# A Phase 2 Trial of Adjuvant Dabrafenib (GSK2118436) in Patients with Surgically Resected AJCC Stage IIIC Melanoma Characterized by a *BRAF*$^{V600E/K}$ Mutation

PROTOCOL FACE PAGE FOR
MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

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| Principal Investigator/Department: | Paul B. Chapman, MD | Medicine/MSO |
| Co-Principal Investigator(s)/Department: | Jedd Wolchok, MD PhD | Medicine/MSO |
| Investigator(s)/Department: | Ping Chi, MD, PhD<br>Sandra D'Angelo, MD<br>Mark Dickson, MD<br>Margaret Callahan, MD<br>James Harding, MD<br>Michael Postow, MD<br>Parisa Momtaz, MD<br>Alexander Shoushtari, MD<br>Charlotte Ariyan, MD, PhD<br>Mary Sue Brady, MD<br>Daniel G. Coit, MD<br>Mario Lacouture, MD<br>Mark Bluth, MD<br>Alyona Weinstein, RN, MSN, FNP-BC<br>Yelena Shames, MS, ANCP-BC, CNRN<br>Nana Prempeh-Keteku, MS, ANP-BC<br>Mimma Errante, MS, NP-C, OCN<br>Jacqueline Bromberg, MD, PhD<br>Klaus J. Busam, MD<br>Jasmine Francis, MD<br>Murk-Hein Heinemann, MD<br>Brian P. Marr, MD<br>David C. Lyden, MD, PhD<br>Taha Merghoub, PhD<br>Katherine Panageas, DrPH<br>David Solit, MD<br>Agnes Viale, PhD<br>Ira J. Dunkel, MD | Medicine/MSO<br>Medicine/MSO<br>Medicine/MSO<br>Medicine/MSO<br>Medicine/MSO<br>Medicine/MSO<br>Medicine/MSO<br>Medicine/MSO<br>Surgery/MSO<br>Surgery/MSO<br>Surgery/MSO<br>Dermatology<br>Radiology<br>Nursing<br>Nursing<br><br>Nursing Nursing Medicine<br>Pathology<br>Ophthalmology<br>Ophthalmology<br>Ophthalmology<br>Pediatrics<br>Medicine<br>Epidemiology and Biostatistics<br>Medicine/GU<br>Genomics Core Laboratory<br>Pediatrics |
| Consenting Professional(s)/Department: | Paul B. Chapman, MD<br>Jedd Wolchok, MD PhD<br>Ping Chi, MD, PhD<br>Sandra D'Angelo, MD<br>Mark Dickson, MD Michael Postow, MD Alexander Shoushtari, MD Ira J. Dunkel, MD | Medicine/MSO<br>Medicine/MSO<br>Medicine/MSO<br>Medicine/MSO<br>Medicine/MSO<br>Medicine/MSO<br>Medicine/MSO<br>Pediatrics |

**Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.**

Memorial Sloan-Kettering Cancer Center
1275 York Avenue
New York, New York 10065

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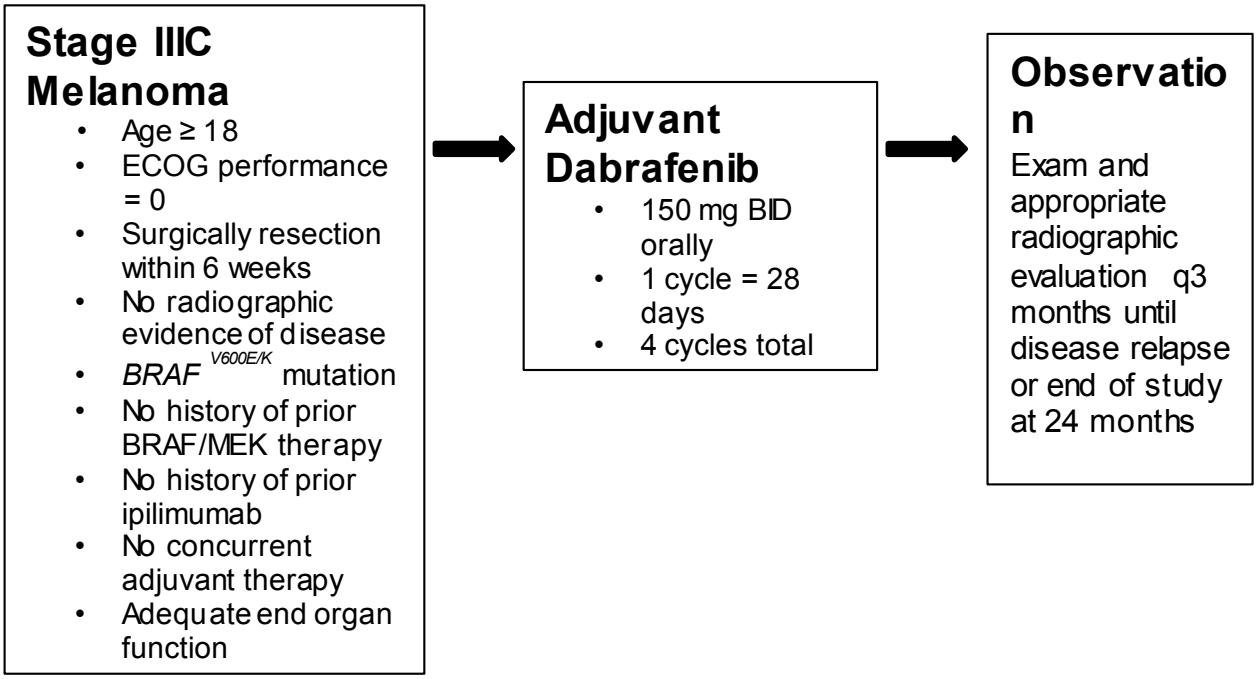
## 1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Inhibition of *BRAF*$^{V600E}$ kinase has emerged as effective therapeutic strategy for patients with metastatic melanoma harboring a *BRAF*$^{V600E}$ mutation. It is reasonable to speculate that *BRAF*$^{V600E}$ kinase inhibitors will benefit molecularly selected melanoma patients at earlier stages of the disease. Patients with stage IIIC melanoma are at an extremely high risk of disease recurrence and death despite definitive surgical resection. Data from our Center indicate that the relapse-free survival (RFS) for stage IIIC disease is only 24% at 2 years. In this single center phase II trial, patients with surgically-resected stage IIIC melanoma characterized by a *BRAF*$^{V600E}$ or *BRAF*$^{V600K}$ mutation will be treated with 4 cycles of adjuvant dabrafenib and monitored clinically and radiographically for disease recurrence for 24 months following surgical resection. We will test the hypothesis that adjuvant *BRAF* kinase inhibition will improve RFS from 24% to 51% at 24 months. The planned accrual is for 23 patients. The primary objective of the study will be to determine the RFS at 24 months. The trial would be considered positive if 9 or more patients are relapse-free and alive at 24 months. The trial would be terminated early if at any time 15 patients relapsed or died before 24 months. Secondary objectives include the assessment of dabrafenib toxicity and the determination of overall survival (OS). In an exploratory fashion, pretreatment tumors biopsies and biopsies at the time of relapse will be obtained to characterize the tumors genetically and to assess for mechanisms of resistance to *BRAF* inhibition. Serial blood samples will also be obtained and used to determine if circulating tumor-derived exosomes can predict melanoma recurrence.

**STUDY SCHEMA**




## 2.0 OBJECTIVES AND SCIENTIFIC AIMS

### 2.1 Primary Objective

To determine the RFS at 24 months for patients with Stage IIIC melanoma harboring a *BRAF*$^{V600E/K}$ mutation who are treated with definitive surgical resection followed by four cycles of adjuvant dabrafenib administration.

### 2.2 Secondary Objectives

To determine overall survival.

To assess toxicity.

### 2.3 Exploratory Objectives

To characterize the genetic heterogeneity of *BRAF*-mutated melanomas and explore mechanisms of intrinsic and acquired resistance to dabrafenib.

To evaluate the ability of circulating tumor-derived exosomes to predict melanoma recurrence.

## 3.0 BACKGROUND AND RATIONALE

### 3.1 Regional metastatic melanoma

It is projected that there will be 76,250 new cases of cutaneous melanoma in the United States in 2012 [1]. Ten to 13% of patients with cutaneous melanoma will present with regional metastatic disease. Regional metastatic melanoma [American Joint Commission on Cancer (AJCC) Stage III disease] is defined by the neoplastic involvement of the regional lymph nodes and/or regional cutaneous disease in-transit. Independent prognostic factors for this stage of disease include the depth of the primary tumor, the presence of ulceration in the primary tumor, the number of tumor-bearing lymph nodes, and the burden of nodal disease [2]. Stages III patients are sub-classified into three groups (i.e. IIIA, IIIB and IIIC) by presence or absence of these important prognostic factors.

