ECOG-ACRIN cancer research group
Reshaping the future of patient care

EA6191

The BAMM2 (BRAF, Autophagy, MEK inhibition in Melanoma) Study: A Randomized Double Blind Phase II Study of Dabrafenib and Trametinib with or without Hydroxychloroquine in Advanced BRAF$^{V600E/K}$ Melanoma with elevated LDH

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STUDY PARTICIPANTS

ALLIANCE / Alliance for Clinical Trials in Oncology
NRG / NRG Oncology
SWOG / SWOG

ACTIVATION DATE

October 23, 2020
Addendum #1
Addendum #2
Addendum #3

Agents	NSC#	Supply
Dabrafenib	763760	Commercial
Trametinib	763093	Commercial
Hydroxychloroquine and matching placebo	4375	Sandoz Inc, Division of Novartis

Study Exempt from IND Requirements per 21 CFR 312.2(b)

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CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. (Sign in at www.ctsu.org, and select the Regulatory Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions. Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS).		
For clinical questions (i.e., patient eligibility or treatment-related) Contact the Study PI of the Coordinating Group.		
For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Web site is located at https://www.ctsu.org		

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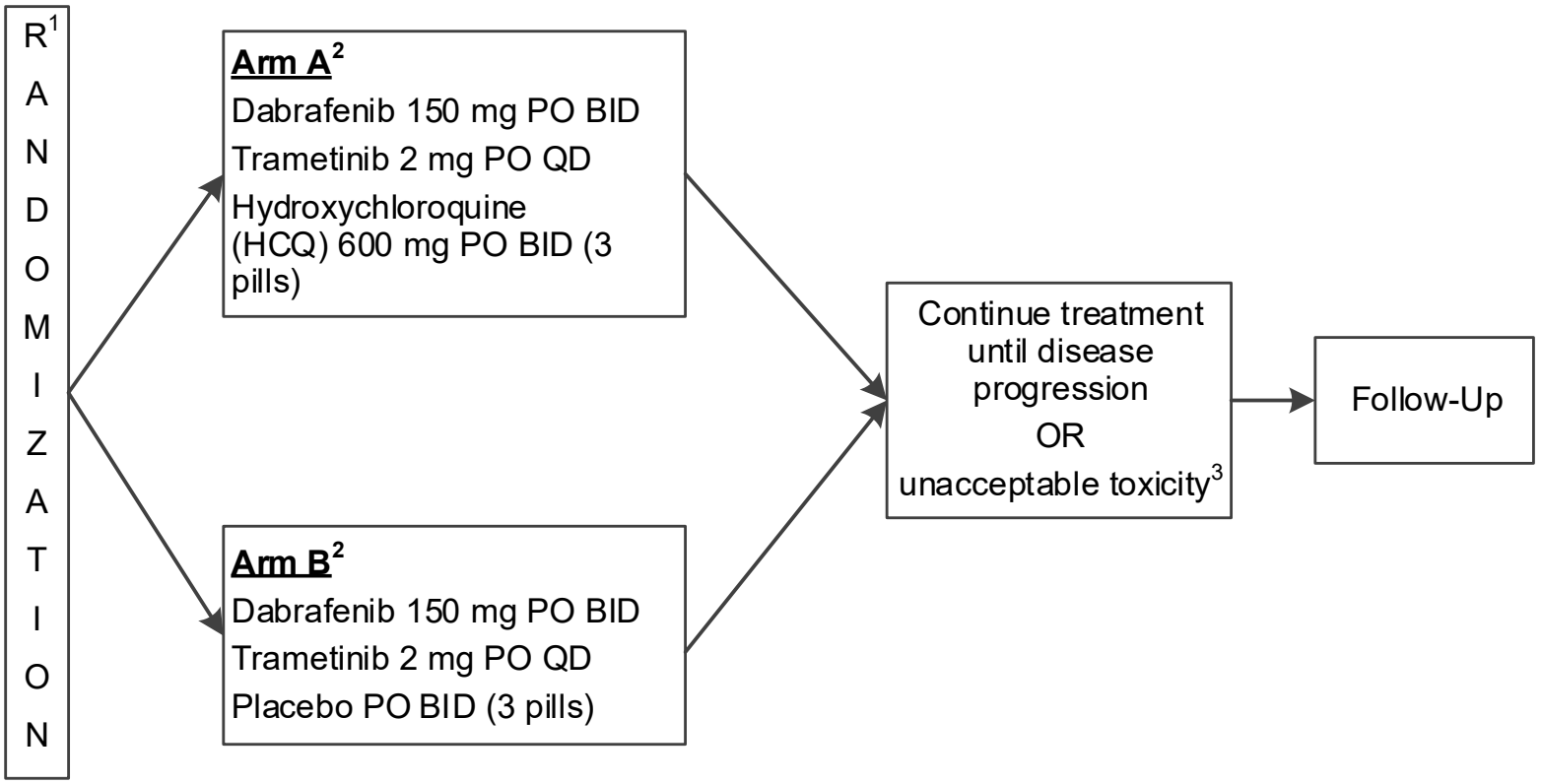
Schema



1. Randomization will be double blinded 1:1.
2. When a patient has been randomized, the confirmation of the registration will indicate that the patient is on Arm X. The patient will actually be on Arm A or B, however, since this is a double-blinded trial, that information cannot be displayed.
3. Dabrafenib and trametinib may be continued indefinitely until progression of disease. Due to the risk of retinal toxicity HCQ/placebo will be administrated for a maximum of 2 years unless there is sufficient evidence from a comprehensive retinal exam that there are no early signs of retinal toxicity and the treating ophthalmologist provides a written plan of monitoring more frequently than yearly for treatment beyond 2 years

Introduction

1.1 Rationale

BRAF and MEK inhibition is a standard of care therapy for *BRAF* mutant melanoma patients. Not every patient responds, and most responses are not complete responses. Eventually the vast majority of patients progress. A new approach to overcome resistance to BRAF and MEK inhibition is needed. Autophagy has been identified as a major resistance mechanism to BRAF and/or BRAF/MEK inhibition in BRAF mutant cancers (1-10) The only clinically available drugs to target autophagy are the chloroquine derivatives. The first 6 clinical trials involving combinations of hydroxychloroquine (HCQ) and cancer drugs (11-15) have been published and have demonstrated the safety of the approach in patients with advanced solid tumors. Finally a series of recent papers has convincingly demonstrated that chloroquine derivatives are not simply weak bases that deacidify the lysosome. In fact they are targeted therapies that bind and inhibit palmitoyl protein thioesterase 1 (PPT1) in the lysosome (16, 17).

As described below the BAMM (BRAF Autophagy and MEK inhibition for Melanoma) trial demonstrates an 85% response rate without significant excess toxicity when dabrafenib and trametinib are combined with HCQ in patients with anti-PD1 Ab naïve or anti-PD1 Ab refractory Stage IV *BRAF* mutant melanoma. In this study while the response rate was higher than previous response rates observed with dabrafenib and trametinib (60-70%), the PFS was not significantly different than historical controls from previous randomized trials of dabrafenib and trametinib (12 months). One possible explanation for this finding was that the BAMM trial had a higher enrollment of subjects with elevated LDH who were previously treated with immunotherapy than most of the published trials with dabrafenib and trametinib (see below for comparisons and references). Post-hoc analysis of the patients with elevated LDH revealed a prolonged PFS compared to historical controls.

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Typically BRAF mutant melanoma patients with elevated LDH have low response rates and short progression-free survival when treated with BRAF and MEK inhibitors. There is an unmet need to develop new therapeutic regimens for patients with elevated LDH. Melanoma tumors from patients with elevated serum LDH are dependent on glycolytic metabolism driven by hypoxia-induced HIF1 alpha signaling (21). Hypoxic tumors drive upregulation of glycolysis, leading to increased lactate production. Excess lactate in the tumor microenvironment is shuttled back into the cancer cell through monocarboxylate transporters. Elevation of intracellular lactate drives expression of LDH which is secreted and measurable in the serum. Mechanistic studies (Brisson Cancer Cell 2016) have demonstrated that elevated LDH within the cancer cell drives lysosomal acidification and increases autophagic flux. Hence melanoma tumors with elevated LDH are possibly more susceptible to autophagy inhibition than tumors with normal LDH. Therefore, with evidence of tolerability and increased response rate established the single arm BAMM study, and a mechanistic rationale as well as a clinical unmet need that supports investigating this regimen in elevated LDH patients, we propose a randomized trial of dabrafenib and trametinib (D+T) with HCQ or placebo in Stage III/IV *BRAF* mutant melanoma patients with elevated LDH.

Only a randomized trial would answer the question of whether or not the addition of HCQ is adding to the activity of targeted therapy in patients with elevated LDH. Here we describe a double-blind placebo-controlled phase II trial in patients with RECIST measurable unresectable stage IIIC or stage IV BRAF inhibitor naïve $BRAF^{V600E/V600K}$ melanoma with elevated LDH who have been previously treated with an immune checkpoint inhibitor. Based on the variability of the control arm outcomes in multiple targeted therapy trials we propose a 1:1 randomization between D+T+ placebo and D+T+HCQ with the primary objective to determine if the addition of HCQ significantly improves the rate of progression-free survival (PFS) at 12 months. Response will be measured by RECIST 1.1 by investigator assessment.

Given the number of durable CRs observed (see below) and the lack of almost any additional grade 3-4 toxicity compared to published reports of D+T toxicity, there are already indications that the median PFS for D + T + HCQ will be longer than the 5.5 months observed in previous trials of D + T alone in patients with LDH for the triple drug combination. The safety of this regimen is in stark contrast to the safety of some immunotherapy based regimens. If this randomized study is positive, a randomized phase III study would be warranted. This trial is designed as a proof of a biological principle and is not a registration trial for regulatory agencies.

Single arm clinical trial data: The BAMM (BRAF, Autophagy MEK inhibition in Melanoma) trial is a four-institution (UPENN, Rutgers, Northwestern, Washington University) phase I/II trial of dabrafenib (D), trametinib (T) and HCQ (NCT02257424). Phase I was completed with no dose limiting toxicities (DLT). The recommended phase II dose was HCQ 600 bid with D+T. Phase II enrollment was halted after 34 evaluable patients were accrued. 38 patients in the phase I and II trial were evaluable for toxicity. Compared to COMBI-V the phase III trial of D + T versus vemurafenib (18) D+T+HCQ was well tolerated with rash (12%) the only grade 3 toxicity that was slightly increased in the triple combination compared to published reports of the standard doublet combination (4% grade 3 rash). An initial long term follow-up of the first 10 patients enrolled was published and reported no clinically significant ocular toxicity (19).

Results of BAMM1 (NCT0225742)

1.1.1 BAMM1 study eligibility criteria includes:

- Must be ≥ 18 years of age.
- Must have histologically confirmed melanoma Stage IV or unresectable Stage III positive for BRAF V600E, V600K V600R or V600D mutation by a CLIA approved assay
- Must have ECOG performance status of 0 or 1
- Must have adequate renal, liver, cardiac and hematological function
- Must be able to provide written informed consent.
- Patients with brain metastases treated with whole brain radiation that have been stable for 2 months are eligible; patients with brain metastases treated with gamma knife or surgery are allowed to participate after 2 weeks have elapsed since their procedure, and must be off steroids for 1 week prior to starting study treatment.

- May have had any number and type of prior anticancer therapies. Patients with prior BRAF or MEK inhibitors are not allowed to participate.

  Exclusions: Porphyria, uncontrolled psoriasis, history of retinal vein occlusion in either eye, concurrent malignancies within the last 2 years except for prostate cancer and breast cancer for which no concurrent therapy is indicated. Taking P450 enzyme-inducing anticonvulsant drugs

1.1.2 Final analysis of the BAMM study demonstrates that dabrafenib, trametinib and HCQ at 600 mg PO BID is well tolerated with no excess toxicities except slightly more grade 1-2 constipation and anorexia than might be expected with dabrafenib and trametinib alone. The efficacy of the regimen was striking with an 85% response rate. However the 11.9 month median progression-free survival did not meet the pre-specified criteria for success. One possible explanation for lack of difference in the PFS compared to historical control is that the BAMM trial had a higher proportion of the patients (47%) had elevated LDH and were pre-treated with immunotherapy. This is a very different patient population than previously reported studies for BRAF and MEK inhibitor combinations, which typically have a lower rate of elevated LDH patients and patients who were immunotherapy naïve. These data warrant further study of this regimen in a randomized phase II setting.

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Patients

- 50 patients consented and screened
- 38 accrued of target 47 and evaluable for toxicity
- 34 of target 47 evaluable for response and PFS

Patients were typical for a stage IV melanoma population (Table 1). Of note there was a lower rate of M1c, elevated LDH and previously treated patients.

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Table 1. Demographics	
Age, Median (Range)	58 (30-83)
Sex	
Female	11/ 38 (29%)
Male	27/38 (71%)
ECOG Performance Status	
ECOG PS 0	27/38 (71%)
ECOG PS 1	11/38 (29%)
LDH at Study Entry	

Table 1. Demographics	
LDH ≤ ULN	20/38 (53%)
LDH > ULN	18/38 (47%)
Stage at Study Entry	
Unresectable Stage IIIC	0/38 (0%)
Stage IV M1a	9/38 (24%)
Stage IV M1b	9/38 (24%)
Stage IV M1c	15/38 (39%)
Stage IV M1d	5/38 (13%)
# Prior systemic therapies	
0	18/38 (47%)
1	9/38 (24%)
2	9/38 (24%)
3	2/38 (5%)
Brain metastases	5/38 (13%)

Comparing the demographics between BAMM and COMBI-V we see that the BAMM population has a much higher percentage of patients with elevated LDH and a much higher percentage of patients previously treated with immunotherapy. Both of these are poor prognostic factors that significantly reduce the PFS to targeted therapy.

1.1.3 Phase I dose escalation

Six patients were enrolled on the phase I dose escalation portion of the BAMM study. No DLTs were reported. The recommended phase II dose of HCQ 600 mg po bid combined with dabrafenib 150 mg po bid and trametinib 2 mg po qd was used for the single arm phase II study. All patients in the phase I and II portions of the study were assessed for response and toxicity below.

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Response

The investigator assessed best overall response rate for the study population was 85% (Table 2). The complete response rate was 41%. Below we provide post-hoc exploratory subgroup analyses of this single arms study. The best overall response rate for patients with elevated LDH (88%), prior therapy (83%), and baseline tumor size ≥ 5

cm (89%), and the complete response rate in elevated LDH (25%), prior therapy (39%), and baseline tumor size ≥ 5 cm (33%) suggests this regimen is effective at eliciting response in the most aggressive Stage IV *BRAF* mutant melanoma patients. Waterfall plots for the overall population and these subgroups demonstrates this further (Figure 1).

Table 2. Response Rates

Response	Investigator Assessed	Rad. Core Assessed*	LDH≤ULN	LDH>ULN	No prior therapy	Prior therapy	BTS< 5 cm	BTS ≥ 5 cm
CR	14/34 (41%)		10/18 (56%)	4/16 (25%)	7/16 (44%)	7/18 (39%)	8/16 (50%)	6/18 (33%)
PR	15/34 (46%)		5/18 (27%)	10/16 (63%)	7/16 (44%)	8/18 (44)%	5/16 (31%)	10/18 (56%)
SD	3 (8%)		2/18 (11%)	1/16 (6%)	2/16 (12%)	1/18 (6%)	2/16 (13%)	1/18 (6%)
PD	2 (5%)		1/18 (6%)	1/16 (6%)	0	2/18 (11%)	1/16 (6%)	1/18 (5%)
N	34		18	16	16	18	16	18
BORR	29/34 (85%)		15/18 (83%)	14/16 (88%)	14/16 (88%)	15/18 (83%)	14/16 (81%)	16/18 (89%)

*In process; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; BORR: Best Overall Response Rate; LDH: lactate dehydrogenase; ULN: upper limit of normal; BTS: Baseline Tumor Size

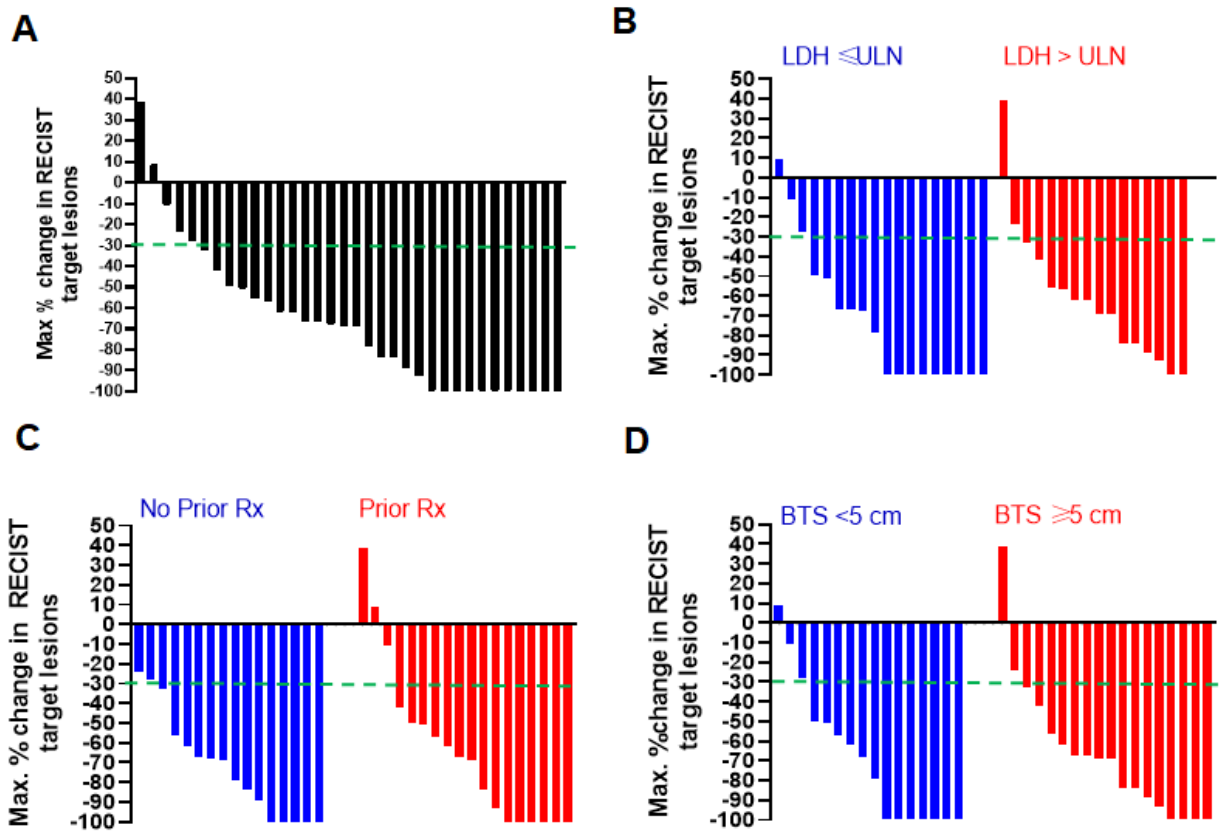

Fig. 1 Waterfall Plots for Maximum change in Target lesions. Overall study population B. According to LDH status C. According to prior therapy D. According to Baseline tumor size as determined by the sum of the RECIST target lesions on baseline scans

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Progression-free survival. The one-year progression-free survival rate for the entire study population was 14/24 (41%). The median PFS for the entire study population was 11.9 months (Figure 2A). We performed post-hoc exploratory sub-group analyses for PFS. The median PFS for patients with elevated LDH (8 Mo.; Figure 2B), prior therapy (15.5 Mo.; Figure 2C), and baseline tumor size > 5 cm (8.5 Mo.; Figure 2D) suggests this regimen may have a role in increasing the duration of response in previously treated patients with elevated LDH.

Overall Survival. With 38 months of median followup the median overall survival was 28 months in the overall population (Figure 3A). We performed post-hoc exploratory sub-group analyses for OS. The median OS for patients with elevated LDH (25 Mo.; Figure 3B), prior therapy (25 Mo.; Figure 3C), and baseline tumor size > 5 cm (25 mo.; Figure 3D) suggests this regimen may have a role in increasing survival of previously treated patients with elevated LDH.

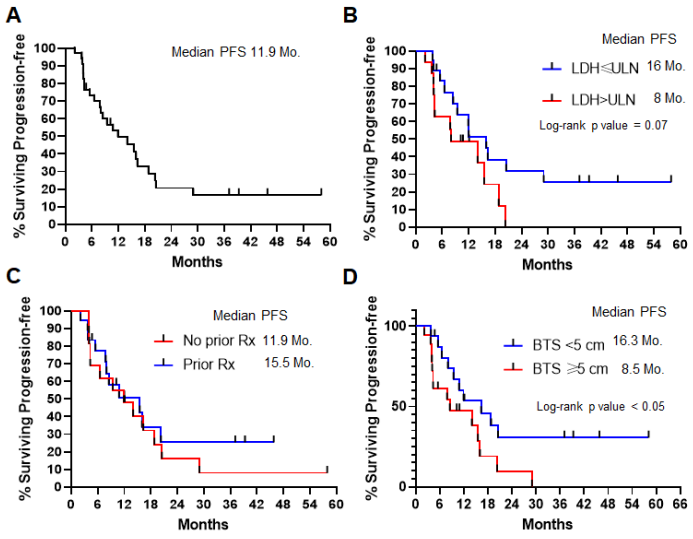

Fig. 2 Progression-free survival A. Overall study population B. According to LDH status C. According to prior therapy D. According to baseline tumor size as determined by the sum of the RECIST target lesions on baseline scans. Tick marks indicate censored patients who never progressed by RECIST criteria.

