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

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

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

Tumor markers Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

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

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

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

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

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

11.1.4 Response Criteria

11.1.4.1 Evaluation of Target Lesions

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

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

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

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

11.1.4.2 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 patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

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

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

11.1.4.3 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 patient's best response

assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response 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	

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

Note: Patients 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.

For Patients with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

11.1.5 Duration of Response

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

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

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

11.1.6 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

11.1.7 Response Review

All partial and complete responses will be reviewed by an independent radiologist at Memorial Sloan Kettering Cancer Center. For patients treated at a site other than MSK, all appropriate radiological studies will be shipped to MSK either as hardcopy or by CD-ROM, as appropriate.

12 DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

12.1.1 Method

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis, either by FTP burst of data or via the CDS web application. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP Web site (http://ctep.cancer.gov/reporting/cdus.html).

MSK will assign a Research Study Assistant (RSA) and Research Project Coordinator (RPC) to manage data entry for this study. Data collected for this study will be entered into a secure database (CRDB) for MSK and outside patients. MSK is responsible for compiling and submitting CDUS data to CTEP for all participants and for providing the data to the Principal Investigator for review.

Note: If your study has been assigned to CDUS-Complete reporting, **all** adverse events (both routine and expedited) that have occurred on the study and meet the mandatory CDUS reporting guidelines must be reported via the monitoring method identified above. If your study has been assigned to CDUS-Abbreviated reporting, no adverse event reporting (routine or expedited) is required to be reported via CDUS.

12.1.2 Responsibility for Data Submission at Participating Sites

The participating site(s) will enter data remotely into MSK's internet-based Clinical Research Database, termed CRDBi-Multicenter. Standardized Case Report Forms (CRFs) and data entry guidelines have been generated for this study. The site staff will receive CRDB training prior to enrolling its first patient. The participating Site PI is responsible for ensuring these forms are completed accurately and in a timely manner. A schedule of required forms is shown in the table below. Participating sites will be responsible for completing the eCRFs and submitting them to MSK per the designated timelines.

Data and Source Documentation Submission for Participating Sites
Participating sites should enter data directly into CRDBi-Multicenter and study-specific paper CRFs (if applicable). Source documentation should be sent to MSK at CTO_MSO_MCT@mskcc.org. Submissions should include a cover page listing relevant records enclosed per participant.

Data Submission Timelines for Participating Sites
Data should be submitted to MSK according to the table below*:*

Data Submission Timelines for Therapeutic Studies	
Time point	Submission requirement
Baseline	Eligibility checklist within 24 hours of ICF signature
Cycle CRFs in EDC	Within 14 days of study visit
SAE	Must be reported in EDC system within 3 days of learning of the event (see section 7.3.2); follow-up as needed

Specific CRFs to be referenced are listed in the Data Management Handbook for CRDBi-MCT.

Source Documentation
Source documentation refers to original records of observations, clinical findings and evaluations that are subsequently recorded as data. Source documentation should be consistent with data entered into CRFs. The participating site is responsible for maintaining adequate and correct source documentation for all submitted data.

Source documentation should include a minimum of two identifiers to allow for data verification. MSK will maintain the confidentiality of any subject-identifiable information it may encounter.

Data Review and Queries for Participating Site Data
Research staff at MSK will review data and source documentation as it is submitted. Data will be monitored against source documentation and discrepancies will be sent as queries to the participating sites. Participating sites should respond to data queries within 14 days of receipt.

Regulatory Documentation
Prior to implementing this protocol at MSK, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the MSK Institutional Review Board/Privacy Board (IRB/PB) and CTEP. Prior to implementing this protocol at the participating sites, approval for the MSK IRB/PB approved protocol must be obtained from the participating site's IRB and submitted to the CTEP PIO. In addition, applicable contractual agreements must be finalized and executed before participating sites implement this protocol.

The following documents must be provided to MSK before the participating site can be initiated and begin enrolling participants:
- Participating Site IRB approval(s) for the protocol, appendices, informed consent form and HIPAA authorization
- Participating Site IRB approved consent form

Upon receipt of the required documents, MSK will formally contact the site and grant permission to proceed with enrollment.

Participating sites that are consulting and/or conducting specimen or data analysis should submit this protocol to their IRB according to local guidelines. Copies of any site IRB correspondence should be forwarded to MSK.

Amendments
Each change to the protocol document must be organized and documented by MSK and first approved by the MSK IRB/PB. Upon receipt of MSK IRB/PB approval, MSK will immediately distribute all non expedited amendments to the participating sites, for submission to their local IRBs.

Participating sites must obtain approval for all non expedited amendments from their IRB within 90 calendar days of MSK IRB/PB approval. If the amendment is the result of a safety issue or makes eligibility criteria more restrictive, sites will not be permitted to continuing enrolling new participants until the participating site IRB approval has been granted.

The following documents must be provided to MSK for each amendment within the stated timelines:
- Participating Site IRB approval
- Participating Site IRB approved informed consent form and HIPAA authorization

Additional IRB Correspondence

Continuing Review Approval
The Continuing Review Approval letter from the participating site's IRB and the most current approved version of the informed consent form should be submitted to MSK within 7 days of expiration. Failure to submit the re-approval in the stated timeline will result in suspension of study activities.

Violations
A protocol violation is any change or departure from the research protocol that occurred without prior approval from the MSK IRB/PB. For protocol violations that are identified after they occur, the participating site should report to MSK as soon as possible. The MSK PI will in turn report the violation to the MSK IRB/PB and CTEP.

Participating sites should report violations to their institution's IRBs as soon as possible per that site's institutional guidelines. Approvals/acknowledgments from the participating site IRB for protocol violations should be submitted to MSK as received.

Other correspondence
Participating sites should submit other correspondence to their institution's IRB according to local guidelines, and submit copies of that correspondence to MSK.

Document maintenance
The MSK PI and the Participating Site PI will maintain adequate and accurate records to enable the implementation of the protocol to be fully documented and the data to be subsequently verified.

The participating sites will ensure that all participating site IRB correspondence (IRB approval letters referencing protocol version date and amendment number, IRB approved protocol, appendices, informed consent forms, deviations, violations, and approval of continuing reviews) is maintained in the regulatory binder on site and sent to MSK.

A regulatory binder for each site will also be maintained at MSK; this binder may be paper or electronic.

After study closure, the participating site will maintain all source documents, study related documents and CRFs for 7 years.

Noncompliance
If a participating site is noncompliant with the data and regulatory requirements set forth in the protocol document, accrual privileges may be suspended until the outstanding issues have been resolved.

Quality Assurance for Participating Sites
Participating N01 contract holders and their affiliates may be audited by MSK.

Response Review
Since therapeutic efficacy is a stated primary objective, all sites participant's responses are subject to review by MSK's Therapeutic Response Review Committee (TRRC). Radiology and possibly additional lab reports will need to be obtained from the participating sites for MSK TRRC review and confirmation of response assessment. These materials must be sent to MSK promptly upon request.