Definitive surgical resection is the only widely accepted modality for long-term disease control and cure. Even in the setting of a complete surgical resection, the risk of disease recurrence and death is extremely high, particularly for patients with stage IIIC disease. Data from our Center show that the 5-year relapse-free survival for stage IIIC melanoma is 15%; the 5-year overall survival is only 11% [3]. This indicates that relapse is almost equivalent to death in patients with stage IIIC melanoma. Preventing disease relapse is thus a key objective.

Patients with surgically resectable stage IIIC melanoma have few tolerable and effective systemic therapies available to alter the natural history of their disease. Adjuvant high dose and pegylated interferon therapy have been shown to offer a modest relapse-free survival benefit in randomized studies [4, 5]. Unfortunately, interferon-based adjuvant therapy is poorly tolerated and no study has demonstrated an overall survival advantage [4-7]. As such interferon is not uniformly accepted as a standard of care, despite being the only FDA approved agent for use in the adjuvant setting. Clinical trials of adjuvant immunotherapies,

vaccines and chemotherapies have also been disappointing and have not modified the risk of recurrence or death from melanoma after definitive surgical resection [8].

As surgically resectable stage IIIC melanoma has a high mortality with minimal effective treatments, novel adjuvant and neoadjuvant therapies are clearly necessary to improve patient outcomes.

### 3.2 Mutations in *BRAF* activate the MAPK pathway in melanoma

A subset of melanoma is driven by constitutive activation of the mitogen-activated protein kinase (MAPK) signaling cascade [9]. Fifty to sixty percent of melanomas harbor activating mutations in *BRAF*. Ninety percent of these mutations occur at codon 600 [10]. The most common mutation at this position is a missense error resulting in a valine to glutamate substitution (i.e. $BRAF^{V600E}$). Other variants have also been observed and include *V600K, V600R and V600D* [11]. It is now well-established that melanomas with $BRAF^{V600}$ mutations are dependent on signaling through the MAPK pathway for cellular proliferation and survival [12] and that blocking signaling through this pathway results in cell cycle arrest and apoptosis *in vitro* and *in vivo* [13]. These preclinical observations have led to the clinical development of two potent inhibitors of mutated-*BRAF* kinase: vemurafenib and dabrafenib.

### 3.3 Vemurafenib and Dabrafenib

*In vitro* studies indicate that vemurafenib and dabrafenib effectively block signaling through the MAPK pathway by inhibiting $BRAF^{V600E}$ kinase activity [14, 15]. The $IC_{50}$ of vemurafenib for $BRAF^{V600E}$ kinase is 31nM [14]. Dabrafenib is a more potent inhibitor of this kinase *in vitro* with a corresponding $IC_{50}$ of 0.7nM [15]. Dabrafenib also effectively inhibits $BRAF^{V600K}$ and $BRAF^{V600D}$ kinase with an $IC_{50}$ of 0.5 and 1.8nM, respectively. Both vemurafenib and dabrafenib induce growth suppression, rapid cell cycle arrest, and apoptosis in melanoma cell lines characterized by a $BRAF^{V600E}$ mutation [15, 16]. Likewise, administration of each of the agents *in vivo* results in profound tumor regression in murine xenograft melanoma models [14, 15].

The completed phase I, II and III clinical trials of vemurafenib have confirmed that this agent is a safe and effective treatment modality for patients with metastatic melanoma [17-19]. The pivotal, randomized, open label, phase III trial (BRIM 3) comparing vemurafenib with dacarbazine in patients with previously untreated, *BRAF*-mutated metastatic melanoma led to FDA licencing of the agent in August of 2012 [18]. Forty-eight percent of patients treated with vemurafenib had a confirmed objective response (2 CR and 104 PR) by RECIST criteria. The median time to response was 1.5 months. At the time of first interim analysis, the median follow-up for patients treated with vemurafenib and dacarbazine was 3.8 months and 2.3 months, respectively. Importantly, vemurafenib was associated with a statistically significant relative risk reduction of 63% in the risk of death and of 74% in the risk of death or progression of disease when compared to dacarbazine. These beneficial effects on outcome

were independent of disease stage [i.e. unresectable stage IIIC, Stage IV (M1a, M1b and M1c)]. In the phase II trial of vemurafenib, nearly 90% of patients achieved a maximal response by 4 months [19].

The safety and clinically efficacy of dabrafenib appears to be equivalent to vemurafenib. A multicenter phase I/II trial assessed the tolerability and activity of dabrafenib in patients with previously-treated *BRAF*-mutated metastatic melanoma and other solid tumor [20]. Although a maximum tolerated dose was not identified, dabrafenib at 150 mg twice a day was ultimately selected as the recommended phase II dose. This schedule was comparable in antitumor activity, pharmacokinetic properties and pharmacodynamic effect to higher doses. Twenty-five of 36 (69%) *BRAF*-mutant metastatic melanoma patients who were treated with the recommend phase II achieved an unconfirmed partial or complete response. The median duration of response was 6.2 months; the median progression-free survival was 5.5 months. Tumor biopsies were obtained prior to treatment and 7 (±4) days into treatment in 12 patients. Importantly, a marked decrease in proliferation with associated necrosis and apoptosis was observed in all samples. Two phase II studies of dabrafenib have since confirmed its antitumor activity in melanoma [21, 22]. Response rates in these studies range from 31% to 58% and thus appear to be equivalent to those observed with vemurafenib, which range from 48 to 57% [17-19].

In a multicenter, open label, randomized phase III clinical trial (BREAK-3) in patients with unresectable stage IIIC or IV *BRAF*-mutated melanoma dabrafenib was found to improve progression-free survival compared dacarbazine [23]. Median progression-free survival was 6.7 months for dabrafenib as compared to 2.9 months with dacarbazine with a hazard ratio for progression of 0.35. These data are equivalent to the data obtained from BRIM-3, the randomized phase III study comparing vemurafenib to dacarbazine in patients with unresectable stage IIIC or IV *BRAF*-mutated melanoma. In BRIM-3, the PFS for patients receiving vemurafenib was 6.9 months versus 1.6 months for dacarbazine (HR 0.38) [18, 24].

### 3.4 Study rationale

Preclinical *in vitro* and *in vivo* data with both vemurafenib and dabrafenib indicate that inhibitors of mutated-*BRAF* kinase induce cell death in melanoma cells harboring a *BRAF* mutation [14, 16]. Clinical data demonstrate that inhibition of mutated-*BRAF* kinase results in rapid and significant tumor shrinkage in more than 50% of patients with advanced melanoma characterized by $BRAF^{V600}$ mutations independent of disease stage [15, 17-19]. Correlative studies show that apoptosis and tumor necrosis are apparent within one week after the initiation of *BRAF* kinase inhibitors. Anecdotally, we have observed several pathologic complete responses following metastasectomy after best response to *BRAF* kinase inhibition. This indicates that inhibitors of mutated-*BRAF* kinase have the ability to eradicate bulky metastatic disease. It is thus reasonable to speculate that inhibition of mutated-*BRAF* kinase will benefit molecularly selected melanoma patients at earlier stages of the disease.

The underlying hypothesis of this trial is that treatment of micrometastatic disease for 4 cycles will be sufficient to improve RFS in stage IIIC patients with *BRAF* mutations who are currently free of disease. Based on our data at MSKCC [3], stage IIIC patients would be expected to have a RFS of only 24% at 24 months. We will test the hypothesis that 4 cycles of adjuvant dabrafenib will result in an improvement in RFS from 24% to 51% at 24 months.

The duration of treatment (i.e. 4 cycles) was based on the time to maximal response in patients with bulky disease treated with BRAF inhibitor as well as the observation that resistance to these agents generally develops after month six. It was also felt that if continuous adjuvant treatment with dabrafenib were necessary to improve relapse-free survival, then treatment at relapse would likely be just as effective and the rationale for adjuvant therapy would be undercut.

### 3.5 Correlative studies

*Resistance to BRAF kinase inhibition*

Despite the major success of *BRAF* inhibition, subsets of melanomas are intrinsically resistant to inhibitors of mutated *BRAF* kinase [25]. Fourteen percent of melanoma patients had primary progressive disease on the phase II trial of vemurafenib [19]. Genetic heterogeneity may in part explain *de novo* resistance. Mutations in other signaling pathways and/or tumor suppressor genes may abrogate the cellular dependence on mutated-*BRAF* activity. To this end, concomitant mutational inactivation of *PTEN* and *RB1* has been observed in *BRAF* mutated cell lines and these co-mutations render these cell lines resistant to *BRAF* kinase inhibition [26, 27].

Melanomas also appear to develop acquired resistance to *BRAF* inhibition. The median progression-free survival to vemurafenib is 5-7 months in the metastatic setting [18]; the progression-free survival to dabrafenib appears to be similar. Investigators have proposed numerous candidate mechanisms for acquired resistance [28-32], however, reactivation of the RAS-RAF-MEK-ERK pathway appears to be a prominent mode of resistance to *BRAF* kinase inhibition. Acquired *N-RAS* (Q61K) and *MEK* (C121S) mutations [30-32] as well as a unique splice variant of $BRAF^{V600E}$ [32] have been shown to up-regulate the MAPK signaling pathway and convey resistance to *BRAF* kinase inhibition.