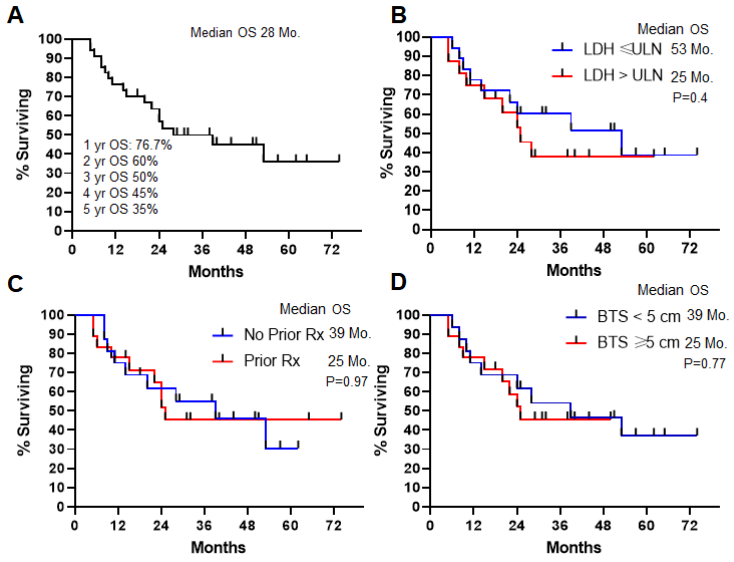

Fig. 3 Overall survival (Median Follow-up 38 months) Overall study population B. According to LDH status C. According to prior therapy D. According to baseline tumor size as determined by the sum of the RECIST target lesions on baseline scans. Tick marks indicate censored patients who have not died.

1.1.4 BAMM1 Adverse Events

The addition of HCQ to dabrafenib and trametinib seems to be very well tolerated, with no significant increase in grade 3 toxicities. The addition of HCQ may result in slightly more GI side effects of constipation and anorexia than would be expected from dabrafenib

and trametinib, but these adverse events were not dose limiting. The most common dose limiting adverse event was fever/ pyrexia which is the most common reason for discontinuation of dabrafenib and trametinib.

Table 3. Adverse Events

	Dabrafenib + trametinib + HCQ (BAMM)			Dabrafenib + trametinib (COMBI-V)*	
Adverse Event	Grade 1-2	Grade 3	Grade 4	Any Grade	Grade 3
Chills	14 (56%)	1 (4%)	0	31%	1%
Diarrhea	13 (52%)	0	0	32%	1%
Fever	13 (52%)	1 (4%)	0	53%	4%
Nausea	12 (48%)	1 (4%)	0	35%	1%
Fatigue	11 (44%)	0	0	NR	NR
Headache	9 (36%)	0	0	NR	NR
Myalgia	9 (36%)	0	0	NR	NR
Rash	9 (36%)	3 (12%)	0	22%	4%
Anorexia	8 (32%)	0	0	NR	NR
Dry mouth	7 (28%)	0	0	NR	NR
Pruritus	7 (28%)	0	0	NR	NR
Arthralgia	6 (24%)	0	0	24%	1%
Abdominal pain	5 (20%)	0	0	NR	NR
Vomiting	5 (20%)	0	0	29%	1%
Constipation	4 (16%)	0	0	NR	NR
Dysgeusia	4 (16%)	0	0	NR	NR
Creatinine increased	3 (12%)	0	0	NR	NR
Dehydration	3 (12%)	2 (8%)	0	NR	NR
Electrocardiogram QT corrected interval prolonged	3 (12%)	1 (4%)	0	NR	NR
Allergic reaction	2 (8%)	0	0	NR	NR
Anemia	2 (8%)	0	0	NR	NR
Dizziness	2 (8%)	0	0	NR	NR
Other, squamous cell carcinoma	2 (8%)	0	0	1%	0
Photosensitivity	2 (8%)	0	0	4%	0
Weight Loss	2 (8%)	0	0	NR	NR
Alanine aminotransferase increased	1 (4%)	2 (8%)	0	NR	NR

Table 3. Adverse Events					
	Dabrafenib + trametinib + HCQ (BAMM)			Dabrafenib + trametinib (COMBI-V)*	
Other, sigmoid polyp	1 (4%)	0	0	NR	NR
Ejection fraction decreased	0	1 (4%)	0	8%	4%

*From Combi-V Study (Robert et al. *NEJM* 2015)

NR: Not reported in the paper

1.1.5 Cardiac adverse events of note

12% of patients experienced asymptomatic Qtc prolongation which could be attributed to either dabrafenib and trametinib or the HCQ or to both. After consultation with a cardiologist all patients with Qtc prolongation were continued on therapy without dose modification and monitored with EKGs every cycle. No evidence of troponin elevation or acute coronary ischemia were noted. One patient experienced a clinically asymptomatic but irreversible drop in ejection fraction (EF) from 55% to 40% starting 8 months into therapy. After consultation with a cardiologist this was deemed as treatment related as there was no evidence of acute cardiac ischemia. The EF stabilized when MEK inhibitor was removed. This patient experienced a complete response and continued on study treated with dabrafenib and HCQ. He was treated on study for 2.5 years.

1.1.6 Additional information on tolerability of therapy

The median duration of therapy (excluding patients who had recently enrolled) was 16 months (with a range of 2-33). There were 2/22 evaluable patients that discontinued therapy earlier than progression and 1 additional patient who continued on BRAF and HCQ after echo showed decreased EF. Responses continued in patients that discontinued treatment early. Treatment was well tolerated enough that 3 patients were treated beyond isolated progression after local therapy (radiation) was administered.

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Comparison to historical data for dabrafenib and trametinib and conclusions. The BAMM trial did not meet its primary objective which was a one-year PFS rate that was significantly different than the historical control of 40%. Table 4 has an efficacy comparison of the BAMM trial data to the data for dabrafenib and trametinib in Robert et al. NEJM 2019 and Shadendrof Eur J Cancer 2017. While the addition of HCQ increased response rates substantially, in many cases responses were transient. However, in patients with elevated LDH, a population of patients that historically has poor outcomes with targeted therapy, there appears to be increased response rate, complete response rate and prolonged PFS with the addition of HCQ that could translate into an overall survival benefit. While examination of this subset of patients was a post-hoc exploratory analysis, there is a mechanistic reason why tumors in patients with elevated LDH may be especially sensitive to autophagy inhibition with HCQ. Since there

is an unmet clinical need to develop treatments for *BRAF* mutant patients with elevated LDH, further study of dabrafenib, trametinib and HCQ is warranted in patients with elevated LDH.

Table 4. Efficacy Comparison

	Overall		LDH> ULN	
	D+T*	BAMM	D+T*	BAMM
% patients with elevated LDH	34	47		
CR (%)	19	41	8[a]	25
BORR (%)	68	85	50-57[a]	88
Median PFS, Mo.	11.1	11.9	5.5	8
1year PFS (%)	45	41	22	31
Median OS, Mo.**	25.9	28	13	25
1 yr OS (%)	79	77	50	75
2 yr OS (%)	52	60	27	60
3 yr OS (%)	44	50	22	38
4 yr OS (%)	37	45	17	38
5 yr OS (%)	34	35	16	38

*All data except (a) for D+T is from Robert et al. N Engl J Med 2019; 381:626-636
DOI: 10.1056/NEJMoa1904059 5 year outcomes of dabrafenib and trametinib in melanoma

**BAMM median F/U for OS 38 months; a- from Schadendorf Eur. J Cancer 2017 Three-year pooled analysis of factors associated with clinical outcomes across dabrafenib and trametinib combination therapy phase 3 randomized trial

1.2 Importance

The treatment regimen of D + T + HCQ appears tolerable and warrants further study in poor-prognosis subsets of BRAF mutant melanoma patients. However all of the data supporting these conclusions comes from a single phase II study conducted at 4 institutions. It could be that the high response rate could have been due to chance in the BAMM phase II cohort. In order to test the hypothesis that the addition of HCQ to D + T will result in a significantly better outcomes for BRAF mutant melanoma patients with elevated LDH, a randomized clinical trial is needed. There is equipoise between the two arms on this study and therefore a double-blind placebo-controlled trial with no crossover allowed while on study will be conducted.

The addition of HCQ to dabrafenib and trametinib will overcome targeted therapy resistance and significantly increase the rate of 12 month progression-free survival for patients with unresectable stage III or stage IV BRAF mutant melanoma with elevated LDH and previously treated with immunotherapy.

Objectives

2.1 Primary Objective

To determine the rate of one year progression-free survival (PFS) when hydroxychloroquine or /placebo is added to dabrafenib and trametinib in advanced *BRAF*$^{V600E/K}$ melanoma with elevated LDH.

2.2 Secondary Objectives

2.2.1 To compare the PFS of both arms.

2.2.2 To evaluate the best overall response rate by treatment arm.

2.2.3 To evaluate the complete response (CR) rate by treatment arm.

2.2.4 To evaluate the adverse event rate by treatment arm.

2.2.5 To evaluate overall survival (OS) by treatment arm.

Selection of Patients

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

ECOG-ACRIN Patient No. _____

Patient's Initials (L, F, M) _____

Physician Signature and Date _____

NOTE: CTEP Policy does not allow for the issuance of waivers to any protocol specified criteria (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm). Therefore, all eligibility criteria listed in Section 0 must be met, without exception. The registration of individuals who do not meet all criteria listed in Section 0 can result in the participant being censored from the analysis of the study, and the citation of a major protocol violation during an audit. All questions regarding clarification of eligibility criteria must be directed to the Group's Executive Officer (EA.ExecOfficer@jimmy.harvard.edu) or the Group's Regulatory Officer (EA.RegOfficer@jimmy.harvard.edu).

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to randomization by the treating physician.

3.1 Eligibility Criteria

_____ 3.1.1 Patient must be ≥ 18 years of age.

_____ 3.1.2 Patient must have locally advanced unresectable stage IIIC to stage IV melanoma.

_____ 3.1.3 Patient must have $BRAF^{V600E}$ or $BRAF^{V600K}$ tumor genotype based on a CLIA approved assay.

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_____ 3.1.4 Patient must have serum LDH > Upper limit of normal per institution standards.

_____ 3.1.5 Patient must have measurable disease by RECIST 1.1. Baseline measurements of sites of disease must be obtained within 3 weeks prior to study randomization.

_____ 3.1.6 Patient must have been treated with prior immune checkpoint inhibitor therapy (anti PD-1 antibody, anti-CTLA-4 antibody or a combination regimen including either or both agents) either in the adjuvant or metastatic setting. Patient may have received investigational agents in combination with standard therapy, as long as it was adhering to the timeframes outlined below in 3.1.6.3.

_____ 3.1.6.1 Patient must have discontinued active immunotherapy (IL-2, interferon, anti-CTLA-4 antibody, anti-PD-1 antibody

etc.) or chemotherapy at least 4 weeks prior to randomization.

_____ 3.1.6.2 Patient must have discontinued any oral targeted therapy at least 2 weeks prior to randomization.

_____ 3.1.6.3 Patients must not receive any other investigational anticancer therapy during the period on study or the 4 weeks prior to randomization.

_____ 3.1.7 Patient may have been treated with prior adjuvant therapy including combined BRAF and MEK inhibitor therapy. Patients will be eligible if they tolerated this therapy and did not discontinue the therapy due to toxicity AND ≥ 6 months have elapsed since the end of adjuvant BRAF and MEK inhibition. If patients received BRAF and MEK inhibitor therapy in the metastastic setting, they are not eligible.

_____ 3.1.8 Patient may have been treated with prior chemotherapy or radiation therapy.

_____ 3.1.9 Patients who are known to be experiencing an objective partial response to immunotherapy at the time of study enrollment are not eligible.

_____ 3.1.10 Patient must have an ECOG performance status of 0 or 1.

_____ 3.1.11 Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.

_____ 3.1.12 Women must not be pregnant or breast-feeding due to the potential harm to an unborn fetus and possible risk for adverse events in nursing infants with the treatment regimens being used.

All females of childbearing potential must have a blood test or urine study within 14 days prior to randomization to rule out pregnancy.

A female of childbearing potential is defined as any woman, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy; or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Female of child bearing potential? _____ (Yes or No)

Date of blood test or urine study: _____

_____ 3.1.13 Women of childbearing potential and sexually active males must not expect to conceive or father children by using accepted and effective method(s) of contraception or abstaining from sexual intercourse for the duration of their participation in the study and for 4 months after the last dose of protocol treatment.

_____ 3.1.14 Patient must have recovered from clinically significant reversible toxicities from previous treatment prior to randomization. Abnormal

laboratory values may be grade 1, as long as they meet the eligibility criteria outlined in Section 3.1.26.

_____ 3.1.15 Patient must not have a history of interstitial lung disease (ILD) or chronic pneumonitis.

NOTE: If there is radiographic evidence of ILD that is clinically insignificant and asymptomatic, the patient would be eligible.

_____ 3.1.16 Patient must not have porphyria or psoriasis due to risk of disease exacerbation unless the disease is well controlled and they are under the care of a specialist for the disorder who agrees to monitor the patient for exacerbations.

_____ 3.1.17 Patient must not have a previously documented retinal vein occlusion.

_____ 3.1.18 Patient must not have a history or evidence of increased cardiovascular risk including:

_____ 3.1.18.1 Left ventricular ejection fraction (LVEF) < institutional lower limit of normal measured within 14 days prior to randomization.

_____ 3.1.18.2 A QT interval corrected for heart rate using the Bazett‘s formula ≥ 480 msec;

_____ 3.1.18.3 Current clinically significant uncontrolled arrhythmias. Exception: Patients with controlled atrial fibrillation for >30 days prior to randomization are eligible.

_____ 3.1.18.4 Acute coronary syndromes (including myocardial infarction and unstable angina), coronary angioplasty, or stenting within 6 months prior to randomization.

_____ 3.1.18.5 Abnormal cardiac valve morphology (≥ grade 2) documented by echocardiogram unless a cardiologist concludes the valve abnormality is not clinically significant. Patients with grade 1 abnormalities (i.e., mild regurgitation/stenosis) are eligible.

_____ 3.1.18.6 Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible for this trial, patients should be class 2B or better.

_____ 3.1.19 Patient must be able to swallow and retain oral medication and must not have any clinically significant gastrointestinal abnormalities that may alter absorption such as malabsorption syndrome or major resection of the stomach or bowels.

_____ 3.1.20 Patient with known serious concurrent infection or medical illness, including psychiatric disorders, which would jeopardize the ability of the patient to receive the treatment outlined in this protocol with reasonable safety are not eligible.

_____ 3.1.21 Patient must not be receiving concurrent therapy for their tumor (i.e. chemotherapeutics or investigational agents). Radiotherapy delivered to palliate pain is allowed as long as it is not targeting a lesion that meets RECIST criteria for progression. Radiation therapy to the surgical bed with gamma knife radiotherapy while on treatment during the first cycle is allowed for small volume surgically resected brain metastases. Gamma knife radiotherapy for known active, asymptomatic small volume CNS lesions may be performed during the first cycle while on study. Radiotherapy for new CNS lesions identified beyond the first cycle is not allowed on study.

_____ 3.1.22 Patient must not have a known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to study drug, or excipients or to dimethyl sulfoxide (DMSO).

_____ 3.1.23 Patient must not have received cytochrome P450 enzyme –inducing anticonvulsant drugs (EIADs) (i.e. phenytoin, carbamazepine, Phenobarbital, primidone or oxcarbazepine) within 4 weeks prior to randomization.

_____ 3.1.24 Patient must not have a current use of a prohibited medication as described in Section 5.5 on Potential for Drug-Drug Interaction.

_____ 3.1.25 Patient must have the ability to understand and the willingness to sign a written informed consent document. Patients with impaired decision-making capacity (IDMC) who have a legally authorized representative (LAR) or caregiver and/or family member available will also be considered eligible.

_____ 3.1.26 Patient must have adequate organ and marrow function as defined below (these labs must be obtained ≤ 14 days prior to protocol randomization):

_____ Absolute neutrophil count ≥ 1,500/mcL

ANC:_____ Date of Test:_____

_____ Platelets ≥ 100,000/mcL

Platelet:_____ Date of Test:_____

_____ Total Bilirubin ≤ institutional upper limit of normal (ULN)

Total Bilirubin:_____ Institutional ULN:_____

Date of Test:_____

_____ AST(SGOT)/ALT(SGPT) ≤ 3.0 × Institutional ULN

ALT:_____ Institutional ULN:_____

Date of Test:_____

AST:_____ Institutional ULN:_____ ___

_____ Creatinine ≤ 1.5 x institutional ULN

Creatinine _____ Institutional ULN:_____

Date of Test:_____

_____ 3.1.27 Human immunodeficiency virus (HIV)-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.

_____ 3.1.28 For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.

_____ 3.1.29 Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.

_____ 3.1.30 Patient with asymptomatic new or progressive brain metastases (active brain metastases) are eligible if the treating physician determines that CNS specific treatment is not required.

NOTE: Patient with treated brain metastases are eligible. No brain imaging is required, however, 1 week must elapse after gamma knife therapy. Patient treated with whole brain radiation that have been stable for 2 months are eligible. Patient are excluded if they have leptomeningeal disease or metastases causing spinal cord compression that are symptomatic or untreated or not stable (documented by imaging) for at least 3 months or requiring corticosteroids. Patients on a stable dose of corticosteroids for at least 1 month or who have been off of corticosteroids for at least 1 week are eligible.

_____ _____

Physician Signature Date

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.

Registration Procedures

Cancer Therapy Evaluation Program Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, Rave, or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five person registration types.

- IVR - MD, DO, or international equivalent;
- NPIVR - advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP - clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System (RUMS), OPEN, Rave; acting as a primary site contact, or with consenting privileges;
- Associate (A) - other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) - individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✔	✔			
Financial Disclosure Form	✔	✔	✔		
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔		
GCP training	✔	✔	✔		
Agent Shipment Form (if applicable)	✔				
CV (optional)	✔	✔	✔		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval

In addition, all investigators act as the Site-Protocol PI, consenting/treating/drug shipment, or as the CI on the DTL must be rostered at the enrolling site with a

participating organization (i.e., Alliance). Additional information can be found on the CTEP website at <https://ctep.cancer.gov/investigatorResources/default.htm>. For questions, please contact the RCR ***Help Desk*** by email at <RCRHelpDesk@nih.gov>.

Cancer Trials Support Unit Registration Procedures

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

IRB Approval:

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by emailing the email address above or calling 1-888-651-CTSU (2878).

Sites using their local IRB or REB, must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation;
- IRB-signed CTSU IRB Certification Form; and/or
- Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria to complete processing of the IRB/REB approval record:

- Holds an Active CTEP status;
- Rostered at the site on the IRB/REB approval (*applies to US and Canadian sites only*) and on at least one participating roster;
- If using NCI CIRB, rostered on the NCI CIRB Signatory record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;

- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); and
- Compliance with all protocol-specific requirements (PSRs).

Protocol Specific Requirements for EA6191 Site Registration

Downloading Site Registration Documents:

- Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a PO on the protocol.
- Log on to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
  - Enter the protocol # in the search field at the top of the protocol tree, or
  - Click on the By Lead Organization folder to expand then select ECOG-ACRIN, and protocol number EA6191;
- Click on Documents, select *Site Registration,* and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load automatically to the CTSU as described above.)

Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU website.

To access the Regulatory Submission Portal log in to the CTSU members' website, go to the Regulatory section and select Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

Checking Your Site's Registration Status:

You can verify your site registration status on the members' section of the CTSU website.

- Log on to the CTSU members' website;
- Click on *Regulatory* at the top of your screen;
- Click on *Site Registration;*
- Enter your 5-character CTEP Institution Code and click on Go

NOTE: The status shown only reflects compliance with site registration requirements as outlined above. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

Patient Enrollment

Patients must not start protocol treatment prior to randomization.

Treatment should start within 7-10 working days after randomization.

Randomization

Please note that no blinded starter supplies will be available for this study. At the time of patient randomization each patient will be assigned a specific blinded drug ID number (e.g. DR117). This blinded drug ID number should be included on the drug request form that is submitted to the ECOG-ACRIN Drug Team. (See Section 0 for complete details.)

NOTE: When a patient has been successfully randomized, the confirmation of randomization will indicate that the patient is on Arm X. The patient will actually be randomized to Arm A or B, but as this is a double-blind trial, that information cannot be displayed.

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the Lead Protocol Organization (LPOs) registration/randomization systems or Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Be on a LPO roster, ETCTN Corresponding roster, or PO roster with the role of Registrar. Registrars must hold a minimum of an AP registration type;
- Have an approved site registration for a protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

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

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

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

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

4.1 Patient Registration

The following information is to be provided at the time of registration to the trial:

4.1.1 Protocol Number

4.1.2 Investigator Identification

- Institution and affiliate name
- Investigator's name

4.1.3 Patient Identification

- Patient's initials (first and last)
- Patient's Hospital ID and/or Social Security number
- Patient demographics
  - Gender
  - Birth date (mm/yyyy)
  - Race
  - Ethnicity
  - Nine-digit ZIP code
  - Method of payment
  - Country of residence

4.1.4 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.1.

4.2 Additional Requirements

4.2.1 Patients must provide a signed and dated, written informed consent form.

NOTE: Copies of the consent are not collected by the ECOG-ACRIN Operations Office – Boston.

4.2.2 Specimens are to be submitted for future undefined research studies as outlined in Section 0.

4.3 Medidata Rave

Medidata Rave is a clinical data management system being used for data collection in this clinical trial. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

- A valid CTEP-IAM account; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as an Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only role must have at a minimum an Associates (A) registration type.

Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent

a study invitation e-mail from iMedidata. To accept the invitation, site staff must log in to the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM username and password, and click on the *accept* link in the upper right-corner of the iMedidata page. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the *Rave EDC* link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will display under the study name.

Site staff that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Rave section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

4.4 Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, and DQP Delinquent Forms modules.

NOTE: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization (LPO) for delinquent form details and reports to be available on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendaring functionality

4.5 Emergency Unblinding

The information provided below is for the use by a physician, nurse, CRA or pharmacist treating the patient. These contact numbers should not be used by patients. Patients should be instructed to call their doctor's office

in the event of an emergency or adverse event that may result in the need to unblind the patient.

In the event of an emergency or severe adverse reaction necessitating identification of the medication for the welfare of the patient, please contact the EA Drug Team at DrugOrder@ecog-acrin.org during business hours (9am-4pm M-F Eastern Time) or AnswerConnect at 1-866-296-8940 outside of those hours. The request will require the protocol number (i.e., EA6191), the patient ID number (5-digit number), patient initials, patient step, your contact information, as well as the reason for unblinding. ECOG-ACRIN staff may contact you for further details in order to determine the validity of the request, and will work to obtain the required approvals to unblind the patient. Once approved, a staff member will provide the unblinded treatment identity. Note that if a patient is unblinded, they must discontinue protocol treatment.

4.6 Instructions for Patients who Do Not Start Assigned Protocol Treatment

If a patient does not receive any assigned protocol treatment, baseline and follow-up data will still be collected and must be submitted through Medidata Rave according to the schedule in the EA6191 Forms Completion Guidelines.

Treatment Plan

5.1 Administration Schedule

NOTE: When a patient has been successfully randomized, the confirmation of registration will indicate that the patient is on Arm X. The patient will actually be randomized to Arm A or B, however, as this is a double-blinded trial, that information cannot be displayed.

NOTE: Dabrafenib, trametinib and hydroxychloroquine/placebo are all oral medications, requiring the patient to keep a study diary documenting their doses. The diary must be submitted at each clinic visit. See Appendix III.

One cycle = 28 days.

5.1.1 Arm A

- Dabrafenib 150 mg by mouth (PO) twice daily (BID)
- Trametinib 2 mg by mouth (PO) once daily (QD)
- Hydroxychloroquine (HCQ) 3 pills by mouth (PO) twice daily (BID)

5.1.2 Arm B

- Dabrafenib 150 mg by mouth (PO) twice daily (BID)
- Trametinib 2 mg by mouth (PO) once daily (QD)
- Placebo 3 pills by mouth (PO) twice daily (BID)

5.1.3 Dabrafenib and Trametinib administration

The starting dose for dabrafenib is 150 mg BID. Capsules of dabrafenib are available in 50 mg and 75 mg strength doses. Dabrafenib will be administered twice daily approximately twelve hours apart on an empty stomach – either one (1) hour before meals or two (2) hours after. Patients will be instructed to swallow the whole capsules in rapid succession without chewing. If a dose is missed, it should not be taken if it is less than 6 hours until the next dose.

The starting dose of trametinib is 2 mg daily. Tablets of trametinib are available in 0.5 mg and 2 mg strength. Trametinib will be administered once daily on an empty stomach – either one (1) hour before meals or two (2) hours after. Patients will be instructed to swallow the whole tablet without chewing. If a dose of trametinib is missed, the dose can be taken if it is more than 12 hours until the next scheduled dose.

5.1.4 Hydroxychloroquine or placebo administration

The starting dose of HCQ/placebo is 600 mg BID. The HCQ/placebo tablets are available in 200 mg strength, therefore patients taking 3 tablets BID will be receiving a starting dose of 600 mg. HCQ/Placebo pills should be taken in the morning and evening (12 hours apart) with or without food. The HCQ/placebo dosing schedule may be adjusted as needed in order to minimize gastrointestinal side effects (see dose modification Section 5.4).

5.1.5 Duration of treatment

Dabrafenib and trametinib may be continued indefinitely until progression of disease. Due to the risk of retinal toxicity HCQ/placebo will be administrated for a maximum of 2 years unless there is sufficient evidence from a comprehensive retinal exam that there are no early signs of retinal toxicity and the treating ophthalmologist provides a written plan of monitoring more frequently than yearly for treatment beyond 2 years.

5.1.6 Concomitant Medication and Procedures

Because HCQ has known effects on P450 enzymes, patients requiring anti-convulsants may be treated with any of the non-enzyme inducing anti-convulsants which include: felbamate, valproic acid, gabapentin, lamotrigine, tiagibine, topiramate, or levetiracetam. The exception is zonisamide which should be avoided, as zonisamide accumulates in red blood cells as does HCQ. For nausea, aprepitant should be avoided. Radiation therapy to the surgical bed with gamma knife radiotherapy while on treatment during the first cycle is allowed for small volume surgically resected brain metastases. Gamma knife radiotherapy for known active, asymptomatic small volume CNS lesions may be performed during the first cycle while on study. If radiotherapy is being delivered while the patient is on study, patients should hold all three study medications for 2 days prior to radiation and resume study medication one day after completion of radiation. Radiotherapy for new CNS lesions identified beyond the first cycle is not allowed on study. All other concomitant medications are permitted.

5.2 Adverse Event Reporting Requirements

All toxicity grades described throughout this protocol and all reportable adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

5.2.1 Purpose

Adverse event (AE) data collection and reporting, which are a required part of every clinical trial, are done so investigators and regulatory agencies can detect and analyze adverse events and risk situations to ensure the safety of the patients enrolled, as well as those who will enroll in future studies using similar agents.

5.2.2 Routine Reporting of Adverse Events (Medidata Rave)

Adverse events are reported in a routine manner at scheduled times during a trial using the Medidata Rave clinical data management system. Please refer to Section 0 of the protocol for more information on how to access the Medidata Rave system and the EA6191 forms packet for instructions on where, when and what adverse events are to be reported routinely on this protocol.

5.2.3 Expedited Reporting of Adverse Events (CTEP-AERS)

In addition to routine reporting, certain adverse events must be also reported in an expedited manner for timelier monitoring of patient safety and care. The remainder of this section provides information and instructions regarding expedited adverse event reporting

5.2.4 Terminology

- **Adverse Event (AE):** Any untoward medical occurrence associated with the use of an agent in humans, whether or not considered agent related. Therefore, an AE can be **ANY** unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- **Attribution:** An assessment of the relationship between the adverse event and the protocol treatment, using the following categories.

ATTRIBUTION	DESCRIPTION
Unrelated	The AE is *clearly NOT related* to treatment.
Unlikely	The AE is *doubtfully related* to treatment.
Possible	The AE *may be related* to treatment.
Probable	The AE is *likely related* to treatment.
Definite	The AE is *clearly related* to treatment.

- **CAEPR (Comprehensive Adverse Events and Potential Risks List):** An NCI generated list of reported and/or potential AEs associated with an agent currently under an NCI IND. Information contained in the CAEPR is compiled from the Investigator's Brochure, the Package Insert, as well as company safety reports.
- **CTCAE:** The NCI Common Terminology Criteria for Adverse Events provides a descriptive terminology that is to be utilized for AE reporting. A grade (severity) is provided for each AE term.
- **Expectedness:** Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes, when either the type of event or the severity of the event is NOT listed in the protocol or drug package insert.

5.2.5 Expedited Adverse Event Reporting Procedure

Adverse events requiring expedited reporting will use CTEP's Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov.

A CTEP-AERS report must be submitted electronically via the CTEP-AERS Web-based application located at http://ctep.cancer.gov., so that ECOG-ACRIN and all appropriate regulatory agencies will be notified of the event in an expeditious manner.

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made by telephone to

- the AE Team at ECOG-ACRIN (857-504-2900)
- the FDA (1-800-FDA-1088)

An electronic report MUST be submitted via CTEP-AERS immediately upon re-establishment of internet connection.

Supporting and follow up data: Any supporting or follow up documentation must be uploaded to the Supplemental Data Folder in Medidata Rave within 48-72 hours. In addition, supporting or follow up documentation must be faxed to FDA (800-332-0178) in the same timeframe.

CTEP Technical Help Desk: For any technical questions or system problems regarding the use of the CTEP-AERS application, please contact the NCI Technical Help Desk at ncictephelp@ctep.nci.nih.gov or by phone at 1-888-283-7457.

Many factors determine the requirements for expedited reporting of adverse events on each individual protocol. The instructions and tables in the following sections have been customized for protocol EA6191and outline the specific expedited adverse event reporting requirements for study EA6191.

5.2.6 Rave-CTEP-AERS integration

The Rave Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) Integration enables evaluation of post-baseline Adverse Events (AE) entered in Rave to determine whether they require expedited reporting and facilitates entry in CTEP-AERS for those AEs requiring expedited reporting.

All AEs that occur after baseline are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment or reporting period and used to collect AEs that start during the period or persist from the previous reporting period. CRA will enter AEs that occur prior to the start of treatment on a baseline form that is not included in the Rave-CTEP-AERS integration. AEs that occur prior to enrollment must begin and end on the baseline Adverse Events form and should not be included on the standard Adverse Events form that is available at treatment unless there has been an increase in grade.

Prior to sending AEs through the rules evaluation process, site staff should verify the following on the Adverse Event form in Rave:

- The reporting period (course/cycle) is correct; and
- AEs are recorded and complete (no missing fields) and the form is query free.

The CRA reports AEs in Rave at the time the Investigator learns of the event. If the CRA modifies an AE, it must be re-submitted for rules evaluation.

Upon completion of AE entry in Medidata Rave, the CRA submits the AE for rules evaluation by completing the Expedited Reporting Evaluation form. Both NCI and protocol-specific reporting rules

evaluate the AEs submitted for expedited reporting. A report is initiated in CTEP-AERS using information entered in Medidata Rave for AEs that meet reporting requirements. The CRA completes the report by accessing CTEP-AERS via a direct link on the Medidata Rave Expedited Reporting Evaluation form.

In the rare occurrence that 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 that was phoned in must be entered immediately into CTEP-AERS using the direct link from Medidata Rave.

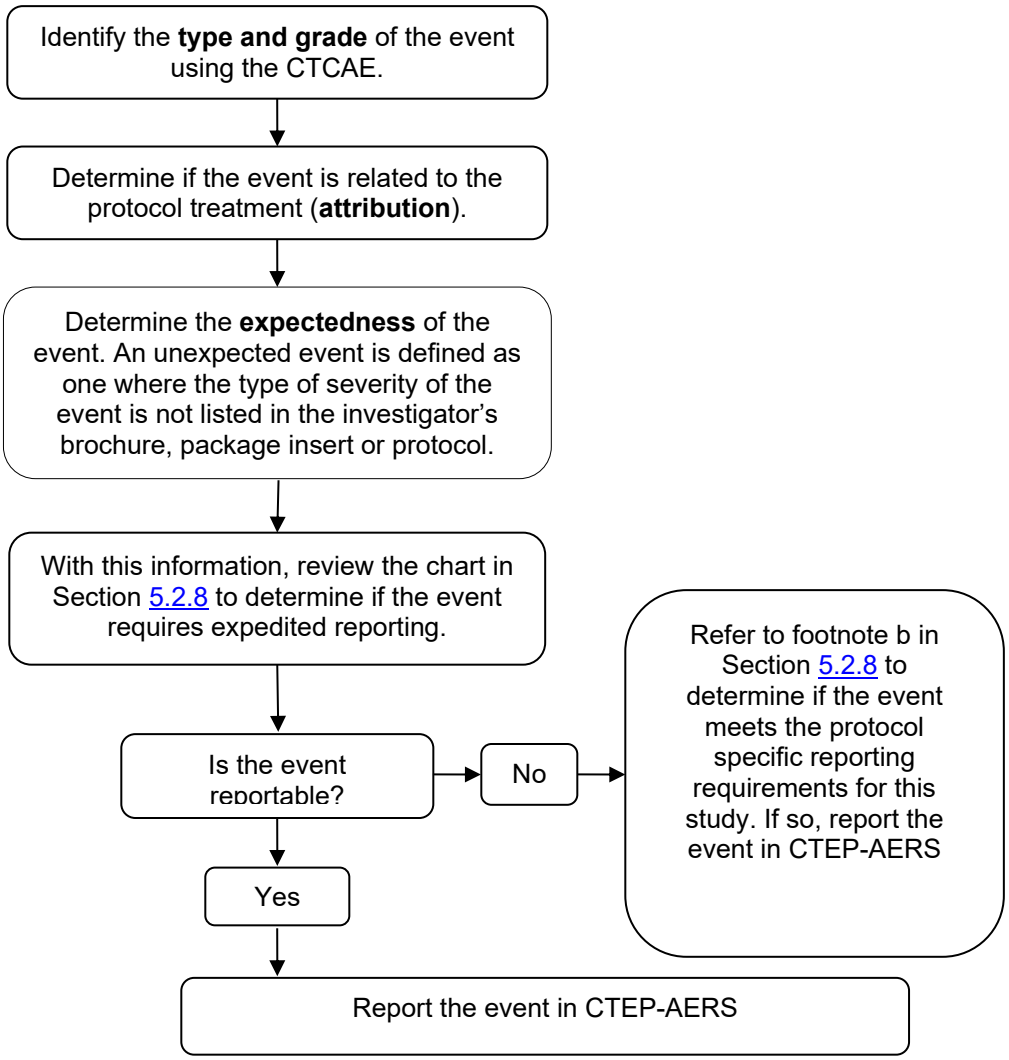
Additional information about the CTEP-AERS integration is available on the CTSU website:

- Study specific documents: Protocols > Documents > Education and Promotion; and
- Expedited Safety Reporting Rules Evaluation user guide: Resources > CTSU Operations Information > User Guides & Help Topics.

NCI requirements for SAE reporting are available on the CTEP website:

- NCI Guidelines for Investigators: Adverse Event Reporting Requirements is available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

5.2.7 Steps to determine if an event is to be reported in an expedited manner



5.2.8 Expedited Reporting Requirements for Arm X (Arm A and Arm B) on protocol EA6191

Commercial/IND Exempt Agents: Dabrafenib, Trametinib, and Hydroxychloroquine (HCQ)/Placebo

Expedited reporting requirements for adverse events experienced by patients on arm(s) with commercial/IND exempt agents only

Attribution	**Grade 4[c]**		**Grade 5[ac]**		**ECOG-ACRIN and Protocol-Specific Requirements**
	Unexpected	Expected	Unexpected	Expected	
Unrelated or Unlikely			7 calendar days	7 calendar days	See footnote (b) for special requirements.
Possible, Probable, Definite	7 calendar days		7 calendar days	7 calendar days	

7 Calendar Days: Indicates a full CTEP-AERS report is to be submitted within 7 calendar days of learning of the event.

a A death occurring while on study or within 30 days of the last dose of treatment requires both routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

NOTE: A death due to progressive disease should be reported as a Grade 5 "*Disease progression*" under the System Organ Class (SOC) "*General disorder and administration site conditions*". 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.

NOTE: Any death that occurs > 30 days after the last dose of treatment and is attributed possibly, probably, or definitely to the treatment must be reported within 7 calendar days of learning of the event.

b Protocol-specific expedited reporting requirements: The adverse events listed below also require expedited reporting for this trial:

Serious Events: Any event following treatment that results in *persistent or significant disabilities/incapacities, congenital anomalies, or birth defects* must be reported in CTEP-AERS accessed via Medidata Rave within 7 calendar days of learning of the event. For instructions on how to specifically report these events, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497. This will need to be discussed on a case-by-case basis.

LVEF Changes: If any of the following circumstances occur, the event(s) must be reported via CTEP-AERS within 7 calendar days

- Asymptomatic: Absolute decrease of >10% in LVEF compared to baseline and ejection fraction below the institution's LLN that does not resolve within 4 weeks (i.e.: defined as LVEF ≥LLN and absolute decrease ≤10% compared to baseline)
- Symptomatic: Grade 3-4 LVEF

Please refer to the dose modification instructions for further information regarding Treatment Modification and Management Guidelines for LVEF Decrease.

Visual Changes: If RPED (retinal pigment epithelial detachments) is suspected or diagnosed or RVO (retinal vein occlusion) is diagnosed, the event(s) must be reported via

CTEP-AERS within 7 calendar days. Please refer to the dose modification instructions for further information regarding Treatment Modification and Management Guidelines for Visual Changes.

Pyrexia: Any occurrence of pyrexia accompanied by hypotension, or dehydration requiring IV fluids, or severe rigors/chills in the absence of an obvious infectious must be reported via CTEP-AERS within 7 calendar days.

Liver Chemistry Changes: If any of the following circumstances occur, the event(s) must be reported via CTEP-AERS within 7 calendar days

- ALT ≥ 3xULN and bilirubin ≥ 2x ULN or > 35% direct bilirubin
- ALT ≥ 3xULN and INR ≥ 1.5, if INR measured (INR threshold does not apply if patient is on anticoagulant)
- ALT > 5xULN
- ALT > 3xULN persistent for > 4 weeks
- ALT > 3xULN associated with symptoms (new or worsening) believe to be related to liver injury of hypersensitivity

Please refer to the dose modification instructions for further information regarding Treatment Modification and Management Guidelines for Liver Chemistry Changes.

c. NOTE: All adverse events meeting the criteria in this table that occurs while the patient is on study treatment and for 30 days after the last dose of protocol treatment must be reported in CTEP-AERs according to the timeframes outlined. Any adverse event meeting the criteria that occurs more than 30 days after the last dose of protocol treatment and is related to Hydroxychloroquine/Placebo must be reported in CTEP-AERS according to the timeframes outlined.

5.2.9 Other recipients of adverse event reports and supplemental data

A drug supporter representative may call a site for additional or supplemental information regarding a serious adverse event. Any additional written AE information requested by the drug supporter MUST be submitted to BOTH ECOG-ACRIN and the drug supporter.

Adverse events determined to require expedited reporting must also be reported by the institution, according to the local policy and procedures, to the Institutional Review Board responsible for oversight of the patient.

5.2.10 Second Primary Cancer Reporting Requirements

All cases of second primary cancers, including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), that occur following treatment on NCI-sponsored trials must be reported to ECOG-ACRIN using Medidata Rave.

- **A <u>second malignancy</u> is a cancer that is UNRELATED to any prior anti-cancer treatment (including the treatment on this protocol). Second malignancies require ONLY routine reporting as follows:**
  1. Complete a Second Primary Form in Medidata Rave within 14 days.
  2. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave confirming the diagnosis.

3. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave.

- **A <u>secondary malignancy</u> is a cancer CAUSED BY any prior anti-cancer treatment (including the treatment on this protocol). Secondary malignancies require both routine and expedited reporting as follows:**
  1. Complete a Second Primary Form in Medidata Rave within 14 days.
  2. Report the diagnosis via CTEP-AERS at http://ctep.cancer.gov.

     Report under a.) leukemia secondary to oncology chemotherapy, b.) myelodysplastic syndrome, or c.) treatment related secondary malignancy
  3. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP confirming the diagnosis.
  4. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP.

NOTE: The ECOG-ACRIN Second Primary Form and the CTEP-AERS report should not be used to report recurrence or development of metastatic disease.

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the ECOG-ACRIN Second Primary Form must be submitted for the most recent trial. ECOG-ACRIN must be provided with a copy of the form and the associated pathology report and cytogenetics report (if available) even if ECOG-ACRIN was not the patient's most recent trial.

NOTE: Once data regarding survival and remission status are no longer required by the protocol, no follow-up data should be submitted in CTEP-AERS or by the ECOG-ACRIN Second Primary Form.

5.3 Comprehensive Adverse Events and Potential Risks lists (CAEPR)

5.3.1 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Dabrafenib NSC763760

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. Frequency is provided based on 1374 patients. Below is the CAEPR for Dabrafenib

Version 2.5, September 30, 2019[1]

Adverse Events with Possible Relationship to Dabrafenib (GSK2118436B) (CTCAE 5.0 Term) [n= 1374]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
	Anemia[2,3]	
EYE DISORDERS		
		Eye disorders - Other (iritis)[4]
		Uveitis[4]
GASTROINTESTINAL DISORDERS		
	Abdominal pain	
		Colitis
		Colonic perforation
	Constipation	
	Diarrhea	
Nausea		
		Pancreatitis
	Vomiting	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
	Chills	
	Edema limbs[5]	
Fatigue		
Fever[6]		
	Flu like symptoms	
IMMUNE SYSTEM DISORDERS		
		Allergic reaction[7]
INFECTIONS AND INFESTATIONS		
	Upper respiratory infection	
INVESTIGATIONS		
	Creatinine increased[3]	
	Neutrophil count decreased[3]	
	Platelet count decreased[3]	
	White blood cell decreased[3]	
METABOLISM AND NUTRITION DISORDERS		
	Anorexia	
	Hyperglycemia[3]	
	Hypokalemia[3]	
	Hyponatremia[3]	

Adverse Events with Possible Relationship to Dabrafenib (GSK2118436B) (CTCAE 5.0 Term) [n= 1374]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
	Hypophosphatemia[3]	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Arthralgia		
	Back pain	
	Myalgia	
	Pain in extremity	
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)		
	Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (squamous cell carcinoma or keratoacanthoma)[8]	
	Skin papilloma	
		Treatment related secondary malignancy (non-SCC)[9]
NERVOUS SYSTEM DISORDERS		
	Dizziness	
Headache		
		Syncope
RENAL AND URINARY DISORDERS		
		Acute kidney injury
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Cough	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Alopecia		
	Dry skin	
	Hair texture abnormal	
	Hyperhidrosis	
Hyperkeratosis		
	Palmar-plantar erythrodysesthesia syndrome	
	Pruritus	
Rash[10]		
		Skin and subcutaneous tissue disorders - Other (drug reaction with eosinophilia and systemic symptoms [DRESS])
		Skin and subcutaneous tissue disorders - Other (neutrophilic panniculitis)[11]
		Stevens-Johnson syndrome
VASCULAR DISORDERS		
	Hypertension	
	Thromboembolic event[12]	
	Vascular disorders - Other (hemorrhage)[13]	

[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] The incidence of anemia is increased when dabrafenib mesylate (GSK2118436B) is used in combination with trametinib dimethyl sulfoxide (GSK1120212B).