12.2 CTEP Multicenter Guidelines

This protocol will adhere to the policies and requirements of the CTEP Multicenter Guidelines. The specific responsibilities of the Principal Investigator and the Coordinating Center (Study Coordinator) and the procedures for auditing are presented in Appendix E.

- The Principal Investigator/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports received from CTEP to all participating institutions for submission to their individual IRBs for action as required.

- Except in very unusual circumstances, each participating institution will order DCTD-supplied agents directly from CTEP. Agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO (PIO@ctep.nci.nih.gov) except for Group studies.

12.3 Collaborative Agreements Language

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

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

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

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

   b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator

to develop, obtain regulatory approval or commercialize its own Agent.

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

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

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

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

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

12.4 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new

policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: *http://www.cancer.gov/clinicaltrials/conducting/dsm-guidelines/page1*. The DSM Plans at MSK were established and are monitored by the Office of Clinical Research. The MSK Data and Safety Monitoring Plans can be found on the MSK Intranet at: http://inside2/clinresearch/Documents/MSKCC%20Data%20and%20Safety%20Monitoring%20Plans.pdf

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

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

13 STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

The prognosis for patients with metastatic disease is poor, but this is an encouraging time and there are many agents which could be examined. Therefore, 2 investigational treatment strategies will be assessed in this trial.

A total of 80 patients with advanced stage melanoma will be randomized to either trametinib plus GSK2141795 or trametinib alone (40 evaluable patients per arm). The primary endpoint of this study is time to progression (PFS) defined from the date of randomization to the date of documented progression or death. Patients will be assessed for progression every 8 weeks. PFS will be calculated as time from randomization to the earlier date of objective disease progression per RECIST criteria or death due to any cause in the absence of progression; patients who have not progressed or died at the time of analysis will be censored at the time of their latest evaluable objective tumor assessment. It is estimated that median PFS for the trametinib arm is 16 weeks based upon the results of CTEP8443 as presented at the 2013 ASCO Annual Meeting which demonstrated a median PFS of 15.9 weeks with selumetinib (n = 47, 95% CI, 8.4 – 23.1 weeks). With 80 patients and with 76 progression events, the probability is 80% that the study will detect a treatment difference at a one-sided 5% significance level, if the true hazard ratio is 0.56.

Overall survival will be analyzed using the same methods as used for PSF. Overall survival will be calculated as time from randomization to death due to any cause; patients who have not died at the time of analysis will be censored based on the last recorded date on which the subject was known to be alive.

This is based on the assumption that the accrual period will be approximately 26 months, the follow up period will be 12 months, and the median PFS for trametinib alone is 16 weeks. It is anticipated that 3 patients per month will be accrued to this study and hence the study accrual will be completed in approximately two years and the trial will be completed in approximately three years.

An early stopping rule for futility will be applied. Clinical benefit rate will be examined in each arm after 40 evaluable patients have been accrued (20 patients per arm). As noted above, early analysis of our on-going trial of selumetinib versus temozolomide in patients with advanced uveal melanoma, 40% of patients treated with selumetinib achieved disease control beyond 16 weeks. If at least two patients have achieved a radiographic response as defined as a RECIST partial or complete response in each arm, then the trial will continue as planned. If zero or one patient achieves a RECIST response among the 20 patients of an arm, then that arm will be terminated. The upper bound of the 95% confidence interval for no clinical benefit out of 20 patients with this early stopping rule is 25%. PFS will also be reviewed at the end of the first stage, and adjustment to the futility rule may be considered if significant PFS prolongation is obtained in the absence of sufficient numbers of RECIST responses. If we stop one arm of the trial due to futility, then we may revert to a single arm phase II study. The alternate arm may continue to accrue 40 patients. The plan for the second stage will be finalized after discussion with the sponsor. At the end of the study we will estimate the progression free survival distribution for that arm and provide the median PFS along with a 95% confidence interval.

13.2 Sample Size/Accrual Rate

This study design requires the accrual of up to 60 patients with advanced uveal melanoma.

This study will be a multi-institution phase II study led by MSK. The Melanoma Service at MSK sees between 2 and 4 patients with uveal melanoma monthly, with 75% or more presenting with metastatic disease. We anticipate accrual of 2 patients monthly from MSK alone. Once the study is open at all participating centers, we conservatively estimate an accrual of 3 patients per month.

13.3 Stratification Factors

Eligible patients will be randomized on a 1:1 ratio, with randomization stratified by presence or absence of liver involvement and LDH (< 2 times the ULN versus ≥ 2 times the upper limit of normal), to one of the two treatment arms.

13.4 Analysis of Secondary Endpoints

Analysis of secondary endpoints will be exploratory and hypothesis-generating.

Progression-free survival and overall survival curves will be generated using Kaplan-Meier methodology. Toxicity across both arms will be reported by type, frequency and severity according to the NCI Common Toxicity Criteria. Response rate (CR+PR) by arm will be calculated along with a

95% confidence interval.

13.5 Analysis of Exploratory Endpoints

For patients who progress on trametinib and crossover to the combination arm clinical outcomes will be summarized. Response rate (CR+PR) will be estimated along with progression-free and overall survival from the start of combination therapy. Toxicity for the crossover patients will be reported by type, frequency and severity according to the NCI Common Toxicity Criteria.

Clinical response will be associated with Gnaq/11 mutational status using Wilcoxon rank sum test. An additional exploratory objective is to assess whether circulating tumor DNA can be detected. If so, these numeric data will be summarized by clinical response.

Using the 30 or more paired tumor biopsies collected on this study, associations between suppression specifically of p-ERK, AKT, Cyclin-D1, and response to treatment will be assessed using Fisher's exact test. Baseline and post-treatment status as well as changes will be reported. Assessment of apoptosis in the paired samples will be performed by caspase3 cleavage; changes will be assessed by a Wilcoxon signed rank test. These correlative studies will be considered exploratory in nature.

13.6 Reporting and Exclusions

13.6.1 Evaluation of Toxicity

All patients will be evaluable for toxicity from the time of their first treatment with trametinib and GSK2141795.

13.6.2 Evaluation of Response

All patients 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 patient will 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). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.]

Intent-to-treat analysis will be performed in all who were randomized and who received at least one dose of study treatment in the main analysis of PFS (evaluable population). Patients in response categories 4-8 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate.

All conclusions should be based on all eligible patients. Subanalyses may then be performed on the basis of a subset of patients, 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 patients from the analysis should be clearly reported. The 95% confidence intervals will be provided.

14 PROTECTION OF HUMAN SUBJECTS

14.1 Privacy

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

15 INFORMED CONSENT PROCEDURES

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

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

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

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

15.1 For Participating Centers

The investigators listed on the protocol cover page and their qualified designees at each participating institution may obtain informed consent and care for the participants according to good clinical practice and protocol guidelines.