Additional mechanisms will likely be postulated in the months to come. Unfortunately, few patient samples have actually been interrogated to date. The proposed trial is uniquely positioned to acquire substantial tumor tissue. Tumors obtained prior to treatment will be genetically characterized by whole exome sequencing to identify co-mutations in *BRAF* mutated melanomas. Tumor will also be obtained in virtually all patients at time of progression since tissue confirmation of progression is a standard of care. Tumor biopsies at progression will allow discovery of resistance mechanisms in a prospective manner.

*Circulating tumor-derived exosomes as a marker of melanoma recurrence*

Exosomes are microvesicles derived from the luminal membrane of the endocytic compartment in both normal and neoplastic cells [33]. These membrane-bound particles range between 30 and 100 nanometers in size and are constitutively released into the extracelluar matrix after fusion of endosome with the cell membrane. Exosomes contain a number of subcellular elements including messenger RNAs, micro-RNAs, DNA, and a variety of proteins involved in multiple cellular processes such as antigen presentation, cell targeting and adhesion, apoptosis, signal transduction, and cell proliferation. Thus, exosomes play a critical role in mediating intercellular communication allowing for the horizontal transfer of information between cells [34].

Peinado and colleagues [34] recently isolated and characterized exosomes from the sera of patients with increasing stages of cutaneous melanoma. Exosome size distribution and absolute number did not differ based on clinical stage. Interestingly, exosomes isolated from patients with advanced stages of melanoma were qualitatively different from normal controls as well as individuals with earlier stages of the disease. Specifically, exosomes from patients with Stage IV disease were characterized by both higher concentrations of proteins and a unique protein signature including tyrosinase-related protein-2 (TYRP2), very late antigen 4 (VLA-4), heat shock protein 70 (HSP70), and the MET oncoprotein. Exosomal levels of TYRP2 were also significantly higher in patients with Stage III disease and in a retrospective analysis of 29 patients correlated with disease progression. In an exploratory fashion, we will obtain serial peripheral blood samples from all patients on this trial to measure and characterize tumor-derived exosomes in patients with surgically resected stage IIIC disease. We will prospectively test the hypothesis that qualitative changes in circulating exosomes will be able to predict melanoma recurrence.

## 4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

### 4.1 Design

This is a single institution, single arm, phase II trial of adjuvant dabrafenib in patients with surgically-resected stage IIIC cutaneous melanoma characterized by a *BRAF*$^{V600E/K}$ mutation.

### 4.2 Intervention

Following definitive surgical resection, eligible patients will receive dabrafenib at 150 mg twice a day by mouth for 4 cycles. One cycle is 28 days.

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## 5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

### 5.1 Mechanism of Action

Dabrafenib, a 4-(3-aminosulfonylphenyl)-5-(pyrimidin-3-yl) thiazole, is an orally bioavailable, small molecule, ATP-competitive inhibitor of *BRAF*$^{V600}$ kinase. Dabrafenib (IND # 105032) is an investigational agent manufactured and supplied by Novartis Pharmaceuticals. Detailed information regarding the pharmacologic properties of dabrafenib can be found in the Investigator's Brochure.

### 5.2 Formulation, Storage and Packaging

Dabrafenib will be provided as 50 mg and 75 mg capsules. Each capsule contains 50 mg or 75 mg as free base present as the mesylate salt. The inactive ingredients include microcrystalline cellulose, magnesium stearate, gelatin, FDA red iron oxide and titanium dioxide. The drug should be stored in a dry location at room temperature not exceeding 25°C.

### 5.3 Administration of Dabrafenib

Dabrafenib will be dosed at 150 mg twice a day by mouth. Patients are instructed to take 150 mg in the morning and 150 mg in the evening, approximately 12 hours apart. Dabrafenib should be administered under fasting conditions, either 1 hour before or 2 hours after a meal. If a study participant vomits after a dose, the patient should be instructed not to retake the dose and should take the next dose at its scheduled time. If a dose is missed, it can be taken up to 6 hours prior to the next dose to maintain the twice daily regimen. Instructions for dose modifications can be found in Section 9.

## 6.0 CRITERIA FOR SUBJECT ELIGIBILITY

### 6.1 Subject Inclusion Criteria

6.1.1 AJCC (2009) stage IIIC cutaneous melanoma rendered free of disease by surgical resection no greater than 90 days prior study enrollment. Patients with unknown primaries will be eligible for this trial. Patients with a history of resected stage I or II cutaneous melanoma who subsequently have their first disease recurrence meeting the criteria for stage IIIC disease will also be eligible for this trial.

6.1.2 Patients must have clear margins after wide local excision. Patients with nodes that are palpable or detectable on radiologic imaging must have an adequate lymphadenectomy.

6.1.3 Patients must be adequately recovered from surgery, radiation therapy, or any surgical complications prior to enrollment. In general, this means patients will be off antibiotics from wound infections and drains removed. However, if necessary, patients can be treated with a drain in place at the discretion of the PI if the 90 days window is about to expire.

6.1.4 Histologic proof of melanoma reviewed and confirmed by MSKCC.

6.1.5 A documented *BRAF*$^{V600E}$ or *BRAF*$^{V600K}$ mutation by genotyping or IHC [35] performed by a CLIA certified laboratory.

6.1.6 Age $\geq$ 16 years old.

6.1.7 ECOG performance status = 0 or Karnofsky Performance Status equivalent (Appendix A).

6.1.8 The ability to swallow pills.

6.1.9 Patients must have adequate organ and marrow function as defined below:

| | |
|---|---|
| Absolute neutrophil count | ≥ 1.5 K/mcL |
| Platelets | ≥ 100 K/mcL |
| Hemoglobin | ≥ 9.0 g/dL |
| Total bilirubin | ≤ 1.5 X institutional upper limit of normal (ULN)<br>≤ 3.0 X institutional ULN if the patient has Gilbert's Syndrome |
| AST (SGOT) and ALT (SGPT) | ≤ 2.5 X institutional ULN |
| Creatinine | ≤ 1.5 X institutional ULN or creatinine clearance (calculated or measured) > 60 ml/min |

6.1.10 Women with child bearing potential and men with reproductive potential must be willing to practice acceptable methods of contraception.

## 6.2 Subject Exclusion Criteria

6.2.1 Patients with a history of stage III melanoma (any primary melanoma with locoregional nodal/subcutaneous disease) treated with surgical resection who subsequently have disease recurrence meeting the criteria for stage IIIC disease.

6.2.2 Prior therapy with ipilimumab, other BRAF inhibitors, or MEK inhibitors.

6.2.3 Concurrent adjuvant immunotherapy, chemotherapy, or radiotherapy.

6.2.4 Current use of a prohibited medication while on dabrafenib (See Section 9, Appendix B).

6.2.5 Presence of active gastrointestinal disease or other condition that will interfere significantly with the absorption of drugs.

6.2.6 A history of known glucose-6-phosphate dehydrogenase (G6PD) deficiency.

6.2.7 Pregnant women and lactating women.

6.2.8 A concurrent second malignancy even if it does not require active therapy. Patients with indolent B-cell malignancies will not be eligible. Prior malignancy will be allowed as long as the patient is known to be free of disease for at least 3 years.

6.2.9 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris,

cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

6.2.10 QTc interval > 500 msec, unless a bundle branch block is also present.

### 6.3 Inclusion of Women and Minorities

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

## 7.0 RECRUITMENT PLAN

Patients will be recruited through the Melanoma Disease Management Team of the Memorial Sloan-Kettering Cancer Center. Melanoma tumors are routinely genotyped for *BRAF* at MSKCC. The Melanoma/Sarcoma service and the Melanoma Disease Management Team each hold weekly interdepartmental meetings to identify study participants for open clinical trials.

## 8.0 PRETREATMENT EVALUATION

The following procedures and assessments must be performed prior to treatment start:

### 8.1 At anytime prior to the start of the study

- Histologic confirmation of melanoma by a MSKCC pathologist.
- Assessment of *BRAF* mutational status (either primary or regional metastases) by CLIA certified laboratory.

### 8.2 Within 90 days of the start of study

- Complete surgical resection of Stage IIIC disease. This can be completed either at MSKCC or at an outside institution.
- Patients may have adjuvant radiation therapy but all treatment must be completed and patients adequately recovered before beginning dabrafenib.

### 8.3 Within 4 weeks of the start of the study

- Written Informed Consent
- A contrast-enhanced CT or MRI of the brain
- ECG

### 8.4 Within 2 weeks of the start of the study

- Updated medical history and physical examination
- A complete skin examination by dermatology or a consenting medical oncologist.
- An eye examination by ophthalmology
- Laboratory studies including a CBC with differential; comprehensive metabolic panel; serum phosphorous, magnesium and LDH levels.