[3] The frequencies of these events are based upon laboratory findings rather than being due to patient-reported outcomes.

[4] Dabrafenib mesylate (GSK2118436B) has been associated with ocular toxicities including chorioretinitis, retinitis, iridocyclitis, iritis, and uveitis.

[5] Edema limbs (peripheral edema) is a risk associated when dabrafenib mesylate (GSK2118436B) is used in combination with trametinib dimethyl sulfoxide (GSK1120212B) compared to dabrafenib mesylate (GSK2118436B) alone.

[6] Fever (pyrexia) can be associated with hypotension and/or (in rare cases) syncope. The frequency of fever and serious febrile events is increased when dabrafenib mesylate (GSK2118436B) is used in combination with trametinib dimethyl sulfoxide (GSK1120212B).

[7] Manifestations of allergic reactions (hypersensitivity) to dabrafenib mesylate (GSK2118436B) may include bullous rash (bullous dermatitis).

[8] Squamous cell carcinoma (SCC), including SCC of the skin, SCC in situ (Bowen's disease), and keratoacanthoma have been observed.

[9] New non-SCC malignancies have been reported including primary melanoma, basal cell carcinoma, and non-cutaneous malignancies.

[10] Rash includes the terms: rash, rash acneiform, rash papular, rash maculo-papular, and erythema.

[11] Recurrent neutrophilic panniculitis has been observed in at least one patient treated with dabrafenib mesylate (GSK2118436B) in combination with the MEK inhibitor trametinib dimethyl sulfoxide (GSK1120212B).

[12] Venous thromboembolic events (including deep vein thrombosis and pulmonary embolism) is a risk associated when dabrafenib mesylate (GSK2118436B) is used in combination with trametinib dimethyl sulfoxide (GSK1120212B).

[13] Treatment with dabrafenib mesylate (GSK2118436B) in combination with trametinib dimethyl sulfoxide (GSK1120212B) resulted in an increased incidence and severity of hemorrhagic events compared to patients treated with dabrafenib mesylate (GSK2118436B) as a single agent. Sites of hemorrhage may include, but are not limited to, intracranial, reproductive tract, respiratory tract, and gastrointestinal hemorrhage.

Adverse events reported on Dabrafenib mesylate (GSK2118436B) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Dabrafenib mesylate (GSK2118436B) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (agranulocytosis); Blood and lymphatic system disorders - Other (pancytopenia); Disseminated intravascular coagulation; Febrile neutropenia; Hemolysis; Leukocytosis

CARDIAC DISORDERS - Atrial fibrillation; Atrial flutter; Chest pain - cardiac; Heart failure; Left ventricular systolic dysfunction; Mitral valve disease; Myocardial infarction; Pericardial effusion; Sinus tachycardia

EAR AND LABYRINTH DISORDERS - Ear pain

ENDOCRINE DISORDERS - Hyperthyroidism; Hypothyroidism

EYE DISORDERS - Blurred vision; Eye disorders - Other (amaurosis fugax); Eye disorders - Other (vitreous detachment); Floaters; Photophobia; Retinal detachment; Retinopathy; Vision decreased

GASTROINTESTINAL DISORDERS - Dry mouth; Dyspepsia; Gastritis; Stomach pain

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Death NOS; Disease progression; Gait disturbance; Localized edema; Malaise; Non-cardiac chest pain; Pain

HEPATOBILIARY DISORDERS - Cholecystitis; Hepatic pain

INFECTIONS AND INFESTATIONS - Bacteremia; Bronchial infection; Catheter related infection; Device related infection; Gallbladder infection; Infections and infestations - Other (bacterial peritonitis); Infections and infestations - Other (blood culture positive); Infections and infestations - Other (croup infectious); Infections and infestations - Other (Epstein-Barr virus infection); Infections and infestations - Other (respiratory tract infection); Lung infection; Otitis media; Pharyngitis; Rash pustular; Rhinitis infective; Sepsis; Skin infection; Urinary tract infection; Viremia

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising; Injury, poisoning and procedural complications - Other (complication associated with device); Injury, poisoning and procedural complications - Other (device occlusion); Injury, poisoning and procedural complications - Other (radiation injury, stroke-like migraine attacks after radiation therapy); Seroma

INVESTIGATIONS - Alanine aminotransferase increased; Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; CD4 lymphocytes decreased; Ejection fraction decreased; Electrocardiogram QT corrected interval prolonged; GGT increased; Lipase increased; Lymphocyte count decreased; Weight gain; Weight loss

METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hyperkalemia; Hypernatremia; Hyperuricemia; Hypocalcemia; Hypoglycemia; Hypomagnesemia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Generalized muscle weakness; Muscle cramp; Muscle weakness lower limb; Muscle weakness upper limb; Neck pain

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Leukemia secondary to oncology chemotherapy; Myelodysplastic syndrome; Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (acrochordon); Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (bile duct adenocarcinoma); Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (mycosis fungoides)

NERVOUS SYSTEM DISORDERS - Ataxia; Cognitive disturbance; Depressed level of consciousness; Dysgeusia; Dysphasia; Hydrocephalus; Lethargy; Nervous system disorders - Other (expressive aphasia); Nervous system disorders - Other (intracranial pressure increased); Paresthesia; Seizure; Somnolence; Stroke

PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Depression; Hallucinations; Insomnia

RENAL AND URINARY DISORDERS - Proteinuria; Renal calculi; Urinary frequency; Urinary retention

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Menorrhagia; Prostatic obstruction; Reproductive system and breast disorders - Other (hematospermia)

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Allergic rhinitis; Dyspnea; Hypoxia; Nasal congestion; Oropharyngeal pain; Pleuritic pain; Productive cough; Pulmonary edema; Respiratory failure; Rhinorrhea; Sore throat; Stridor; Voice alteration

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Bullous dermatitis[7]; Eczema; Erythroderma; Photosensitivity; Purpura; Skin and subcutaneous tissue disorders - Other (palmoplantar keratoderma); Skin and subcutaneous tissue disorders - Other (sunburn); Skin hyperpigmentation

VASCULAR DISORDERS - Flushing; Hot flashes; Hypotension

NOTE: Dabrafenib (GSK2118436B) 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.

5.3.2 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. Frequency is provided based on 1111 patients. Below is the CAEPR for Trametinib (GSK1120212B).

Version 2.6, October 10, 2019[1]

Adverse Events with Possible Relationship to Trametinib (GSK1120212B) (CTCAE 5.0 Term) [n= 1111]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
	Anemia	
CARDIAC DISORDERS		
		Heart failure
		Left ventricular systolic dysfunction
	Sinus bradycardia	
EYE DISORDERS		
	Blurred vision	
	Dry eye	
		Eye disorders - Other (chorioretinopathy also known as retinal pigment epithelial detachment)
		Eye disorders - Other (retinal vein occlusion)
	Eye disorders - Other (visual disorders)[2]	
		Papilledema
	Periorbital edema	
GASTROINTESTINAL DISORDERS		
	Abdominal pain	
		Colitis
		Colonic perforation
	Constipation	
Diarrhea		
	Dry mouth	
	Dyspepsia	
	Mucositis oral	
Nausea		
	Vomiting	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
	Chills	

Adverse Events with Possible Relationship to Trametinib (GSK1120212B) (CTCAE 5.0 Term) [n= 1111]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
	Edema face	
Fatigue		
	Fever	
Generalized edema[3]		
IMMUNE SYSTEM DISORDERS		
	Allergic reaction[4]	
INFECTIONS AND INFESTATIONS		
	Folliculitis	
	Lung infection	
	Paronychia	
	Skin infection	
INVESTIGATIONS		
	Alanine aminotransferase increased	
	Alkaline phosphatase increased	
	Aspartate aminotransferase increased	
	CPK increased	
	Ejection fraction decreased	
METABOLISM AND NUTRITION DISORDERS		
	Anorexia	
	Dehydration	
	Hypoalbuminemia	
	Hypomagnesemia	
	Hyponatremia	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Arthralgia	
	Back pain	
	Pain in extremity	
		Rhabdomyolysis
NERVOUS SYSTEM DISORDERS		
	Dizziness	
	Headache	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Cough	
	Dyspnea	
		Pneumonitis
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Alopecia	
	Dry skin	
	Nail changes	
		Palmar-plantar erythrodysesthesia syndrome
	Pruritus	

Adverse Events with Possible Relationship to Trametinib (GSK1120212B) (CTCAE 5.0 Term) [n= 1111]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
		Skin and subcutaneous tissue disorders - Other (drug reaction with eosinophilia and systemic symptoms [DRESS])
Skin and subcutaneous tissue disorders - Other (rash)[5]		
		Stevens-Johnson syndrome[6]
VASCULAR DISORDERS		
	Hypertension	
		Thromboembolic event (venous)
	Vascular disorders - Other (hemorrhage)[7]	

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

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

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

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

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

[6] Stevens-Johnson syndrome has been observed in patients treated with trametinib and dabrafenib combination.

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

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

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Disseminated intravascular coagulation; Febrile neutropenia; Leukocytosis

CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Myocardial infarction; Restrictive cardiomyopathy; Sinus tachycardia

EYE DISORDERS - Corneal ulcer; Eyelid function disorder; Flashing lights; Floaters; Glaucoma; Photophobia

GASTROINTESTINAL DISORDERS - Ascites; Duodenal ulcer; Esophageal necrosis; Esophageal ulcer; Esophagitis; Gastric hemorrhage[7]; Gastric ulcer; Gastritis; Gastrointestinal disorders - Other (intestinal obstruction); Gastrointestinal disorders - Other (pneumatosis intestinalis); Gastrointestinal fistula; Gingival pain; Hemorrhoidal hemorrhage[7]; Ileus; Obstruction gastric; Pancreatitis; Small intestinal obstruction

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Flu like symptoms; General disorders and administration site conditions - Other (axillary pain); Localized edema; Malaise; Non-cardiac chest pain; Pain

HEPATOBILIARY DISORDERS - Cholecystitis; Hepatic failure; Hepatic pain; Hepatobiliary disorders - Other (hepatic encephalopathy)

INFECTIONS AND INFESTATIONS - Biliary tract infection; Catheter related infection; Device related infection; Endocarditis infective; Enterocolitis infectious; Hepatitis viral; Infections and infestations - Other (abscess limb); Infections and infestations - Other (necrotizing fasciitis); Infections and infestations - Other (oral infection); Pharyngitis; Sepsis; Upper respiratory infection; Urinary tract infection

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising

INVESTIGATIONS - Blood bilirubin increased; Blood lactate dehydrogenase increased; Creatinine increased; Electrocardiogram QT corrected interval prolonged; GGT increased; Lipase increased; Lymphocyte count decreased; Platelet count decreased; Serum amylase increased; White blood cell decreased

METABOLISM AND NUTRITION DISORDERS - Hyperglycemia; Hyperkalemia; Hyperphosphatemia; Hyperuricemia; Hypocalcemia; Hypoglycemia; Hypokalemia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Generalized muscle weakness; Muscle cramp; Musculoskeletal and connective tissue disorder - Other (compression fracture); Myalgia; Neck pain

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor hemorrhage[7]; Tumor pain

NERVOUS SYSTEM DISORDERS - Dysgeusia; Encephalopathy; Intracranial hemorrhage[7]; Lethargy; Nervous system disorders - Other (diplopia); Seizure; Somnolence; Stroke; Syncope; Transient ischemic attacks

PSYCHIATRIC DISORDERS - Anxiety; Confusion; Delirium; Depression; Hallucinations; Insomnia; Personality change

RENAL AND URINARY DISORDERS - Acute kidney injury; Cystitis noninfective; Dysuria; Hematuria; Proteinuria; Urinary incontinence

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Vaginal fistula; Vaginal hemorrhage[7]

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage[7]; Hypoxia; Laryngeal edema; Oropharyngeal pain; Pleural effusion; Pneumothorax; Productive cough; Pulmonary hypertension; Respiratory failure; Sinus disorder

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Bullous dermatitis; Photosensitivity; Purpura; Skin and subcutaneous tissue disorders - Other (erythema nodosum); Skin ulceration; Urticaria

VASCULAR DISORDERS - Hematoma; Hot flashes; Hypotension

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

5.4 Dose Modifications

5.4.1 General Instructions

5.4.1.1 Dabrafenib/Trametinib Dose Reduction Procedures

- If treatment related toxicities occur when dabrafenib and trametinib are used in combination, then both

agents should be simultaneously dose reduced, interrupted or discontinued with the exception of the following:

- Dose modifications are required for dabrafenib only (and not trametinib) for these events: pyrexia and, RAS mutation positive non-cutaneous malignancies
- Dose modifications are required for trametinib only (and not dabrafenib) for these events: left ventricular rejection fraction (LVEF) reduction, retinal vein occlusion (RVO) retinal pigment epithelial detachment (RPED) and interstitial lung disease (ILD)/pneumonitis (primarily related to trametinib).

NOTE: Dose modifications are not recommended for adverse reactions of cutaneous squamous cell carcinoma (cuSCC) or new primary melanoma.

5.4.1.2 Dose Level Reduction Tables

Table 1: Dabrafenib Dose Level Reductions

Dose Level	Dose/Schedule
Starting Dose	150 mg twice daily
First Reduction	100 mg twice daily
Second Reduction	75 mg twice daily
Third Reduction	50 mg twice daily
If unable to tolerate 50 mg twice daily	Discontinue dabrafenib

Trametinib Dose Reductions

Table 2: Trametinib Dose Reductions

Dose Level	Dose/Schedule
Starting Dose	2 mg twice daily
First Reduction	1.5 mg twice daily
Second Reduction	1.0 mg twice daily
Third Reduction	0.5 mg twice daily
If unable to tolerate 0.5 mg once daily	Discontinue trametinib

Hydroxychloroquine/Placebo Dose Reductions

Table 3: HCQ/placebo Dose Reductions

Dose Level	Dose/Schedule
Starting Dose	600 mg twice daily
First Reduction	600 mg once daily in the morning and

Dose Level	Dose/Schedule
	400 mg once daily in the evening
Second Reduction	400 mg twice daily
Third Reduction	A third dose reduction to 400 mg once a day (qd) may be pursued in patients deemed to be deriving clinical benefit at the discretion of the treating physician.

For any AE with a grade ≥ 3, HCQ/placebo dose will be held until the toxicity resolves to ≤ grade 1 before restarting, after which HCQ/placebo may be restarted at a reduced dose as described in table 3.

5.4.1.3 Dose reductions for toxicities that overlap between D+T and HCQ/placebo

Some toxicities overlap between dabrafenib, trametinib and HCQ/placebo making it difficult to accurately assign association. In these cases table 3 in conjunction with table 4 should be used to dose reduce in the appropriate fashion. In general HCQ/placebo dose should be reduced and if this does not reduce the toxicity to < grade 2 or the toxicity returns after being reduced to < grade 2 then dose modifications of both dabrafenib and trametinib will be made together. Non-hematological toxicities having an attribution to trametinib of possible, probable or definite will result in dose modifications as described below.

5.4.1.4 Dose Delays, Missed Doses, and Dose Reescalation

Major Events are grade 3 and 4 hematologic and non-hematologic toxicities that are not treatment related. Treatment should be delayed for major events if HCQ may further complicate the non-treatment related event. If a major event requires a delay of treatment, treatment must be delayed until toxicity is resolved (≤ Grade 2 or ≤ Baseline). Missed doses do not need to be made up but the missed doses should be documented in the diaries. Dose reescalation following resolution to ≤ Grade 1 toxicity is allowed.

5.4.2 General Guidelines for Toxicities and Dose Modifications

Guidelines for specific toxicities are outlined below, but general guidelines for toxicities not listed are provided in Table 5.

Table 4: General Dose modification guidelines for dabrafenib and trametinib for toxicities attributable to only dabrafenib and/or trametinib. These are general guidelines but for specific toxicities dose modification instructions may be different and are provided in the subsequent sections.

CTCAE Grade	Action and Dose Modification
Grade 1	• Continue dabrafenib, trametinib and HCQ/placebo at current dose level • Monitor closely

CTCAE Grade	Action and Dose Modification
	• Provide supportive care according to institutional standards
Grade 2	• Interrupt dabrafenib and trametinib if clinically indicated, continue HCQ/placebo • Monitor closely • Provide supportive care according to institutional standards • When toxicity resolves to Grade 1 or baseline, restart dabrafenib and trametinib treatment at current dose level
Grade 3	• Interrupt dabrafenib and trametinib if clinically indicated, continue HCQ/placebo • Monitor closely • Provide supportive care according to institutional standards • When toxicity resolves to Grade 1 or baseline, restart dabrafenib and trametinib both reduced by one dose level • If the Grade 3 toxicity recurs, interrupt study treatment • When toxicity resolves to Grade 1 or baseline, restart dabrafenib and trametinib both reduced by another dose level
Grade 4	• Interrupt dabrafenib and trametinib, continue HCQ/placebo • Monitor closely • Provide supportive care according to institutional standards • If event resolves to Grade 1 or baseline patient may continue dabrafenib and trametinib both reduced by one dose level • If event does not resolve permanently discontinue study treatment

5.4.3 Guidelines and Dose Modifications for Specific Toxicities

5.4.3.1 Management and Dose Modification Guidelines for Pyrexia

- Pyrexia is defined as a body temperature equal to or above 38.5◦ Celsius or 101.3° Fahrenheit
- Pyrexia is an adverse event associated with dabrafenib and is increased in frequency and severity in patients receiving dabrafenib in combination with trametinib. In a minority of cases, pyrexia was accompanied by symptoms such as severe chills/rigors, dehydration, hypotension, dizziness or weakness and required hospitalization
- Patients should be instructed on the importance of immediately reporting febrile episodes. In the event of a fever, the patient should be instructed to take anti-pyretics (e.g. ibuprofen or acetaminophen/paracetamol) as appropriate to control fever. The use of oral corticosteroids should be considered in those instances in which anti-pyretics are insufficient. Monitor serum creatinine and other evidence of renal function during and following severe events of pyrexia

Table 5: Management and Dose Modification Guidelines of Dabrafenib only for Pyrexia

Management and Dose Modification Guidelines of Dabrafenib only for Pyrexia	
Work up: • Clinical evaluation for infection and hypersensitivity, especially if pyrexia is complicated by rigors, severe chills, dehydration, *etc.* • Laboratory work-up (should include full-blood-count, electrolytes, creatinine, BUN, CRP, liver-function tests, blood and urine culture). ***Management***: • Anti-pyretic treatment should be started immediately at the first occurrence. Anti-pyretic treatment may include acetaminophen (paracetamol), ibuprofen, or suitable anti-pyretic medication per institutional standards. • Oral hydration is encouraged in patients without evidence of dehydration. Intravenous hydration is recommended if pyrexia is complicated by dehydration/hypotension. • In patients experiencing pyrexia complicated by rigors, severe chills, *etc.*, which cannot be controlled with anti-pyretic medication, oral corticosteroids should be started at the 2nd event and doses should be gradually increased for subsequent events. Prophylactic anti-pyretic treatment is recommended after the 2nd event, or after the 1st event if complicated by rigors or severe chills. Prophylactic anti-pyretics may be discontinued after three days in absence of pyrexia. ***Notes*** • Escalation of dabrafenib is allowed if no episode of pyrexia is observed in the 4 weeks subsequent to dose reduction from the dose level you were on before. Pyrexia accompanied by hypotension, or dehydration requiring IV fluids, or severe rigors/chills in the absence of an obvious infectious cause should be reported as an SAE.	
All Events • Clinical evaluation for infection and hypersensitivity • Laboratory work-up • Hydration as required	
Event Management	**Action and Dose Modification**
1st Event • Administer anti-pyretic treatment as clinically indicated and initiate prophylactic treatment if associated with rigors, renal failure, dehydration or hypotension[f]	1st Event • **Interrupt dabrafenib** • Continue trametinib and HCQ/placebo • Once pyrexia resolves to baseline, restart dabrafenib at the same dose level • If fever was associated with rigors, renal failure, dehydration or hypotension, reduce dabrafenib **to** 100 mg BID

2nd Event:
• Within 3 days of onset of pyrexia
  • Optimize anti-pyretic therapy
  • Consider oral corticosteroids (i.e., prednisone 10 mg) for at least 5 days or as clinically indicated[e]
	2nd Event:
	• **Interrupt dabrafenib**
	• Continue trametinib and HCQ/placebo
	• Once pyrexia resolves to baseline, restart dabrafenib at 100 mg BID
	  • If fever was associated with rigors, renal failure, dehydration or hypotension, **reduce dabrafenib** to 75 mg BID

3rd Event:
• Within 3 days of onset of pyrexia
  • Optimize anti-pyretic therapy
	3rd Event:
	• **Interrupt dabrafenib**
	• Continue trametinib and HCQ/ placebo; start prednisone 20 mg PO qday for at least 5 days or as clinically indicated
	• Once pyrexia resolves to baseline, restart dabrafenib **at 75 mg BID; continue prednisone 20 mg PO qday as clinically indicated**
	  • If fever was associated with rigors, renal failure, dehydration or hypotension, reduce dabrafenib to **50** mg BID.