Signed copies of the informed consent should be distributed as follows: One copy will be given to the participant to be retained for their personal records. One copy will be maintained on file at the MSK. The third copy will be confidentially maintained by the participating institution.

A note will be placed in the medical record documenting that informed consent was obtained for this study, and that the participant acknowledges the risk of participation.

REFERENCES

1. Strickland D, Lee JA: Melanomas of eye: stability of rates. Am J Epidemiol 113:700-2, 1981
2. Chang AE, Karnell LH, Menck HR: The National Cancer Data Base report on cutaneous and noncutaneous melanoma: a summary of 84,836 cases from the past decade. The American College of Surgeons Commission on Cancer and the American Cancer Society. Cancer 83:1664-78, 1998
3. Singh AD, Topham A: Survival rates with uveal melanoma in the United States: 1973-1997. Ophthalmology 110:962-5, 2003
4. Singh AD, Turell ME, Topham AK: Uveal melanoma: trends in incidence, treatment, and survival. Ophthalmology 118:1881-5, 2011
5. Kujala E, Makitie T, Kivela T: Very long-term prognosis of patients with malignant uveal melanoma. Invest Ophthalmol Vis Sci 44:4651-9, 2003
6. Salmon RJ, Levy C, Plancher C, et al: Treatment of liver metastases from uveal melanoma by combined surgery-chemotherapy. European Journal of Surgical Oncology 24:127-30, 1998
7. Nathan F, Sato T, Hart E, et al: Response to combination chemotherapy of liver metastasis from chorhoidal melanoma compared with cutaneous melanoma. Proc Am Soc Clin Oncol 13:394, 1994
8. Bedikian AY, Legha SS, Mavligit G, et al: Treatment of uveal melanoma metastatic to the liver: a review of the M. D. Anderson Cancer Center experience and prognostic factors. Cancer 76:1665-70, 1995
9. Albert DM, Ryan LM, Borden EC: Metastatic ocular and cutaneous melanoma: a comparison of patient characteristics and prognosis. Arch Ophthalmol 114:107-8, 1996
10. Gragoudas ES, Egan KM, Seddon JM, et al: Survival of patients with metastases from uveal melanoma. Ophthalmology 98:383-9; discussion 390, 1991
11. Collaborative Ocular Melanoma Study G: Assessment of metastatic disease status at death in 435 patients with large choroidal melanoma in the Collaborative Ocular Melanoma Study (COMS): COMS report no. 15.[see comment]. Archives of Ophthalmology 119:670-6, 2001
12. Rietschel P, Panageas KS, Hanlon C, et al: Variates of survival in metastatic uveal melanoma. Journal of Clinical Oncology 23:8076-80, 2005
13. Homsi J, Bedikian AY, Papadopoulos NE, et al: Phase 2 open-label study of weekly docosahexaenoic acid-paclitaxel in patients with metastatic uveal melanoma. Melanoma Res 20:507-10, 2010
14. Penel N, Delcambre C, Durando X, et al: O-Mel-Inib: a Cancero-pole Nord-Ouest multicenter phase II trial of high-dose imatinib mesylate in metastatic uveal melanoma. Invest New Drugs 26:561-5, 2008
15. Schmittel A, Schmidt-Hieber M, Martus P, et al: A randomized phase II trial of gemcitabine plus treosulfan versus treosulfan alone in patients with metastatic uveal melanoma. Ann Oncol 17:1826-9, 2006
16. O'Neill PA, Butt M, Eswar CV, et al: A prospective single arm phase II study of dacarbazine and treosulfan as first-line therapy in metastatic uveal melanoma. Melanoma Res 16:245-8, 2006
17. Schmittel A, Scheulen ME, Bechrakis NE, et al: Phase II trial of cisplatin, gemcitabine and treosulfan in patients with metastatic uveal melanoma. Melanoma Res 15:205-7, 2005

18. Schmidt-Hieber M, Schmittel A, Thiel E, et al: A phase II study of bendamustine chemotherapy as second-line treatment in metastatic uveal melanoma. Melanoma Res 14:439-42, 2004
19. Bedikian AY, Papadopoulos N, Plager C, et al: Phase II evaluation of temozolomide in metastatic choroidal melanoma. Melanoma Res 13:303-6, 2003
20. Kivela T, Suciu S, Hansson J, et al: Bleomycin, vincristine, lomustine and dacarbazine (BOLD) in combination with recombinant interferon alpha-2b for metastatic uveal melanoma. Eur J Cancer 39:1115-20, 2003
21. Flaherty KT, Robert C, Hersey P, et al: Improved survival with MEK inhibition in BRAF-mutated melanoma. N Engl J Med 367:107-14, 2012
22. Gopal YN, Deng W, Woodman SE, et al: Basal and treatment-induced activation of AKT mediates resistance to cell death by AZD6244 (ARRY-142886) in Braf-mutant human cutaneous melanoma cells. Cancer Res 70:8736-47, 2010
23. Ebi H, Corcoran RB, Singh A, et al: Receptor tyrosine kinases exert dominant control over PI3K signaling in human KRAS mutant colorectal cancers. J Clin Invest 121:4311-21, 2011
24. Engelman JA, Chen L, Tan X, et al: Effective use of PI3K and MEK inhibitors to treat mutant Kras G12D and PIK3CA H1047R murine lung cancers. Nat Med 14:1351-6, 2008
25. Hoeflich KP, O'Brien C, Boyd Z, et al: In vivo antitumor activity of MEK and phosphatidylinositol 3-kinase inhibitors in basal-like breast cancer models. Clin Cancer Res 15:4649-64, 2009
26. Tolcher A, Bendell J, Patnaik A, et al: A phase Ib study of the MEK inhibitor GSK1120212 combined with gemcitabine in patients with solid tumors: Interim results. . J Clin Oncol. 29:Abstract 278., 2011
27. Bendell J, LoRusso P, Kwak E, et al: Clinical combination of the MEK inhibitor GDC-0973 and the PI3K inhibitor GDC-0941: A first-in-human phase Ib study in patients with advanced solid tumors. AACR Meeting Abstracts. Abstract LB-89., 2011
28. Gilmartin AG, Bleam MR, Groy A, et al: GSK1120212 (JTP-74057) is an inhibitor of MEK activity and activation with favorable pharmacokinetic properties for sustained in vivo pathway inhibition. Clin Cancer Res 17:989-1000, 2011
29. Yamaguchi T, Kakefuda R, Tajima N, et al: Antitumor activities of JTP-74057 (GSK1120212), a novel MEK1/2 inhibitor, on colorectal cancer cell lines in vitro and in vivo. Int J Oncol 39:23-31, 2011
30. Brochure Is: GSK1120212. GlaxoSmithKline. Version 04. September 5, 2012., 2012
31. Infante J, Fecher L, Nallapareddy S, et al: Safety and efficacy results from the first-in-human study of the oral MEK 1/2 inhibitor GSK1120212. J Clin Oncol. 28:Abstract 2503., 2010
32. Messersmith W, Falchook G, Fecher L, et al: Clinical activity of the oral MEK1/MEK2 inhibitor GSK1120212 in pancreatic and colorectal cancer. J Clin Oncol. 29:Abstract 246., 2011
33. Borthakur G, Foran J, Kadia T, et al: GSK1120212, a MEK1/MEK2 inhibitor, demonstrates acceptable tolerability and preliminary activity in a dose rising trial In subjects with AML and other hematologic malignancies. . Blood (ASH Annual Meeting Abstracts). 116:Abstract 3281., 2010
34. Kirkwood JM, Bastholt L, Robert C, et al: Phase II, open-label, randomized trial of the MEK1/2 inhibitor selumetinib as monotherapy versus temozolomide in patients with advanced melanoma. Clin Cancer Res 18:555-67, 2012