- A serum pregnancy test for woman of child-bearing potential.
- Appropriate radiologic assessment to assure no evidence of disease. In general, this will involve a CT scan (with contrast) of the chest, abdomen and pelvis; if the patient is not able to undergo a CT scan, a MRI with and without gadolinium may be used. For patients with a primary melanoma below the knee, a PET scan with a non-contrast chest CT will also be acceptable.

## 9.0 TREATMENT/INTERVENTION PLAN

### 9.1 Adjuvant Dabrafenib

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 11. Appropriate dose modifications for dabrafenib are described below in Section 9.2. No investigational or commercial therapies other than those described below may be administered with the intent to treat the patient's malignancy.

If all eligibility criteria are met, study participants will self-administer dabrafenib by mouth at a dose of 150 mg twice a day. Four weeks of treatment is one full cycle. After each cycle (± 5 days) the study participant will be seen in clinic for a complete clinical evaluation as detailed in section 10.0. A pill diary will be provided to the patient and will be reviewed at the completion of each cycle (Appendix C). This will be used to assure compliance with the regimen. In the absence of treatment delays due to adverse event(s), dabrafenib will continue for 4 cycles or until one of the criteria listed in Section 13 apply.

### 9.2 Dose Modification

#### 9.2.1 Dose Modifications Algorithm

Management of symptomatic adverse drug reactions may require temporary interruption and dose reduction of dabrafenib treatment. Table 1 describes the dose levels to be used for any necessary dose modifications.

**Table 1: Dabrafenib Dose Reduction Algorithm**

| Dose Level | Dose/Schedule |
|---|---|
| 0 | 150 mg BID |
| -1 | 100 mg BID |
| -2 | 75 mg BID |
| -3 | 50 mg BID |

### 9.2.2 Dose Modifications/Interruption for Toxicity

The severity of adverse events will be graded utilizing the CTCAE version 4.0. Guidelines for dose modifications and interruptions for management of toxicities associated with the study treatment other than fever, neutropenia, rash, hand-foot syndrome, renal dysfunction, and QTc elongation are provided in Table 2. Dose modifications for fever and neutropenia are provided in Table 3 and 4, respectively. Dose modifications for rash and hand foot syndrome are provided in Table 5 and Table 6, respectively. Table 7 contains guidelines for the management of renal insufficiency.

Dabrafenib must be withheld if the QTc exceeds 530 milliseconds. This will be based on the average QTc value of triplicate ECGs. For example, if an ECG demonstrates a prolonged QT interval, obtain 2 more ECGs over a brief period, and then use the averaged QTc values of the 3 ECGs to determine whether the subjects should have study medication withheld.

If the QTc prolongation resolves to Grade 1 or baseline, the subject may be re-started on the study medication if the Investigator and Novartis Medical Monitor agree that the subject will benefit from further treatment.

**Table 2: Dose Modification for non-hematologic and hematologic toxicity (except neutropenia)**

| Non-hematologic and hematologic Toxicity (except neutropenia) | Dose Modification Algorithms[a, b, d, e] |
|---|---|
| Grade 1 | Continue dabrafenib at full dose, monitor as clinically indicated. |
| Grade 2 | **For Grade 2 Diarrhea with accompanying risk factors[c]** Hold dabrafenib until return to ≤ Grade 1, provide supportive care.<br><br>**For all other toxicities:** Consider holding dabrafenib until resolution to Grade 1 or baseline; provide supportive care as clinically indicated. Monitoring of laboratory values should occur as clinically indicated.<br><br>**For Grade 2 or higher respiratory symptoms (i.e. cough, dyspnea, hypoxia etc.),** evaluation by a CT scan is recommended. |
| Grade 3 | **For Grade 3 toxicity,** hold dabrafenib until toxicity is Grade 1 or baseline then reduce dose of dabrafenib by 1 dose level. The subject may be continued at the same dose if, in the judgment of the investigator, the toxicity is considered to be unrelated to dabrafenib. Continue to monitor as clinically indicated.<br><br>**If any Grade 3 toxicity recurs,** hold dosing until Grade 1 or baseline, then reduce current dose of dabrafenib by one dose level. |
| Grade 4 | Discontinue dabrafenib. Continue to monitor as clinically indicated, and provide supportive care as needed<br><br>If in the investigator's judgment the toxicity is unlikely to recur then, hold until toxicity is Grade 1 or baseline, then reduce dose of dabrafenib by 1 dose level. If Grade 4 toxicity recurs after dose reduction, discuss continuation of study drug with the Novartis Medical Monitor. |

a. The minimum dose is 50mg BID. If a subject requires dose reduction below 50mg BID then the subject must be discontinued from study medication.
b. For adverse events of abdominal pain or suspected pancreatitis, amylase and lipase laboratory samples should be collected.
c. Risk factors for cancer treatment-induced diarrhea include: fever, orthostatic symptoms (i.e. dizziness), abdominal pain/cramping, or weakness.
d. If the subject has a Grade 3 or 4 laboratory abnormalities that, in the judgment of the investigator, is not considered clinically significant, dose modification is not required.
e. For subjects who develop symptoms associated with uveitis including blurry vision, eye pain or erythema ophthalmologic consult is required.

**Table 3: Dose Modification and Guidelines for Management of Neutropenia**

| Grade | ANC value K/mcl | Management of Neutropenia | Dabrafenib Dose Adjustment |
|---|---|---|---|
| 1 | 1.5 to LLN | • Monitor per protocol study calendar. | • Continue at current dose |
| 2 | 1.0 to <1.5 | • Re-check ANC in 1 week. If improvement to grade 1, continue to monitor per study calendar.<br>• If stable at grade 2, monitor ANC every 2 weeks until resolution to grade 1 or until stable for 4 weeks<br>• If worsens to grade 3 or 4 follow below. | • Any occurrence: continue at current dose |
| 3 | 0.5 to <1.0 | • Re-check ANC at least weekly during dose interruption.<br>• If resolved to grade 1, re-check ANC 3 days after rechallenge with dabrafenib and then 1 week later. | • Any occurrence: hold until return to grade 1, then reduce one dose level<br>• 1st recurrence: discontinue dabrafenib or hold until return to grade 1, then reduce one dose level<br>• 2nd recurrence: discontinue dabrafenib. |
| 4 | < 0.5 | • Re-check ANC at least weekly<br>• If resolved to grade 1, re-check ANC 3 days after rechallenge with dabrafenib and then 1 week later. | • Discontinue or hold until return to grade 1, then reduce dabrafenib by one dose level.<br>• 1st recurrence discontinue dabrafenib |

**Table 4: Dose Modification and Guidelines for Management of Fever**

| | Definition | Dose Modification Algorithms | Dabrafenib Dose Adjustment |
|---|---|---|---|
| Complicated fever. (≥38.5°C or 101.3°F) | Grade ≥3 or any grade with signs and symptoms including; rigors, dehydration, hypotension, dizziness or weakness | • Subject must be evaluated in clinic<br>• Labs: Obtain blood sample to assess ANC, serum creatinine and BUN if sample was not collected within 3 days of the fever.<br>• Evaluate for signs and symptoms of infection and consider work up as clinically indicated.<br>• If signs and symptoms of dehydration occur, consider intravenous hydration.<br>• When restarting drug, administer acetaminophen 500 mg or ibuprofen 400 mg (or suitable alternative) prophylactically BID with study drug for 2-3 days.<br>• Re-check ANC 1 week after the start of fever; encourage subject to take oral temperature daily for 4 weeks after restarting dabrafenib. | • Interrupt dabrafenib immediately and hold until fever resolves to <38.0°C or 100.4°F and accompanying symptoms resolve<br>• At rechallenge reduce dose of dabrafenib by one dose level. |
| Uncomplicated Fever (≥38.5°C or 101.3°F) | defined as grade≤ 2 without signs and symptoms as described above | • Encourage oral hydration.<br>• If subject is seen in the clinic, obtain blood sample to assess ANC, serum creatinine and BUN if sample was not collected within 3 days of the fever<br>• Evaluate for signs and symptoms of infection and consider work up as clinically indicated.<br>• If signs and symptoms of dehydration occur, follow algorithm for complicated fever.<br>• When restarting drug, administer acetaminophen 500 mg or ibuprofen 400 mg (or suitable alternative) prophylactically BID | • Hold until fever resolves to <38.0°C or 100.4°F.<br>• Dabrafenib may be restarted at the original dose level or reduced one dose level as clinically indicated. |

| | | | |
|---|---|---|---|
| | | with study drug for 2-3 days.<br>• Re-check ANC 1 week after the start of fever; encourage subject to take oral temperature daily for 4 weeks after restarting dabrafenib. | |

1. If fever does not recur after 3 days, prophylactic antipyretics may be discontinued or tapered.

**Table 5: Guidelines for Skin Rash Management**

| Skin Toxicity Grade (CTCAE v 4.0) | Guideline for Management | Dose Reduction |
|---|---|---|
| 1 | Topical corticosteroids (mometasone, betamethasone, or fluocinonide creams) | None |
| 2 | As for grade 1, with the addition of diphenhydramine 50 mg bid, oral prednisone (short course) | None: if unacceptable to subject or medically concerning then hold until recovery to ≤Grade 1. Restart at same dose. |
| ≥3 | | Hold until recovery to ≤Grade 1. Then reduce the dose by one dose level. |