4th Event[f]
• Within 3 days of onset of pyrexia
  • Optimize anti-pyretic therapy
	4th Event:
	• **Interrupt dabrafenib**
	• Continue trametinib and HCQ/ placebo; start prednisone 20 mg PO qday for at least 5 days or as clinically indicated
	  • Once pyrexia resolves to baseline, restart dabrafenib **reduced to 50 mg BID; continue with prednisone 20 mg PO qday as clinically indicated**

5.4.3.2 Management and Dose Modification Guidelines for Rash

Rash is a frequent AE observed in patient receiving trametinib, dabrafenib, or the combination of both agents. HCQ can also cause a rash.

Table 6: Management and Dose Modification Guidelines for Rash

Management and Dose Modification Guidelines for Rash
Supportive care: **Prevention:** • 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) **Symptom management:** • 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 oral antibiotics; if no improvement, consult dermatologist or surgeon • Infected lesions: appropriate bacterial/fungal culture-driven systemic or topical antibiotics **Notes:** • Rash prophylaxis is recommended for the first 6 weeks of study treatment • Subjects who develop rash/skin toxicities should be seen by a qualified physician and should receive evaluation for symptomatic/supportive care management

CTCAE Grade	Adverse Event Management	Action and Dose Modification
Grade 1	• Initiate prophylactic and symptomatic treatment measures • Use moderate strength topical steroid.[2] • Reassess after 2 weeks.	• Continue HCQ/placebo, dabrafenib and trametinib • If rash does not recover to baseline within 2 weeks despite best supportive care, **reduce HCQ/placebo by one dose level**.[2]
Grade 2	• Initiate prophylactic and symptomatic treatment measures. • Use moderate strength topical steroid.[1] • Reassess after 2 weeks.	• **Continue dabrafenib and trametinib at the same dose, but reduce HCQ/placebo by one dose level.** • If rash recovers to ≤ grade 1 within 2 weeks, increase HCQ/placebo dose to previous dose level. • If no recovery to ≤ grade 1 within 2 weeks, interrupt HCQ/placebo until recovery to ≤ grade 1. • **Restart study treatment with HCQ/placebo at reduced dose level.[2]** • If no improvement in rash then reduce darbrafenib and trametinib by one dose level and restart the HCQ/placebo at reduced level.
Grade ≥ 3	• Use moderate strength topical steroids PLUS oral methyl-prednisolone dose pack.[1] • Consult dermatologist.	• Interrupt HCQ/placebo, dabrafenib and trametenib until rash recovers to ≤ grade 1. • **Restart with all three study agents reduced by one dose level** • If no recovery to ≤ grade 2 within 2 weeks, **permanently discontinue study treatment**.

1. Moderate-strength topical steroids: Hydrocortisone 2.5% cream or fluticasone propionate concentration 0.05% cream.
2. Study treatment may be escalated to previous dose level if no rash is evident 4 weeks after restarting study treatment.

5.4.3.3 Management and Dose Modification Guidelines for Renal Insufficiency

Cases of renal insufficiency have occurred in patients receiving dabrafenib and the combination of dabrafenib and trametinib. Prior to start of study treatment, concomitant medications should be reviewed for the potential risk of inducing nephrotoxicity and concomitant medications should be modified if clinically possible.

Table 7: Management and Dose Modification Guidelines for Renal Insufficiency

Serum Creatinine Level	Adverse Event Management	Action and Dose Modification
Serum creatinine increase > 0.2 mg/dL (18 umol/L) but ≤ 0.5 mg/dL (44 umol/L) above baseline	• Recheck serum creatinine within 1 week • Serum creatinine increase > 1 week: contact Study chair. If elevation persists beyond 4 weeks, recommend evaluation (consider renal biopsy) for etiology; consider nephrology consultation.	Continue HCQ/placebo, dabrafenib and trametinib at the same dose level

Serum Creatinine Level	Adverse Event Management	Action and Dose Modification
	• If pyrexia is present, treat pyrexia as per guidelines[a]	

Serum creatinine increase
> 0.5 mg/dL (44 umol/L) above baseline or serum creatinine
> 2 mg/dL
(> 177 umol/L)
	• Monitor serum creatinine ≥ 2-times per week
	• Hospitalization may be necessary if serum creatinine cannot be monitored frequently
	• If pyrexia is present, treat pyrexia per guidelines[a]
	• Consult nephrologist if clinically indicated
	• Perform renal biopsy if clinically indicated, for example:
	  • Renal insufficiency persists despite volume repletion
	  • Patient has new rash or signs of hypersensitivity (such as elevated eosinophil count)
		Interrupt HCQ/placebo, dabrafenib and trametinib
		• until serum creatinine recovers to baseline
		• Restart with HCQ, dabrafenib and trametinib[b]

a. NSAIDs can induce renal insufficiency, especially in patients with dehydration; encourage oral fluids or consider intravenous fluids as clinically indicated. See guidelines for pyrexia Section 5.4.3.1.

b. Investigator may restart at either the same or a reduced dose level of dabrafenib. Escalation of study treatment to previous dose level is allowed if another episode of renal insufficiency does not occur after 4 weeks of dose reduction. Study treatment may not be restarted if there is evidence of thrombotic microangiopathy.

5.4.3.4 Management and Dose Modification Guidelines for Hepatic Insufficiency

Cases of hepatic insufficiency have occurred in patient receiving dabrafenib and the combination of dabrafenib and trametinib. Prior to start of study treatment, concomitant medications should be reviewed for the potential risk of inducing hepatic toxicity and concomitant medications should be modified if clinically possible.

Table 8: Management and Dose Modification Guidelines for Hepatic Toxicity

Criteria –		**Actions**	**Follow Up Assessments**
ALT-absolute	ALT ≥ 5xULN	Immediately discontinue dabrafenib, trametinib and HCQ/placebo Report the event in CTEP-AERS within 7 calendar days. Perform liver event follow up assessments. Monitor the patient until liver chemistries resolve, stabilize, or return to within baseline (see MONITORING below). Do not restart/rechallenge	Viral hepatitis serology Blood sample for pharmacokinetic (PK) analysis, obtained within 48 hours after last dose. Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). Fractionate bilirubin, if total bilirubin≥2xULN Obtain complete blood count with differential to assess
ALT Increase	ALT ≥ 3xULN persists for ≥ 4 weeks		
Bilirubin	ALT ≥ 3xULN and bilirubin ≥ 2xULN (> 35% direct bilirubin)		
INR	ALT ≥ 3xULN and INR>1.5, if INR measured		

***Criteria* –**		**Actions**	**Follow Up Assessments**
Cannot Monitor	ALT ≥ 3xULN and cannot be monitored weekly for 4 weeks	patient with study treatment If restart/rechallenge not allowed per protocol or not granted, permanently discontinue study treatment and may continue patient in the study for any protocol specified follow up assessments. MONITORING: <u>For bilirubin or INR criteria</u>: Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24 hrs. A specialist or hepatology consultation is recommended. Monitor patient twice weekly until liver chemistries resolve, stabilize or return to within baseline. <u>For All other criteria</u>: Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24-72 hrs Monitor patient weekly until liver chemistries resolve, stabilize or return to within baseline	eosinophilia Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form. Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. Record alcohol use on the liver event alcohol intake case report form. <u>For bilirubin or INR criteria</u>: Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in patients with definite or likely acetaminophen use in the preceding week). Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen): quantitative hepatitis B DNA and hepatitis delta antibody. Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy eCRF forms.
Symptomatic	ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity		

5.4.3.5 Management and Dose Modification Guidelines for Pneumonitis

Pneumonitis has been observed in patient receiving trametinib. To reduce the risk of pneumonitis, patient will be monitored closely for symptoms, evaluated with imaging and functional tests.

Table 9: Management and Dose Modification Guidelines for Pneumonitis of Trametinib only

CTCAE Grade	Adverse Event Management	Action and Dose Modification
Grade 1	• CT scan (high-resolution with lung windows) recommended • Clinical evaluation and laboratory work-up for infection • Monitoring of oxygenation via pulse-oximetry recommended • Consultation with pulmonologist recommended	• Continue trametinib at current dose
Grade 2	• CT scan (high-resolution with lung windows) • Clinical evaluation and laboratory work-up for infection • Consult pulmonologist • Pulmonary function tests -if < normal, repeat every 8 weeks until ≥ normal • Bronchoscopy with biopsy and/or bronchioaveloar lavage (BAL) recommended • Symptomatic therapy including corticosteroids if clinically indicated	• Interrupt trametinib until recovery to grade ≤1 • Restart treatment with trametinib reduced by one dose level
Grade 3	• CT scan (high-resolution with lung windows) • Clinical evaluation and laboratory work-up for infection • Consult pulmonologist • Pulmonary function tests-if < normal, repeat every 8 weeks until ≥ normal • Bronchoscopy with biopsy and/or BAL if possible • Symptomatic therapy including corticosteroids as clinically indicated	• Interrupt trametinib until recovery to grade ≤1, then restart at reduced dose. • If no recovery to grade ≤1 within 4 weeks, permanently discontinue trametinib
Grade 4	• Same as grade 3	• Permanently discontinue trametinib • Unblinding may be allowed to improve medical care. See Section 4.5

5.4.3.6 Management and Dose Modification Guidelines for Reduced Left ventricular ejection fraction (LVEF)

Decreases in left ventricular ejection fraction have been seen with the use of trametinib with an incidence of 9% with the combination of trametinib and dabrafenib compared to 0% with dabrafenib alone. Therefore, transthoracic echo must be performed at baseline and repeated every 3 months while on study or as clinically indicated. More frequent evaluation is warranted if there are signs or symptoms suggestive of clinical CHF. The same procedure (either ECHO or MUGA, although ECHO

is preferred) should be performed at baseline and at follow-up visit(s).

Table 10: Management and Dose Modification Guidelines of Trametinib for LVEF Decrease

Clinic	LVEF-drop (%) or CTCAE grade	Action and Dose Modification
Asymptomatic	Absolute decrease of > 10% in LVEF compared to baseline and ejection fraction below the institution's LLN	Interrupt trametinib and repeat ECHO within 2 weeks[a,b] If the LVEF **recovers** within 4 weeks (defined as LVEF ≥LLN and absolute decrease ≤10% compared to baseline) then restart at a reduced dose level of trametinib. • Repeat ECHO at 2, 4, 8 and 12 weeks after re-start; continue in intervals of 12 weeks thereafter If LVEF **does not recover** within 4 weeks • Consult with cardiologist • **Permanently discontinue trametinib** • **Report as SAE** • Repeat ECHO after 2, 4, 8, 12, and 16 weeks or until resolution
Symptomatic[b]	Grade 3: resting LVEF 39-20% or >20% absolute reduction from baseline Grade 4: resting LVEF < 20%	**Permanently discontinue trametinib** **Report as SAE** **Interrupt dabrafenib.[c]** **Consult with cardiologist** **Repeat ECHO after 2, 4, 8, 12, and 16 weeks or until resolution** **Grade 4 toxicity will trigger unblinding per Section** 4.5

a. If ECHO does not show LVEF recovery after 2 weeks, repeat ECHO 2 weeks later.

b. Symptoms may include: dyspnea, orthopnea, and other signs and symptoms of pulmonary congestion and edema.

c. Once LVEF recovers, including resolution of symptoms, restart of dabrafenib monotherapy will be at the discretion of the study investigator.

5.4.3.7 Management and Dose Modification Guidelines for QTc prolongation

Both dabrafenib and trametinib have been shown to prolong the QTc interval. However, to date, there are no clinical adverse event reports attributable to QTc interval prolongation or manifest cardiac arrhythmias. However, the following recommendations have been developed to minimize the risk of ventricular tachyarrhythmias in patients with metastatic melanoma treated with this regimen:

- Avoid combination with other drugs with potential to lead to prolongation of QTc interval, if possible.
- ECG should be monitored at baseline, and each cycle (monthly) thereafter.

- Monitor ECG weekly until the QTc interval decreases to < 500 msec, or a cardiologist provides documentation that it is safe to resume therapy before reinstituting therapy at a reduced dose.

Table 11: Management and Dose Modification Guidelines for QTcB-Prolongation

(QT interval on electrocardiogram corrected using the Bazett's formula) QTc-Prolongation [a]	Action and Dose Modification
QTcB ≥501 msec (milliseconds)	Interrupt all three study agents until QTcB prolongation resolves to grade 1 or baseline Test serum potassium, calcium, phosphorus and magnesium. If abnormal correct per routine clinical practice to within normal limits. Review concomitant medication usage for agents that prolong QTc. If event resolves, restart study treatment at current dose level[b] If event does not resolve, discuss with a cardiologist, if deemed clinically significant then discontinue study treatment If event recurs, discuss with a cardiologist, if deemed clinically significant then permanently discontinue study treatments

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

b If the QTc prolongation resolves to grade 1 or baseline, the patient may resume study treatment.

5.4.3.8 Management and Dose Modification Guidelines for Hypertension

For patient experiencing an increase in systolic and/or diastolic blood pressure that is persistent and may be associated with the study treatment, recommendations for the clinical management of hypertension are described in Table 12.

Table 12: Management and Dose Modification Guidelines for Hypertension

Hypertension	Action and Dose Modification
(Scenario A) Asymptomatic and persistent[a] SBP of ≥ 140 and < 160 mmHg, or DBP ≥ 90 and < 100 mmHg, or Clinically significant increase in DBP of 20 mmHg (but DBP still <100 mmHg).	Continue dabrafenib and trametinib and HCQ/placebo at the current dose Adjust current or initiate new antihypertensive medication Titrate antihypertensive medication(s) during the next 2 weeks as indicated to achieve well-controlled[b] BP If BP is not well controlled within 2 weeks, consider referral to a specialist and go to scenario (B).
(Scenario B) Asymptomatic SBP ≥ 160 mmHg, or DBP ≥100 mmHg, or	Interrupt dabrafenib and trametinib if clinically indicated but continue HCQ/placebo Adjust current or initiate new antihypertensive medication(s)

Hypertension	Action and Dose Modification
Failure to achieve well-controlled BP within 2 weeks in Scenario A	Titrate antihypertensive medication(s) during the next 2 weeks to achieve well-controlled BP Once BP is well controlled[b], restart dabrafenib and trametinib **reduced by one dose level[c] and continue HCQ/placebo**
(Scenario C) Symptomatic[d] hypertension or Persistent SBP ≥160 mmHg, or DBP ≥ 100 mmHg, despite antihypertensive medication and dose reduction of study treatment	Interrupt dabrafenib, trametinib and HCQ/placebo treatment Adjust current or initiate new antihypertensive medication(s) Titrate antihypertensive medication during the next 2 weeks to achieve well-controlled BP Referral to a specialist for further evaluation and follow-up is recommended Once BP is well controlled, restart 3 study treatments **reduced by one dose level[c]**
(Scenario D) Refractory hypertension unresponsive to above interventions, or having hypertensive crisis.	**Permanently discontinue study treatment** Continue follow-up per protocol.

a. Hypertension detected in two separate readings during up to three consecutive visits
b. Well-controlled blood pressure defined as SBP ≤140 mm Hg and DBP ≤90 mm Hg in two separate readings during up to three consecutive visits.
c. Escalation of study treatment to previous dose level can be considered if BPs remain well-controlled for 4 weeks after restarting of study treatment.

Symptomatic hypertension defined as hypertension aggravated by symptoms (e.g., headache, light-headedness, vertigo, tinnitus, episodes of fainting) that resolve after the blood pressure is controlled within the normal range.

5.4.3.9 Other dabrafenib-specific adverse events and recommended management

Palmar plantar erythrodysesthesia (PPES) – Measures for PPES should include:

Lifestyle modification: avoidance of hot water, traumatic activity, constrictive footwear, or excessive friction on the skin and the use of thick cotton socks and gloves, and shoes with padded insoles

- Symptomatic treatments: apply moisturizing creams frequently, topical keratolytics (e.g. urea 20-40% cream, salicylic acid 6%, tazarotene 0.1% cream, fluorouracil 5% cream), clobetasol propionate 0.05% ointment for erythematous areas, topical lidocaine 2%, and / or systemic pain medication such as nonsteroidal anti-inflammatory drugs, codeine, and pregabalin for pain.
- Dose modification may also be required.

Pancreatitis – In the event of abdominal pain or suspected pancreatitis, amylase and lipase laboratory samples should be collected for confirmation of the

diagnosis. Patients should be closely monitored when re-starting dabrafenib after an episode of pancreatitis.

Uveitis: Treatment with dabrafenib has been associated with the development of uveitis, including iritis. Monitor patients for visual signs and symptoms (such as, change in vision, photophobia and eye pain) during therapy.

Hyperglycemia: Hyperglycemia requiring an increase in the dose of, or initiation of insulin or oral therapy can occur with dabrafenib. Monitor serum glucose levels as clinically appropriate during treatment with dabrafenib in patient with pre-existing diabetes or hyperglycemia. Advise patients to report symptoms of severe hyperglycemia such as excessive thirst or any increase in the volume or frequency of urination.

Investigators should always err on the side of caution in these settings if treatment-related toxicity is a possibility.

5.4.3.10 Ocular Toxicity

Due to the known ocular toxicities associated with BRAF and MEK inhibitors and the potential for toxicity with HCQ, an ophthalmic exam at baseline and yearly thereafter is required. The standard of care for patients on HCQ is that the ophthalmologist performs visual field 10-2 test, plus one of the three other highly sensitive screening tests: the FAF (fundus autofluorescence imaging), the SD-OCT (spectral domain optical coherence), or the multifocal electroretinogram (mfERG). Episodes of visual changes have been observed in patientreceiving trametinib, dabrafenib, and combination therapy. An ophthalmologist should be consulted if changes in vision develop. However, if the visual changes are clearly unrelated to study treatment (e.g., allergic conjunctivitis), then monitor closely as it may be reasonable to defer ophthalmic examination. Treatment with dabrafenib has been associated with the development of uveitis, including iritis. Monitor patients for visual signs and symptoms (such as, change in vision, photophobia and eye pain) during therapy. 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).

With particular regard to visual field deficits patients should be cautioned to report any visual symptoms, particularly difficulty seeing entire words or faces, intolerance to glare, decreased night vision, or loss of peripheral vision. **These symptoms of retinal toxicity or subclinical evidence of retinal toxicity on eye exams should prompt drug discontinuation and ophthalmologic evaluation.** Patients who discontinue HCQ/placebo permanently may

stay on dabrafenib and/or trametinib at the discretion of the treating physician in consultation with an ophthalmologist.

Guidelines regarding management and dose reduction for visual changes and/or ophthalmic examination findings considered to be related to study treatment are provided in Tables 13, 14, and 15.

Table 13: Management and Dose Modification Guidelines for Visual Changes and/or Ophthalmic Examination Findings

CTCAE Grade[a]	Adverse Event Management	Action and Dose Modification
Grade 1[b]	• Consult ophthalmologist within 7 days of onset	• If dilated fundus examination cannot be performed within 7 days of onset, interrupt trametinib and hydroxychloroquine until RPED, RVO, and visual field deficit can be excluded by retina specialist/ophthalmologist. Dabrafenib may be continued. • If RPED and RVO excluded, continue (or restart) trametinib and HCQ/placebo at same dose level • If RPED suspected or diagnosed: see RPED dose modification table 14 below; **report as SAE if diagnosed**. • If RVO diagnosed: **Permanently discontinue trametinib and report as SAE.**
Grade 2 and Grade 3	• Consult ophthalmologist immediately • Interrupt trametinib and HCQ/placebo. Dabrafenib may be continued.	• If RPED and RVO excluded, restart trametinib and HCQ at same dose level. • If RPED diagnosed, see RPED dose modification table below; **report as SAE**. • If RVO diagnosed: **Permanently discontinue trametinib and report as SAE**
Grade 4	• Consult ophthalmologist immediately • Interrupt trametinib and HCQ/placebo. Dabrafenib may be continued.	• If RPED and RVO excluded, may consider restarting trametinib at same or reduced dose • **If RVO or RPED diagnosed, permanently discontinue trametinib and report as SAE.**

Abbreviations: RPED = retinal pigment epithelial detachment; CTCAE = Common Terminology Criteria for Adverse Events; RVO= retinal vein occlusion; SAE = serious adverse event

a Refers to the CTCAE 'Eye disorders – Other, specify'

b If visual changes are clearly unrelated to study treatment (e.g., allergic conjunctivitis), monitor closely but ophthalmic examination is not required.

Table 14: Recommended dose modifications for trametinib for retinal pigment epithelial detachments (RPED)

CTCAE Grade	Action and Dose Modification
Grade 1 RPED (Asymptomatic; clinical or diagnostic observations only)	• Continue treatment with retinal evaluation each cycle (monthly) until resolution. If RPED worsens follow instructions below
Grade 2-3 RPED (Symptomatic with mild to moderate decrease in visual acuity; limiting instrumental ADL)	• Interrupt trametinib and hydroxychloroquine/placebo • Retinal evaluation each cycle (monthly) • If improved to ≤ Grade 1, restart trametinib at lower dose (reduced by 0.5 mg) or discontinue in patients taking trametinib 1 mg daily

Table 15: Management of Ocular Toxicities

Ocular Toxicity	Action
Uveitis, conjunctivitis	• Continue all therapies as long as effective local therapies can control inflammation
Retinal Vein occlusion, retinal pigment epithelial detachment (RPED), papilledema	• See table 13 and 14
Visual field deficits	• Discontinue HCQ/placebo

5.4.3.11 Cutaneous Squamous Cell Carcinoma (cuSCC)

Cases of cuSCC (which include those classified as keratoacanthoma or mixed keratoacanthoma subtype) have been observed in patient treated with dabrafenib. Approximately 70% of events occurred within the first 12 weeks of treatment with a median time to onset of 8 weeks. Dose modification or interruption of study treatment is not required for cuSCC or KA, however cuSCC should be reported as an SAE if it meets the reporting requirements outline in Section 5.2.10.

The cuSCC risk management plan includes (at a minimum) regular, thorough skin examinations by a dermatologist or melanoma oncology specialist trained to diagnose and treat these lesions, regular head and neck exams by the treating physician, In patients who develop cuSCC or any suspicious skin lesions during the trial, definitive treatment (i.e., surgical excision) of any SCC/KA or other suspicious lesion(s) is required (shave biopsies are not recommended), and the excised tissue is to be sent to a pathology laboratory. A complete dermatological history of prior medications and cuSCC risk factors (i.e., radiation therapy, sun exposure, immunosuppression, prior SCC, use of tanning beds, precursor lesions and photochemotherapy for psoriasis) must be collected.

- A designated dermatologist or the treating medical oncologist, if he/she is adept at skin exams will be available to perform skin exams to monitor for cuSCC,

BCC, actinic keratosis, keratoacanthoma and second primary melanomas. Any lesion suspected of being a SCC, BCC, actinic keratosis, keratoacanthoma or second primary melanoma should be appropriately mapped, photographed, with the photos stored digitally and made available upon request.

- Any suspicious lesions identified at baseline and while on D+T+ placebo or D+T+HCQ must be fully excised and sent for pathological examination (shave biopsies are not recommended).
- Actinic keratosis, keratoacanthoma or other skin conditions should be treated as per local standard of care.

5.4.3.12 New primary melanoma

New primary melanomas have been reported in patients treated with dabrafenib. These were identified within the first 5 months of therapy and did not require treatment modification other than excision. Monitoring for skin lesions should occur as described for cuSCC.

5.5 Drug interactions:

Table 16: Prohibited medications with CYP3A or CYP2C* Interactions

PROHIBITED – Strong inducers of CYP3A or CYP2C8, since concentrations of dabrafenib may be decreased	
Class	**Drugs**
Antibiotics	Rifamycin class agents (e.g., rifampin, rifabutin, rifapentine),
Anticonvulsant	Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, s-mephenytoin
Miscellaneous	bosentan, St-John's wort
PROHIBITED – Strong inhibitors of CYP3A, or CYP2C8 since concentrations of dabrafenib may be increased	
Class/Therapeutic Area	**Drugs/Agents**
Antibiotics	Clarithromycin, telithromycin, troleandomycin
Antidepressant	Nefazodone
Antifungals	Itraconazole, ketoconazole, posaconazole, voriconazole
Hyperlipidemia	Gemfibrozil
Antiretroviral	ritonavir, saquinavir, atazanavir
Miscellaneous	Conivaptan

Table 17: USE WITH CAUTION: Moderate inhibitors of CYP3A, or CYP2C8 since concentrations of dabrafenib may be increased

Class/Therapeutic Area	**Moderate CYP3A and CYP2C8 Inhibitors**
Antiarrhythmics	Diltiazem, verapamil
Antibiotic	Erythromycin

Class/Therapeutic Area	Moderate CYP3A and CYP2C8 Inhibitors
Antifungal	Fluconazole
Miscellaneous	Aprepitant
USE WITH CAUTION: Co-administration of these drugs with study treatment may result in loss of efficacy. Monitor patient for loss of efficacy or substitute with another medication.	
Class/Therapeutic Area	**CYP3A4, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or Transporter Substrates that May be Affected by Induction**
Analgesics	Alfentanil, buprenorphine, celecoxib, codeine, fentanyl, methadone, oxycodone
Antiarrhythmics	Disopyramide, dronedarone, mexiletine, propafenone, quinidine
Antibiotics	Chloramphenicol, doxycycline, erythromycin, moxifloxacin
Anticoagulants/ Antiplatelets	Cilostazole, warfarin
Anticonvulsants	Divalproex, lamotrigine, valproate, zonisamide
Antidepressants and Antipsychotics	Aripiprazole, bupropion, buspirone, desipramine, haloperidol, mirtazapine, pimozide, quetiapine, trazodone, amitriptyline, clomipramine, imipramine
Antidiabetics	Glyburide, saxagliptin, tolbutamide, nateglinide, pioglitazone, repaglinide, rosiglitazone
Antifungals	Caspofungin, fluconazole, terbinafine
Antihistamines	Astemizole, chlorpheniramine, ebastine
Antihypertensives	Amlodipine, diltiazem, felodipine, nifedipine, nilvadipine, nisoldipine, verapamil
Antimigraine Agents	Diergotamine, eletriptan, ergotamine
Corticosteroids	Dexamethasone, methylprednisolone, oral budesonide
Erectile Dysfunction Agents	Sildenafil, tadalafil, vardenafil
HMG-CoA Reductase Inhibitors	Atorvastatin, lovastatin, simvastatin, rosuvastatin, pravastatin
Hypnotics and Sedatives	Alprazolam, brotizolam, diazepam, estazolam, midazolam, triazolam, zolpidem, zopiclone
Immunosuppressants	Everolimus, sirolimus, tacrolimus
Miscellaneous	Aprepitant, cisapride, darifenacin, digoxin, disopyramide, leflunomide, methohexital, oral contraceptives, quinine, ranitidine, solifenacin, sulfasalazine, tramadol, tolvaptan, chloroquine, zopiclone
Selective Aldosterone Blockers	Eplerenone
USE WITH CAUTION: Co-administration of drugs that increase gastric pH should be used with caution when administered with dabrafenib as exposure to dabrafenib may be decreased	
pH altering agents	dexlansoprazole. esomeprazole, famotidine, ilaprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole, ranitidine

5.6 Supportive Care

All supportive measures consistent with optimal patient care will be given throughout the study.

5.7 Duration of Therapy

Patients will receive protocol therapy unless:

- Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued. In this event submit forms according to the instructions in the EA6191 Forms Packet.
- Patient withdraws consent.
- Patient experiences unacceptable toxicity.
- Non-protocol therapies are administered.
- Treatment will continue until disease progression.

5.8 Duration of Follow-up

For this protocol, all patients, including those who discontinue the protocol therapy early, will be followed for response until progression, even if non-protocol-therapy is initiated. Patients will be evaluated for at least 6 months after discontinuation of study treatment and will be followed for a minimum of one year from the start of treatment, unless disease progression is reported prior to one year. One year survival information will be extracted from the medical record or by phone call for patient who have discontinued protocol treatment and completed the 6 month follow-up evaluations prior to one year from the start of treatment.

Measurement of Effect

6.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 8 (+/-1) weeks. In addition to a baseline scan, confirmatory scans should also be obtained not less than 4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [Eur J Ca 45:228-247, 2009]. 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 RECIST.

The following general principles must be followed:

1. To assess objective response, it is necessary to estimate the overall tumor burden at baseline to which subsequent measurements will be compared. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than four weeks before registration.
2. Measurable disease is defined by the presence of at least one measurable lesion.
3. All measurements should be recorded in metric notation by use of a ruler or calipers.
4. The same method of assessment and the same technique must be used to characterize each identified lesion at baseline and during follow-up.

6.1.1 Definitions

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 lesion assessment. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

6.1.2 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, as

≥ 10 mm with CT scan, or ≥ 10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters.

NOTE: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol.

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. Non-measurable also includes lesions that are < 20 mm by chest x-ray.

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

of the 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 or absence of unequivocal progression of each should be noted throughout follow-up.

6.1.3 Methods for Evaluation of Disease

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

The same method of assessment and the same technique must 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 in 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.

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 must 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.

6.1.4 Response Criteria

6.1.4.1 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 progression, See Section 6.1.4.3.

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. (Note: a change of 20% or more that does not increase the sum of the diameters by 5 mm or more is coded as stable disease)

To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval of 8 weeks.

6.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR)

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

Non-CR/Non-PD

Persistence of one or more non-target lesion(s).

Progressive Disease (PD)

Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions (see

Section 6.1.4.3). Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

When the patient also has measurable disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient only has non-measurable disease, the increase in overall disease burden should be comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden from "trace" to "large", an increase in nodal disease from "localized" to "widespread", or an increase sufficient to require a change in therapy.

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).

6.1.4.3 Evaluation of New Lesions

The appearance of new lesions constitutes Progressive Disease (PD).

A growing lymph node that did not meet the criteria for reporting as a measurable or non-measurable lymph node at baseline should only be reported as a new lesion (and therefore progressive disease) if it:

a) increases in size to ≥ 15 mm in the short axis, or

b) there is new pathological confirmation that it is disease (regardless of size).

New effusion or ascites that appears during treatment should only be reported as a new lesion (and therefore progressive disease) if it has cytological confirmation of malignancy.

6.1.4.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence or non-protocol therapy (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*	Best Overall Response	Remarks
CR	CR	No	CR	
CR	Non-CR/Non-PD***	No	PR	
CR	Not evaluated	No	PR	
PR	Non-PD***/not evaluated	No	PR	
SD	Non-PD***/not evaluated	No	SD	Documented at least once ≥ 8 weeks from randomization
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.

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

*** PD in non-target lesions should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase. Please refer to the Evaluation of Non-Target Lesions – Progressive Disease section for further explanation.

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.

6.1.4.5 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.

To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval 8 weeks.

Study Parameters

7.1 Therapeutic Parameters

1. Prestudy CXR and/or scans should be done ≤ 3 weeks prior to randomization.
2. Prestudy CBC (with differential and platelet count) should be done ≤ 14 days prior to randomization.
3. All required prestudy chemistries, as outlined in Section 0, should be done ≤ 14 days prior to randomization.

Assessment	Baseline	X= Each 28-day Cycle (Monthly)[1] /alternative interval	End of treatment[7] (for any reason) or disease progression	Post Treatment/ Follow-up[6]
History and physical examination	X	X		
Vital Signs (including BP)	X	X		
EKG	X	X		
LVEF	X			
Standard ophthalmological exam[10]	X	Yearly or as clinically indicated		
Transthoracic echo[8]	X	Every 3 months or as clinically indicated	As clinically indicated	As clinically indicated
Brain CT or MRI	X	Every 4 cycles if brain metastases are present on baseline scan, or more often as clinically indicated	As clinically indicated	As clinically indicated
Chest CT[2]	X	Every 2 cycles or more often as clinically indicated. Confirmatory scans at least 4 weeks following initial documentation of objective response[9]	As clinically indicated	Every 2 months until 6 months after completion of study treatment and as clinically indicated per protocol Section 5.4.3.11 for cuSCC risk management
Abdomen/pelvis CT or MRI[2]	X	Every 2 cycles and as clinically indicated Confirmatory scans at least 4 weeks	As clinically indicated	As clinically indicated

Assessment	Baseline	X= Each 28-day Cycle (Monthly)[1] /alternative interval	End of treatment[7] (for any reason) or disease progression	Post Treatment/ Follow-up[6]
		following initial documentation of objective response[9]		
CBC with differential[4]	X	X	X	
Serum chemistry[5]	X	X	X	
PT/PTT[9]	X	X		
Serum or Urine Pregnancy Test[3]	X			
Biological Sample Submissions	See Sections 7.2 and 0			

1. Day 1 of cycle 1 begins the first day of treatment. A cycle constitutes 28 days or 4 weeks of D+T+HCQ/ placebo therapy. Monthly tests and procedures should be done on Day 1 of each cycle, however, account for major holidays and unforeseen events such as inclement weather, scheduled visits and testing can occur +/- 1 week from the start of each cycle, as long as there is documentation as to why they did not occur according to intended schedule.
2. Standard of care imaging will be utilized for tumor measurements while on study. The preferred type of imaging is high resolution CT scans of the chest abdomen and pelvis with contrast. In cases of elevated creatinine or anaphylactic reaction to contrast dye, CT scans without contrast or MRI with gadolinium may be substituted for the abdomen and non-contrast CT for the chest. PET/CT scans may not be substituted unless the CT portion of the PET/CT is a high resolution scan with contrast.

   NOTE: All visceral areas originally involved by tumor should be re-imaged every 2 cycles.
3. All females of childbearing potential must have a negative [blood test or urine test] within 14 days prior to study randomization to rule out pregnancy.
4. CBCs (with differential and platelet count) which includes WBC, ANC, Platelets, Hgb, and Hct.
5. Serum chemistries include: sodium, potassium, BUN, serum creatinine, glucose, SGOT (AST), SGPT (ALT), total bilirubin, alkaline phosphatase, LDH, albumin.
6. Follow-up: all patient will be evaluated for at least 6 months after discontinuation of study treatment and will be followed for a minimum of one year from the start of treatment, unless disease progression is reported prior to one year. One year survival information will be extracted from the medical record or by phone call for patient who have discontinued protocol treatment and completed the 6 month follow-up evaluations prior to one year from the start of treatment.
7. An End of Treatment (EOT) visits should occur 30 days (+/- 7 days) from the last dose for all patients. For patients experiencing toxicities, EOT visits should occur every 2 weeks (+/-3 days) until toxicities resolve.
8. Transthoracic echocardiogram must be completed within 28 days before starting therapy. They should be repeated every 3 months or as clinically indicated

9. As clinically indicated, with documentation of the medical necessity.
10. Any abnormalities found on standard of care eye exams will be graded and attributed to study medication by the investigator. NO additional data from routine eye exams needs to be captured.

7.2 Biological Sample Submissions

1. Specimens are to be submitted as outlined in Section 0.
2. All specimens submitted must be entered and tracked via the online ECOG-ACRIN Sample Tracking System (STS).

Rev Add2

Biological Materials	Prior to Start of Treatment	Cycle 1, Day 7 (+/- 2 days)	Cycle 2, prior to start of treatment (+/-1 week)	Cycle 3, prior to start of treatment (+/-1 week)	Progression
Submit from patients who answer 'Yes' to 'I agree that my tissue and blood samples and related health information may be kept in a Biobank for use in future health research.'[5]					
Archival Tumor Tissue Biopsy[1]	X				
Plasma (one 10mL EDTA purple top tube)[2]	X	X[6]	X[6,7]	X[7]	
Submit from patients who answer 'Yes' to 'I agree biopsies may be done to obtain research samples.'					
Serial Tumor Tissue Biopsy[1,4]	X	X[3]			X

1. Tumor tissue and related pathology reports are to be submitted within one month of randomization or collection.
2. Kits are being provided for the collection and shipment of the plasma specimens. See Appendix VI for instructions. Kit orders will on average be delivered within three (3) business days from when the order was placed.
3. Either week 1 +/- 2 days or week 4 +/-1 week or both. The investigator will use clinical judgement to choose time points for the second on-treatment biopsy and whether both may be collected.
4. Serial biopsies are to be obtained from patients that have easily accessible lesions.
5. As outlined in the Informed Consent patient participation in tumor tissue and plasma submissions is optional. Institutions must offer participation in these optional studies to all patients.
6. For patients submitting tumor tissue from serial research biopsies plasma collection will be prior to start of treatment, Cycle 1 Day 7 (+/- 2 days, and prior to start of Cycle 2 treatment (+/-1 week).
7. For patients not submitting tumor tissue from serial research biopsies plasma collection will be prior to start of treatment, prior to start of Cycle 2 treatment (+/- 1 week), and prior to Cycle 3 treatment (+/- 1 week).

Drug Formulation and Procurement

8.1 Dabrafenib mesylate (NSC 763760)

8.1.1 Chemical Name

N-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzene sulfonamide, methanesulfonate salt

8.1.2 Other Names

GSK2118436B, GSK2118436A (free base), Tafinlar®

8.1.3 Classification

BRAF inhibitor

8.1.4 CAS Registry Number

1195768-06-9

8.1.5 Molecular Formula

$C_{23}H_{20}F_3N_5O_2S_2 \cdot CH_4O_3S$

8.1.6 M.W.

615.68 (mesylate salt)

8.1.7 Mode of Action: Dabrafenib mesylate is a potent and selective BRAF kinase inhibitor. This inhibition suppresses downstream activity of pERK, a biomarker, and has antiproliferative activity against BRAF mutant tumors. The mode of action is consistent with ATP-competitive inhibition.

8.1.8 How Supplied

Commercially available as capsules.

50 mg capsules: Dark red capsule imprinted with ‘GSTEW’ and ‘50mg’ available in bottles of 120 (NDC 0078-0682-66). Each bottle contains a silica gel desiccant.

75 mg capsules: Dark pink capsule imprinted with ‘GSLHF’ and ‘75mg’ available in bottles of 120 (NDC 0078-0681-66). Each bottle contains a silica gel desiccant.

8.1.9 Storage

Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F)

8.1.10 Stability

Refer to the package label for expiration.

8.1.11 Route and Method of Administration

Oral administration. Take dabrafenib mesylate can be taken on an empty stomach either 1 hour before or 2 hours after a meal. If a dose is missed, it should not be taken later.

8.1.12 Potential Drug Interactions

In vivo data shows that metabolism of dabrafenib mesylate and its metabolites is mediated by CYP3A4 and CYP2C8 with minor contributions by CYP 2C9 and 2C19. Use caution if strong inducers or inhibitors of CYP2C8 or 3A4 are co-administered with dabrafenib. Although *in vitro* studies indicate dabrafenib mesylate and its metabolites are substrates for P-glycoprotein (P-gp) and BCRP transporters, the apparent high oral bioavailability and permeability indicate modulation of efflux transporters will have minimal impact on dabrafenib pharmacokinetics.

Dabrafenib mesylate and its metabolites showed moderate inhibition of CYP 2C8, 2C9, 2C19 and 3A4 in human liver microsomes. Use caution in patients who are taking sensitive substrates of these enzymes. Additionally, dabrafenib and its metabolites showed inhibition of OATP1B1, OATP1B3, OAT1, OAT3 and OCT2 transporter systems; however, the drug-drug interaction risk is believed to be low based on clinical exposures.

Neither dabrafenib nor its metabolites show inhibition of P-gp *in vitro*, but are moderate inhibitors of BCRP. Dabrafenib may affect the pharmacokinetics of co-medications with narrow therapeutic index whose absorption or clearance depends on BCRP-mediated transport.

In vitro, dabrafenib mesylate induces CYP 2B6 and 3A4 and possibly CYP 2C8, 2C9 2C19, UDP glucuronosyltransferase and P-gp.; although *in vivo*, the overall effect of dabrafenib induction is as a mild inducer of CYP2C9 and moderate inducer of CYP3A4. Use caution in patients who are taking substrates of these pathways, such as warfarin or hormonal contraceptives and monitor for loss of efficacy.

Dabrafenib solubility is pH-dependent but is not expected to be reduced when co-administered with pH elevating agents like proton pump inhibitors.

8.1.13 Patient Care Implications

In the case of overdose, patients should be treated symptomatically since there is no specific antidote. Hemodialysis is likely to be ineffective since dabrafenib mesylate is highly bound to plasma proteins.

Advise women study participants of reproductive potential to use effective non-hormonal contraception methods while receiving study treatment and for 2 weeks after the last dose of dabrafenib. Hormonal contraceptives can be ineffective when taken concurrently with dabrafenib. Male study participants (including those who have had a vasectomy) must use a condom during intercourse while taking dabrafenib and for 2 weeks after the last dose and should not father a child during this period.

Patients should be instructed on the importance of immediately reporting febrile episodes. In the event of a fever, the patient should be instructed to take anti-pyretics (e.g. ibuprofen or

acetaminophen/paracetamol) as appropriate to control fever. The use of oral corticosteroids should be considered in those instances in which anti-pyretics are insufficient. Monitor serum creatinine and other evidence of renal function during and following severe events of pyrexia.

8.1.14 Side effects

See Section 5.3.1

8.2 Trametinib dimethyl sulfoxide (NSC 763093)

8.2.1 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

8.2.2 Other Names

trametinib, GSK1120212B, TMT212-NXA, JTP-74057, JTP-78296, JTP-75303, Mekinist®

8.2.3 CAS Registry Number

1187431-43-1

8.2.4 Classification

MEK inhibitor

8.2.5 Molecular Formula

C26H23FIN5O4 • C2H6OS

8.2.6 M.W.

693.53 (DMSO solvate form)

8.2.7 Approximate Solubility

Trametinib dimethyl sulfoxide is almost insoluble in aqueous media at pH range of 2-8.

8.2.8 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.

8.2.9 Description

Trametinib dimethyl sulfoxide is a white to almost white powder.

8.2.10 How Supplied

Commercially available

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.

8.2.11 Storage

Store tablets at 2°C -8°C (36° F to 46° F) in the original bottle. Do not repackage tablets or remove desiccant. Bottles should be protected from light and moisture.

8.2.12 Stability

Refer to the package label for expiration.

8.2.13 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, it should not be taken later.

8.2.14 Potential Drug Interactions

In vitro studies suggest that trametinib 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). 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 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 CYP 2B6 and 3A4 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 MRP2 or BSEP, but an in vitro inhibitor of P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT2 and MATE1 at systemic concentrations that are not clinically relevant. No clinically relevant inhibition by trametinib is predicted in the liver or kidney and a low risk of intestinal drug-drug interaction is possible with BCRP.

Trametinib is highly bound to plasma proteins (97.3%) and has the potential to interfere with other highly protein-bound drugs. Use caution in patients taking concomitant drugs that are highly protein-bound and have narrow therapeutic ranges.

8.2.15 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. Advise women not to breastfeed while receiving study treatment and for 4 months after the last dose of trametinib. Advise men study participants to use barrier contraception and not to father a child while taking study treatment and for 4 months after the last dose of trametinib. Patients should be instructed on the importance of immediately reporting febrile episodes. In the event of a fever, the patient should be instructed to take anti-pyretics (e.g. ibuprofen or acetaminophen/paracetamol) as appropriate to control fever. The use of oral corticosteroids should be considered in those instances in which anti-pyretics are insufficient.

Monitor serum creatinine and other evidence of renal function during and following severe events of pyrexia.

8.2.16 Side Effects

See Section 0

8.3 Hydroxychloroquine and Matching Placebo

All orders for HCQ and placebo must be placed using the EA6191 Drug Request Form and submitted to EA Drug team at DrugOrder@ecog-acrin.org.

8.3.1 Chemical name

Hydroxychloroquine sulfate

8.3.2 Other names

PLAQUENIL®

8.3.3 Molecular Formula

C18H26ClN3O.H2SO4

8.3.4 Molecular weight

433.95

8.3.5 Mode of Action

Chloroquine has been shown to be a catalytic inhibitor of DNA repair enzymes (topoisomerase II).

8.3.6 Storage and stability

Store at room temperature [20° to 25°C (68° to 77°F), allows excursions between 15° and 30°C (59° to 86°F)

8.3.7 Route of administration

Oral. Take three (3) tablets by mouth that contains 200 mg of hydroxychloroquine sulfate/placebo (600 mg total). Take with or without food.

8.3.8 Potential Drug Interactions

Drug Interactions Digoxin: Concomitant HCQ/placebo and digoxin therapy may result in increased serum digoxin levels: serum digoxin

levels should be closely monitored in patients receiving combined therapy.

Insulin or antidiabetic drugs: As HCQ/placebo may enhance the effects of a hypoglycemic treatment, a decrease in doses of insulin or antidiabetic drugs may be required.

Drugs that prolong QT interval and other arrhythmogenic drugs: HCQ/placebo prolongs the QT interval and should not be administered with other drugs that have the potential to induce cardiac arrhythmias. Also, there may be an increased risk of inducing ventricular arrhythmias if HCQ/placebo is used concomitantly with other arrhythmogenic drugs.

Mefloquine and other drugs known to lower the convulsive threshold: HCQ/placebo can lower the convulsive threshold. Co-administration of HCQ/placebo with other antimalarials known to lower the convulsion threshold (e.g., mefloquine) may increase the risk of convulsions.

Antiepileptics: The activity of antiepileptic drugs might be impaired if co-administered with HCQ/placebo.

Methotrexate: Combined use of methotrexate with HCQ/placebo has not been studied and may increase the incidence of adverse effects.

Cyclosporin: An increased plasma cyclosporin level was reported when cyclosporin and HCQ/placebo were co-administered.

The following interactions have been observed on treatment with the structurally related substance chloroquine phosphate, and therefore cannot be ruled out for hydroxychloroquine.

Praziquantel: Chloroquine has been reported to reduce the bioavailability of praziquantel.

Antacids and kaolin: Antacids and kaolin can reduce absorption of chloroquine; an interval of at least 4 hours between intake of these agents and chloroquine should be observed.

Cimetidine: Cimetidine can inhibit the metabolism of chloroquine, increasing its plasma level. Concomitant use of cimetidine should be avoided.

Ampicillin: In a study of healthy volunteers, chloroquine significantly reduced the bioavailability of ampicillin.

8.3.9 Patient Care Implications:

Patients should be informed of the early signs and symptoms of toxicity such as rash or visual changes. Patients must see their physicians promptly in case of the appearance of these or of any unusual effects. Periodic laboratory tests may be recommended in some patients. Patients should be fully informed of the potential risks of the use ofHCQ/placebo, especially in pregnancy and in children.

Teratogenic Effects: Human pregnancies resulting in live births have been reported in the literature and no increase in the rate of birth defects has been demonstrated. Embryonic deaths and malformations

of anophthalmia and microphthalmia in the offspring have been reported when pregnant rats received large doses of chloroquine.

Nursing Mothers: Caution should be exercised when administering HCQ/placebo to nursing women. It has been demonstrated that hydroxychloroquine administered to nursing women is excreted in human milk and it is known that infants are extremely sensitive to the toxic effects of 4-aminoquinolines.

Pediatric Use: Safety and efficacy have not been established in the chronic use of HCQ/placebo for systemic lupus erythematosus and juvenile idiopathic arthritis in children. Children are especially sensitive to the 4-aminoquinoline compounds. Most reported fatalities followed the accidental ingestion of chloroquine, sometimes in small doses (0.75 g or 1 g in one 3-year-old child). Patients should be strongly warned to keep these drugs out of the reach of children.

Geriatric Use: Clinical studies of HCQ/placebo did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. However, this drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and it may be useful to monitor renal function.

8.3.10 Side Effects

The following adverse events have been identified during post-approval use of HCQ/placebo or other 4-aminoqunoline compounds. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and lymphatic system disorders: Bone marrow failure, anemia, aplastic anemia, agranulocytosis, leukopenia, and thrombocytopenia. Hemolysis reported in individuals with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency.

Cardiac disorders: Cardiomyopathy which may result in cardiac failure and in some cases a fatal outcome. PLAQUENIL prolongs the QT interval. Ventricular arrhythmias and torsade de pointes have been reported in patients taking HCQ/placebo.

Ear and labyrinth disorders: Vertigo, tinnitus, nystagmus, nerve deafness, deafness.

Eye disorders: Irreversible retinopathy with retinal pigmentation changes (bull's eye appearance), visual field defects (paracentral scotomas) and visual disturbances (visual acuity), maculopathies (macular degeneration), decreased dark adaptation, color vision abnormalities, corneal changes (edema and opacities) including corneal deposition of drug with or without accompanying symptoms (halo around lights, photophobia, blurred vision).

Gastrointestinal disorders: Nausea, vomiting, diarrhea, and abdominal pain.

General disorders and administration site conditions: Fatigue.

Hepatobiliary disorders: Liver function tests abnormal, hepatic failure acute.

Immune system disorders: Urticaria, angioedema, bronchospasm.

Metabolism and nutrition disorders: Decreased appetite, hypoglycemia, porphyria, weight decreased.

Musculoskeletal and connective tissue disorders: Sensorimotor disorder, skeletal muscle myopathy or neuromyopathy leading to progressive weakness and atrophy of proximal muscle groups, depression of tendon reflexes and abnormal nerve conduction.

Nervous system disorders: Headache, dizziness, seizure, ataxia and extrapyramidal disorders such as dystonia, dyskinesia, and tremor have been reported with this class of drugs.

Psychiatric disorders: Affect/emotional lability, nervousness, irritability, nightmares, psychosis, suicidal behavior.

Skin and subcutaneous tissue disorders: Rash, pruritus, pigmentation disorders in skin and mucous membranes, hair color changes, alopecia. Dermatitis bullous eruptions including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), photosensitivity, dermatitis exfoliative, acute generalized exanthematous pustulosis (AGEP). AGEP has to be distinguished from psoriasis, although HCQ/placebo may precipitate attacks of psoriasis. It may be associated with pyrexia and hyperleukocytosis.

8.3.11 Drug Orders/How Supplied

HCQ and matching placebo are being provided free of charge for this study by Sandoz Inc. a division of Novartis, and distributed by Patwell Pharmaceutical Solutions LLC. Each capsule contains 200 mg of HCQ or placebo and will be packaged in 100 count bottles. Each shipment will contain 6 bottles of either HCQ or matching placebo for 3 months of treatment. The label will include:

- Study Number
- Med ID #
- The Number of Tablets
- Administration instructions (i.e. ‘Administer as Directed per Protocol’)
- IND caution statement and/or local regulatory statements
- Expiration Date
- Storage instructions

8.3.12 IND Status

When used in this protocol, HCQ/placebo are each classified as an “unapproved use of an approved agent” and by definition considered investigational agents. However, while it is not an indication currently approved by the FDA, the use of HCQ/placebo in this protocol is

exempt from the requirements of an IND and described under Title 21 CFR 312.2(b).

8.3.13 Initial Orders

Following submission of the required regulatory documents and patient randomization, a supply of HCQ and matching placebo may be ordered from the ECOG-ACRIN Drug Team. Institutions must email the completed EA6191 Drug Request Form to the ECOG-ACRIN Drug Team at DrugOrder@ecog-acrin.org. The drug order form is available for download on the CTSU website under the protocol specific Pharmacy tab. If email is not available, the completed form may be faxed to ATTN: ECOG-ACRIN Drug Team at 617-589-0919. No blinded starter supplies are available for this protocol.

8.3.14 Important Information for Drug Orders

At the time of randomization each patient will be assigned a patient specific Blinded Drug ID number, example DR1117. The Blinded Drug ID number will appear on the patient's Confirmation of Registration Form.

The EA6191 Drug Request Form must include the patient specific Blinded Drug ID number with each drug request in order for the drug order to be processed. Failure to provide this information on the drug order form will result in a delay of the drug order being processed and shipped.

This study is a double-blinded treatment protocol. Blinded 100 count bottles of HCQ and matching placebo MAY NOT be transferred from one patient to another patient.

Each shipment will contain 6 bottles for a 3-month supply of HCQ and matching placebo. Study drug is provided in 100 count bottles. Each capsule contains 200 mg of HCQ or placebo.

8.3.15 Reorders

Once it is determined that the patient will continue treatment, reorders should be made by submitting the EA6191 Drug Request Form should be emailed to the ECOG-ACRIN Drug Team at DrugOrder@ecog-acrin.org.

Each shipment will contain 6 bottles for a 3-month supply of HCQ/placebo. Study drug is provided in 200 mg capsules of 100 capsules/bottle.

For both initial orders and reorders, Patwell will ship orders received prior to 2 pm ET Monday-Thursday the same day for next day delivery. Patwell will ship orders received after 2 pm ET Monday-Thursday or on Friday will be shipped the following business day for next day delivery. There will be no weekend or holiday deliveries.

8.3.16 Drug Inventory Records

Investigational Product Records at Investigational Site(s): It is the responsibility of the Investigator to ensure that a current record of

investigational product disposition is maintained at each study site where investigational product is inventoried and disposed. Records or logs must comply with applicable regulations and guidelines.

8.3.17 Drug Destruction and Return

At the completion of the patient's treatment at your institution, all unused drugs, partially used, or empty blister packs must be destroyed at the site according to the institution's policy for drug destruction. Please maintain appropriate records of the disposal, including dates and quantities.

8.3.18 Emergency Unblinding

See Section 4.5.

Statistical Considerations

9.1 Study Design and Objectives

Rev Add2

In this randomized phase II study, 84 patients with advanced BRAF V600E/K melanoma and serum LDH > ULN will be randomized to: dabrafenib + trametinib + HCQ (Arm A) and dabrafenib + trametinib + placebo (Arm B). The primary objective is to compare the rate of one-year progression-free survival (PFS) between the two arms. It is hypothesized that HCQ will overcome resistance and significantly improve the rate of one year PFS.

Secondary objectives are to evaluate: PFS, best overall response rate, complete response rate, treatment duration, adverse event rate and overall survival (OS) by treatment arms.

9.2 Study Endpoints

PFS is defined as the time from randomization to progression or death (whichever occurs first). Patients who have not had an event will be censored at the date of last disease assessment documenting the patient was free of progression. Progression will be evaluated based on international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) as described in Section 0. One-year PFS rate in each arm will be estimated from the Kaplan-Meier PFS curve.

Response will be defined by the RECIST guidelines (version 1.1) as described in Section 0. Treatment duration will be measured from treatment start to treatment end dates on protocol. For patients who have progressed, information on treatment type and duration on off-protocol therapies will be collected in the long-term follow up. Adverse events will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE). Overall Survival (OS) will be defined as the time from randomization to death from any cause. Patients who have not died will be censored at the date last known to be alive.

9.3 Sample Size Considerations and Monitoring Plan

Rev Add2

In patients with elevated LDH, the null hypothesis is a 1-year PFS rate of 20% in the control arm and the targeted effect size is 25% improvement in the treatment arm (i.e. alternate hypothesis is 45% 1-year PFS rate).

Eighty-four patients (for 80 eligible and evaluable) will be equally randomized to HCQ vs. placebo arms. It is expected to accrue 84 patients in 28 months (target accrual 3 patients per month). We expect the number of patients who will be censored before one-year will be very small (less than 4 out of 84 accrued). The sample size of 80 eligible and evaluable patients will provide 81.7% power for the comparison of one-year PFS rate of 20% to 45%. To be conservative, we used the power calculation based on the Fisher's exact test, assuming 80 patients with one-year PFS assessed. One-sided type I error rate of 0.10 was used. It is likely PFS follows a cure rate model with a mixture of patients who have progression and cured. As there is limited data to evaluate the cure rate model parameters, a landmark analysis based on the one-year PFS rate was used for the sample size calculation.

One interim analysis for futility will be conducted when one-year PFS rate is assessed in the first 40 patients at 50% information time. We will adopt a stopping rule proposed by Wieand et al. (Statistics in Medicine vol 13: 1453-1458, 1994). That is, if one-year PFS rate in the HCQ arm is lower than the one-year PFS rate in the placebo arm, an early stopping will be considered. Conditional power will be also estimated.

9.4 Statistical Analysis Plan

As a primary analysis, one-year PFS rates estimated from the Kaplan-Meier curves will be compared by treatment arm. A test statistic of the difference in one-year PFS rates divided by the square root or the sum of the variances will be used with a normal approximation. As a secondary analysis, PFS distribution will be estimated using the method of Kaplan-Meier by treatment arm and compared using the log-rank test. In this analysis, all cases with PFS assessed (including cases with censored < one-year) will be included.

For the secondary endpoints, overall response and complete response rates will be estimated by treatment arm and 95% CIs will be provided. Overall survival will be described using the method of Kaplan-Meier by treatment arm. Adverse events will be monitored carefully throughout the study and will be summarized by treatment arm. Treatment duration will be estimated by treatment arm.

9.5 Gender and Ethnicity

Based on previous data from E1608, E3611, the anticipated accrual in subgroups defined by gender and race is:

EXAMPLE
PLANNED ENROLLMENT REPORT

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	1	0	1	1	3
Asian	3	2	0	0	5
Native Hawaiian or Other Pacific Islander	1	0	0	0	1
Black or African American	6	5	0	0	11
White	40	25	1	1	67
More Than One Race	4	3	3	3	13
Total	55	35	5	5	100

9.6 Study Monitoring

This study will be monitored by the ECOG-ACRIN Data Safety Monitoring Committee (DSMC). The DSMC meets twice each year. For each meeting, all monitored studies are reviewed for safety and progress toward completion. When appropriate, the DSMC will also review interim analyses of outcome data. Copies of the toxicity reports prepared for the DSMC meetings are included in the study

reports prepared for the ECOG-ACRIN group meeting (except that for double blind studies, the DSMC may review unblinded toxicity data, while only pooled or blinded data will be made public). These group meeting reports are made available to the local investigators, who may provide them to their IRBs. Only the study statistician and the DSMC members will have access to interim analyses of outcome data. Prior to completion of this study, any use of outcome data will require approval of the DSMC. Any DSMC recommendations for changes to this study will be circulated to the local investigators in the form of addenda to this protocol document. A complete copy of the ECOG-ACRIN DSMC Policy can be obtained from the ECOG-ACRIN Operations Office – Boston.

Specimen Submissions

Representative archival tumor tissue, serial tumor tissue research biopsies and plasma specimens are to be submitted per patient consent for future undefined research studies.

All specimens must be clearly labeled with the ECOG-ACRIN protocol number EA6191, the patient's initials and ECOG-ACRIN patient sequence number, the collection date, and specimen type. For pathology materials, it is strongly recommended that full patient names be provided.

It is required that all specimens submitted on this trial be entered and tracked via the ECOG-ACRIN Sample Tracking System (STS) Section 10.5. An STS shipping manifest form is to be included with every submission.

10.1 Submissions to ECOG-ACRIN Central Biorepository and Pathology Facility (CBPF)

If you have any questions concerning tumor tissue and peripheral blood submissions please contact the ECOG-ACRIN CBPF at (844) 744-2420 or eacbpf@mdanderson.org

10.1.1 Pathology Material Submissions

Guidelines for pathologists are provided in Appendix I.

Rev Add2

Submit per patient consent within one month of randomization or collection. Tissue requested is archival diagnostic tumor tissue and tumor tissue from serial research biopsies collected at:

- Baseline
- Cycle 1 Day 7 (+/- 2 days) and/or Cycle 2 prior to treatment (+/-1 week)
- Progression

NOTE: Information regarding the reimbursements associated with the research biopsies is provided in Appendix VI.

Submitting pathologist and clinical research associate may refer to Appendix I which outlines the Pathology Submission Guidelines.

The tumor tissue specimens are to be labeled with the institution's assigned pathology ID number as well as the information above.

10.1.1.1 Required Forms:

The following forms must be submitted with all pathology submissions:

- STS generated Shipping Manifest Form
- Copy of the institutional pathology reports
- Immunological study reports, if available

10.1.1.2 **Tumor Tissue Submissions (archival and research biopsies):**

- Representative formalin-fixed paraffin-embedded (FFPE) tumor tissue blocks

NOTE: Reimbursement guidelines for research biopsies are outlined in Appendix VII. Biopsies to obtain specimens for research must be determined to be minimal risk prior to performance.

NOTE: **Only blocks will be accepted from serial research biopsies eligible for reimbursement,** though institutions are allowed to keep an H&E slide.

NOTE: If archival blocks are unavailable for submission, cores and slides are to be submitted. All cores and slides must be adequately labeled, with slides numbered sequentially in the order cut. Alternative submission requirements:

- One (1) H&E slide
- Twenty (20) 5 µm and five (5) 4 µm unstained, positively charged, air-dried plus slides from the thickest part of the tumor.
- One (1) or more core punches (minimum of 4mm diameter). If core punch tool is unavailable, request core punch kit from the ECOG-ACRIN CBPF (844) 744-2420. Adequately label every slide and core submitted.

If these criteria cannot be met, please contact the ECOG-ACRIN CBPF (eacbpf@mdanderson.org) to obtain alternative submission requirements.

10.1.2 Plasma Submissions

Kits for the collection and shipment of the plasma specimens are ordered online from Cenetron Central Laboratories. Instructions are provided in Appendix VI. Questions regarding kits can be directed to projectmanagement@cenetron.com or call the Cenetron Clinical Trials Group at (512) 439-2000. Kits must be ordered after the patient has been randomized to the trial and will generally arrive within three (3) business days from when the order was placed.

10.1.2.1 Plasma Collection Time Points:

Rev Add2

- Prior to Start of Treatment
- Cycle 1, Day 7 (+/- 2 days) (from patients submitting tumor tissue from serial research biopsies)
- Cycle 2, prior to treatment (+/-1 week)
- Cycle 3, prior to treatment (+/-1 week) (from patients not submitting tumor tissue from serial research biopsies)

10.1.2.2 Plasma Preparation Guidelines

- Collect 10mL of whole blood into one (1) EDTA Purple Top tube
- Invert tube gently 8-10 times to ensure proper mixing
- Centrifuge within 20 minutes of collection at 1000-1500g (approximately 3000 rpm) for 15 minutes or longer at 4˚C
- Carefully pipette the top plasma layer and aliquot into each of four (4) cryovials
- Replace the stopper on the EDTA tube containing the residual cells
- Place plasma and residual cells upright in -70°C freezer and ship overnight on dry ice (at least five pounds) or batch for subsequent shipping. If -70°C freezer is not available, store blood at -20°C and ship with 24 hours. If dry ice is not available, please contact the ECOG-ACRIN CBPF at (844) 744-2420 for shipping alternatives.

10.2 Shipping Procedures

Tumor tissue specimens (both archival and research biopsies) are to be shipped overnight at ambient temperature (cool pack in warm weather) within one (1) month following randomization or collection.

Batch ship plasma specimens overnight frozen on dry ice.

The laboratory is open Monday through Friday to receive specimens. Do not ship on Fridays or Saturdays, or the day before legal holidays.

Friday shipments are ill advised, similarly shipping before holidays is often problematic. The laboratory is closed Saturday, Sunday, and holidays.

Ship using the CBPF's FedEx account using the FedEx on-line ship manager.

Access to the FedEx shipping account for specimen shipments to the ECOG-ACRIN CBPF at MD Anderson Cancer Center can only be obtained by logging into fedex.com with an account issued by the ECOG-ACRIN CBPF. For security reasons, the account number will no longer be given out in protocols, over the phone, or via email. If your institution needs to have an account created, please contact the ECOG-ACRIN CBPF by email at eacbpf@mdanderson.org

Ship to:

Rev Add2

MD Anderson Cancer Center CBPF
Mike Balco
Life Science Plaza - Suite 910
2130 West Holcombe Boulevard, LSP9.4227
Houston, TX 77030
Phone: Toll Free (844) 744-2420 (713-745-4440 Local or International Sites)
Fax: (713)-563-6506

An STS Shipping Manifest Form must be generated and shipped with all specimen submissions.

10.3 Use of Specimens in Research

An amendment or proposal for any additional correlative science studies to be performed on biological specimens will be submitted to CTEP/NCI for review and approval according to NCTN guidelines. Amendments to the protocol and/or proposals for use of biological specimens will include the appropriate background, experimental plans with assay details, and detailed statistical section. Specimens for testing will not be released until the appropriate NCI approvals have been obtained.

The proposed future studies will assess the biological effects of the triple drug regimen, and generate candidate predictive markers of efficacy.

Specimens submitted will be processed to maximize their utility for current and future research projects and may include, but not limited to, extraction of plasma, serum, DNA and RNA.

Specimens from patients who consented to allow their specimens to be used for future approved research studies will be retained in an ECOG-ACRIN designated central repository. For this trial, specimens will be retained at the ECOG-ACRIN Central Biorepository and Pathology Facility. Specimens will be de–identified prior to distribution for any approved research projects.

If future use is denied or withdrawn by the patient, the specimens will be removed from consideration for use in any future study. Pathology materials may be retained for documentation purposes or returned to the institution. All other specimens will be destroyed per guidelines of the respective repository.

10.4 ECOG-ACRIN Sample Tracking System

It is **required** (barring special circumstances) that all specimens submitted on this trial be entered and tracked using the ECOG-ACRIN Sample Tracking System (STS). As of June 2007, the software will allow the use of either 1) an ECOG-ACRIN username and password previously assigned (for those already using STS), or 2) CTSU username and password.

When you are ready to log the collection and/or shipment of the specimens required for this study, please access the Sample Tracking System software by clicking https://webapps.ecog.org/Tst.

Important: Please note that the STS software creates pop-up windows, so you will need to enable pop-ups within your web browser while using the software. A user manual and interactive demo are available by clicking this link: http://www.ecog.org/general/stsinfo.html. Please take a moment to familiarize yourself with the software prior to using the system.

An STS generated Shipping Manifest must be generated and shipped with all specimen submissions.

Please direct your questions or comments pertaining to the STS to ecog.tst@jimmy.harvard.edu.

Study Specific Notes

Generic Specimen Submission Form (#2981v3) will be required only if STS is unavailable at time of specimen submission. Notify the laboratory of the shipment by faxing a copy of the completed form to the laboratory.

Retroactively enter all specimen collection and shipping information when STS is available.

10.5 Sample Inventory Submission Guidelines

Inventories of all specimens submitted will be tracked via the ECOG-ACRIN STS and receipt and usability verified by the receiving laboratory. Inventories of specimens forwarded and utilized will be submitted by the investigating laboratories to the ECOG-ACRIN Operations Office - Boston on a monthly basis in an electronic format defined by the ECOG-ACRIN Operations Office - Boston.

Electronic Data Capture

Please refer to the EA6191 Forms Completion Guidelines for the forms submission schedule. Data collection will be performed exclusively in Medidata Rave

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 by FTP burst of data. 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).

For studies assigned **Demography** monitoring **and** enrolling patients via **OPEN**:

Required submission of patient demographic data for this study will be submitted automatically via OPEN.

NOTE: Serious adverse events must be submitted via CTEP-AERS per protocol guidelines.

Patient Consent and Peer Judgment

Current FDA, NCI, state, federal and institutional regulations concerning informed consent will be followed.

References

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The BAMM2 (BRAF, Autophagy, MEK inhibition in Melanoma) Study: A Randomized Double Blind Phase II Study of Dabrafenib and Trametinib with or without Hydroxychloroquine in Advanced BRAF$^{V600E/K}$ Melanoma with elevated LDH

Appendix I

Pathology Submission Guidelines

The following items are included in Appendix I:

1. Guidelines for Submission of Pathology Materials (instructional sheet for Clinical Research Associates [CRAs])
2. Instructional memo to submitting pathologists
3. ECOG-ACRIN Generic Specimen Submission Form (#2981v3)

Guidelines for Submission of Pathology Materials

The following pathology materials are to be submitted within one (1) month of randomization or collection.

Pathology Submissions

1. Representative formalin-fixed paraffin-embedded (FFPE) from the archival pretreatment tumor tissue biopsy and serial tumor tissue research biopsies from baseline, weeks one and/or four, and progression

NOTE: Reimbursement guidelines for research biopsies are outlined in Appendix VII. Biopsies to obtain specimens for research must be determined to be minimal risk prior to performance.

NOTE: Only blocks will be accepted from research biopsies eligible for reimbursement, though institutions are allowed to keep an H&E slide.

NOTE: If blocks are unavailable for submission, cores and slides are to be submitted. All cores and slides must be adequately labeled, with slides numbered sequentially in the order cut. Alternative submission requirements:

- One (1) H&E slide
- Twenty (20) 5 µm and five (5) 4 µm unstained, positively charged, air-dried plus slides from the thickest part of the tumor
- One (1) or more core punches (minimum of 4mm diameter). If core punch tool is unavailable, request core punch kit from the ECOG-ACRIN CBPF (844) 744-2420. Adequately label every slide and core submitted.

If these criteria cannot be met, please contact the ECOG-ACRIN CBPF (eacbpf@mdanderson.org) to obtain alternative submission requirements.

2. Forms and Reports

Adequate patient identifying information must be included with every submission to retain chain of custody. It is strongly recommended that full patient names be provided. The information will be used only to identify patient materials and will expedite any required communications with the institution (including pathologists).

The following items are to be included with the pathology materials:

- Institutional Pathology Report
- ECOG-ACRIN Generic Specimen Submission Form (#2981v3) [If STS is unavailable]
- Sample Tracking System (STS) Shipping Manifest Form
- Immunological study reports, if available

3. Mail pathology materials to:

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MD Anderson Cancer Center CBPF
Mike Balco
Life Science Plaza - Suite 910
2130 West Holcombe Boulevard, LSP9.4227
Houston, TX 77030
Phone: Toll Free (844) 744-2420 (713-745-4440 Local or International Sites)
Fax: (713) 563-6506
Email: eacbpf@mdanderson.org

If you have any questions concerning the above instructions, contact the Pathology Coordinator at the ECOG-ACRIN Central Biorepository and Pathology Facility by telephone: (844) 744-2420 or email: eacbpf@mdanderson.org

Robert L. Comis, MD, and Mitchell D. Schnall, MD, PhD
Group Co-Chairs

MEMORANDUM

TO: _____
(Submitting Pathologist)

FROM: Stanley Hamilton, M.D., Chair
ECOG-ACRIN Laboratory Science and Pathology Committee

DATE: _____

SUBJECT: Submission of Pathology Materials for EA6191: *The BAMM2 (BRAF, Autophagy, MEK inhibition in Melanoma) Study: A Randomized Double Blind Phase II Study of Dabrafenib and Trametinib with or without hydroxychloroquine in Advanced BRAF V600E/K Melanoma*

The patient named on the attached request has been entered onto an ECOG-ACRIN protocol by _____ (ECOG-ACRIN Investigator). This protocol requires the submission of pathology materials for future undefined research studies.

Please return the pathology reports, the slides and/or blocks and any other required materials to the Clinical Research Associate (CRA). The CRA will forward all required pathology materials to the ECOG-ACRIN Central Biorepository and Pathology Facility.

Blocks and/or slides submitted for this study will be retained at the ECOG-ACRIN Central Biorepository and Pathology Facility for undefined future research studies. Paraffin blocks will be returned upon written request for purposes of patient management.

If you have any questions regarding this request, please contact the ECOG-ACRIN Central Biorepository and Pathology Facility at (844) -744-2420 (713-745-4440 Local or International Sites) or email: eacbpf@mdanderson.org

The ECOG-ACRIN CRA at your institution is:

Name:_____

Address: _____

Phone: _____

Thank you.

ECOG-ACRIN Generic Specimen Submission Form

Form No. 2981v3

Institution Instructions: This form is to be completed and submitted with **all specimens** ONLY if the Sample Tracking System (STS) is not available. **Use one form per patient, per time- point.** All specimens shipped to the laboratory must be listed on this form. Enter all dates as MM/DD/YY. Keep a copy for your files. Retroactively log all specimens into STS once the system is available. **Contact the receiving lab to inform them of shipments that will be sent with this form.**

Protocol Number _____ **Patient ID** _____ **Patient Initials** Last _____ First _____

Date Shipped _____ **Courier** _____ **Courier Tracking Number** _____

Shipped To (Laboratory Name) _____ **Date CRA will log into STS** _____

FORMS AND REPORTS: Include all forms and reports as directed per protocol, e.g., pathology, cytogenetics, flow cytometry, patient consult, etc.

Required fields for all samples				**Additional fields for tissue submissions**				**Completed by Receiving Lab**
Protocol Specified Timepoint:								
Sample Type (fluid or fresh tissue, include collection tube type)	**Quantity**	**Collection Date and Time 24 HR**		**Surgical or Sample ID**	**Anatomic Site**	**Disease Status** (e.g., primary, mets, normal)	**Stain or Fixative**	**Lab ID**

Fields to be completed if requested per protocol. Refer to the protocol-specific sample submissions for additional fields that may be required.					
Leukemia/Myeloma Studies:	**Diagnosis**	**Intended Treatment Trial**	**Peripheral WBC Count (x1000)**	**Peripheral Blasts %**	**Lymphocytes %**
Study Drug Information:	**Therapy Drug Name**	**Date Drug Administered**	**Start Time 24 HR**	**Stop Time 24HR**	
Caloric Intake:	**Date of Last Caloric Intake**		**Time of Last Caloric Intake 24HR**		

CRA Name _____ **CRA Phone** _____ **CRA Email** _____

Comments

9/12/14

The BAMM2 (BRAF, Autophagy, MEK inhibition in Melanoma) Study: A Randomized Double Blind Phase II Study of Dabrafenib and Trametinib with or without Hydroxychloroquine in Advanced BRAF$^{V600E/K}$ Melanoma with elevated LDH

Appendix II

Patient Thank You Letter

We ask that the physician use the template contained in this appendix to prepare a letter thanking the patient for enrolling in this trial. The template is intended as a guide and can be downloaded from the web site at http://www.ecog.org. As this is a personal letter, physicians may elect to further tailor the text to their situation.

This small gesture is a part of a broader program being undertaken by ECOG-ACRIN and the NCI to increase awareness of the importance of clinical trials and improve accrual and follow-through. We appreciate your help in this effort.

[PATIENT NAME] [DATE]

[PATIENT ADDRESS]

Dear [PATIENT SALUTATION],

Thank you for agreeing to take part in this important research study. Many questions remain unanswered in cancer. With the participation of people like you in clinical trials, we hope to improve treatment and quality of life for those with your type of cancer.

We believe you will receive high quality, complete care. I and my research staff will maintain very close contact with you. This will allow me to provide you with the best care while learning as much as possible to help you and other patients.

On behalf of ***[INSTITUTION]*** and ECOG-ACRIN, we thank you again and look forward to helping you.

Sincerely,

[PHYSICIAN NAME]

The BAMM2 (BRAF, Autophagy, MEK inhibition in Melanoma) Study: A Randomized Double Blind Phase II Study of Dabrafenib and Trametinib with or without Hydroxychloroquine in Advanced BRAF$^{V600E/K}$ Melanoma with elevated LDH

Appendix III

Patient Pill Calendar

Pill Calendar Directions

1. Take your scheduled dose of each pill.
   - Dabrafenib should be taken twice daily, about 12 hours apart on an empty stomach (1 hour before or 2 hours after meals)
   - Trametinib should be taken once daily, on an empty stomach (1 hour before or 2 hours after a meal)
   - Hydroxchloroquine (HCQ or placebo) should be taken twice daily, about 12 hours apart (in the morning and evening). It can be taken with or without food.
2. If you forget, the missed pills will not be taken later.
3. Please bring the empty bottles or any leftover capsules/ tablets and your pill calendar to your next clinic visit.

Patient Pill Calendar

This is a calendar on which you are to record the time and number of tablets you take each day. You should take your scheduled dose of each pill. **Note the times and the number of tablets that you take each day.** If you develop any side effects, please record them and anything you would like to tell the doctor in the space provided. Bring any unused tablets and your completed pill calendar to your doctor's visits.

DAY	Date Month	Day	Year	Drug Name	Time pills taken AM	PM	Number of pills taken AM	PM	Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.)
1				Dabrafenib (twice daily)					
				Trametinib (once daily)					
				HCQ or placebo (twice daily)					
2				Dabrafenib (twice daily)					
				Trametinib (once daily)					
				HCQ or placebo (twice daily)					
3				Dabrafenib (twice daily)					
				Trametinib (once daily)					
				HCQ or placebo (twice daily)					
4				Dabrafenib (twice daily)					
				Trametinib (once daily)					
				HCQ or placebo (twice daily)					
5				Dabrafenib (twice daily)					
				Trametinib (once daily)					
				HCQ or placebo (twice daily)					

DAY	Date Month	Day	Year	Drug Name	Time pills taken AM	PM	Number of pills taken AM	PM	Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.)
6				Dabrafenib (twice daily)					
				Trametinib (once daily)					
				HCQ or placebo (twice daily)					
7				Dabrafenib (twice daily)					
				Trametinib (once daily)					
				HCQ or placebo (twice daily)					
8				Dabrafenib (twice daily)					
				Trametinib (once daily)					
				HCQ or placebo (twice daily)					
9				Dabrafenib (twice daily)					
				Trametinib (once daily)					
				HCQ or placebo (twice daily)					
10				Dabrafenib (twice daily)					
				Trametinib (once daily)					
				HCQ or placebo (twice daily)					
11				Dabrafenib (twice daily)					
				Trametinib (once daily)					
				HCQ or placebo (twice daily)					

DAY	Date Month	Day	Year	Drug Name	Time pills taken AM	PM	Number of pills taken AM	PM	Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.)
12				Dabrafenib (twice daily)					
				Trametinib (once daily)					
				HCQ or placebo (twice daily)					
13				Dabrafenib (twice daily)					
				Trametinib (once daily)					
				HCQ or placebo (twice daily)					
14				Dabrafenib (twice daily)					
				Trametinib (once daily)					
				HCQ or placebo (twice daily)					
15				Dabrafenib (twice daily)					
				Trametinib (once daily)					
				HCQ or placebo (twice daily)					
16				Dabrafenib (twice daily)					
				Trametinib (once daily)					
				HCQ or placebo (twice daily)					

DAY	Date Month	Day	Year	Drug Name	Time pills taken AM	PM	Number of pills taken AM	PM	Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.)
17				Dabrafenib (twice daily)					
				Trametinib (once daily)					
				HCQ or placebo (twice daily)					
18				Dabrafenib (twice daily)					
				Trametinib (once daily)					
				HCQ or placebo (twice daily)					
19				Dabrafenib (twice daily)					
				Trametinib (once daily)					
				HCQ or placebo (twice daily)					
20				Dabrafenib (twice daily)					
				Trametinib (once daily)					
				HCQ or placebo (twice daily)					
21				Dabrafenib (twice daily)					
				Trametinib (once daily)					
				HCQ or placebo (twice daily)					
22				Dabrafenib (twice daily)					
				Trametinib (once daily)					
				HCQ or placebo (twice daily)					

DAY	Date Month	Day	Year	Drug Name	Time pills taken AM	PM	Number of pills taken AM	PM	Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.)
23				Dabrafenib (twice daily)					
				Trametinib (once daily)					
				HCQ or placebo (twice daily)					
24				Dabrafenib (twice daily)					
				Trametinib (once daily)					
				HCQ or placebo (twice daily)					
25				Dabrafenib (twice daily)					
				Trametinib (once daily)					
				HCQ or placebo (twice daily)					
26				Dabrafenib (twice daily)					
				Trametinib (once daily)					
				HCQ or placebo (twice daily)					
27				Dabrafenib (twice daily)					
				Trametinib (once daily)					
				HCQ or placebo (twice daily)					
28				Dabrafenib (twice daily)					
				Trametinib (once daily)					
				HCQ or placebo (twice daily)					

The BAMM2 (BRAF, Autophagy, MEK inhibition in Melanoma) Study: A Randomized Double Blind Phase II Study of Dabrafenib and Trametinib with or without Hydroxychloroquine in Advanced BRAF$^{V600E/K}$ Melanoma with elevated LDH

Appendix IV

ECOG Performance Status

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

The BAMM2 (BRAF, Autophagy, MEK inhibition in Melanoma) Study: A Randomized Double Blind Phase II Study of Dabrafenib and Trametinib with or without Hydroxychloroquine in Advanced BRAF$^{V600E/K}$ Melanoma with elevated LDH

Appendix V

EA6191 Collection and Shipping Kit Order Instructions

Specimen Collection/Shipping Kits are being provided by CENETRON CENTRAL LABORATORIES and are to be ordered ONLINE.

Starter kits are not available. Kit requests are to be made after patient randomization.

Questions regarding kits can be directed to projectmanagement@cenetron.com or call the Cenetron Clinical Trials Group at (512) 439-2000.

Ordering Process:

- Following randomization of the patient to the trial, go to the website www.cenetron.com and click on the 'Order Kits' button at the top right. It is recommended that kits be ordered same day as patient randomization.
- The order form is not study specific and can be used for any study. Complete the online form as follows:
  - Sponsor (REQUIRED): ECOG-ACRIN
  - Contact Name (REQUIRED): Name of the institution kit contact
  - Protocol Number (REQUIRED): EA6191
  - Phone Number (REQUIRED): Phone number of the kit contact. Please ensure that this is a number that can be reached from an external caller
  - FAX Number: Fax number of the kit contact
  - Investigator: Last name of the kit contact is adequate
  - Email (REQUIRED): Email of the institution kit contact. Must be entered twice to confirm
  - Date Supplies Needed (REQUIRED): Add three (3) business days or more to order date. (Reminder that weekends and holidays must also be considered in this timeline)
  - KIT NAME (REQUIRED): Type in the kit type needed
    - EA6191 Collection Kit
- Quantity: 1
- Comments: Provide EA6191 Patient Case ID# and Full Shipping Address
  - Patient Case ID = #####
  - 'Ship Kit to' name of the individual to whom the kit is being shipped. (May be different than the kit contact provided above)
  - Full street address, town, state and zip code
- Answer the security question

Please complete this form correctly, including the valid ECOG-ACRIN patient case number and complete shipping address. If information is missing the kit processing will be delayed.

The BAMM2 (BRAF, Autophagy, MEK inhibition in Melanoma) Study: A Randomized Double Blind Phase II Study of Dabrafenib and Trametinib with or without Hydroxychloroquine in Advanced BRAF$^{V600E/K}$ Melanoma with elevated LDH

Appendix VI

Tumor Tissue Research Biopsy Reimbursement Instructions

Biopsies performed to obtain research specimens from patients who answer 'Yes' to 'I agree biopsies may be done to obtain research samples' at:

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- Baseline (following registration, prior to start of treatment)
- Cycle 1 Day 7 (+/- 2 days) and/or prior to start of treatment on Cycle 2 (+/- 1 week)
- Progression

Biopsies are reimbursable at the following research rates per biopsy:

- Radiology Assisted = $4,000

Biopsies that are performed as part of the patient's standard of care are not eligible for reimbursement.

All institutions are eligible for the reimbursement for applicable research biopsies regardless of cooperative group.

Prior to performing the research biopsies, the following conditions must be met:

a. The research rates outlined above are deemed acceptable by the institution's central research office. Costs above these reimbursement rates are not to be billed to the patient or patient's insurance.

b. The research rate is reported to the institution's financial office and an account established under the designated Investigator's name.

   Reminder that the institution must set up the mechanism for the 'billing' of these research biopsies. ECOG-ACRIN recommends billing the cooperative group Principal Investigator (PI) of the institution. Contact your coordinating group's operations office and ask to whom this account should be named.

Expenses for research biopsies will be paid only to participating institutions, not to any other persons or entities, at the above stated research rates.

Distribution of the reimbursements requires:

- Submission and receipt of the research biopsies via the ECOG-ACRIN Sample Tracking System (STS)
- Completion and submission of the EA6191 Biopsy Reimbursement Form to the ECOG-ACRIN Operations Office - Boston
- Supporting documentation, if requested

Rev Add2

EA6191 Biopsy Reimbursement Form

This form is to be used to request reimbursement for the performance and submission of the tumor tissue biopsies at baseline, weeks one and/or four, and progression as outlined in Section 0. Reimbursements are NOT applicable for biopsies performed as part of standard of care, and thus billed to the patient or their insurance.

If you have questions about the reimbursement process, please contact the EA funding team at *ea.fundingsheet@jimmy.harvard.edu*

Please fax the completed form to the ECOG-ACRIN Translational Science Team (TST), FAX: (617) 589-0914

Institution CTEP ID: _____

Name of Investigator: _____

NCI Investigator ID: _____

Payee Address

Payee/W-9 Name: _____

Payee Tax ID #: _____

Attention To: _____

Street Address: _____

City, State, Zip: _____

Any Requested Reference on Payment (i.e. Invoice #): _____

	ECOG-ACRIN Case ID	Date of Service	Time Point	Service Performed	Amount Requested
#1			Baseline	Radiology Assisted	$4,000
#2			C1 D7	Radiology Assisted	$4,000
#3			Prior to C2	Radiology Assisted	$4,000
#4			Progression	Radiology Assisted	$4,000

I confirm that these patients are registered to the protocol referenced above, the patient numbers and procedure dates are correct, and the biopsies were performed for the purposes of the trial only, following registration of the patient to the lowest step of the trial, and that the biopsy was NOT standard of care and was NOT billed to insurance or the patient.

Signature: _____ **Date:** _____

If there are problems with this invoice, please contact:

Name	Phone	Fax	Email

ECOG-Operations Office Use Only: **TST Reviewer:** _____ **Date:** _____

Patient	#1	#2	#3	#4
Date of Registration to Step 1				
Registering/Tracking Institution				
Data in STS indicates 'Not billed to insurance'	☐	☐	☐	☐
Performed post-registration & per protocol	☐	☐	☐	☐
Specimen received by CBPF	☐	☐	☐	☐
Approved	☐	☐	☐	☐