35. Falchook GS, Lewis KD, Infante JR, et al: Activity of the oral MEK inhibitor trametinib in patients with advanced melanoma: a phase 1 dose-escalation trial. Lancet Oncol 13:782-9, 2012
36. Infante JR, Fecher LA, Falchook GS, et al: Safety, pharmacokinetic, pharmacodynamic, and efficacy data for the oral MEK inhibitor trametinib: a phase 1 dose-escalation trial. Lancet Oncol 13:773-81, 2012
37. Carvajal R: A Randomized Phase II Trial of Temozolomide versus AZD6244 in Patients with Metastatic Uveal Melanoma. CTEP EDD Fall Meeting, 2011
38. Infante JR, Falchook GS, Lawrence DP, et al: Phase I/II study to assess safety, pharmacokinetics, and efficacy of the oral MEK 1/2 inhibitor GSK1120212 (GSK212) dosed in combination with the oral BRAF inhibitor GSK2118436 (GSK436). ASCO Meeting Abstracts 29:Abstract CRA8503, 2011
39. Weber J, Flaherty K, Infante J, et al: Updated safety and efficacy results from a phase I/II study of the oral BRAF inhibitor dabrafenib (GSK2118436) combined with the oral MEK 1/2 inhibitor trametinib (GSK1120212) in patients with BRAFi-naïve metastatic melanoma. J Clin Oncol. 30:Abstract 8510., 2012
40. Brochure Is: GSK2118436. GlaxoSmithKline. Version 04. May 15, 2012., 2012
41. Kurzrock R, Patnaik A, Rosenstein L, et al: Phase I dose-escalation of the oral MEK1/2 inhibitor GSK1120212 (GSK212) dosed in combination with the oral AKT inhibitor GSK2141795 (GSK795). J Clin Oncol. 29:Abstract 3085., 2011
42. Davies H, Bignell GR, Cox C, et al: Mutations of the BRAF gene in human cancer. Nature 417:949-54, 2002
43. Rimoldi D, Salvi S, Lienard D, et al: Lack of BRAF mutations in uveal melanoma. Cancer Res 63:5712-5, 2003
44. Cruz F, 3rd, Rubin BP, Wilson D, et al: Absence of BRAF and NRAS mutations in uveal melanoma. Cancer Res 63:5761-6, 2003
45. Zuidervaart W, van Nieuwpoort F, Stark M, et al: Activation of the MAPK pathway is a common event in uveal melanomas although it rarely occurs through mutation of BRAF or RAS. Br J Cancer 92:2032-8, 2005
46. Onken MD, Worley LA, Long MD, et al: Oncogenic mutations in GNAQ occur early in uveal melanoma. Invest Ophthalmol Vis Sci 49:5230-4, 2008
47. Raamsdonk CDV, Bezrookove V, Green G, et al: Frequent somatic mutations of GNAQ in uveal melanoma and blue naevi Nature *A*dvance online publication 10 December 2008 (doi:10.1038/nature07586), 2008
48. Van Raamsdonk CD, Griewank KG, Crosby MB, et al: Mutations in GNA11 in uveal melanoma. N Engl J Med 363:2191-9, 2010
49. Van Raamsdonk CD, Bezrookove V, Green G, et al: Frequent somatic mutations of GNAQ in uveal melanoma and blue naevi. Nature 457:599-602, 2009
50. Van Raamsdonk CD, Fitch KR, Fuchs H, et al: Effects of G-protein mutations on skin color. Nat Genet 36:961-8, 2004
51. Ambrosini G, Schwartz GK: The MEK inhibitor AZD6244 (selumetinib) is active in GNAQ mutant ocular melanoma cells. American Association for Cancer Research (abstr 5035), 2010
52. Patel M, Smyth E, Chapman PB, et al: Therapeutic implications of the emerging molecular biology of uveal melanoma. Clin Cancer Res 17:2087-100, 2011
53. Carvajal R, Sosman J, Quevedo F, et al: Phase II study of selumetinib (sel) versus

temozolomide (TMZ) in gnaq/Gna11 (Gq/11) mutant (mut) uveal melanoma (UM). J Clin Oncol 31, 2013 (suppl; abstr CRA9003), 2013
54. Carvajal R, Ambrosini G, Wolchok J, et al: Pharmacodynamic activity of selumetinib to predict radiographic response in advanced uveal melanoma. J Clin Oncol 30, 2012 (suppl; abstr 8598), 2012
55. Ambrosini G, Pratilas CA, Qin LX, et al: Identification of Unique MEK-Dependent Genes in GNAQ Mutant Uveal Melanoma Involved in Cell Growth, Tumor Cell Invasion, and MEK Resistance. Clin Cancer Res, 2012
56. Calipel A, Mouriaux F, Glotin AL, et al: Extracellular signal-regulated kinase-dependent proliferation is mediated through the protein kinase A/B-Raf pathway in human uveal melanoma cells. J Biol Chem 281:9238-50, 2006
57. Ivey K, Tyson B, Ukidwe P, et al: Galphaq and Galpha11 proteins mediate endothelin-1 signaling in neural crest-derived pharyngeal arch mesenchyme. Dev Biol 255:230-7, 2003
58. Shin MK, Levorse JM, Ingram RS, et al: The temporal requirement for endothelin receptor-B signalling during neural crest development. Nature 402:496-501, 1999
59. Schwarzenbach H, Hoon DS, Pantel K: Cell-free nucleic acids as biomarkers in cancer patients. Nat Rev Cancer 11:426-37, 2011
60. Kaiser J: Medicine. Keeping tabs on tumor DNA. Science 327:1074, 2010
61. Madic J, Piperno-Neumann S, Servois V, et al: Pyrophosphorolysis-activated polymerization detects circulating tumor DNA in metastatic uveal melanoma. Clin Cancer Res, 2012
62. Lacouture ME, Anadkat MJ, Bensadoun RJ, et al: Clinical practice guidelines for the prevention and treatment of EGFR inhibitor-associated dermatologic toxicities. Support Care Cancer 19:1079-95, 2011
63. Balagula Y, Barth Huston K, Busam KJ, et al: Dermatologic side effects associated with the MEK 1/2 inhibitor selumetinib (AZD6244, ARRY-142886). Invest New Drugs 29:1114-21, 2011
64. Rapaport F, Khanin R, Liang Y, et al: Comprehensive evaluation of differential expression analysis methods for RNA-seq data. http://arxiv.org/abs/1301.5277. 2013
65. Diehl F, Schmidt K, Choti MA, et al: Circulating mutant DNA to assess tumor dynamics. Nat Med 14:985-90, 2008
66. Eisenhauer EA, Therasse P, Bogaerts J, et al: New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 45:228-47, 2009

APPENDIX A – PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
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).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active 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.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B – POTENTIAL DRUG-DRUG INTERACTIONS

B.1 Potential CYP-Mediated Interactions

In vitro data indicate that GSK2141795 is a CYP3A4 substrate (GSK2141795 Investigator's Brochure, 2012). 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 [IC50] 3 mcM) and CYP3A4 (IC50 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.