**Table 6: Guidelines for Hand-Foot Syndrome**

| Grade | Occurrence | Dose Modification |
|---|---|---|
| Grade 1: Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain | Any occurrence. | Continue treatment with dabrafenib and start topical therapy[a] for symptomatic relief. |
| Grade 2: Skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting instrumental ADL | 1st occurrence. | Continue treatment with dabrafenib and start topical therapy[a] for symptomatic relief. Instruction on life-style modifications should also be given.[b]<br>If no improvement within 28 days, see below |
| | No improvement within 28 days or additional occurrence. | Interrupt dabrafenib treatment until toxicity resolves to Grade 0-1.[c]<br>When resuming treatment, decrease dabrafenib dose by one dose level. Continue topical therapy[a] for symptomatic relief. Instruction on life-style modifications should also be given[b] |
| Grade 3 or intolerable grade 2: Severe skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting self care ADL | 1st or 2nd occurrence. | Interrupt dabrafenib treatment until toxicity resolves to Grade 0-1.[c]<br>When resuming treatment, decrease dabrafenib dose by one dose level. Continue topical therapy[a] for symptomatic relief. Instruction on life-style modifications should also be given.[b] |
| | 3rd occurrence. | Discontinue dabrafenib treatment. |

a. Topical therapy includes the following options; keratolytics (e.g. urea 40%), high potency corticosteroids (fluocinonide, clobetasol)oral analgesia (non-steroidal anti-inflammatories or narcotics)

b. Lifestyle modifications include; avoidance of excessive temperatures, exercise, and ill-fitting clothing/shoes. Use of soft slippers (Tempurpedic or Crocs), friction-relieving measures (calfskin,

gels ).

c. HSFR usually resolves within 2-4 weeks of drug cessation.

**Table 7: Renal Insufficiency Guidelines**

| Creatinine | Guidelines for Management |
|---|---|
| For subjects with serum creatinine increase > 0.2 mg/dL but ≤ 0.5 mg/dL above baseline: | 1. Continue dabrafenib and re-check serum creatinine within 1 week<br>2. If subject has fever (T >/= 38.5C): treat pyrexia as per guidelines (please note NSAIDs can induce renal insufficiency, especially in subjects with dehydration); encourage oral fluids<br>3. If elevation in serum creatinine persists beyond 1 week, please contact medical monitor |
| For subjects with serum creatinine rise >0.5 mg/dL above baseline or serum creatinine >2 mg/dL: | 1. Interrupt dabrafenib<br>2. If subject has fever (T >/= 38.5C): treat pyrexia as per guidelines (please note NSAIDs can induce renal insufficiency, especially in subjects with dehydration); consider IV hydration<br>3. Follow serum creatinine at least twice weekly (or consider hospitalization if serum creatinine cannot be monitored frequently)<br>4. Consider renal consultation<br>5. If serum creatinine returns to baseline, may restart study treatment at the same dose, or reduced by one dose level at the investigator's discretion.<br>6. Consider renal biopsy if clinically indicated , for example:<br>a. Renal insufficiency persists despite volume repletion<br>b. Subject has new rash or signs of hypersensitivity (such as elevated eosinophil count)<br>7. Prior approval of Medical Monitor is required to re-initiate therapy if<br>c. Subject's serum creatinine has not returned to baseline<br>d. There is evidence of thrombotic microangiopathy |

## 9.3 Drug Interactions

### 9.3.1 Prohibited Medications

The pathways for metabolism and elimination of dabrafenib are presently unknown in humans. Preclinical *in vitro* data indicate that dabrafenib is primarily metabolized by CYP2C8, CYP3A4, and CYP2C19. Dabrafenib is also a substrate of two cell membrane drug transporter proteins; human P-glycoprotein (PGP) and murine breast cancer resistant protein 1 (BCRP1) *in vitro*. Drugs that are strong inhibitors or inducers of CYP3A, CYP2C8, PGP or BCRP1, are prohibited because they may increase or decrease dabrafenib concentrations, respectively (see Appendix B).

### 9.3.2 Cautionary Medications

The following medications should be used with caution (see Appendix B):

- Drugs that are mild/moderate inhibitors or inducers of CYP3A, CYP2C8, PGP or BCRP because they may alter dabrafenib concentrations.

- *In vitro* dabrafenib inhibits CYP2C8, CYP2C9, and CYP2C19 activity. Concentration of medications metabolized by these enzymes may be altered by dabrafenib.

- *In vitro* dabrafenib induces CYP3A4, CYP2B6, CYP2C8, CYP2C9, and CYP2C19. Co-administration of dabrafenib and medications which are affected by the induction of these enzymes may result in loss of efficacy. If co-administration of these medications is necessary, investigators should monitor subjects for loss of efficacy or consider substitutions of these medications.

## 10.0 EVALUATION DURING TREATMENT/INTERVENTION

### 10.1 Standard Evaluation

Study participants will be evaluated at the start of each 4 week cycle (± 5 days, see Table 8). At these visits, patients will be assessed clinically for melanoma recurrence, toxicity, and performance status. A full physical examination with standard vital signs will also be performed in addition to an ECG and standard laboratories including a CBC, comprehensive metabolic panel, phosphorous, magnesium, and LDH. Radiographic evaluation of disease status will occur at the end of cycles 2 and 4. Dermatological exams (to assess toxicity and to screen for squamous cell carcinoma/keratoacanthomas) will also be done at the completion of cycles 2 and 4 or more frequently as indicated clinically. Ophthalmologic exams will be done at the completion of Cycle 1 and 3 or more frequently as indicated clinically. Dabrafenib will be discontinued after 4 cycles of adjuvant therapy or sooner for disease recurrence or the development of any of the conditions listed in Section 13.0.

After the completion of adjuvant dabrafenib, study participants will undergo active surveillance for disease recurrence. Patients will present at 6 months for a medical history, physical examination with standard vital signs, standard laboratories, and a radiographic evaluation of disease status. This assessment will be repeated every 3 months until the completion of the active follow-up period at 24 months from the date of surgical resection or at recurrence. These assessments and radiographic studies can occur 2 weeks earlier or later without being considered a protocol violation. After 24 months, patients who remain free of disease will continue to undergo routine follow-up and disease assessment at the discretion of their treating physician. Their charts will be reviewed by research staff biannually to monitor for disease relapse and survival and data collection will be limited to survival status until the completion of the study.

**Table 8: Pretreatment Evaluation/Evaluation during Treatment**

| | Screen [i] | Adjuvant Dabrafenib [j] | | | | Observation [h] | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Cycle** | | *Cycle 1* | *Cycle 2* | *Cycle 3* | *Cycle 4* | | | | |
| **Month** | | | | | | 6 | Every 3 months | 24 months/ End of Study | Survival (every 6 months) |
| **Week** | | 1 2 3 4 | 5 6 7 8 | 9 10 11 12 | 13 14 15 16 | | | | |
| Medical History | X | X | X | X | X | X | X | X | |
| Pill Diary | | X | X | X | X | | | | |
| ECOG Performance Status | X | X | X | X | X | X | X | X | |
| Physical Exam [a] | X | X | X | X | X | X | X | X | |
| Laboratory Evaluation [b, c] | X | X | X | X | X | X | X | X | |
| ECG | X | X | X | X | X | | | | |
| Radiologic Evaluation [d] | X | | X[k] | | X[k] | X | X | X | |
| Dermatology Evaluation [h] | X | | X | | X | | | | |
| Ophthalmologic Evaluation [h] | X | X | | X | | | | | |
| MRI Brain [e] | X | | | | | | | X | |
| Tumor Biopsy [f] | | | | | | | | X | |
| Research Bloods [g] | | X | X | X | X | X | X | X | |
| Survival Review | | | | | | | | | X |

a: Complete physical examination with standard vital signs
b: CBC, CMP, Phosphorous, Magnesium and LDH
c: Serum β-HCG if applicable
d: CT-C/A/P with contrast (preferred) or MRI with and without gadolinium (if contrast allergy) or PET scan with non-contrast CT of the chest (if below the knee melanoma primary)
e: Contrast enhanced CT-head is an acceptable alternative
f: Mandatory tumor biopsy at relapse of disease
g: One 10cc lavender top, 2 cell-free DNA BCT tubes (Streck, Inc.), and 2 10 cc green top tubes at the first research blood draw; two 10cc green top tubes and 2 cell-free DNA BCT tubes (Streck, Inc.) thereafter as indicated on the study calendar.
h: ± 2 weeks
i: Refer to Section 8.0, laboratories and ECG performed at screening do not need to be performed at Cycle 1, week 1 if these studies were completed within 7 days of Cycle 1, week 1.
j: Treatment window ± 5 days for each cycle
k: ± 1 week

### 10.2 Correlative Studies and Tumor Biopsies at Progression of Disease

Pre-treatment tumor material will be available from the biopsy used to establish that the patient had stage IIIC melanoma or from the initial surgical resection of residual disease. In patients who relapse, the standard of care is to obtain a biopsy to confirm progression. This will also be available. Biopsies will be performed either by the Principal Investigator or staff members from surgery, dermatology, or interventional radiology. Tissue samples will either be collected from the Tissue Procurement Service (TPS) after appropriate pathological review or directly delivered to the Wolchok Lab by a Research Study Assistant or lab member. We shall coordinate samples within Pathology through Dr. Klaus Busam and/or any other appropriate members of the pathology service. Tissue samples will be analyzed with the appropriate assays described in this protocol, and stored in the Immune Monitoring Facility in the Zuckerman Research Building under the supervision of Dr. Jedd Wolchok and Dr. Taha Merghoub.