Therefore, drugs that potently inhibit CYP3A4 could lead to increased GSK2141795 exposure in subjects, and drugs which are strong inducers of CYP3A are prohibited (see Tables below). Furthermore, drugs that are substrates of CYP3A4 or CYP2C8 with a narrow therapeutic index are prohibited (see Tables below).

Whether or not GSK2141795 is a substrate of hepatic uptake transporter OATP is unknown, therefore co-administration of OATP potent inhibitors should be performed with caution.

Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated list such as http://medicine.iupui.edu/clinpharm/ddis/table.aspx; medical reference texts such as the Physicians' Desk Reference may also provide this information. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product.

B.2 Oral Steroids

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.

B.3 Herbal and Dietary Supplements

Because the composition, PK, and metabolism of many herbal supplements are unknown, the concurrent use of all herbal supplements is prohibited during the study (including, but not limited to, St. John's wort, kava, ephedra [ma huang], gingko biloba, dehydroepiandrosterone [DHEA], yohimbe, saw palmetto, or ginseng). 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). For example, specific dietary supplements for evaluable deficiencies or imbalances (e.g. Vitamin D, zinc, omega 3) are not prohibited. The investigator should contact a CTEP Medical Monitor before initiating treatment with any herbal preparation.

B.4 Other Prohibited Medications

Other anti-cancer therapy while on study treatment (note: megestrol [Megace] if used as an appetite stimulant is allowed).

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

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

B.5 Tables

The following concurrent medications are **prohibited** while patients are receiving study drugs:

Metabolism Class	Therapeutic Area	Agents
CYP3A Substrate	Hypnotics and Sedatives	Cisapride
	Antidepressant, Antipsychotics, Antianxiety Agents	Pimozide
	Antihistamine	Astemizole
Strong CYP3A Inhibitor/Inducer	Antibiotics	Clarithromycin Telithromycin Rifamycin class agents (*e.g.*, rifampin, rifabutin, rifapentine) Troleandomycin
	Antifungals	Itraconazole ketoconazole
	Antidepressants	Nefazodone
	Antivirals	Atazanzvir Delaviridine Indinavir Lopinavir Nelfinavir Ritonavir Saquinavir Nevirapine
	Anticonvulsants	Carbamazepine Phenobarbital Phenytoin
BCRP Substrates	HMG-CoA Reductase Inhibitors, gastrointestinal agents	Rosuvastatin Sulfasalazine

The following concurrent medications (including, but not limited to) should be administered with caution while patients are receiving study drugs:

Metabolism Class	Therapeutic Area	Agents
CYP3A Inhibitors	Antivirals	Amprenavir Fosamprevanir
	Antibiotics	Erythromycin
	Antifungals	Fluconazole Voriconazole
	Calcium Channel Blockers	Mibefradil Diltiazem Verapamil
	Miscellaneous	Aprepitant
	Antibiotics	Erythromycin
	Antifungals	Fluconazole Voriconazole
	Calcium Channel Blockers	Mibefradil Diltiazem Verapamil
CYP3A Inducers	Antivirals	Efavirenz
CYP2C8 Substrates	HMG CoA-reductase inhibitors	Cerivastatin
	Thiazolidinediones	Rosiglitazone Pioglitazone
	Miscellaneous	Chloroquine Zopiclone Repaglinide

The following additional concurrent medications (including, but not limited to) should be administered with caution while patients are receiving study drugs:

Drugs Potentially Affecting 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
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
Drugs that may have their concentrations altered by trametinib or GSK2141795	
repaglinide, rosiglitazone, pioglitazone	Antidiabetics
alfentanil, fentanyl	Analgesics
quinidine	Antiarrhythmics
cilostazol	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
eplerenone	Selective Aldosterone Blockers
chloroquine, zopiclone	Thiazolidinediones

APPENDIX C – NEW YORK HEART ASSOCIATION CLASSIFICATIONS

Clinical Evaluation of Functional Capacity of Patients with Heart Disease in Relation to Ordinary Physical Activity

Class	Cardiac Symptoms	Limitations	Need for Additional Rest*	Physical Ability to work**
I	None	None	None	Full time
II	Only moderate	Slight	Usually only slight or occasional	Usually full time
III	Defined, with less than ordinary activity	Marked	Usually moderate	Usually part time
IV	May be present even at rest, and any activity increases discomfort	Extreme	Marked	Unable to work

* To control or relieve symptoms, as determined by the patient, rather than as advised by the physician.

** At accustomed occupation or usual tasks.

Reference: Bruce, R. A.: Mod. Concepts Cardiovasc. Dis. 25:321, 1956.
(Modified from New York Heart Association, 1953).

APPENDIX D – INFORMATION ON POSSIBLE DRUG INTERACTIONS

Information on Possible Interactions with Other Agents for Patients and Their Caregivers and Non-Study Healthcare Team

The patient _____ is enrolled on a clinical trial using the experimental agent **GSK2141795 and Trametinib.** This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

GSK2141795 interacts with many drugs that are processed by your liver. Because of this, it is very important to tell your study doctors about all of your medicine before you start this study. It is also very important to tell them if you stop taking any regular medicine, or if you start taking a new medicine while you take part in this study. When you talk about your medicine with your study doctor, include medicine you buy without a prescription at the drug store (over-the-counter remedy), or herbal supplements such as St. John's wort.

Many health care prescribers can write prescriptions. You must also tell your other prescribers (doctors, physicians' assistants or nurse practitioners) that you are taking part in a clinical trial. **Bring this paper with you and keep the attached information card in your wallet**. These are the things that you and they need to know:

GSK2141795 interacts with certain specific enzymes in your liver. The enzymes in question are **CYP3A4 and 2C8**. CYP3A4 is responsible for breaking down GSK2141795 in your liver. GSK2141795 may prevent other drugs from being broken down in your liver by CYP2C8

- GSK2141795 must be used very carefully with other medicines that need these liver enzymes to be effective or to be cleared from your system.
- Other medicines may also affect the activity of the enzyme.
    - Substances that increase the activity of CYP 3A4 ("inducers") could reduce the effectiveness of GSK2141795, while substances that decrease that enzyme's activity ("inhibitors") could result in high levels of the active drugs, increasing the chance of harmful side effects.
- You and healthcare providers who prescribe drugs for you must be careful about adding or removing any drug in this category.
- Before you start the study, your study doctor will work with your regular prescriber to switch any medicines that are considered "strong inducers/inhibitors" of **CYP 3A4** or substrates of **CYP 2C8**.
- Your prescribers should look at this web site http://medicine.iupui.edu/clinpharm/ddis/table.aspx or consult a medical reference to see if any medicine they want to prescribe is on a list of drugs to avoid.
- Please be very careful! Over-the-counter drugs have a brand name on the label—it's usually big and catches your eye. They also have a generic name—it's usually small and located above or below the brand name, and printed in the ingredient list. Find the generic name and determine, with the pharmacist's help, whether there could be an adverse interaction.
- Be careful:

- If you take acetaminophen regularly: You should not take more than 4 grams a day if you are an adult or 2.4 grams a day if you are older than 65 years of age. Read labels carefully! Acetaminophen is an ingredient in many medicines for pain, flu, and cold.
- If you drink grapefruit juice or eat grapefruit: Avoid these until the study is over.
- If you take herbal medicine regularly: You should not take St. John's wort while you are taking GSK2141795.

Other medicines can be a problem with your study drugs.

- You should check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.
- Your regular prescriber should check a medical reference or call your study doctor before prescribing any new medicine for you. Your study doctor's name is _____ and he or she can be contacted at _____.

INFORMATION ON POSSIBLE DRUG INTERACTIONS	
You are enrolled on a clinical trial using the experimental agents trametinib **and GSK2141795**. This clinical trial is sponsored by the NCI. **Only** GSK2141795 interacts with drugs that are processed by your liver. Because of this, it is very important to: ➢ Tell your doctors if you stop taking regular medicine or if you start taking a new medicine. ➢ Tell all of your prescribers (doctor, physicians' assistant, nurse practitioner, pharmacist) that you are taking part in a clinical trial. ➢ Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.	GSK2141795 interacts with a specific liver enzyme called **CYP 3A4 and 2C8**, and must be used very carefully with other medicines that interact with this enzyme. ➢ Before you start the study, your study doctor will work with your regular prescriber to switch any medicines that are considered "strong inducers/inhibitors or substrates of **CYP3A4 and 2C8**." ➢ Before prescribing new medicines, your regular prescribers should go to http://medicine.iupui.edu/clinpharm/ddis//table.aspx for a list of drugs to avoid, or contact your study doctor. ➢ Your study doctor's name is _____ and can be contacted at _____.

APPENDIX E – CTEP MULTICENTER GUIDELINES

If an institution wishes to collaborate with other participating institutions in performing a CTEP sponsored research protocol, then the following guidelines must be followed.

Responsibility of the Protocol Chair

- The Protocol Chair will be the single liaison with the CTEP Protocol and Information Office (PIO). The Protocol Chair is responsible for the coordination, development, submission, and approval of the protocol as well as its subsequent amendments. The protocol must not be rewritten or modified by anyone other than the Protocol Chair. There will be only one version of the protocol, and each participating institution will use that document. The Protocol Chair is responsible for assuring that all participating institutions are using the correct version of the protocol.
- The Protocol Chair is responsible for the overall conduct of the study at all participating institutions and for monitoring its progress. All reporting requirements to CTEP are the responsibility of the Protocol Chair.
- The Protocol Chair is responsible for the timely review of Adverse Events (AE) to assure safety of the patients.
- The Protocol Chair will be responsible for the review of and timely submission of data for study analysis.

Responsibilities of the Coordinating Center

- Each participating institution will have an appropriate assurance on file with the Office for Human Research Protection (OHRP), NIH. The Coordinating Center is responsible for assuring that each participating institution has an OHRP assurance and must maintain copies of IRB approvals from each participating site.
- Prior to the activation of the protocol at each participating institution, an OHRP form 310 (documentation of IRB approval) must be submitted to the CTEP PIO.
- The Coordinating Center is responsible for central patient registration. The Coordinating Center is responsible for assuring that IRB approval has been obtained at each participating site prior to the first patient registration from that site.
- The Coordinating Center is responsible for the preparation of all submitted data for review by the Protocol Chair.
- The Coordinating Center will maintain documentation of AE reports. There are two options for AE reporting: (1) participating institutions may report directly to CTEP with a copy to the Coordinating Center, or (2) participating institutions report to the Coordinating Center who in turn report to CTEP. The Coordinating Center will submit AE reports to the Protocol Chair for timely review.
- Audits may be accomplished in one of two ways: (1) source documents and research records for selected patients are brought from participating sites to the Coordinating Center for audit, or (2) selected patient records may be audited on-site at participating sites. If the NCI chooses to have an audit at the Coordinating Center, then the Coordinating Center is responsible for having all source documents, research records, all IRB approval documents, NCI Drug Accountability Record forms, patient registration lists, response assessments scans, x-rays, etc. available for the audit.

Inclusion of Multicenter Guidelines in the Protocol

- The protocol must include the following minimum information:
  - The title page must include the name and address of each participating institution and the name, telephone number and e-mail address of the responsible investigator at each participating institution.
  - The Coordinating Center must be designated on the title page.
  - Central registration of patients is required. The procedures for registration must be stated in the protocol.
  - Data collection forms should be of a common format. Sample forms should be submitted with the protocol. The frequency and timing of data submission forms to the Coordinating Center should be stated.
  - Describe how AEs will be reported from the participating institutions, either directly to CTEP or through the Coordinating Center.
  - Describe how Safety Reports and Action Letters from CTEP will be distributed to participating institutions.

Agent Ordering

- Except in very unusual circumstances, each participating institution will order DCTD-supplied investigational agents directly from CTEP. Investigational agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO.

APPENDIX F – PATIENT'S MEDICATION DIARY
Pill Diary for IRB #13-144: A Randomized Two-Arm Phase II Study of Trametinib Alone and in Combination with GSK2141795 in Patients with Advanced Uveal Melanoma

Participant Dosing Diary- Arm A		
This section to be completed by clinic staff	**Section completed by: _____**	
Participant ID #: _____	**Participant Initials: _____-_____-_____**	**CYCLE: _____**
Start on Day: _____/_____/_____ MM DD YY	**Circle the day participant starts medication:** **SUN MON TUES WED THURS FRI SAT**	**Number of tablets returned:** _____

Trametinib: 2 mg, by mouth once a day on an empty stomach one hour before a meal or two hours after a meal with water only

Medication Instructions:

- Your nurse or physician will review your prescribed dose with you.
- Record all your doses in this pill diary.
- Bring your study pills and this diary to every clinic visit. You will take Trametinib with a nurse (not at home) on the days you come in for appointments.
- Open only one bottle at a time when taking out your dose. Do not transfer pills from one bottle to another.
- Do not throw away any study pill bottles. We will collect them.
- If you think you are having a side effect, feel sick, or have any other questions about your pills please call your study doctor.
- Trametinib should be taken by mouth on an empty stomach one hour before a meal or two hours after a meal with water only.
- Trametinib tablets should be refrigerated in the original container.