In addition, peripheral blood will be obtained on the first day of therapy and then every 3 months for the duration of the study. One 10cc lavender top tube and 2 10cc green top tubes of peripheral blood will be collected on the first day of treatment. The lavender top tube will be utilized to extract germline DNA to serve a control for the genetic analyses described below. This tube of blood will be delivered by the research staff to the Wolchok Lab for storage and processing as described below. The green top tubes and all additional research bloods will be used for exosomes analysis. These blood samples will be delivered to the laboratory of Dr. Jacqueline Bromberg for storage and processing as described below.

DNA from pretreatment tumor, germline DNA from peripheral blood, and tumor DNA from progressing melanoma will be analyzed. These studies will be performed in the laboratory of Dr. David Solit and Michael Berger using an exon capture assay. This assay, designed by Dr. Berger, currently sequences all coding exons of 230 cancer-associated genes including *PTEN*, *PIK3CA*, *AKT1*, *RB1*, *NF1, TP53, ERBB4* and others. In brief, tumor and normal DNA from each patient is used to generate a bar-coded library for sequencing analysis. Libraries are then subjected to exon capture of all coding exons for the 230 gene panel using custom-designed probes generated using the Agilent SureSelect Target Enrichment system [31]. Hybridized DNA is then sequenced using Illumina HiSeq 2000 instrumentation to generate paired-end 75-bp reads. Read pairs are assigned to the corresponding tumor samples according to the identity of each barcode and then aligned to the reference human genome (hg19) using the BWA algorithm [36], and performance metrics are calculated using the publically available suite of Picard tools (http://picard.sourceforge.net). Sequence variants, sequence coverage, and copy number alterations in tumor samples are determined using additional algorithms developed by the Medical and Population Genetics and Cancer Genome Analysis groups at the Broad Institute, including the Genome Analysis Toolkit (GATK) [37, 38]. Both tumor and matching normal DNA are analyzed simultaneously to identify germline single nucleotide polymorphisms (SNPs). In preliminary studies, we have generated average mean read coverage of over 500X using a DNA input of 250-500

nanograms. Importantly, this assay can be carried in FFPE-derived DNA, underscoring the utility of exon capture sequencing in identifying genetic aberrations from FFPE tissue.

Exosome analysis will be completed in the laboratories of Drs. David Lyden and Jacqueline Bromberg. Exosomes will be purified and analyzed as previously described [34]. Briefly, fresh or frozen human plasma will be isolated by centrifugation followed by serial ultracentrifugation with or without filtration. The LM10 nanoparticle characterization system (NanoSight) will be used for real-time analysis of particle size, concentration and aggregation. Exosomes will be further characterized by multiple methods including flow cytometry, immunoblotting, electron microscopy, reverse phase high pressure liquid chromatography with mass spectrometry (HPLC-MS), and gene expression profiling analysis. Importantly, the concentrations of exosomal levels of TYRP2, VLA-4, HSP70, and the MET oncoprotein will be determined over time in each patient in an effort to prospectively evaluate exosomal content as biomarker of melanoma recurrence.

Two tubes of blood (cell-free DNA BCT tubes (Streck, Inc.) or another appropriate tube for cFDNA) will be collected pre-treatment and every time research bloods are collected thereafter as shown in Table 8, in order to measure circulating tumor-derived DNA. Plasma will be stored until needed. DNA will be extracted from plasma and analyzed by digital PCR in the Genomics Core Laboratory (Agnes Viale, head). Probes will be used specific for both mutated and wild-type BRAF V600E or V600K to allow quantification of tumor-derived and non-tumor-derived DNA. The hypothesis to be tested is that detection of circulating tumor-derived DNA will be an accurate measure of tumor recurrence.

## 11.0 TOXICITIES/SIDE EFFECTS

### 11.1 Adverse Events

An Adverse Event (AE) is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the patient that emerge during the protocol specified AE reporting period, including signs or symptoms associated with recurrence of melanoma that were not present prior to the AE reporting period.
- Complications that occur during the study as a result of protocol-mandated interventions (e.g., invasive procedures such as biopsies).
- AEs that occur prior to assignment of study treatment that are related to a protocol-mandated intervention (e.g., invasive procedures such as biopsies or medication washouts).
- Preexisting medical conditions that are judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

### 11.2 Serious Adverse Event

Serious Adverse Events (SAEs) as defined by the FDA will be recorded and reported as detailed in section 17.2. Recurrent melanoma will not be considered an SAE. However, development of a new primary melanoma will be reported as a SAE.

### 11.3 Assessment of Adverse Events

All adverse events encountered during the study will be evaluated according to the NCI Common Toxicity Grading system version 4.0. Grade, duration and treatment will be recorded. Life threatening toxicities and serious adverse events should be reported immediately to the Principal Investigator.

### 11.4 Previously Reported Toxicities Associated with Dabrafenib

The interim results of a phase I/II trial of the dabrafenib in patients with metastatic melanoma and other solid tumors were reported at ASCO in 2010 [15]. Dabrafenib was generally well tolerated with a manageable toxicity profile. The majority of all AEs were reported as Grade 1 and 2. Acute adverse events have been reversible upon discontinuation of dabrafenib and in most instances the drug can be re-started with a dose reduction.

A comprehensive list of the previously reported drug-related toxicities associated with dabrafenib as well as their relative frequencies is presented below. In addition, a more complete discussion will follow regarding a subset of important adverse events with guidelines for management and prevention.

#### 11.4.1 Likely Toxicities (>10%)

- Anemia
- Diarrhea
- Nausea
- Vomiting
- Anorexia
- Constipation
- Rash
- Actinic keratosis
- Hyperkeratosis
- Squamous Cell Carcinoma (SCC) of the skin
- Alopecia
- Pruritus
- Fatigue
- Headaches
- Pyrexia
- Syncope
- Arthralgias
- Myalgias
- Chills

#### 11.4.2 Less Likely Toxicities (≥1% and <10%)

- Leukopenia and Neutropenia
- Hypophosphatemia
- Abdominal Pain
- Influenza-like Symptoms
- Renal Dysfunction/Acute Renal Failure
- Acrochordon
- Cutaneous papillomas
- Grover's Disease
- Palmar-Plantar Erythrodysesthesia (PPE)
- Uveitis

#### 11.4.3 Rare But Serious (< 1%)

- Pancreatitis
- Drug Hypersensitivity Reactions
- Uveitis/Iritis
- Retinal Vein Occlusion

### 11.5 Pyrexia

Pyrexia has been observed in several patients on a number of ongoing clinical trials. Fevers have occasionally been associated with hypotension, rigors, renal insufficiency/renal failure, weakness, dizziness, syncope, presyncope, dehydration, nausea, vomiting, and/or an influenza-like illness. Generally, this syndrome is observed within 30 days of initiating dabrafenib. Study participants with pyrexia should be evaluated as detailed in Table 4.

### 11.6 Acute Renal Failure

Acute renal failure and granulomatous interstitial nephritis have been reported in study participants receiving dabrafenib. In some cases, pyrexia may be associated with renal insufficiency/renal failure, possibly secondary to dehydration or hypotension. Renal function should be monitored carefully, especially in patients with pyrexia. Guidelines for the management of renal dysfunction can be found in Table 7.

### 11.7 Squamous Cell Carcinoma of the Skin

*BRAF* inhibition is associated with the development of squamous cell carcinoma (SCC) of the skin, keratoacanthomas (KA) and cutaneous papillomas [39]. The median time to appearance is approximately 8 weeks into treatment. All suspicious lesions should be completely resected by a dermatologist and submitted for pathologic review. A dose reduction is not indicated for this adverse event.

### 11.8 Ophthalmologic Effects

Ophthalmologic effects including blurred vision (2%), uveitis and iritis (<1%), eye pain (<1%), visual impairment (<1%) and reduced visual acuity (<1%) have been observed in clinical studies to date, with all events Grade 1 or 2. Retinal vein occlusions have also been reported with RAF inhibitors. An ophthalmologic consult is required for subjects developing symptoms associated with uveitis including blurry vision, eye pain or erythema.

### 11.9 Reproductive Risk

Preclinical data indicate that dabrafenib is detrimental to the developing fetus. Thus, fertile patients must not become pregnant or father a child while on study. Contraception should be utilized for the duration of the study and for at least 6 months after study completion. Women should not breastfeed while on study.

## 12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

### 12.1 Assessment of Relapse Free Survival

Relapse free survival is defined as the time from surgical resection to the first recurrence or death as assessed by physical examination and radiographic evaluation. All recurrences will be confirmed by biopsy and histologic evaluation.

### 12.2 Assessment of Overall Survival

Overall survival is defined as the time from surgical resection to death or last follow-up. Follow up will continue until the completion of the study.

### 12.3 Assessment of Toxicity

Toxicity will be graded by the NCI Common Toxicity Criteria (CTC) version 4.0 with each cycle of adjuvant dabrafenib.

## 13.0 CRITERIA FOR REMOVAL FROM STUDY

- Recurrence of the underlying malignancy.
- Unacceptable toxicity not improved with the recommended dose reductions will require cessation of the study drug.
- Development of a secondary malignancy whose systemic treatment would interfere with the study. This does not apply to the development of cutaneous SCC, a known adverse event associated with dabrafenib.
- Development of an intercurrent medical illness in which further administration of the study drug, in the opinion of the Investigator and the treating physician, would be detrimental to the patient.
- Treatment delay of more than 14 days (longer delays must be approved by the Principal Investigator).
- Request of the patient to stop the study.
- Inability of the patient to comply with the requirements of the protocol for treatment or evaluation.

## 14.0 BIOSTATISTICS

This is a single institution phase II trial assessing the efficacy of adjuvant dabrafenib (GSK2118436) in patients with surgically resected AJCC stage IIIC melanoma characterized by a *BRAF*$^{V600E/K}$ mutation. The primary endpoint is 24 month relapse-free survival rate. Patients will be enrolled within 90 days of surgical resection and monitored clinically and radiographically for relapse for recurrence for 24 months. Data from our Center indicate that the relapse-free survival (RFS) for stage IIIC disease is only 24% at 2 years.

A single stage design will be employed whereby a 24% relapse-free rate at 24 months is considered not promising, a 51% relapse-free rate at 24 months is considered promising, and the probabilities of a type I error (falsely accepting a non-promising therapy) and type II error (falsely rejecting a promising therapy) are set at 0.10 and 0.10, respectively. Twenty-three patients will be accrued. All patients will be followed for a minimum of 24 months. At the end of the trial, if 9 or more patients are relapse-free at 24 months out of a total of 23 patients then the treatment will be considered worthy of further investigation. If 8 or fewer patients are relapse-free at 24 months in then the treatment will be declared negative. The trial would be terminated early if at any time 15 patients relapsed or died before 24 months. This design yields a 0.90 probability of a positive result if the true relapse-free survival is at least 51% and yields a 0.90 probability of a negative result if the true relapse-free survival is 24%.

With the exception of those patients who elect to withdraw consent, all patients will be followed with an intention-to-treat and will be evaluated for the primary endpoint as per the protocol study calendar. This includes patient who develop unacceptable toxicity from the agent, secondary malignancies, or an intercurrent illness as listed in section 13.0. Patients who elect to withdraw consent will be evaluated as follows. If patients relapse on study before withdrawing consent (failure), or if they withdraw consent after month 24 without relapsing (success), they are counted as events. If patients withdraw consent before month 24 and before they relapse, then they are not events and will be replaced. Patients, who are lost to follow up at 24 months or later, are counted as successes and will be censored beyond that point.

Toxicities will be tabulated according to the NCI Common Toxicity version 4.0. Overall survival and relapse-free survival will be estimated using Kaplan-Meier methodology. Overall survival will be assessed from surgical resection to death or last follow-up; relapse-free survival will be assessed from surgical resection to relapse, death or last follow-up. Explorative correlative studies examining the genetic heterogeneity of *BRAF*-mutated melanoma, genetic mechanisms of intrinsic and acquired resistance to dabrafenib, and circulating tumor-derived exosomes as a biomarker of disease recurrence will be reported in a descriptive manner.

A total of 23 patients will be accrued to this study. Enrollment is anticipated to take 6 to 12 months and the study is expected to be completed in 30 to 36 months.

## 15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

### 15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

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

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

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

### 15.2 Randomization

Not applicable.

## 16.0 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team. The data collected for this study will be entered into a secure database. Source documentation will be available to support the computerized patient record.

### 16.1 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action. Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

### 16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled “Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials” which can be found at: http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and

Safety Monitoring Plans can be found on the MSKCC Intranet at: http://mskweb5.mskcc.org/intranet/_assets/_tables/content/359709/DSMPlans07.pdf

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

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

## 17.0 PROTECTION OF HUMAN SUBJECTS

Participation in the research study is voluntary. The patients will be explained the risk, benefits, toxicities/side effects, treatment alternatives/options, financial costs/burdens and the voluntary nature of the study. Informed consent will be obtained as detailed in section 18.0.

Benefits: It is possible that treatment with dabrafenib will result in improved relapse-free survival. This could lead to improvement in overall survival.

Costs: Dabrafenib is an investigational drug that will be provided by Novartis to all study participants. Costs for venipuncture for research bloods will not be billed to the patient unless part of by clinical blood test venipuncture. All other standard medical costs will be the responsibility of the study participants. Biopsies performed at progression of disease are a standard of care and will be billed to the patient. Research testing on the tissue will not be charged to the subject. BRAF testing, if not done prior to enrollment, performed to determine subject eligibility will not be billed to the patient.

Incentives: No incentives will be provided to participants in the trial.

Alternatives: Other treatment options are available for patients with stage IIIC melanoma who choose not to participate in this investigational study. Other alternatives include participation in another clinical trial, adjuvant high dose or pegylated interferon, adjuvant radiotherapy, or expectant observation.

Confidentiality: All research and medical records are confidential in accordance with Health Insurance Portability and Accountability Act. Protected information will not be released or reported in any presentations or publications that may result from this study.

### 17.1 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of

protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

### 17.2 Serious Adverse Event (SAE) Reporting

Any SAE must be reported to the IRB/PB as soon as possible but no later than 5 calendar days. The IRB/PB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office at sae@mskcc.org. The report should contain the following information:

Fields populated from CRDB:

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

Data needing to be entered:

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

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

For IND/IDE protocols:
The CRDB AE report should be completed as above and the FDA assigned IND/IDE number written at the top of the report. If appropriate, the report will be forwarded to the FDA by the SAE staff through the IND Office.

#### 17.2.1 Definition of SAEs/Reporting to Novartis and the National Comprehensive Cancer Network (NCCN)

All AEs and SAEs will be collected from the initiation of the study drug until 28 days after discontinuation of the last dose of the study drug. Definitions for adverse events can be found in Section 11. A serious adverse event is defined as any adverse event that:

- Results in death
- Is life-threatening

- Requires hospitalization or prolongation of an existing hospitalization
- Results in disability/incapacity
- Results in congenital anomaly or birth defect
- Any event which requires intervention to prevent the previously stated outcomes

In addition to standard institutional practice and reporting, all SAEs must be reported to Novartis and NCCN within 24 hours. The SAE should be recorded on an MSK CRDB SAE report and after de-identification faxed to the attention of:

- Local Novartis Drug Safety and Epidemiology Safety Desk
  - Fax#: 877-778-9739
  - Should the designated SAE Fax# be non-functional please send SAEs to the designated SAE mailbox: clinicalsafetyop.phuseh@novartis.com
  - Please include Novartis SAE report coversheet for any SAE report

*And:*

*NCCN at ORPReports@nccn.org or fax to 215-358-7699*

Novartis may contact the PI/research staff for additional information, clarification, or current status of the subject for whom and adverse event was reported.

## 18.0 INFORMED CONSENT PROCEDURES

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

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

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

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

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## 20.0 APPENDICES

**Appendix A: ECOG/KPS Conversion Table**

**Appendix B: Prohibited and Cautionary Medications**

**Appendix C: Pill Diary**

## Appendix A: ECOG/KPS Conversion Table

| ECOG Performance Status Scale | | Karnofsky Performance Scale | |
|---|---|---|---|
| Grade | Description | Percent | Description |
| 0 | Normal activity. Fully active, able to carry on all pre-disease performance without restriction. | 100 | Normal, no complaints, no evidence of disease. |
| | | 90 | Able to carry on normal activity; minor signs or symptoms of disease. |
| 1 | Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work). | 80 | Normal activity with effort; some signs or symptoms of disease. |
| | | 70 | Cares for self, unable to carry on normal activity or to do active work. |
| 2 | In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours. | 60 | Requires occasional assistance, but is able to care for most of his/her needs. |
| | | 50 | Requires considerable assistance and frequent medical care. |
| 3 | In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. | 40 | Disabled, requires special care and assistance. |
| | | 30 | Severely disabled, hospitalization indicated. Death not imminent. |
| 4 | 100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. | 20 | Very sick, hospitalization indicated. Death not imminent. |
| | | 10 | Moribund, fatal processes progressing rapidly. |
| | Dead. | | Dead. |

| | | | |
|---|---|---|---|
| 5 | | 0 | |

**APPENDIX B: Prohibited and Cautionary Medications**

| **PROHIBITED MEDICATIONS** | |
|---|---|
| **Strong CYP2C8/3A/PGP/BCRP1 Inhibitor/Inducer. May alter levels of DABRAFENIB** | **Therapeutic Area** |
| Clarithromycin, telithromycin, rifamycin class agents (e.g. rifampin, rifabutin, rifapentine), troleandomycin | Antibiotics |
| Itraconazole, ketoconazole, posaconazole, voriconazole | Antifungals |
| Nefazodone | Antidepressants |
| Gemfibrozil | Hyperlipidemia |
| Carbamazepine, phenobarbital, amiodarone, , phenytoin, s-mephenytoin, bosentan, mibefradil, conivaptan | Miscellaneous |
| Cyclosporine | Immunosuppressive agents |

| **CAUTIONARY MEDICATIONS** | |
|---|---|
| **CYP2C8/C9/C19 Substrates; these drugs may be altered (increased or decreased) by DABRAFENIB** | **Therapeutic Area** |
| Cerivastatin | HMG-CoA Reductase Inhibitors |
| Tolbutamide, nateglinide, repaglinide | Antidiabetics |
| Amitriptyline, clomipramine, imipramine | Antidepressants |
| | |
| **Mild/Moderate Inhibitor of CYP3A, CYP2C8, PGP and BCRP1; These drugs may increase concentrations of DABRAFENIB** | **Therapeutic Area** |
| Erythromycin | Antibiotic |
| Fluconazole | Antifungal |

| | |
|---|---|
| Diltiazem, verapamil | Antiarrhythmics |
| Aprepitant, cimetidine, montelukast | Miscellaneous |
| | |
| **Substrates of CYP3A4/CYP2B6/CYP2C8/CYP2C9/CYP2C19 that may be affected by induction by DABRAFENIB; These drugs may lose efficacy when co-admistered with by DABRAFENIB** | **Therapeutic Area** |
| Chloramphenicol, doxycycline, erythromycin, moxifloxacin | Antibiotics |
| Caspofungin, fluconazole, terbinafine | Antifungals |
| Amlodipine, diltiazem, felodipine, nifedipine, nilvadipine, nisoldipine, verapamil | Antihypertensives |
| Aripiprazole, bupropion, buspirone, desipramine, haloperidol, mirtazapine, pimozide, quetiapine, trazodone | Antidepressants and Antipsychotics Agents |
| Glyburide, saxagliptin, tolbutamide | Antidiabetics |
| Lamotrigine, valproate, divalproex, zonisamide, | Anticonvulsants |
| Alfentanil, buprenorphine, celecoxib, codeine, fentanyl, methadone, oxycodone | Analgesics |
| Aprepitant, cisapride, darifenacin, disopyramide, leflunomide, methohexital, oral contraceptives, quinine, ranitidine, solifenacin, sulfasalazine, tramadol, tolvaptan | Miscellaneous |
| Alprazolam, brotizolam, diazepam, estazolam, midazolam, triazolam, zolpidem, zopiclone | Hypnotics and Sedatives |
| Diergotamine, ergotamine, eletriptan | Antimigraine agents |
| Everolimus, sirolimus, tacrolimus | Immunosuppressive agents |
| Astemizole, chlorpheniramine, ebastine | Antihistamine |
| Oral budesonide, methylprednisolone | Corticosteroids |
| Sildenafil, tadalafil, vardenafil | Erectile Dysfunction agents |
| Eplerenone | Selective Aldosterone Blockers |
| Disopyramide, dronedarone, mexiletine, propafenone, quinidine | Antiarrhythmics |
| Lovastatin, atorvastatin, simvastatin | HMG-CoA Reductase Inhibitors |
| Cilostazole, warfarin | Anticoagulants and Antiplatelets |
| Ritonavir, nevirapine, efavirenz, zidovudine | Antiretrovirals |

**APPENDIX C**

**Pill Diary for IRB #12-124 A(5): A Phase 2 Trial of Adjuvant Dabrafenib (GSK2118436) in Patients with Surgically Resected AJCC Stage IIIC Melanoma Characterized by a *BRAF*$^{V600E/K}$ Mutation**

Number of Pills Given: Pill Bottle(s) returned: Circle **Yes** or **No**
Total Daily Dose: Number of Pills returned: _____
*(To be completed by RN)*

**PLEASE FILL OUT AND BRING THIS SHEET AT YOUR NEXT VISIT.**

**SPECIAL INSTRUCTION:** DABRAFENIB is made as a 50 and 75 mg capsules. Your study doctor will give you instruction on the number of pills you will take twice a day. The doses should be taken about 12 hours apart. Taking the medication twice a day for four weeks is one complete cycle. If you forget to take a dose, you should take the dose as soon as possible. The next dose can then be taken at its regularly scheduled time as long as it is at least 6 hours from the last dose. You must not eat anything for 1 hour before you take the medicine or for 2 hours after you take the medicine. If you vomit after you have taken the study medication, **do not** take an additional dose before your next scheduled dose. Please bring this completed log and any unused pill to each appointment.

**CYCLE#: _____ # of WEEK_____**

| DAY | MEDICATION | DATE | TIME | | NUMBER of 50 mg tablets taken | NUMBER of 75 mg tablets taken |
|---|---|---|---|---|---|---|
| Example | DABRAFENIB | 01/01/2010 | 9:00 | AM | 3 | |
| | DABRAFENIB | | 9:00 | PM | 3 | |
| Day 1 | DABRAFENIB | | | AM | | |
| | DABRAFENIB | | | PM | | |
| Day 2 | DABRAFENIB | | | AM | | |
| | DABRAFENIB | | | PM | | |
| Day 3 | DABRAFENIB | | | AM | | |
| | DABRAFENIB | | | PM | | |
| Day 4 | DABRAFENIB | | | AM | | |
| | DABRAFENIB | | | PM | | |
| Day 5 | DABRAFENIB | | | AM | | |
| | DABRAFENIB | | | PM | | |
| Day 6 | DABRAFENIB | | | AM | | |
| | DABRAFENIB | | | PM | | |
| Day 7 | DABRAFENIB | | | AM | | |
| | DABRAFENIB | | | PM | | |
| Day 8 | DABRAFENIB | | | AM | | |
| | DABRAFENIB | | | PM | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Day 9** | DABRAFENIB | | | **AM** | | |
| | DABRAFENIB | | | **PM** | | |
| **Day 10** | DABRAFENIB | | | **AM** | | |
| | DABRAFENIB | | | **PM** | | |
| **Day 11** | DABRAFENIB | | | **AM** | | |
| | DABRAFENIB | | | **PM** | | |
| **Day 12** | DABRAFENIB | | | **AM** | | |
| | DABRAFENIB | | | **PM** | | |
| **Day 13** | DABRAFENIB | | | **AM** | | |
| | DABRAFENIB | | | **PM** | | |
| **Day 14** | DABRAFENIB | | | **AM** | | |
| | DABRAFENIB | | | **PM** | | |
| **Day 15** | DABRAFENIB | | | **AM** | | |
| | DABRAFENIB | | | **PM** | | |
| **Day 16** | DABRAFENIB | | | **AM** | | |
| | DABRAFENIB | | | **PM** | | |
| **Day 17** | DABRAFENIB | | | **AM** | | |
| | DABRAFENIB | | | **PM** | | |
| **Day 18** | DABRAFENIB | | | **AM** | | |
| | DABRAFENIB | | | **PM** | | |
| **Day 19** | DABRAFENIB | | | **AM** | | |
| | DABRAFENIB | | | **PM** | | |
| **Day 20** | DABRAFENIB | | | **AM** | | |
| | DABRAFENIB | | | **PM** | | |
| **Day 21** | DABRAFENIB | | | **AM** | | |
| | DABRAFENIB | | | **PM** | | |
| **Day 22** | DABRAFENIB | | | **AM** | | |
| | DABRAFENIB | | | **PM** | | |
| **Day 23** | DABRAFENIB | | | **AM** | | |
| | DABRAFENIB | | | **PM** | | |
| **Day 24** | DABRAFENIB | | | **AM** | | |
| | DABRAFENIB | | | **PM** | | |
| **Day 25** | DABRAFENIB | | | **AM** | | |
| | DABRAFENIB | | | **PM** | | |
| **Day 26** | DABRAFENIB | | | **AM** | | |
| | DABRAFENIB | | | **PM** | | |
| **Day 27** | DABRAFENIB | | | **AM** | | |
| | DABRAFENIB | | | **PM** | | |
| **Day 28** | DABRAFENIB | | | **AM** | | |
| | DABRAFENIB | | | **PM** | | |

**Patient Signature:** _____ **Date:** _____

**Consenting Professional Signature:** _____ **Date:** _____

**Consenting Professional Comments:** _____