How to complete the diary:

- Record the Date for each day of dosing in the Month – Day –Year (MM - DD - YY) format.
- Trametinib may be provided in different strengths. You may be asked to take a combination of strengths in a single dose. Please write the number of pills taken for each mg strength in the space provided.
- If you miss a dose, write "0" in the number of pills taken and add a comment for why the dose was missed.
- Add a comment if you vomited after taking drug and if so, how long after taking drug you vomited.
- Your doctor may change the amount of drug or how often you will be taking the drugs. Always record the actual amount of pills you took for each day.
- If you forget to complete the diary, leave it blank.

IF YOU HAVE QUESTIONS AT ANY TIME PLEASE CONTACT YOUR DOCTOR

Protocol IRB#: 13-144 Cycle: _____

Trametinib: 2 mg, by mouth, once a day

Date:	Pill taken:	Time taken:	Dose/Quantity:	Comments:
___/___/___ Day 1	☐Yes ☐No	___:___AM/PM	___0.5 mg ___2 mg	
___/___/___ Day 2	☐Yes ☐No	___:___AM/PM	___0.5 mg ___2 mg	
___/___/___ Day 3	☐Yes ☐No	___:___AM/PM	___0.5 mg ___2 mg	
___/___/___ Day 4	☐Yes ☐No	___:___AM/PM	___0.5 mg ___2 mg	
___/___/___ Day 5	☐Yes ☐No	___:___AM/PM	___0.5 mg ___2 mg	
___/___/___ Day 6	☐Yes ☐No	___:___AM/PM	___0.5 mg ___2 mg	
___/___/___ Day 7	☐Yes ☐No	___:___AM/PM	___0.5 mg ___2 mg	
___/___/___ Day 8	☐Yes ☐No	___:___AM/PM	___0.5 mg ___2 mg	
___/___/___ Day 9	☐Yes ☐No	___:___AM/PM	___0.5 mg ___2 mg	
___/___/___ Day 10	☐Yes ☐No	___:___AM/PM	___0.5 mg ___2 mg	
___/___/___ Day 11	☐Yes ☐No	___:___AM/PM	___0.5 mg ___2 mg	
___/___/___ Day 12	☐Yes ☐No	___:___AM/PM	___0.5 mg ___2 mg	
___/___/___ Day 13	☐Yes ☐No	___:___AM/PM	___0.5 mg ___2 mg	
___/___/___ Day 14	☐Yes ☐No	___:___AM/PM	___0.5 mg ___2 mg	
___/___/___ Day 15	☐Yes ☐No	___:___AM/PM	___0.5 mg ___2 mg	

Protocol IRB#: 13-144 Cycle: _____

Trametinib: 2 mg, by mouth, once a day

Date:	Pill taken:	Time taken:	Dose/Quantity:	Comments:
___/___/___ Day 16	☐Yes ☐No	___:___AM/PM	___0.5 mg ___2 mg	
___/___/___ Day 17	☐Yes ☐No	___:___AM/PM	___0.5 mg ___2 mg	
___/___/___ Day 18	☐Yes ☐No	___:___AM/PM	___0.5 mg ___2 mg	
___/___/___ Day 19	☐Yes ☐No	___:___AM/PM	___0.5 mg ___2 mg	
___/___/___ Day 20	☐Yes ☐No	___:___AM/PM	___0.5 mg ___2 mg	
___/___/___ Day 21	☐Yes ☐No	___:___AM/PM	___0.5 mg ___2 mg	
___/___/___ Day 22	☐Yes ☐No	___:___AM/PM	___0.5 mg ___2 mg	
___/___/___ Day 23	☐Yes ☐No	___:___AM/PM	___0.5 mg ___2 mg	
___/___/___ Day 24	☐Yes ☐No	___:___AM/PM	___0.5 mg ___2 mg	
___/___/___ Day 25	☐Yes ☐No	___:___AM/PM	___0.5 mg ___2 mg	
___/___/___ Day 26	☐Yes ☐No	___:___AM/PM	___0.5 mg ___2 mg	
___/___/___ Day 27	☐Yes ☐No	___:___AM/PM	___0.5 mg ___2 mg	
___/___/___ Day 28	☐Yes ☐No	___:___AM/PM	___0.5 mg ___2 mg	

Final Review and Collection:

Participant/LAR Signature: _____ Date: _____/_____/_____

MD/RN Signature: _____ Date: _____/_____/_____

MD/RN Name (print): _____

Additional Comments:

APPENDIX G – OPHTHALMOLOGY EXAMS

Instructions: This worksheet can be used to record the findings during the ophthalmology exam.

Contact Information for Study Staff:
PI: _____
Coordinator (RSA): _____
Participant: _____
Return form to: _____

Date of Exam: _____

	Right Eye	**Left Eye**
Visual Acuity (Record Values)		
Tonometry (Record Values)		
Slit Lamp Exam	□ Normal □ Abnormal – not clinically significant □ Abnormal Explain:	□ Normal □ Abnormal – not clinically significant □ Abnormal Explain:
Indirect Funduscopy	□ Normal □ Abnormal – not clinically significant □ Abnormal Explain:	□ Normal □ Abnormal – not clinically significant □ Abnormal Explain:
Visual Field	□ Normal □ Abnormal – not clinically significant □ Abnormal Explain:	□ Normal □ Abnormal – not clinically significant □ Abnormal Explain:
New Optic Disc Cupping?	□ Yes □ No	□ Yes □ No
New Visual Field Defect?	□ Yes □ No	□ Yes □ No
Intraocular Pressure >21mmHg?	□ Yes □ No	□ Yes □ No
Other Risk Factors for RVO/RPED?	□ Yes □ No	□ Yes □ No

Signature of Person Conducting Exam: _____ Date: _____

APPENDIX H– IMF/LCCI MSK RESEARCH LABORATORY REQUISITION

Protocol 13-144: A Randomized Two-Arm Phase II Study of Trametinib Alone and in Combination with GSK2141795 in Patients with Advanced Uveal Melanoma (NCI #9445)

Name:
MRN:
DOB:

Send all samples to:
Drs. Jedd Wolchok, Phillip Wong & Jianda Yuan
Immune Monitoring Core Lab, room Z-1513
ext. 125-3106
Attention: Teresa Rasalan ext. 125-3106 (pager 2877)
Or Rosemarie Ramsawak 125-3106

Dr. _____ RSA Contact info: _____
Arm:_____ Timepoint: _____

Request (Please be Specific)

DRAWN BY:_____ ext.____
Please Print Name

DATE:_____TIME:_____

For Research Lab use only:
Lab Number:
Received by:
Date/Time
Sample Type

Requisition visit type must be checked for samples to be processed

- ☐ **Day 1:** 2 CPT tubes
- ☐ **Cycle ____ :** 2 CPT tubes
- ☐ Other time points

Research Sample Collection Instructions:

1. Invert all tubes several times immediately after collection
2. Write patient initials, date, and time of collection on each tube
3. Fill in date and time of collection in requisition form
4. Place all collected tubes in biohazard ziplock bag
5. Please send all specimens via Stat Messengers to Immune Monitoring Core located at Zuckerman Research Building, Room 1513. (Place at blood bin on table.)
   Notify Teresa or Rosemarie above of sample delivery
   Please drop off samples by 4pm M-F; otherwise late processing fees will be applied.

MEMORIAL SLOAN KETTERING CANCER CENTER
RESEARCH LABORATORY REQUISITION

DR. _____

REFRIGERATE _____

C _____

H _____

K _____

M _____

S _____

OTHER

Send all samples to
Z-1523
Attn: Dr Merghoub x125-2581

Name:
MRN:
DOB:

Protocol 13-144

Arm:
Treatment Medication:

Timepoint:

REQUEST (BE SPECIFIC)

Please collect:

2 Lavender Top Tube 10 ml

BY: _____ x_____

(Please Print Name and extension)

DATE: _____TIME:_____

Fold Here ⇓

56-09250

13-144

Research Samples Collection Instructions

1. Write Patient Initials on each tube, date and time of collection
2. Fill in date and time of collection in requisition form
3. Place all collected tubes in biohazard ziplock bag
4. Please send all specimen via Stat Messengers x 0732 to
   Zuckerman 1523
   ATTN: Dr Merghoub
   x 125-2580

APPENDIX I – PARTICIPATING SITE SHIPPING REQUISITIONS

Laboratory Requisition: Tumor/Blood (U.S. Respository)

Laboratory Requisition: Circulating Tumor DNA

Laboratory Requisition: Exosomal/Proteomic Analysis

MSK IRB Protocol 13-144 (NCI 9445): A Randomized Two-Arm Phase II Study of Trametinib Alone and in Combination with GSK2141795 in Patients with Advanced Uveal Melanoma

US Repository Samples: Tumor and Blood
LAB Project Name: GSK Uveal Protocol

Shipping Instructions:
Complete the below requisition and include with sample. Label all samples with Protocol #9445, MSK-Assigned Participant ID, Initials, Date of Collection, and Time Point. All samples are to be prepared and shipped as per protocol section 9.0. Notify laboratory of each shipment.

Ship Samples to:
Taha Merghoub, MD
415 East 68th Street
New York, NY 11065
646-888-2580

Notify via E-mail:
merghout@mskcc.org
shoushta@mskcc.org
medmctcore@mskcc.org

Participant Information	**Shipment Information**
Institution: _____	Shipment Date: _____
Participant Initials: _____	Shipping Method: _____
MSK-Assigned Participant ID: _____	Tracking Number: _____
Date of Birth (MM/DD/YYYY): _____	**Sender's Contact Information:**
*MSK Laboratory/ID: _____ *(Leave Laboratory ID blank for **first** shipment for each participant. Laboratory ID will be assigned once the first samples for each participant are received at the lab)*	Name: _____ Email: _____ Telephone Number: _____ Address: _____

Study Time Point (Check One)

☐Pretreatment/Screening Visit ☐During Treatment, Day 1 of Cycle List Cycle # _____ ☐End of Treatment Visit

Specimen Type and Information

☐Tumor
List Organ/Site of Collection: _____
List Number of Cores Fixed in Formalin: _____
List Number of Cores Flash-Frozen: _____
Block ID/Accession #: _____

☐Blood
List Number of Aliquots: _____

For Laboratory Use:		
Date Received:	MEL # Assigned:	Date Entered into Database:

MSK IRB Protocol 13-144 (NCI 9445): A Randomized Two-Arm Phase II Study of Trametinib Alone and in Combination with GSK2141795 in Patients with Advanced Uveal Melanoma

Circulating Tumor DNA

Shipping Instructions:
Complete the below requisition and include with sample. Label all samples with Protocol #9445, MSK-Assigned Participant ID, Initials, Date of Collection, and Time Point. All samples are to be prepared and shipped as per protocol section 9.0. Notify laboratory of each shipment.

Ship Samples to:	**Shipment Information**
Marc-Henri Stern, MD PhD Institut Curie Immunologie 4ème étage 26 rue d'Ulm 75005 Paris cedex 05 France	Shipment Date: _____ Shipping Method: _____ Tracking Number: _____
Notify via E-mail: maud.milder@curie.net aurore.rampanou@curie.fr delphine.louis@curie.net isabelle.peguillet@curie.net medmctcore@mskcc.org	**Sender's Contact Information:** Institution: _____ Name: _____ Email: _____ Telephone Number: _____ Address: _____ _____

Contents

Participant Initials	MSK-Assigned Participant ID	Date of Birth	**Study Time Point** (ie. Pre-treatment, Cycle #___, or End of Treatment)	**Specimen Type**	**# Tubes**
				Plasma	
				Plasma	
				Plasma	
				Plasma	
				Plasma	
				Plasma	
				Plasma	
				Plasma	

For Laboratory Use:	Date Received:

MSK IRB Protocol 13-144 (NCI 9445): A Randomized Two-Arm Phase II Study of Trametinib Alone and in Combination with GSK2141795 in Patients with Advanced Uveal Melanoma

Exosomal/Proteomic Analysis

Shipping Instructions:
Complete the below requisition and include with sample. Label all samples with Protocol #9445, MSK-Assigned Participant ID, Initials, Date of Collection, and Time Point. All samples are to be prepared and shipped as per protocol section 9.0. Notify laboratory of each shipment.

Ship Samples to:	**Shipment Information**
Professor Sarah Coupland Department of Molecular and Clinical Cancer Medicine Institute of Translational Medicine University of Liverpool 6th Floor Duncan Building, Daulby Street Liverpool L69 3GA	Shipment Date: _____ Shipping Method: _____ Tracking Number: _____
Notify via E-mail: S.E.Coupland@liverpool.ac.uk medmctcore@mskcc.org	**Sender's Contact Information:** Institution: _____ Name: _____ Email: _____ Telephone Number: _____ Address: _____ _____

Contents

Participant Initials	MSK-Assigned Participant ID	Date of Birth	**Study Time Point** (ie. Pre-treatment, Cycle #___, or End of Treatment)	**Specimen Type**	**# Tubes**
				Plasma	
				Plasma	
				Plasma	
				Plasma	
				Plasma	
				Plasma	
				Plasma	
				Plasma	

For Laboratory Use:	Date Received: