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**TITLE:** A Phase I/II Study of MCS110 with BRAF/MEK Inhibition in Patients with Melanoma after Progression on BRAF/MEK Inhibition

**Coordinating Center:** Dana-Farber Cancer Institute

***Principal Investigator (PI):** Elizabeth Buchbinder MD
Melanoma Program
Dana-Farber Cancer Institute
Elizabeth_Buchbinder@dfci.harvard.edu

**Statistician:**
Anita Giobbie-Hurder
Dana-Farber Cancer Institute
Telephone: 617-632-2193
Fax: 617-632-2444
agiohur@jimmy.harvard.edu

**Project Manager:**
Jennifer Maattala
Dana-Farber Cancer Institute
Telephone: 617-632-3992
Fax: 617-582-8216
jennifera_maattala@dfci.harvard.edu

**Agents:**
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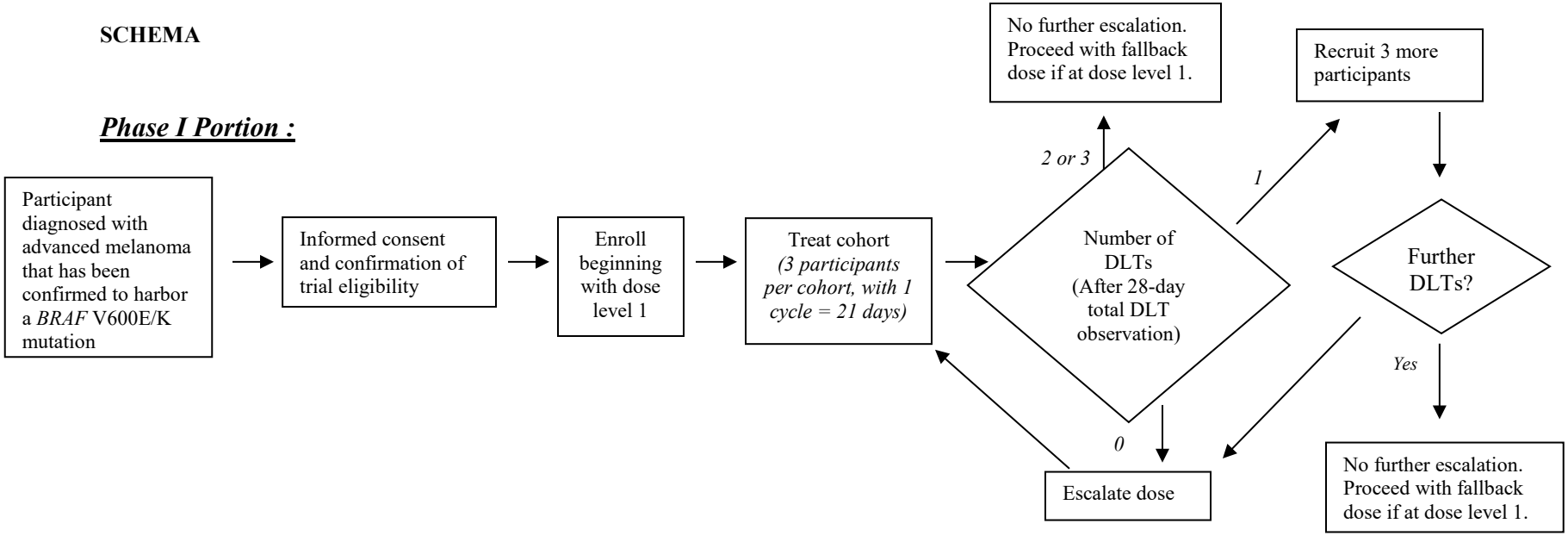
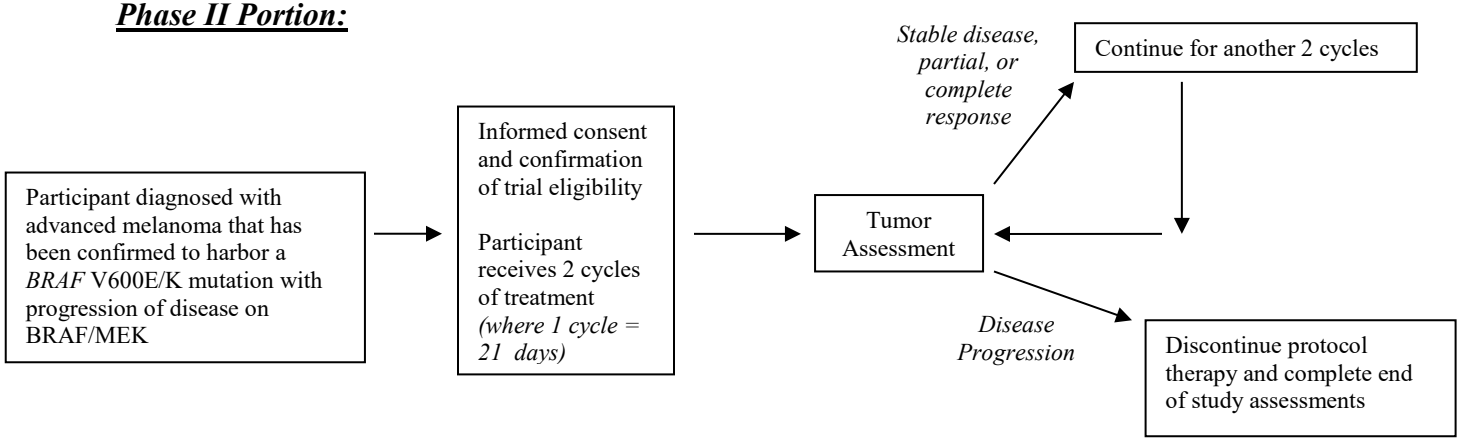
**SCHEMA**

***Phase I Portion :***




***Phase II Portion:***



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# 1. OBJECTIVES

## 1.1 Study Design

This is an open-label, phase I/II study investigating the combination of colony-stimulating factor-1 (CSF-1) inhibition using MCS110 with BRAF/MEK inhibitor therapy using dabrafenib and trametinib in patients with advanced melanoma harboring a BRAF V600 E/K mutation . In phase I, the BRAF and MEK inhibition will be maintained at standard dosing with the addition of the MCS110 using the "3+3" trial design. Once the maximum tolerated dose (MTD) is reached and a recommended phase II dose (RP2D) is chosen, a single-arm phase II study in patients with *BRAF* mutant melanoma whose disease has progressed on BRAF/MEK inhibition will move forward.

## 1.2 Primary Objectives

Phase I:

- To determine the MTD and RP2D of the combination of MCS110 with dabrafenib and trametinib.

Phase II:

- To evaluate the overall response rate (ORR) to the combination of MCS110 with dabrafenib and trametinib in patients with *BRAF* V600E or V600K mutated melanoma who have had progression on BRAF/MEK

## 1.3 Secondary Objectives

Phase I:

- To evaluate the preliminary overall response rate (ORR) and PFS to the combination of MCS110 with dabrafenib and trametinib in patients with *BRAF* V600E or V600K mutated melanoma who have had progression on BRAF/MEK.

Phase II:

- To evaluate the progression free survival (PFS) to the combination of MCS110 with dabrafenib and trametinib in patients with *BRAF* V600E or V600K mutated melanoma who have had progression on BRAF/MEK.
- To evaluate the overall survival (OS) to the combination of MCS110 with dabrafenib and trametinib in patients with *BRAF* V600E or V600K mutated melanoma who have had progression on BRAF/MEK.
- To continue to evaluate the safety and tolerability of the combination of MCS110 with dabrafenib and trametinib in patients with *BRAF* V600E or V600K mutated melanoma who have had progression on BRAF/MEK.

## 1.4 Exploratory Objectives

- To investigate the effect of the combination of MCS110 with dabrafenib and trametinib on mitogen-activated protein kinase (MAPK) pathway signaling and

the immune tumor microenvironment via collection of blood, archival tumor tissue, and optional pre and on-treatment tissue biopsies obtained during both phases of the trial.

- To investigate the relationship between the levels of tumor DNA in serially collected plasma samples and the observed clinical outcomes during both phases of the trial.

## 2. BACKGROUND

### 2.1 Study Disease

Melanoma is the most deadly form of skin cancer, with over 10,000 deaths estimated in the US in 2016[1]. About 40 - 60% of cutaneous melanomas carry mutations in *BRAF* that lead to constitutive activation of downstream signaling through the MAPK pathway. Approximately 90% of these mutations result in the substitution of glutamic acid for valine at codon 600 (*BRAF* V600E), however other activating mutations are known to occur (e.g., *BRAF* V600K)[2,3].

BRAF inhibitor therapy with dabrafenib or vemurafenib has an improved overall survival in patients with *BRAF* mutations with an even larger effect observed when combined with MEK inhibition using trametinib or cobimetinib[2,4,5]. The response rate to the combination is 64 - 68%; however, these responses are of limited duration. The median PFS for combination BRAF/MEK inhibitor therapy is only 9.9 - 11.4 months. Progression on therapy is thought to occur primarily due to the development of acquired resistance through reactivation of the MAPK pathway[4,5].

### 2.2 MCS110

CSF-1R is a receptor tyrosine kinase expressed on monocyte/macrophage and granulocyte cell lineages in normal as well as tumor cells[6,7]. When colony-stimulating factor-1 (CSF-1) or interleukin 34 (IL-34) binds to CSF-1R, the receptor is phosphorylated, initiating downstream signaling events which result in the regulation of proliferation, differentiation, survival and migration of monocytes/macrophages[8-10].

In cancer, increased infiltration of macrophages within and surrounding the tumor mass correlates with increased tumor invasiveness, growth, and poor prognosis. In breast, prostate, ovarian, and cervical cancer, there is a correlation between tumor-associated macrophages (TAMs) and poor prognosis[11-13]. Clinical evidence of TAM participation in tumor growth is corroborated in animal models where CSF-1R/CSF-1 signaling is inhibited or knocked out. Mice with null mutations in the CSF-1 gene have similar initiation rates of virally induced mammary tumors as normal mice, but the tumors do not progress to advanced carcinoma stages and the number of metastases are greatly reduced[14]. In addition to the effects of CSF-1R on macrophages, there are numerous reports of CSF-1R expression on cancer cells. For example breast, ovarian, endometrial, and leukemia cells of myeloid origin express CSF-1R and proliferate in response to CSF-1[6,15-18]. Targeting CSF-1 or CSF-1R have the potential to limit cancer progression.

While CSF-1R levels are infrequently increased on tumor cells compared to analogous normal cells, increased CSF-1 ligand in sera of cancer patients is frequently observed and is associated with poor prognosis and severity of disease in multiple cancers[19,20]. This suggests that circulating CSF-1 modulates the stroma (i.e., macrophages) that contribute to tumor progression. For example, in breast cancer, CSF-1 expression correlated with increased leukocytic infiltration, high tumor grade, and poor clinical outcome[21]. It is hypothesized that the CSF-1 produced by tumor cells suppresses dendritic cell maturation and recruits TAMs that are immunosuppressive, thus promoting angiogenesis and tumor growth[22]. The association of high levels of CSF-1 with poor prognosis in cancer patients may be a consequence of elevated CSF-1 production by tumor cells. Moreover, elevated CSF-1 levels in sera of cancer patients may be an indicator of individuals more likely to benefit from anti-CSF-1 treatment.

MCS110 is a high-affinity, humanized monoclonal antibody directed against human macrophage colony stimulating factor (M-CSF; also known as colony-stimulating factor-1 [CSF-1]). CSF-1 and IL-34 bind to the receptor tyrosine kinase CSF-1R (CSF-1 Receptor) to drive the differentiation, migration and survival of tissue macrophages. MCS110 neutralizes multiple forms of human CSF-1, inhibiting its effect on monocytes and macrophages.

### 2.2.1 Non-Clinical Studies

*In vitro* pharmacology
*In vitro*, the ability of MCS110 to neutralize the activity of CSF-1 was established using two different assays. The first assay involved CSF-1-dependent proliferation of the mouse myelogenous leukemia cell line M-NFS-60. This cell line responds to various recombinant forms of CSF-1, as well as CSF-1 forms present in serum, in medium conditioned by tumor cell lines, and on the cell surface. MCS110 potently inhibited the proliferation of M-NFS-60 cells in response to all human forms of CSF-1 tested. Cell proliferation in response to 10 ng/mL recombinant human CSF-1 could be completely blocked by MCS110. MCS110 blocks the activity of cynomolgus CSF-1 but has no ability to neutralize recombinant mouse CSF-1. The second assay, *in vitro* osteoclastogenesis, was set up to reflect the principal *in vivo* function of CSF-1: regulation of the survival, proliferation and differentiation of cells of the mononuclear phagocyte lineage. MCS110 induced potent inhibition of the osteoclastogenesis process as well as the morphological changes associated with the differentiation into osteoclasts.
*In vivo pharmacology*
Given (a) the lack of activity against mouse CSF-1, and (b) the likely immune response that would develop with long-term dosing of mice with a humanized monoclonal Antibody (mAb), *in vivo* efficacy studies in human tumor cell xenograft models were conducted using two surrogate mAbs rather than MCS110 itself. These two surrogate mAbs were 5A1, a rat monoclonal IgG1antibody which neutralizes mouse (host) CSF-1, and 5H4, a mouse monoclonal IgG1 antibody which neutralizes human (tumor-derived) CSF-1. Using a combination of these two mAbs, inhibition of tumor-induced osteolysis was demonstrated in mice injected intratibially with a human breast cancer cell line (MDA-MB-231Luc). Treatment with a combination of neutralizing antibodies directed against both the host mouse source of CSF-1 and human tumor-derived CSF-1 had the lowest mean osteolytic score and a reduced number of individual animals with clearly evident bone lesions.

To evaluate the competence of TAMs for signaling via the CSF1/CSF1R pathway, macrophages from spontaneous tumors arising in MMTV-PyMT mice were analyzed for CSF1R expression by flow cytometry. CD45+CD11b+F4/80+ positive TAMs stained positively for CSF1R while CD45− tumor cells showed no expression of the receptor. The functional dependence of TAMs on signaling mediated by the CSF1/CSF1R pathway was assessed after 6 days of treatment with the 5A1 Anti MCSF antibody to show a significant reduction in macrophages (CD45+CD11b+F4/80+ cells) suggesting a functional interdependency between CSF1 and CSF1R in regulating TAMs in this breast cancer model (Strachan 2013).

#### 2.2.1.1 Pharmacokinetics

The preclinical pharmacokinetics (PK) and pharmacodynamics (PD) of MCS110 were evaluated in cynomolgus monkeys following single intravenous (i.v) bolus injection of 0.2, 2 or 20 mg/kg, or multiple weekly iv bolus injections of 10 mg/kg for 3 weeks and 2, 20 or 100 mg/kg for up to 13 weeks. Free MCS110 (unbound to target CSF-1) exhibited dose-dependent PK, with decreasing clearance (CL) and increasing mean residence time (MRT) or effective t1/2 when dose increased. The PK profiles of free MCS110 were notably nonlinear at concentrations below approximately 20 μg/mL, presumably due to target-mediate disposition.

In the 13-week study, 2 out of 22 animals tested had anti-drug antibodies detected in serum, which correlated with lower MCS110 exposure at the corresponding time points. For PD, time and dose dependent increase in total CSF-1 was observed in the 13-week study following MCS110 administration, presumably due to slower clearance of the CSF-1 after it formed immune complexes with MCS110, indicating target engagement. Decreases in other downstream biomarkers such as circulating monocytes and serum NTx were also observed following MCS110 administration.

#### 2.2.1.2 Safety Pharmacology and Toxicology

The cynomolgus monkey was selected as the relevant species for toxicology studies because MCS110 showed similar functional activity against cynomolgus monkey and human CSF-1 in *in vitro* bioassays. In cynomolgus monkey studies there were no severe toxicological effects in any animal given MCS110 intravenously as a single dose or as multiple doses once weekly up to 13 weeks and up to doses of 100 mg/kg, showing good tolerability of MCS110 given systemically. Mild increases in liver enzymes were seen in all studies without histopathological correlates, which resolved with clearance of the drug. This included consistent mild/moderate, dose-dependent increases in lactate dehydrogenase (LD), mild increases in AST, and minimal increases in gamma-glutamyl transpeptidase (GGT) and ALT. All parameters returned to baseline levels with the clearance of MCS110 from the serum. The most likely cause of these increases is reduced clearance rate of the serum enzymes due to the diminished numbers of Kupffer cells in the liver. This was demonstrated in cynomolgus monkey study with a single intravenous dose of MCS110, which showed a decreased clearance of histidine-tagged creatine kinase injected in parallel to MCS110. After 13 weekly doses, minimal or mild interstitial edema was seen in multiple organs histopathologically in all dose groups, including the low-dose group. Although periorbital swelling was observed to occur sporadically in all groups (including controls), the increased incidence and severity of periorbital swelling observed at 100 mg/kg

suggested a relationship of this effect to MCS110 administration. No interstitial or periorbital edema was present at the end of the recovery period showing the reversal of this effect. All other effects seen, such as bone morphology changes and monocyte depletion were due to the expected pharmacological effects of MCS110. The data support the intravenous use of MCS110 in clinical trials at the doses selected.

### 2.2.2 Clinical Studies

Five clinical trials with MCS110 have been initiated. Brief information on clinical experience of relevant MCS110 studies is provided below. For additional information, please refer to MCS110 Investigator Brochure.

**Table 1 Clinical trials with MCS110**

| Trial | Study Type | Study Objectives | Patients | MCS110 dose range and schedule |
|---|---|---|---|---|
| [MCS110A2101] Closed | First in human, dose escalation | MTD, safety, PK/PD, preliminary efficacy | Prostate cancer with bone metastases, n=3 | 0.01mg/kg every 14 days |
| [MCS110X2101] Completed | Healthy volunteers, dose escalation | MTD, safety, PK/PD | Healthy, n= 52 | 0.01-20 mg/kg, 1-2 iv infusions every 21-56 days |
| [MCS110X2201] Ongoing | Efficacy study | Safety, tolerability, PK/PD, efficacy | Pigmented Villonodular Synovitis (PVNS), n=37 | 3mg/kg - 10 mg/kg, 1-4 iv infusions every 28 days |
| [MCS110Z2201] Ongoing | Efficacy study | Safety, tolerability, PK/PD, efficacy | Triple Negative Breast Cancer (TNBC), n=100 | 10 mg/kg iv infusions every 21 days |
| [MCS110Z2102] Ongoing | Dose escalation efficacy | Safety tolerability, establish dose for phase 2 and efficacy | TNBC, pancreatic, endometrial, melanoma N=95 | MCS110: 3mg/kg starting dose to 10mg/kg every 21 days. PDR001: 100 mg flat dose to 300 mg flat dose every 21 days |

Brief information on clinical experience of MCS110 will be provided below. For additional information, please refer to the Investigator's Brochure (IB).

#### 2.2.2.1 **MCS110A2101, a first in human clinical trial**

CMCS110A2101 was a first in human study in prostate cancer with bone metastases, designed to evaluate safety, tolerability and MTD of MCS110. MCS110 was administered at doses 0.01 mg/kg repeated every 2 weeks in a 28 day cycle for a total of 3 cycles. The study was closed after 3 patients due to prioritization within Novartis. No MTD was established.

**Clinical safety and tolerability**
MCS110 was well-tolerated and all patients completed the 3-cycle treatment. The only adverse event suspected to be related to MCS110 was an infusion reaction with chills (Grade 1), dizziness (Grade 2) and hypotension (Grade 2). No DLTs were reported. One patient experienced an infusion reaction starting 1 hour after completing the first MCS110 infusion, which resolved 1 hour after occurrence.

**Clinical pharmacokinetics**
Formal PK analysis was not conducted due to small number of serum samples with measurable concentrations.

**Clinical pharmacodynamics**
No consistent changes in monocyte count were observed in the 3 patients treated. All patients' peripheral monocytes were within 70% of baseline levels throughout the study.

**Clinical efficacy**
Biologic activity of MCS110 was not observed. No consistent direction of change was seen in bone markers.

#### 2.2.2.2 MCS110X2101, a clinical trial in healthy volunteers

CMCS110X2101 was a phase I study designed to evaluate safety, tolerability and MTD of MCS110 in 52 healthy volunteers (HV). MCS110 was delivered to 27 HV at increasing single doses from 0.01-20 mg/kg. Additionally, 6 HV received 2 doses (5 mg/kg) given 21 days apart, and another 6 received 2 doses (10 mg/kg) given 56 days apart.

**Clinical safety and tolerability**
Asymptomatic and reversible creatine kinase (CK) elevations were seen in 15 of 52 HV. The CK elevation did not appear to reflect muscle damage since neither troponin T (marker for cardiac muscle damage) nor aldolase (marker for skeletal muscle tissue damage) was elevated. The CK elevations are thought to be caused by the pharmacological effect of MCS110.

Mild periorbital edema was observed in 4 of 52 HV and was transient, lasting between 2 and 158 days. None of the subjects who presented with periorbital edema had developed anti-drug antibodies. The dose limiting toxicity was identified at 20 mg/kg, based on CK elevations exceeding more than 5 times the upper limit of normal. The recommended dose for future studies was set at 10mg/kg.

**Clinical pharmacokinetics**
Following intravenous administration of MCS110 in healthy volunteers, serum free MCS110 exhibited concentration/dose-dependent PK, with decreasing CL (clearance) and increasing MRT (mean residence time) or effective t1/2 when doses increased from 0.01 to 20 mg/kg across 8 dose levels. The shape of the serum free MCS110 PK profiles indicated target mediated disposition, where the MCS110 concentration declined more rapidly at concentrations lower than approximately 10 μg/mL. This was presumably due to binding of MCS110 to the target, suggesting that serum free MCS110 concentrations above approximately 10 μg/mL is required to

saturate circulating CSF-1. At the 10 mg/kg single dose level, MCS110 concentrations were maintained above 10 μg/mL for up to 42 days post dose. As expected, total CSF-1 exhibited dose-dependent increase in plasma following MCS110 treatment, presumably due to slower clearance of CSF-1 after it formed immune complexes with MCS110, indicating successful target engagement. The total CSF-1 concentration reached plateau at the single-dose level at or above 10 mg/kg, and it maintained at the plateau for at least 42 days at the 10 mg/kg dose.

**Clinical pharmacodynamics**
Expected pharmacological responses were observed in downstream biomarkers including dose-dependent decreases in circulating CD14+ or CD14+CD16+ monocytes and C-terminal telopeptide of type I collagen (CTX-1), a bone resorption marker. In addition, dose-dependent increases in CK were observed. Simulation of steady-state dose-response relationships for biomarkers showed that with the once-every-4 week (Q4W) iv administration of MCS110, the response of PD biomarkers (CD14+ and CD14+CD16+ monocytes, and CTX-1) was expected to be close to maximal at the doses at or above 5 mg/kg and minimal at doses at or below 1 mg/kg.

#### 2.2.2.3 MCS110X2201, a phase II study in pigmented villonodular synovitis

**CMCS110X2201** is an ongoing phase II study designed to evaluate safety, tolerability and efficacy with MCS110 in pigmented villonodular synovitis (PVNS). PVNS is a benign tumor consisting of macrophages and multinucleated giant cells, most commonly located to joints. As of 04-Feb-2016, 18 PVNS patients have been dosed. Seven patients received a single dose of 10 mg/kg MCS110 - (5) or placebo (2). Eleven patients received multiple doses of 10 mg/kg MCS110; nine patients received up to 4 i.v. doses and two patients received 6 doses of 10 mg/kg MCS110.

**Clinical safety and tolerability**

Four SAEs were reported, but were not considered related to MCS110. They include hospitalization for anterior and posterior synovetomy, acute cholecystitis, nausea and vomiting with fever and dehydration, and hospitalization for chest pain, dizziness and head congestion (this SAE was reported 7 months after the patient received the last dose).
Common adverse events reported include asymptomatic and reversible CK elevation; mild and reversible periorbital edema; skin adverse reactions (e.g. rash); mild or moderate nausea and vomiting; fever; and headaches. Only one patient was discontinued due to an adverse event (periorbital edema).

**Clinical pharmacokinetics**

PK analysis is ongoing. Preliminary data show serum concentration of free MCS110 was similar to that observed in the HV study. Serum PK profiles after repeated doses were consistent with anticipated PK profiles on single dose PK.

**Clinical pharmacodynamics**

Data from the ongoing study in PVNS patients showed an expected decrease in monocytes and CTX-1, and an increase in CK in patients treated with MCS110. Maximum CK values were generally observed at Day 28 or Day 43 and then returned back to baseline.

**Clinical efficacy**

After receiving a single dose of 10 mg/kg of MCS110, all 18 patients showed mean reduction in tumor volume of 32.8%. In contrast, the 5 patients who received a single dose of placebo, showed tumor volume changes of < 20%, with a mean reduction of -7.7%.

Data from a third interim analysis demonstrated the same reduction in tumor volume when multiple doses of MCS110 were administered. Nine patients given multiple doses of MCS110 who completed the primary endpoint of 8-weeks, showed a clear reduction of tumor volume ranging from 25% to 75%. Two of these patients showed a moderate response of 25% tumor volume decrease; but all other patients show reduction of > 50%.

In parallel with the reduction in tumor size, there were also meaningful clinical improvements of symptoms related to PVNS.

#### 2.2.2.4 MCS110Z2201, a phase II study of MCS110 combined with carboplatin and gemcitabine in Triple Negative Breast Cancer

MCS110Z2201 is a randomized, open label, phase II study of MCS110 combined with carboplatin and gemcitabine in patients with advanced triple negative breast cancer. The study targets TNBC patients with TAM high tumors, who have not previously been treated with chemotherapy for advanced breast cancer. The aim of the study is to investigate whether the addition of MCS110 improves the efficacy of carboplatin and gemcitabine by activating the immune system.

All patients will be given carboplatin (AUC 2) and gemcitabine (1000 mg/m2) on Days 1 and 8 in 21-day cycles. Additionally, patients randomized to Arm 1 (experimental arm) will receive MCS110 10 mg/kg Day 1 in 21-day cycles with an additional dose of MCS110 10 mg/kg on Cycle 1 Day 8. As of 3 May 2016, 10 patients were enrolled; 7 to arm 1 and 3 to arm 2.

**Clinical safety and tolerability**

As required by the protocol, an early safety review was performed on May 25, 2016. The data cutoff was May 3, 2016 and data was collected from seven patients treated with carboplatin/gemcitabine/MCS110 and two patients treated with carboplatin/gemcitabine for 2 full cycles or until discontinuation earlier. After reviewing the safety data, the sponsor and investigators jointly proposed to remove the additional dose of MCS110 on cycle 1/day 8 (C1D8) and to continue optional prophylaxis to prevent infusion reactions.

The Steering Committee reviewed the patient data on May 31, 2016 and found no immediate safety concern with the current dosing. Limited data showed some instances of recurrent increase of liver transaminases after the C1D8. This increase was not seen in all patients, however, and additional data would be necessary to establish any potential relationship. Review of the PK parameters indicate a slightly increased Cmax compared to historical data, which implies that desired exposures can be achieved without the C1D8 administration. Given this information, the Steering Committee agreed with the recommendation to remove C1D8 additional dose.

Grade 1-2 infusion reactions related to MCS110 were observed in 3 patients. Additional is

needed, however, to establish the rate and severity of these events. As all patients have been able to continue on MCS110 dosing with appropriate prophylaxis and without dose reductions, the Steering Committee deemed no further actions were necessary.

**Clinical pharmacokinetics**

A preliminary review of the PK parameters indicates a slightly increased Cmax compared to historical data.

**Clinical pharmacodynamics**

No data is available as May 2016

#### 2.2.2.5 Drug Interactions

Specific studies to investigate drug-drug interactions (DDI) have not been conducted with MCS110. Antibodies that modulate cytokines, which may regulate cytochrome P450 (CYP) enzymes, may cause DDI with small molecule drugs because of the potential to alter CYP-mediated metabolism (lee et al 2010; Huang et al 2010). However, MCS110 specifically neutralizes CSF-1 and hence it is not expected to modulate cytokines. In addition, as an antibody, MCS110 is eliminated through protein catabolism and target-mediated disposition.

### 2.3 Dabrafenib

Dabrafenib mesylate (GSK2118436B, Tafinlar®; referred to as dabrafenib hereafter), a 4-(3-aminosulfonylphenyl)-5-(pyrimidin-3-yl) thiazole, is an ATP-competitive, selective inhibitor of RAF kinase currently in clinical development. On May 29, 2013, the U.S. FDA approved dabrafenib for the treatment of patients with unresectable or metastatic melanoma with BRAFV600E mutation as detected by an FDA-approved test (FDA, 2013). On January 10, 2014, the FDA granted accelerated approval to dabrafenib and MEK inhibitor trametinib for use in combination to treat patients with unresectable or metastatic melanoma with either BRAFV600E or BRAFV600K mutation as detected by an FDA-approved test (FDA, 2014).

Dabrafenib has been FDA approved for patients with unresectable or metastatic melanoma with a *BRAF* V600E mutation and is commercially available.

#### 2.3.1 Pharmacokinetics

Following single-dose oral administration of dabrafenib HPMC capsules, plasma concentrations peaked approximately 2.0 hours post-dose. Oral bioavailability is near complete (94.5%) relative to an intravenous (IV) microdose.

Dabrafenib is highly bound to plasma proteins (99.6%). Its volume of distribution after IV dosing is 45.5 L. Intravenous plasma clearance (12.0 L/hr) is low relative to liver blood flow, suggesting a low hepatic extraction ratio drug. Median terminal half-life is approximately 8 hours after a single oral dose.

Three metabolites of dabrafenib were characterized and may contribute to activity. GSK2285403 (hydroxy-metabolite [M7]) PK paralleled that of dabrafenib, while the carboxy- (GSK2298683 [M4]) and desmethyl- (GSK2167542 [M8]) metabolites exhibited a longer t1/2 (21-22 hours) and accumulated following repeat dosing. M7 is the most abundant, accounting for 54% of the three metabolites. Similar to dabrafenib concentrations, exposure for all metabolites showed a less than dose proportional increase with repeat dosing.

Fecal excretion was a major route of dabrafenib elimination in humans, accounting for 71.1% of the dose administered, and renal excretion accounted for about 20% of drug elimination.

Administration of dabrafenib with a high-fat, high-calorie meal reduced the oral bioavailability of dabrafenib when compared to the fasted state with a decrease in Cmax and AUC of 51% and 31%, respectively, and delayed its absorption. Therefore, the current recommendation is to administer dabrafenib under fasting conditions, either 1 h before or 2 h after a meal.

### 2.3.2 Drug Interactions

Dabrafenib induces CYP3A4 and CYP2C9. Dabrafenib decreased the systemic exposures of midazolam (a CYP3A4 substrate), S-warfarin (a CYP2C9 substrate), and Rwarfarin (a CYP3A4/CYP1A2 substrate). Co-administration of dabrafenib 150 mg twice daily for 15 days and a single dose of midazolam 3 mg (a CYP3A4 substrate) decreased midazolam AUC by 74%. Co-administration of dabrafenib 150 mg twice daily for 15 days and a single dose of warfarin 15 mg decreased the AUC of S-warfarin (a CYP2C9 substrate) by 37% and the AUC of R-warfarin (a CYP3A4/CYP1A2 substrate) by 33%.

*In vitro* studies show that dabrafenib is a substrate of CYP3A4 and CYP2C8 while hydroxy-dabrafenib and desmethyl-dabrafenib are CYP3A4 substrates. Co-administration of dabrafenib 75 mg twice daily and ketoconazole 400 mg once daily (a strong CYP3A4 inhibitor) for 4 days increased dabrafenib AUC by 71%, hydroxy-dabrafenib AUC by 82%, and desmethyl-dabrafenib AUC by 68%. Co-administration of dabrafenib 75 mg twice daily and gemfibrozil 600 mg twice daily (a strong CYP2C8 inhibitor) for 4 days increased dabrafenib AUC by 47%, with no change in the AUC of dabrafenib metabolites. Dabrafenib is a substrate of human P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) in vitro.

### 2.3.3 Clinical activity

The single-agent MTD for dabrafenib was not reached. A dose of 150 mg BID was selected for further single-agent development, based on the following PK/pharmacodynamics, safety, and activity: a) dose increases beyond 150 mg BID yielded no increase in $C_{max}$ and <50% increase in AUC; b) incidence and severity of AEs was similar at 100-300 mg BID; c) pERK target suppression was >80%; and d) the tumor response rate (RR) was 50% at 150 mg BID.

*Activity in patients with BRAF V600E or V600K melanoma in* the FTIH monotherapy study

(BRF112680). The study enrolled 114 patients with BRAFV600 mutant melanoma in the dose escalation phase (Part 1), and 70 patients at the RP2D (150 mg BID) in Part 2. Within this study, a cohort of 10 patients with previously untreated asymptomatic brain metastasis was evaluated for intracranial response to dabrafenib (Long *et al.,* 2011). All patients had decreases in the size of the brain metastasis; three patients achieved complete radiographic resolution of brain lesions as well as reduction in extracranial disease. The response rates in patients treated at 150 mg BID were 50% in 77 patients treated with V600E mutation, 20% in 14 patients treated with V600K mutation. When dabrafenib was used at 50 mg BID (Part 2, Cohort C) in patients with BRAFV600E mutant melanoma, the response rate was only 17%.

*Correlative studies in the phase 1 monotherapy trial:*
Preliminary genomic analysis was performed on 37 patients with melanoma, using a Sequenom mutation analysis for 11 genes (AKT, BRAF, CDK4, CDKN2A, GNAQ, GNA11, Kit, MEK1, MEK2, and NRAS), and PTEN analysis by sequencing, comparative genomic hybridization (CGH), and multiplex ligation-dependent probe amplification (MPLA) (Nathanson *et al.,* 2011). Nine patients (24%) had PTEN genetic alterations including mutation, hemi-/homozygous deletion. PTEN deficiency was associated with lower responses (ORR of 11% and 54% in patients with and without PTEN alteration, respectively).

*Phase III trial of dabrafenib versus chemotherapy in patients with advanced BRAFV600 mutant melanoma (BREAK3 Trial):* Patients with previously untreated, unresectable stage III or IV BRAFV600E-mutated melanoma were randomized (3:1) and stratified by stage to dabrafenib (150 mg PO BID) or dacarbazine (DTIC) (1000 mg/m2, IV, every 3 weeks [Q3W]). Of 250 patients, 187 received dabrafenib and 63 received DTIC from February to September 2011. The hazard ratio for PFS was 0.30 (95% CI: 0.18-0.53; $P$<0.0001), with median PFS of 5.1 months for dabrafenib and 2.7 for DTIC. OS data were immature, with 30 deaths reported. Confirmed RR was 53% for dabrafenib and 19% for DTIC. Benefits in PFS and RR were observed in all subgroups evaluated.

## 2.4 Trametinib

Trametinib (Mekinist) is a dimethyl sulfoxide (DMSO) solvate compound (ratio 1:1) with potent, allosteric and ATP non-competitive inhibition of MEK1/2 (IC50 of 0.7 and 0.9 nM against MEK1 and MEK2, respectively) (Gilmartin *et al.,* 2011). Trametinib inhibited MEK1/2 kinase activity and prevented RAF-dependent MEK phosphorylation (S217 for MEK1), producing prolonged pERK1/2 inhibition. Trametinib showed better potency against unphosphorylated MEK1/2 (u-MEK1/2) when compared with preactivated diphosphorylated MEK (pp-MEK), suggesting that u-MEK affords a higher affinity binding site for trametinib than does pp-MEK.

The specificity of trametinib was confirmed against a panel of 183 kinases, including MEK5 (the closet kinase homolog to MEK1/2), CRAF, BRAF, ERK1, and ERK2 (Yamaguchi *et al.,* 2011). Trametinib demonstrated equal potency against activated MEK1- and MEK2-mediated phosphorylation of ERK (sequence identity of 85% across the whole protein and 100% in the active site for humans). Trametinib demonstrated preferential inhibition of RAF-mediated MEK1 activation (IC50 = 0.60 nM) over pMEK1 kinase activity (IC50 = 13 nM) (Investigator's Brochure, 2012a).

Pharmacodynamic studies were performed in mice treated with trametinib for 14 days (Gilmartin *et al.,* 2011). In the A375P F11s xenograft model, the first dose of trametinib (3 mg/kg) significantly reduced pERK for more than 8 hours on Day 1. pERK inhibition was more sustained (over 24 hours) after the Day 7 dose, probably due to an increase in the steady-state levels of trametinib after repeated doses. The average Cmax in blood was 1,410 nM on Day 7, with an estimated half-life (t1/2) of 33 hours. In addition, immunohistochemistry (IHC) also confirmed inhibition of cell proliferation (reduced Ki67) and G1 cell cycle arrest (elevated p27Kip1/CDKN1B) following 4 days of treatment.

Trametinib has been FDA approved for patients with unresectable or metastatic melanoma with a *BRAF* V600E or V600K mutation and is commercially available.

### 2.4.1 Pharmacokinetics

PK measurements were conducted under fasting conditions. After a single dose (Day 1), AUC0-24 and Cmax values were dose-proportional up to 6 mg, lower than dose proportional following 8 mg, and greater than dose proportional following the 10 mg dose. Median Tmax was 1.5 hours.

After repeat doses (Day 15), trametinib accumulated with a mean accumulation ratio of 6.6 at the RP2D of 2 mg QD. Between-subject variability in exposure ranged from 27- 50% for Cmax and 20-41% for AUC0-24 across all dosing regimens. The effective t1/2 was approximately 4.5 days, and steady state was reached by approximately Day 15. Trametinib had a small peak:trough ratio of ~2 (Infante *et al.,* 2010). At 2 mg QD on Day 15, mean AUC0-24 was 376 ng•h/mL and Cmax 23 ng/mL, and the mean trough concentrations ranged from 10.0 to18.9 ng/mL. The long half-life and small peak:trough ratio of trametinib allowed constant target inhibition within a narrow range of exposure.

### 2.4.2 Drug Interactions

Trametinib is metabolized predominantly via deacetylation (non-cytochrome P450 [CYP450]-mediated) with secondary oxidation or in combination with glucuronidation biotransformation pathways (Investigator's Brochure, 2012a). The deacetylation is likely mediated by hydrolytic esterases, such as carboxylesterases, or amidases. Based on *in vitro* studies, trametinib is not an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2D6, and CYP3A4. Although trametinib was found to be an *in vitro* inhibitor of CYP2C8, CYP2C9, and 2C19; inducer of CYP3A4; and inhibitor of transporters (OATP1B1, OATP1B3, P-glycoprotein [P-gp], and breast cancer resistance protein [BCRP]), its low efficacious dose, and low clinical systemic concentration (22.2 ng/mL or 0.04 mcM at 2 mg) relative to the *in vitro* inhibition/induction potency suggests an overall low potential for drug-drug interactions.

### 2.4.3 Clinical Activity

In the FTIH phase 1 trial, 14 patients with BRAF-mutant melanoma received trametinib at 2 mg QD (2 mg/day continuously, or 2 mg for 21 days followed by a 1 week break). The overall objective response rate (ORR) was 43% (6/14), including 2 complete responses (CRs)

(Investigator's Brochure, 2012a). In 9 patients with BRAF wt melanoma, 2 patients achieved a partial response (PR), and 3 stable disease (SD) (Infante *et al.,* 2010). In 26 evaluable pancreatic cancer patients, there were 2 PRs (1 PR was KRAS mutation-positive) and 11 SD (2 achieved ≥20% tumor reduction) (Messersmith *et al.,* 2011). Among the 27 CRC patients (without selection of RAS or RAF mutations), 8 SD were observed.

In a phase 3 trial, patients with unresectable stage IIIC or IV cutaneous melanoma with a BRAF V600E or V600K mutation were randomized (2:1) to trametinib (2 mg, PO, QD) or chemotherapy (dacarbazine or paclitaxel) (Flaherty *et al.*, 2012). There were 322 patients in the intention-to-treat (ITT) population, of whom 273 (85%) were in the primary efficacy population (patients with BRAFV600E-positive cancer who did not have brain metastases at baseline). In the ITT analyses, the ORR was 22% in the trametinib group and 8% in the chemotherapy group; the median duration of PFS was 4.8 months in the trametinib group as compared with 1.5 months in the chemotherapy group; and the 6- month OS rate was 81% in the trametinib group and 67% in the chemotherapy group.

## 2.5 Rationale

The tumor microenvironment is known to play a role in innate or acquired resistance to BRAF inhibition[29,30]. Tumor cells can control the surrounding milieu by producing cytokines that suppress cytolytic T-cells and recruit immunosuppressive cells, and CSF-1 is one such cytokine that is secreted by melanoma. CSF-1 induces the proliferation and differentiation of immunosuppressive myeloid cells, such as M2 polarized macrophages and myeloid-derived suppressor cells (MDSCs), by binding to CSF-1R on the surface of the cell. This results in the ability of the tumor cell to evade the immune response and allows for subsequent metastasis[31].

Pre-clinical data by Mok et al. showed a dramatic reduction in tumor infiltrating myeloid cells when treated with CSF-1R inhibition. When this was combined with BRAF inhibition superior antitumor responses and increased tumor-infiltrating lymphocytes were observed[31]. Inhibitors to CSF-1R have been shown to deplete certain populations of TAMs and in established tumors, the combination of CSF-1R inhibitors with chemotherapy has been shown to dramatically enhance responses[32].

Additional pre-clinical data from Wang et al. demonstrated that macrophages play a role in resistance to BRAF inhibitor therapy through paradoxical activation of the MAPK pathway leading to increased production of vascular endothelial growth factor (VEGF). Targeting macrophages in a pre-clinical model led to increased tumor activity of BRAF inhibition in mouse and human tumor models[33]. These data together suggest that targeting macrophages in combination with BRAF inhibition in patients with melanoma may reduce baseline resistance and increase efficacy. Prior BRAF inhibition has also been shown to lead to increased TAMs, suggesting a potential role of combination therapy in patients with acquired resistance[34].

## 2.6 Correlative Studies Background

Use of immune and targeted therapies in patients with genomically complicated tumors presents a variety of confounding variables that could contribute to success or failure of the therapy.

Correlative studies are designed to both enable better understanding of the possible reasons that MCS110 in combination with dabrafenib and trametinib may prove to be effective or ineffective in individual patients, and to enable the development of more effective targeting strategies in the future.

*Collection of Tumor Tissue*

In order to retrospectively explore the determinants of response and resistance to MCS110 combination therapy, archival tumor tissue will be collected at baseline from all patients enrolling to the trial. In addition, optional fresh tumor biopsies will be obtained from patients enrolled to either the phase I or phase II portion of the trial. These biopsies will be obtained on-treatment and again at the time of disease progression. The genetic and immune characteristics identified in the tumor tissue will be correlated to clinical outcome.

Analysis of tumor tissue samples taken at distinct points enables addressing of key questions including: (1) the genomic lesions and immune cell presence at baseline in samples studied and their potential impact upon response, (2) the identification of immediate pathways/gene expression programs activated by tumors following MCS110 combination therapy, and (3) mechanisms of acquired resistance to therapy.

The first correlative question relates to the genetic and immune diversity of the patients enrolled in this study. It is the anticipation that most patients on this study will have had their tumor genomically characterized by either the OncoPanel test at DFCI/BWH (a custom hybrid capture panel which via next-generation sequencing will identify mutations and copy-number alterations in cancer associated genes) or via another CLIA-certified method at the time of enrollment. The archival tissue collected will be analyzed to look at the TAMs present at baseline. Macrophages are among the most abundant normal cells in the tumor micoenvironment. Substantial evidence has indicated that macrophages adopt a pro-tumoral phenotype, suppressing T cell response and promoting tumor progression via angiogenesis, tumor cell invasion, motility, intravasation, and promotion of persistent growth[32]. The levels of certain TAMs present at baseline can be correlated to the clinical response observed with the combination therapy, and this data may enable us to identify immune characteristics that may also impact clinical response.

Another key rationale for performance of biopsies in patients after initiating drug therapy is to address mechanisms of resistance to MCS110 combination therapy. The emergence of resistance to therapy is a profound problem in oncology. Such resistance can follow not only acquisition of secondary mutations but also from the ability of cancer cells to activate immediate compensatory signaling tracts following targeted inhibition of a key pathway[39]. Identification of these compensatory reactions is a necessary step in order to design subsequent rational therapies that may lead to even more durable and long-lasting clinical benefit. The optional on-treatment tissue samples will be examined for changes in MAPK activation as well as levels of TAMs and tumor immune infiltrates.

Optional biopsies obtained at the time of disease progression will be used to characterize the change in the tumor at the time of resistance. Such changes could stem from the acquisition of novel genomic alterations, from activation of other signaling pathways, or the production of anti-

inflammatory and immunosuppressive mediators. Biopsies obtained at progression will be analyzed for MAPK reactivation, other mechanisms of resistance (e.g., alternate kinase domain mutations), and tumor immune infiltrates. The information collected from these biopsies will be vital to understanding the methods of resistance to the combination therapy and planning subsequent treatment strategies in this population.

*Collection of Blood*

Cell-free DNA (cfDNA) will be collected and analyzed for *BRAF* V600E or V600K mutations. Levels of tumor DNA will decline longitudinally over time if there is a response to the treatment administered. To further assess this concept, plasma will be collected from participants to evaluate whether circulating free plasma DNA declines with the administration of MCS110, dabrafenib, and trametinib and this information will be compared to clinical outcome.

Blood samples will also be collected to look at circulating immune cells including MDSCs. MDSCs are a heterogeneous group of myeloid-derived cells which are greatly expanded in experimental models of cancer. Studies in humans carried out thus far have reported an increased frequency as well as immune-suppressive activity in some of the myeloid-derived subsets of MDSCs present in the peripheral blood of patients with cancer. In the case of metastatic melanoma, both monocytic as well as granulocytic blood MDSCs with immune-suppressive function have been studied independently and proposed to exert an immune-regulatory role[40]. To further explore the relationship of circulating immune cells including MDSCs and their potential correlation to clinical outcomes, peripheral blood levels will be serially collected from patients enrolled to the trial.

## 3. PARTICIPANT SELECTION

### 3.1 Eligibility Criteria

Baseline evaluations are to be conducted within 14 days prior to start of protocol therapy, with the exception of the informed consent, echocardiogram, ophthalmologic exam, and baseline tumor imaging which may be obtained up to 28 days prior to the start of protocol therapy.

3.1.1 For enrollment to the phase I portion: participants must have a histologically confirmed melanoma with a *BRAF* V600E or *BRAF* V600K mutation (identified via NextGen sequencing using the DFCI/BWH OncoPanel or any CLIA-certified method) that is metastatic or unresectable and for which standard curative measures do not exist or are no longer effective.

3.1.2 For enrollment to the phase II portion: participants must have a histologically confirmed melanoma with a *BRAF* V600E or *BRAF* V600K mutation (identified via NextGen sequencing using the DFCI/BWH OncoPanel or any CLIA-certified method) and have had progression of disease on prior BRAF and MEK inhibitor therapy.

3.1.3 Participants enrolling to the phase I portion of the trial must have evaluable or measurable disease.

3.1.4 Participants enrolling to the phase II portion of the trial must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥ 10 mm with spiral CT scan, MRI, or calipers by clinical exam. See Section 11 for the evaluation of measurable disease.

3.1.5 Age ≥ 18 years. As no dosing or adverse event data are currently available in participants < 18 years of age, children are excluded from this study but will be eligible for future pediatric trials.

3.1.6 ECOG performance status 0 - 2 (see Appendix A).

3.1.7 Life expectancy of greater than 8 weeks.

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

| | |
|---|---|
| – Absolute neutrophil count | ≥ 1.5 K/uL |
| – Platelets | ≥ 100 K/uL |
| – Hemoglobin | ≥ 9 g/dL |
| – Total bilirubin | ≤ 1.5 × institutional upper limit of normal (ULN) |
| – AST(SGOT)/ALT(SGPT) | ≤ 2.5 × institutional ULN |
| – Serum creatinine | ≤ 1.5 × institutional ULN |
| – PT-INR | ≤ 1.5 × institutional ULN (for participants on anticoagulation therapy, ≤ 1.5 × their baseline value) |
| – aPTT | ≤ 1.5 × institutional ULN (for participants on anticoagulation therapy, ≤ 1.5 × their baseline value) |

3.1.9 Participants must have a left ventricular ejection fraction (LVEF) ≥ 50%.

3.1.10 Participants must have a QTc of ≤ 480 msec for both females and males on the screening EKG.

3.1.11 The effects of MCS110, trametinib and dabrafenib on the developing human fetus are unknown. For this reason and because anti-cancer agents are known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for 4 months after the last dose of MCS110. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 4 months after completion of MCS110 administration. Highly Effective contraception methods include:

a. Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception

b. Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment

c. Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject

d. Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception. In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

e. Double-barrier contraception: condom and occlusive cap (diaphragm or cervical/vault caps) with a vaginal spermicidal agent (foam/gel/cream/suppository).

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

3.1.13 Participants must have archival tumor tissue available. Participants without archival tissue may be enrolled at the discretion of the principal investigator.

3.1.14 All prior anti-cancer treatment-related toxicities (except alopecia and laboratory values as listed on Table 1) must be ≤ Grade 1 according to the Common Terminology Criteria for Adverse Events version 4 (CTCAE version 4.0; NCI, 2009) at the time of randomization.

## 3.2 Exclusion Criteria

3.2.1 Participants who have had chemotherapy, radiotherapy, biologic therapy, major surgery, or another investigational agent within 3 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study. Previous BRAF/MEK inhibitor use is allowed with no washout period for the phase I and II portions.

3.2.2 Participants who have not recovered to ≤ CTCAE grade 1 or baseline from toxicity as a result of previous cancer treatment prior to entering the study (with the exception of alopecia and peripheral neuropathy which can be ≤ grade 2).

3.2.3 For enrollment to the phase II portion: participants who have not received prior BRAF or MEK inhibitor therapy.

3.2.4 Participants with known untreated brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events. Participants with a history of brain metastases that have been treated, are no longer taking corticosteroids, and have been stable on imaging for ≥ 4 weeks following the last date of treatment are permitted.

3.2.5 History of allergic reactions attributed to compounds of similar chemical or biologic composition to MCS110, dabrafenib, or trametinib.

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

3.2.7 Pregnant women are excluded from this study because MCS110, dabrafenib and trametinib are anti-cancer agents with the potential for teratogenic or abortifacient effects. Pregnancy status will be verified at various points in the trial and a serum pregnancy test will be required. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with MCS110, dabrafenib or trametinib, breastfeeding should be discontinued if the mother is treated with MCS110, dabrafenib or trametinib.

3.2.8 Participants with a known history of HIV are ineligible because of the potential for pharmacokinetic interactions with MCS110, dabrafenib, and trametinib with antiretroviral agents. In addition, these participants are at increased risk of lethal infections when treated with marrow-suppressive therapy.

3.2.9 Participants with a personal or family history of long QT syndrome.

3.2.10 Participants with a history of a second primary malignancy. Exceptions include: patients with a history of malignancies that were treated curatively and have not recurred within 3 years prior to study entry; resected basal and squamous cell carcinomas of the skin, and completely resected carcinoma *in situ* of any type.

3.2.11 Participants with impairment of GI function or GI disease that may significantly alter the absorption of dabrafenib and trametinib in the opinion of the treating investigator (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection).

3.2.12 Participants who are unable to swallow or retain oral medication.

3.2.13 Participants that require co-administration of strong or moderate CYP3A inhibitors, as these medications may alter dabrafenib and trametinib concentrations.

3.2.14 Participants who require treatment with medications that are strong or moderate CYP3A inducers, as these medications may alter the concentration of trametinib.

3.2.15 Participants with evidence of retinal pathology on ophthalmologic examination that is considered a risk factor for neurosensory retinal detachment/central serous chorioretinopathy (CSCR), retinal vein occlusion (RVO), or neovascular macular degeneration. This includes participants with a history of or current evidence of retinal vein occlusion or retinal pigment epithelial detachment.

3.2.16 Participants taking corticosteroids (≥ 10 mg of prednisone or equivalent). Exceptions may be discussed with the Overall PI on a case by case basis.

### 3.3 Inclusion of Women and Minorities

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

# 4. REGISTRATION PROCEDURES

## 4.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Registration cancellations must be made in OnCore as soon as possible.

## 4.2 Registration Process for DF/HCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

## 4.3 General Guidelines for Other Investigative Sites

Not Applicable.

## 4.4 Registration Process for Other Investigative Sites

Not Applicable.

# 5. TREATMENT PLAN

## 5.1 Treatment Regimen

**MCS110** will be administered intravenously every 3 weeks. The doses of MCS110 will be calculated for each cohort and will be based on the subject's weight. Standard institutional policy can be used for weight based dosing. MCS110 should be administered in a 1 hour (± 5 min) infusion.

Table 2 Treatment and treatment schedule

| Study treatments | Pharmaceutical form and route of administration | Dose | Frequency and/or regimen |
|---|---|---|---|
| MCS110 | Liquid concentrate in a vial, Intravenous infusion | 10 mg/kg, 5 mg/kg or 2.5 mg/kg | Every 3 weeks |

**Table 3: Phase I Dose Escalation Schedule**

| Dose Level | Dose | | |
|---|---|---|---|
| | **MCS110** | **Dabrafenib** | **Trametinib** |
| **-1** | 1.25 mg/kg IV every 3 weeks | 150 mg BID | 2 mg daily |
| **1 (Starting Dose Level)** | 2.5 mg/kg IV every 3 weeks | 150 mg BID | 2 mg daily |
| **2** | 5 mg/kg IV every 3 weeks | 150 mg BID | 2 mg daily |
| **3** | 10 mg/kg IV every 3 weeks | 150 mg BID | 2 mg daily |

Three patients will be enrolled to dose level 1. Enrollment to the dose level can occur in parallel with no observation period or delay between the start of therapy for each enrolled patient. The patients will be observed during the first cycle of therapy for toxicity consistent with a dose-limiting toxicity (DLT) definition, located in Section 5.4. There will be an added 7 days for DLT observation (28 days total) before each new dose escalation cohort begins. This will not pause the 21 day dosing cycle of the current cohort under DLT observation.

Dose escalation will proceed in a standard 3+3 fashion according to the scheme in Table 1.

**Table 4: Phase I Dose Escalation Decision Criteria**

| Number of Participants with DLT at a Given Dose Level | Escalation Decision Rule |
|---|---|
| 0 out of 3 | Enter 3 participants at the next dose level. |
| ≥ 2 | Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional participants will be entered at the next lowest dose level if only 3 participants were treated previously at that dose. |
| 1 out of 3 | Enter at least 3 more participants at this dose level.<br>• If 0 of these 3 participants experience DLT, proceed to the next dose level.<br>• If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional participants will be entered at the next lowest dose level if only 3 participants were treated previously at |

| Number of Participants with DLT at a Given Dose Level | Escalation Decision Rule |
|---|---|
| | that dose. |
| ≤ 1 out of 6 at highest dose level below the maximally administered dose | This is generally the RP2D. At least 6 participants must be entered at the RP2D. |

The maximally administered dose (MAD) of the study medications will be defined as the dose level where at least two participants develop toxicities consistent with a DLT definition. In this situation, the dose level immediately below the MAD will be defined as the MTD. In the event that dose level 1 is found to be intolerable (with either 2/3 or ≥ 2/6 patients experiencing a DLT), the fallback dose level -1 will be explored. If the fallback dose level is also found to be intolerable, the trial will be discontinued. In the situation where none of the dose levels have ≥ 2 DLTs, the MTD will be the highest dose administered (i.e. dose level 3). The MTD will be defined in a minimum of six patients.

Upon declaring the MTD, the Overall Principal Investigator will review safety data generated during the phase 1 portion of the trial to decide the RP2D. This review will include a review of the DLTs that occurred among the dose levels in conjunction with toxicities experienced among participants beyond the DLT time frame. Once the RP2D has been defined, the phase II portion of the trial will begin with enrollment of 25 patients with either *BRAF* V600E or V600K mutant melanoma who have progressed on prior BRAF/MEK inhibition. Patients enrolling into the phase II portion of the trial will be treated at the RP2D identified during the phase I portion of the study.

Patients enrolled to the phase I dose escalation portion of the trial will be required to have received at least 75 percent of their doses of dabrafenib and trametinib, and must complete the MCS110 infusion during the first cycle to be considered evaluable for DLT purposes. Patients who do not meet these parameters during cycle 1 for reasons other than toxicity (for example, withdrawal of consent for participation on the trial, or rapid disease progression and subsequent removal from the trial) will be replaced.

Participants will be requested to maintain a study medication diary that will indicate each dose of oral medication taken to illustrate treatment compliance. The medication diary should be returned to appropriate research staff for review at the end of each treatment cycle.

## 5.2 Pre-Treatment Criteria

### 5.2.1 Cycle 1, Day 1

Patients who completed screening assessments > 72 hours prior to cycle 1 day 1 should have cycle 1 day 1 laboratory values that re-meet eligibility criteria. If screening assessments were completed ≤ 72 hours prior to cycle 1 day 1, laboratory tests do not need to be repeated on cycle 1 day 1 and the screening laboratory values can be used as the cycle 1 day 1 values.

#### 5.2.2 Subsequent Cycles

To be eligible to begin subsequent cycles of treatment, toxicity considered at least possibly related to the study regimen must have recovered to ≤ grade 2 or baseline. Management of specific toxicities considered at least possibly related to the study regimen is outlined in Section 6.1.

## 5.3 Agent Administration

### 5.3.1 MCS110

MCS110 will be given once on day 1 of the 21 day cycle. On days where MCS110, dabrafenib, and trametinib are all to be given, order of administration does not matter.

MCS110 will be administered via IV infusion.

Mild infusion reactions were reported in 2 patients in the MCS110A2101 study, where all symptoms (dizziness, chills, hypotension) resolved within 1 hour. One patient was re-challenged with MCS110 and did not have any infusion reactions during subsequent infusions. Patients should be monitored for hypersensitivity reactions according to local guidelines. Appropriate treatment for hypersensitivity reactions should be available at bedside and a physician readily available. Prophylaxis to prevent infusion reactions is only recommended for subsequent doses in patients who previously experienced an infusion reaction to MCS110.

A pharmacy manual will be provided with details on how to administer MCS110

### 5.3.2 Dabrafenib

Dabrafenib will be given as per package instructions. Dabrafenib should be taken orally every 12 hours. A missed dose can be taken up to 6 hours prior to the next dose. Doses that would be administered outside of that timeframe should be considered missed and should not be taken. Tablets should not be crushed or chewed. A vomited dose should not be retaken, patients should continue with the next scheduled dose. Dabrafenib should be taken orally with approximately 200 mL of water under fasted conditions (an empty stomach either one hour before or two hours after a meal). Do not replace water with juice (especially not orange, grapefruit or other fruit juices), soda or other beverages. On days where MCS110, dabrafenib, and trametinib are all to be given, order of administration does not matter.

### 5.3.3 Trametinib

Trametinib will be given as per package instructions. Trametinib should be taken orally daily. A missed dose can be taken up to 12 hours prior to the next dose. Doses that would occur outside of this timeframe should be considered missed and should not be taken. Tablets should not be crushed or chewed. A vomited dose should not be retaken, patients

should continue with the next scheduled dose. Trametinib can be taken with or without food. Trametinib should be taken with a cup of water (approximately 200 mL of water). Do not replace water with juice (especially not orange, grapefruit or other fruit juices), soda or other beverages. On days where MCS110, dabrafenib, and trametinib are all to be given, order of administration does not matter.

## 5.4 Definition of Dose-Limiting Toxicity (DLT)

Dose-limiting toxicity is based on version 4.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE). DLT refers to toxicities experienced during the first cycle of treatment that are possibly, probably, or definitely related to the study medication regimen. A DLT will be defined as follows:

- ≥ Grade 3 non-hematological toxicity. Exceptions will be made for:
  - Nausea, vomiting, diarrhea, or constipation that can be controlled with appropriate care. Grade 3 and grade 4 nausea, vomiting, diarrhea, or constipation should be considered a DLT if persisting more than 48 hours despite maximum supportive intervention.
  - Grade 3 rash or photosensitivity lasting fewer than 8 days, or that can be controlled with appropriate care. Grade 3 rash or photosensitivity should be considered a DLT if it persists for more than 8 days and cannot be managed despite maximum supportive intervention.
- Grade 3 thrombocytopenia with clinically significant bleeding
- Grade 4 thrombocytopenia
- ≥ Grade 3 febrile neutropenia
- Grade 4 anemia
- Holding of any study medication due to toxicity for a period of greater than 8 consecutive days or two separate periods of any duration during the first cycle.
- Any other significant toxicity deemed by the principal investigator to be dose limiting (for example, any toxicity that is at least possibly related to the study medication regimen that results in the withdrawal of the patient from the study during cycle 1).

Management and dose modifications associated with the above adverse events are outlined in Section 6.

## 5.5 General Concomitant Medication and Supportive Care Guidelines

In general, concomitant medications and therapies deemed necessary for the supportive care (e.g. such as anti-emetics, anti-diarrhea) and safety of the patient are allowed. The administration of bisphosphonates is permitted.

Subjects should receive full supportive care during the study, including transfusions of blood and blood products, and treatment with antibiotics, anti-emetics, anti-diarrheals, and analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines. Use of anticoagulants such as warfarin is permitted however, caution should be exercised and additional International Normalized Ratio (INR) monitoring is recommended when dabrafenib is used concomitantly with warfarin.

The patient must be told to notify the investigational site about any new medications, herbal remedies and dietary supplements he/she takes after the start of the study treatment. All medications (other than study treatment) and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered during the study must be listed in the subject's study records. Prior antineoplastic therapies including medications, radiotherapy, and surgery are also to be recorded. Medication entries should be specific to trade name, dose and unit, the frequency and route of administration, the start and discontinuation date and the reason for therapy.
Radiation skin injury has been reported with concurrent use of dabrafenib and radiation. It is recommended that dabrafenib be held for seven days before and two days after XRT in subjects receiving dabrafenib monotherapy or in combination with trametinib. These recommendations can be modified based on the physician's assessment of the risk of radiation skin injury.

### 5.5.1 MCS110 Guidelines

Anticoagulation is permitted if the patients are already at stable doses of low molecular weight heparin (LMWH) for >2 weeks at time of first dose. However, ongoing anticoagulant therapy should be temporarily discontinued to allow tumor biopsy according to the institutional guidelines.

Statins should be used with caution since CK elevations are commonly seen.

Any other anticancer or investigational treatment is not permitted while on study treatment. Additionally, other biologics (e.g.: antibodies and proteins) and immunosuppressive medication are not permitted while on this study.

Concomitant chronic corticosteroids (≥10 mg of prednisone or equivalent) are not allowed.

Treatment with hematopoietic colony-stimulating growth factors (e.g. G-CSF), may not be initiated unless the investigator deems it necessary.

The use of live vaccines is not allowed through the whole duration of the study.

## 5.6 Criteria for Taking a Participant Off Protocol Therapy

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

- Disease progression, unless the patient is deriving clinical benefit as agreed upon with the principal investigator
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s) including those described in Sections 5.4 and Section

6

- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

When a participant is removed from protocol therapy and/or is off of the study, the relevant Off-Treatment/Off-Study information will be updated in OnCore.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI, Dr. Elizabeth Buchbinder at DFCI pager number 40221.

### 5.7 Duration of Follow Up

Participants will be followed for safety monitoring for 30 days after removal from protocol therapy. After the 30 days they will enter into long term follow up and will be followed until death after removal from protocol therapy. This follow up will be performed by review of the medical record, contact with care providers, and/or telephone contact as needed every 3-4 months.

### 5.8 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Lost to follow-up
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF).

For Centralized Subject Registrations, the research team submits a completed Off Treatment/Off Study form to ODQ when a participant comes off study. This form can be found on the ODQ website or obtained from the ODQ registration staff.

For Decentralized Subject Registrations, the research team updates the relevant Off Treatment/Off Study information in OnCore.

## 6. DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made as indicated in the following table. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

### 6.1 Specific Toxicity Management

Dose delays and modifications due to toxicity considered at least possibly related to MCS110, dabrafenib, and/or trametinib will be made as indicated in the following tables. Please also see Sections 6.2 and 6.3 for further guidance on allowed treatment delays and dose modifications:

**Table 5: Management of Elevated AST**

| AST (SGOT) and/or ALT (SGPT) Increase | Medication Management |
|---|---|
| **≤ Grade 2** | No change. |
| **Grade 3, *increase lasting less than 14 days without evidence of other hepatic injury*** | Hold study medications until resolution to ≤ grade 1 or baseline. Resume study medications at the same dose level. |
| **Grade 3, *increase lasting 14 or more days without evidence of other hepatic injury***<br>***-OR-***<br>**Grade 4, *without evidence of other hepatic injury*** | Hold study medications until resolution to ≤ grade 1; resume study medications with one dose level reduction. |
| **≥ Grade 3, *with evidence of other hepatic injury*** | Discontinue protocol therapy. |

**Table 6: Management of Elevated ALT**

| AST (SGOT) and/or ALT (SGPT) Increase | Medication Management |
|---|---|
| **≤ Grade 2** | No change. |
| **Grade 3, *without evidence of other hepatic injury***<br>***-OR-***<br>**Grade 4, *without evidence of other hepatic injury*** | Hold study medications until resolution to ≤ grade 1; resume study medications with one dose level reduction. |
| **≥ Grade 3, *with evidence of other hepatic injury*** | Discontinue protocol therapy. |

Liver transaminase elevations have been associated with all three study medications in previous clinical trials. Patients should be monitored for increases in their liver function tests and for other signs of possible hepatic injury (elevated bilirubin, coagulation abnormalities, encephalopathy,

etc.) as clinically appropriate and as indicated in the Study Calendar – Section 10.

**Table 7: Management of Neutropenia**

| Neutrophil Count Decrease | Medication Management |
|---|---|
| **≤ Grade 2** | No change. |
| **Grade 3, *no associated fever or infection***<br>***-OR-***<br>**Grade 4, *decrease lasting less than 8 consecutive days*** | Hold study medications until recovery to ≤ grade 2. Upon recovery, restart at the same dose level. |
| **≥ Grade 3, *associated with a fever or infection***<br>***-OR-***<br>**Grade 4, *decrease lasting 8 or more consecutive days*** | Hold study medications until recovery to ≤ grade 2. Upon recovery, resume with one dose level reduction. |

**Table 1: Management of Thrombocytopenia**

| Platelet Count Decrease | Medication Management |
|---|---|
| **≤ Grade 2** | No change. |
| **Grade 3, *no clinically significant bleeding*** | Hold study medications until recovery to ≤ grade 2. Upon recovery, restart at the same dose level. |
| **Grade 3, *associated with clinically significant bleeding***<br>***-OR-***<br>**Grade 4** | Hold study medications until recovery to ≤ grade 2. Upon recovery, resume with one dose level reduction. |

**Table 9: Management of Rash or Photosensitivity**

| Rash or Photosensitivity | Medication Management |
|---|---|
| **≤ Grade 2** | No change.* Implement appropriate supportive care (e.g., topical or oral antibiotics or steroids, use of protective clothing/sunscreen). |
| **Grade 3, *not optimally managed or lasting fewer than 8 consecutive days*** | Implement appropriate supportive care (e.g., topical or oral antibiotics or steroids). Hold study medications until recovery to ≤ grade 2. Upon recovery, restart at the same dose level. |
| **Grade 3, *optimally managed or lasting 8 or more consecutive days***<br>***-OR-***<br>**Grade 4** | Hold study medications until recovery to ≤ grade 2. Upon recovery, resume with one dose level reduction. |
| **If a patient is experiencing intolerable grade 2 rash or photosensitivity despite optimal medical management, their study medication may be held at the treating investigator's discretion. Upon resolution to grade 1 or baseline, the study medication can be dose reduced at the treating* | |

| |
|---|
| *investigator's discretion.* |

**Table 10: Management of QTc Increase (Associated with Dabrafenib)**

| QTc Interval Prolonged | Dabrafenib Management |
|---|---|
| **≤ Grade 2** | No change. |
| **Grade 3, *increase is ≤ 60 msec from pre-treatment value or QTc ≥ 501 msec*** | Hold dabrafenib until recovery to ≤ grade 2. Upon recovery, restart at current dose level reduction.* |
| **Grade 3, *increase is > 60 msec from pre-treatment value***<br>***-OR-***<br>**Grade 4** | Discontinue dabrafenib. |
| *Interrupt all study treatments until QTc prolongation resolves to grade 1 or baseline<br>Test serum potassium, calcium, phosphorus and magnesium. If abnormal correct per routine clinical practice to within normal limits.<br>Review concomitant medication usage for agents that prolong QTc.<br>If event resolves, restart study treatment at current dose level[b]<br>If event does not resolve, permanently discontinue study treatments. Consider evaluation with cardiologist.<br>If event recurs, permanently discontinue study treatments. Consider evaluation with cardiologist. | |

**Table 11: Management of Nausea**

| Nausea | Medication Management |
|---|---|
| **≤ Grade 2** | No change.* Implement appropriate supportive care (e.g., antiemetics) as clinically indicated. |
| **Grade 3, *not optimally managed*** | Hold study medication and implement appropriate supportive care (including antiemetics and IV hydration if indicated). Upon resolution to ≤ grade 2, resume study medication at the same dose level. |
| **≥ Grade 3, *optimally managed***<br>***-OR-***<br>**Grade 4** | Hold study medication until resolution to ≤ grade 2; resume study medication with one dose level reduction if ≥ grade 3 nausea persisted for more than 48 hours despite maximum supportive intervention. |
| **If a patient is experiencing intolerable grade 2 nausea despite optimal medical management, their study medication may be held at the treating investigator's discretion. Upon resolution to grade 1 or baseline, the study medication can be dose reduced at the treating investigator's discretion.* | |

**Table 12: Management of Vomiting**

| Vomiting | Medication Management |
|---|---|
| **≤ Grade 2** | No change.* Implement appropriate supportive care (e.g., antiemetics) as clinically indicated. |
| **Grade 3, *not optimally managed*** | Hold study medication and implement appropriate supportive care (including antiemetics and IV hydration if indicated). Upon resolution to ≤ grade 1, resume study medication at the same dose level. |
| **≥ Grade 3, *optimally managed***<br>***-OR-***<br>**Grade 4** | Hold study medication until resolution to ≤ grade 1; resume study medication with one dose level reduction if ≥ grade 3 vomiting persisted for more than 48 hours despite maximum supportive intervention. |
| **If a patient is experiencing intolerable grade 2 vomiting despite optimal medical management, their study medication may be held at the treating investigator's discretion. Upon resolution to grade 1 or baseline, the study medication may be dose reduced at the treating investigator's discretion.* | |

**Table 13: Management of Diarrhea**

| Diarrhea | Medication Management |
|---|---|
| **≤ Grade 2** | No change.* Implement appropriate supportive care (e.g., antidiarrheals) as clinically indicated. |
| **Grade 3, *not optimally managed*** | Hold study medication and implement appropriate supportive care (including antidiarrheals and IV hydration if indicated). Upon resolution to ≤ grade 1, resume study medication at the same dose level. |
| **≥ Grade 3, *optimally managed***<br>***-OR-***<br>**Grade 4** | Hold study medication until resolution to ≤ grade 1; resume study medication with one dose level reduction if ≥ grade 3 diarrhea persisted for more than 48 hours despite maximum supportive intervention. |
| **If a patient is experiencing intolerable grade 2 diarrhea despite optimal medical management, their study medication may be held at the treating investigator's discretion. Upon resolution to grade 1 or baseline, the study medication may be dose reduced at the treating investigator's discretion.* | |

**Table 14: Management of Constipation**

| Constipation | Medication Management |
|---|---|
| **≤ Grade 2** | No change.* Implement appropriate supportive |

| | |
|---|---|
| | care (e.g., laxatives) as clinically indicated. |
| **Grade 3, *not optimally managed*** | Hold study medication and implement appropriate supportive care (including laxatives and enemas if indicated). Upon resolution to ≤ grade 2, resume study medication at the same dose level. |
| **≥ Grade 3, *optimally managed***<br>***-OR-***<br>**Grade 4** | Hold study medication until resolution to ≤ grade 2; resume study medication with one dose level reduction if ≥ grade 3 constipation persisted for more than 48 hours despite maximum supportive intervention. |
| **If a patient is experiencing intolerable grade 2 constipation despite optimal medical management, their study medication may be held at the treating investigator's discretion. Upon resolution to grade 1 or baseline, the study medication may be dose reduced at the treating investigator's discretion.* | |

**Table 15: Management of CK elevation**

| CK elevation | Medication Management |
|---|---|
| **CK elevation ≤ Grade 2** | No change.§ |
| **CK elevation ≥ Grade 3 (CK ≥ 5XULN)** | Monitor CK-MB, troponin (I and T) and creatinine<br><br>*If CK-MB and troponin (I or T) are normal, creatinine ≤ 1.5 baseline and patient asymptomatic continue treatment<br>*If CK-MB and troponin (I or T) ere abnormal or creatinine ≥1.5X baseline and > ULN or patient symptomatic, hold therapy and explore alternative causes for elevated CK (for example myositis and rhabdomyolysis)<br>After recovery of CK-MB, troponin (I or T) and creatinine to grade 1 or baseline, study treatment may be resumed with MCS110 at 50% of the previous dose. |
| *§If a patient is experiencing a new grade 2 or greater increase in CPK, both urine and serum myoglobin laboratory tests should be performed. Additional tests may also be performed or repeated at the treating investigator's discretion.* | |

* MCS110 treatment results in CK and AST elevations without any association to muscle damage (Radi 2011). The CK/AST elevations are caused by reduced clearance rate from the circulation due to the diminished numbers of macrophages (Kupffer cells) in the liver.

**Table 16: Managment of LVEF reduction**

| LVEF decrease | Medication Management |
|---|---|
| **Asymptomatic with absolute LVEF decrease of > 10% compared to baseline and < 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)<br>• Consult with the GSK medical monitor and request approval for restart<br>• If approved, restart treatment with trametinib reduced by one dose level<br>• Repeat ECHO at 2 , 4, 8 and 12 weeks after re-start; continue in intervals of 12 weeks thereafter<br>• If LVEF **does not recover** within 4 weeks<br>• Consult with cardiologist<br>• **Permanently discontinue trametinib**<br>• **Report as SAE**<br>• Repeat ECHO after 2, 4, 8, 12, and 16 weeks or until resolution |
| **Symptomatic, Grade 3: resting LVEF 39-20% or >20% absolute reduction from baseline<br>-OR-<br>Grade 4: resting LVEF <20%** | • **Permanently discontinue trametinib**<br>• **Interrupt dabrafenib.**[d]<br>• **Report as SAE**<br>• **Consult with cardiologist**<br>Repeat ECHO after 2, 4, 8, 12, and 16 weeks or until resolution[b,d] |

a. If ECHO does not show LVEF recovery after 2 weeks, repeat ECHO 2 weeks later.
b. If recurrent episodes of LVEF reduction occur in subjects receiving dabrafenib monotherapy, consult medical monitor.
c. Symptoms may include: dyspnea, orthopenea, and other signs and symptoms of pulmonary congestion and edema.
*d.* Once LVEF recovers, including resolution of symptoms, restart of dabrafenib monotherapy only can be considered in consultation with GSK medical monitor.

**Table 17: Management of Renal Insufficiency**

| Creatinine elevation | Medication Management |
|---|---|
| **Grade 1, creatinine level increase of >0.3mg/dL, creatinine 1.5-2.0 X ULN** | • Recheck serum creatinine within 1 week<br>• Serum creatinine increase > 1 week: contact Novartis Clinical Team. If elevation persists beyond 4 weeks, recommend evaluation (consider renal biopsy) for etiology; consider nephrology consultation.<br>• If pyrexia is present, treat as per Table 27.<br>Continue study medication at same dose level |
| **Grade 2, creatinine 2-3 X ULN** | • Monitor serum creatinine ≥ 2-times per week |

| | |
|---|---|
| | • Hospitalization may be necessary if serum creatinine cannot be monitored frequently<br>• If pyrexia is present, treat as per Table 27<br>• Consult nephrologist if clinically indicated<br>• Perform renal biopsy if clinically indicated, for example:<br>o Renal insufficiency persists despite volume repletion or signs of hypersensitivity<br>Hold study medication. Upon resolution to ≤ grade 1, resume study medication at same dose level |
| **Grade 3, Creatinine >3XULN or > 4.0mg/dL** | Hold study medication. Upon resolution to ≤ grade 1, resume study medication with one dose level reduction. ** |
| *NSAIDs can induce renal insufficiency, especially in subjects with dehydration; encourage oral fluids or consider intravenous fluids as clinically indicated. See guidelines for pyrexia Section 5.8.5.1.<br>Investigator may restart at either the same or a reduced dose level. 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. Consultation with GSK Medical Monitor is required before restarting study treatment if there is evidence of thrombotic microangiopathy. | |

**Table 18: Management of Pneumonitis**

| Pneumonitis | Medication Management |
|---|---|
| **Grade 1** | • CT scan (high-resolution with lung windows) recommended<br>• Clinical evaluation and laboratory work-up for infection<br>• Monitoring of oxygenation via pulse-oximetry recommended<br>• Consultation of pulmonologist recommended<br>Continue study medication at same dose level |
| **Grade 2** | • CT scan (high-resolution with lung windows)<br>• Clinical evaluation and laboratory work-up for infection<br>• Consult pulmonologist<br>• Pulmonary function tests –if < normal, repeat every 8 weeks until ≥ normal<br>• Bronchoscopy with biopsy and/or BAL recommended<br>• Symptomatic therapy including corticosteroids if clinically indicated<br>• Hold study medication. Upon resolution to ≤ grade 1, resume trametinib at one dose reduction.<br>• Escalation to previous dose level after 4 |

| | |
|---|---|
| | weeks and consultation with Lead Investigator<br>If no recovery to grade ≤1 within 4 weeks, permanently discontinue study treatment |
| **Grade 3** | • CT scan (high-resolution with lung windows)<br>• Clinical evaluation and laboratory work-up for infection<br>• Consult pulmonologist<br>• Pulmonary function tests –if < normal, repeat every 8 weeks until ≥ normal<br>• Bronchoscopy with biopsy and/or BAL recommended<br>• Symptomatic therapy including corticosteroids if clinically indicated<br><br>Hold study medication. Upon resolution to ≤ grade 1, resume trametinib at one dose reduction.<br><br>If no recovery to grade ≤1 within 4 weeks, permanently discontinue study treatment |
| **Grade 4** | • CT scan (high-resolution with lung windows)<br>• Clinical evaluation and laboratory work-up for infection<br>• Consult pulmonologist<br>• Pulmonary function tests –if < normal, repeat every 8 weeks until ≥ normal<br>• Bronchoscopy with biopsy and/or BAL recommended<br>• Symptomatic therapy including corticosteroids if clinically indicated<br>Permanently discontinue trametinib |

**Table 19: Management of Other Toxicity**

| Other Toxicity | Medication Management |
|---|---|
| **≤ Grade 2** | No change.* |
| **≥ Grade 3** | Hold study medication. Upon resolution to ≤ grade 2, resume study medication with one dose level reduction. ** |
| **If a patient is experiencing intolerable grade 2 toxicity, their study medication may be held at the treating investigator's discretion. Upon resolution to grade 1 or baseline, the study medication can be dose reduced at the treating investigator's discretion.*<br>***Patients who experience a ≥ grade 3 infusion-related reaction should be discontinued from* | |

*protocol therapy.*

MCS110 can cause periorbital edema which is generally mild but should be monitored:

| Periorbital edema | |
|---|---|
| Grade 2-3 | Delay treatment until resolved to ≤ Grade 1. Decrease MCS110 1 dose level. |
| Grade 4 | Discontinue from treatment. |

Episodes of visual changes have been observed in subjects receiving 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). For events of visual changes (regardless of severity) for which an ophthalmic examination is conducted, a blood sample for PK analysis must be drawn as close as possible to the time of the event. Guidelines regarding management and dose reduction for visual changes and/or ophthalmic examination findings considered to be related to study treatment are provided in Appendix B.

**Dose modifications and action for toxicities suspected to be related to MCS110**

| Toxicity | CTCAE Grade | Action |
|---|---|---|
| **CK elevation** | Grade ≥3 (CK>5 x ULN) | Monitor CK-MB, troponin (I or T) and creatinine.<br>● If CK-MB and troponin (I or T) are normal, creatinine < 1.5 x baseline and patient asymptomatic, maintain dose level.<br>● If CK-MB and troponin (I or T) are abnormal or creatinine (> 1.5 x baseline and > ULN) or patient symptomatic, withhold drugs and explore alternative causes for elevated CK (for example myositis and rhabdomyolysis) according to local guidelines.<br>After recovery of CK-MB, troponin (I or T) and creatinine to Grade 1 or baseline, study treatment may be resumed: chemotherapy at previous doses and MCS110 at 50%a of the previous dose |

Episodes of pyrexia have been observed in subjects receiving dabrafenib monotherapy, and is increased in incidence and severity in subjects receiving dabrafenib in combination with trametinib (see dabrafenib and trametinib FDA Labels). In a minority of cases the pyrexia was accompanied by symptoms such as severe chills, dehydration, hypotension, dizziness or weakness.

Subjects should be instructed on the importance of immediately reporting febrile episodes. In the event of a fever, the subject 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.

### 6.2 Treatment Delays

The study medications may be held for toxicity for up to four weeks before the participant must be removed from the study. Exceptions to this requirement are possible should the principal investigator agree that the patient may continue despite the length of time off drug. Treatment may be held for grade 2 AST and/or ASLT increases at the treating investigator's discretion following the DLT period.

Study medications may be held independently of each other if toxicity is felt by the treating investigator to be attributed to one or two of the three medications (e.g., a patient may continue to receive their MCS110 on schedule while holding their dabrafenib and/or trametinib).

If the study medication(s) is/are placed on hold for toxicity, the counting of cycle days and assessment schedule will continue without interruption (including tumor evaluations). For example, a patient who does not receive their cycle 2 day 1 infusion of MCS110 due to toxicity will proceed with their next scheduled infusion and visit (cycle 3 day 1). Additional interim visits will be conducted as clinically necessary to manage toxicity. The cycle will not restart for dosing delays due to toxicity. Exceptions to this are possible for significant treatment delays ($\geq$ 2 weeks) after a discussion with the principal investigator.

### 6.3 Dose Modifications

The first dose reduction for any specific toxicity must include a reduction in MCS110 unless the toxicity is clearly causes by dabrafenib or trametinib in which case these medications should be reduced. Further dose reductions will be based on the offending medication(s) according to the schedule outlined in table 20. In the event the treating investigator feels all three medications are responsible for the toxicity, all medications can be reduced. Dose reductions below 25 mg once per week of MCS110 will not be permitted. Reductions below 50 mg BID of dabrafenib or 1 mg daily of trametinib will not be permitted.

A maximum of two dose reductions will be allowed with any one of the medications. If a patient requires more than two dose reductions with any one of the study medications, they should be discontinued from protocol therapy. Exceptions are possible in the event a patient is not tolerating the dabrafenib and/or trametinib despite maximal dose reductions but is deriving clinical benefit. In this circumstance, a patient may be allowed to continue on protocol therapy and receive MCS110 either alone or in combination with just the dabrafenib or trametinib if agreed upon with the principal investigator.

Patients undergoing dose reductions for toxicities may not be re-escalated.

Participants enrolled to the phase I portion of the trial may undergo intra-patient dose escalation if subsequent higher dose levels are proven safe as per the guidelines in Section 5.1 and 5.4. Participants may only undergo dose escalations to a dose level where ≤ 1 DLT have been observed among 6 patients, two dose levels below a dose level where < 1 out of 3 patients have experienced DLTs, or the dose level that has been declared the RP2D. Under no circumstances may a patient escalate to a dose level above the MTD. Patients must have been on study for at least two cycles with no DLTs or DLT-equivalent toxicity to be eligible for dose escalation. If toxicities at a lower dose level are observed and make the dose intolerable, intra-patient dose escalation will stop and patients on higher dose levels will need to dose to reduce to a tolerable level.

**Table 20: Dose Modifications**

| Original Dose Level | MCS110 Reduction | Dabrafenib Reduction* | Trametinib Reduction* |
|---|---|---|---|
| **-1** | 1st Reduction: 0.625 mg/kg IV every 3 weeks | 1st Reduction: 100 mg BID | 1st Reduction: 1.5 mg once daily |
| | 2nd Reduction: Discontinue protocol therapy | 2nd Reduction: 50 mg BID | 2nd Reduction: 1 mg once daily |
| **1** | 1st Reduction: 1.25 mg/kg IV every 3 weeks | 2nd Reduction: 100 mg BID | 1st Reduction: 1.5 mg once daily |
| | 2nd Reduction: 0.625 mg/kg IV every 3 weeks | 2nd Reduction: 50 mg BID | 2nd Reduction: 1 mg once daily |
| **2** | 1st Reduction: 2.5 mg/kg IV every 3 weeks | 1st Reduction: 100 mg BID | 1st Reduction: 1.5 mg once daily |
| | 2nd Reduction: 1.25 mg/kg IV every 3 | 2nd Reduction: 50 mg BID | 2nd Reduction: 1 mg once daily |

| | | | |
|---|---|---|---|
| | weeks | | |
| **3** | 1st Reduction: 5 mg/kg IV every 3 weeks | 1st Reduction: 100 mg BID | 1st Reduction: 1.5 mg once daily |
| | 2nd Reduction: 2.5 mg/kg IV every 3 weeks | 2nd Reduction: 50 mg BID | 2nd Reduction: 1 mg once daily |
| *: Dabrafenib and trametinib may be reduced as per the FDA prescribing information | | | |

### 6.4 Overdose management

There are no known antidotes for over-dosage of MCS110, dabrafenib, or trametinib. In the case of suspected overdose, monitor hematologic parameters, serum chemistry, vital signs, cardiac function, and provide supportive care as necessary.

In the event of a dabrafenib overdose, defined as administration of more than 300 mg as a single dose or 600 mg per day (the highest dose tested in clinical studies to date), and/or a trametinib overdose, defined as administration of more than 3.0 mg once daily (the maximum tolerated dose defined in the MEK111054 Study), the investigator should contact the NOVARTIS Clinical Team immediately and closely monitor the subject for AEs/SAEs and laboratory abnormalities. NOVARTIS does not recommend specific treatment. The investigator will use clinical judgment to treat any overdose. Haemodialysis is not expected to enhance the elimination of either dabrafenib or trametinib as both are highly bound to plasma proteins.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the NOVARTIS Clinical Team based on the clinical evaluation of the subject. A plasma sample for PK analysis may be requested by the NOVARTIS Clinical Team on a case-by-case basis. This plasma sample should be collected as soon as possible, but within 10 days from the date of the last dose of on-study dosing.
Information regarding the quantity of the excess dose as well as the duration of the overdosing should be documented in the eCRF.

## 7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Sections 7.2 and 7.3) will determine whether the event requires expedited reporting **in addition** to routine reporting.

## 7.1 Definition

### 7.1.1 Adverse Event (AE)

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

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

## 7.2 Expected Toxicities

**MSC110**

| | **"Adverse Events considered to be Expected for Reporting Purposes"** | | |
|---|---|---|---|
| **MedDRA system organ class** | **Event** | **n/N (%)** | **Frequency Category*** |
| General disorders and administration site conditions | Swelling (peripheral, general) | 3/16 (19%)** | Very common |
| Investigations | CK (CPK, creatine kinase) increased | *** | Very common |
| Skin and subcutaneous disorders | Periorbital edema** | 7/16 (44 %) | Very common |
| | Rash | 4/16 (25%) | Very common |

* frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000). Unknown - insufficient data to determine the frequency of the ADR
** 3 out of the 7 patients with periorbital edema also developed peripheral or general swelling;
*** not consistently reported as AE
There is no "Adverse Events with a fatal outcome considered to be Expected for Reporting Purposes". Information from MCS110 Investigator's Brochure Edition 11, Dated 14 April 2016

**Trametinib**

| | **"Adverse Events considered to be Expected for Reporting** |
|---|---|

| | **Purposes"** | |
|---|---|---|
| **MedDRA system organ class** | **Event** | **Frequency Category*** |
| Infections and infestations | Folliculitis, paronychia, cellulitis, rash pustular | Common |
| Blood and lymphatic system disorders | Anaemia | Common |
| Immune system disorders | Hypersensitivity<br>*May present with symptoms such as fever, rash, increased liver function tests, and visual disturbances* | Uncommon |
| Metabolism and nutrition disorders | Dehydration | Common |
| Eye disorders | Vision blurred, periorbital oedema, visual impairment | Common |
| | Chorioretinopathy, retinal vein occlusion, papilloedema, retinal detachment | Uncommon |
| Cardiac disorders | Left ventricular dysfunction, ejection fraction decreased, bradycardia | Common |
| | Cardiac failure | Uncommon |
| Vascular disorders | Hypertension, haemorrhage<br>*The majority of bleeding events were mild. Major events, defined as symptomatic bleeding in a critical area or organ, and fatal intracranial haemorrhages have been reported.* | Very common |
| | Lymphoedema | Common |
| Respiratory, thoracic and mediastinal disorders | Cough, dyspnoea | Very common |
| | Epistaxis, pneumonitis | Common |
| | Interstitial lung disease | Uncommon |
| Gastrointestinal disorders | Diarrhoea, nausea, vomiting, constipation, abdominal pain, dry mouth | Very common |
| | Stomatitis | Common |
| | **Colitis, gastrointestinal perforation** | Uncommon |
| Skin and subcutaneous tissue disorders | Rash, dermatitis acneiform, dry skin, pruritus, alopecia | Very common |
| | Skin chapped, erythema, palmar-plantar erythrodysaesthesia syndrome, skin fissures | Common |
| Musculoskeletal and connective tissue disorders | Blood creatinine phosphokinase increased | Common |
| General disorders and administration site conditions | Fatigue, oedema peripheral, pyrexia | Very common |
| | Face oedema, mucosal inflammation, asthenia | Common |
| Investigations | Aspartate aminotransferase increased, alanine aminotransferase increased, blood alkaline | Common |

| | | |
|---|---|---|
| | phosphatase increased | |

* frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000). Unknown - insufficient data to determine the frequency of the ADR. Information taken from Trametinib Investigator's Brochure Edition 8, Dated 11 August 2016. New events to IB Edition 8 are in bold font.

## Dabrafenib

| | **"Adverse Events considered to be Expected for Reporting Purposes"** | |
|---|---|---|
| **MedDRA system organ class** | **Event** | **Frequency Category*** |
| Infections and infestations | Nasopharyngitis | Common |
| Neoplasms benign and malignant (including cysts and polyps) | Papilloma | Very common |
| | Acrochordon (skin tags), cutaneous squamous cell carcinoma (SCC) including SCC of the skin, SCC in situ (Bowen's disease) and keratoacanthoma, seborrhoeic keratosis | Common |
| | New primary melanoma | Uncommon |
| Immune system disorders | Hypersensitivity | Uncommon |
| Metabolism and nutrition disorders | Decreased appetite | Very common |
| | Hypophosphataemia<br>Hyperglycaemia | Common |
| Nervous system disorders | Headache | Very common |
| Eye disorders | Uveitis | Uncommon |
| Respiratory, thoracic and mediastinal disorders | Cough | Very common |
| Gastrointestinal disorders | Nausea, vomiting, diarrhoea | Very common |
| | Constipation | Common |
| | Pancreatitis | Uncommon |
| Skin and subcutaneous tissue disorders | Skin effects (rash, hyperkeratosis), alopecia, palmarplantar erythrodysaesthesia syndrome | Very common |
| | Skin effects (actinic keratosis, skin lesion, dry skin, erythema, pruritus) | Common |
| | Panniculitis | Uncommon |
| Musculoskeletal and connective tissue disorders | Arthralgia, myalgia, pain in extremity | Very common |
| Renal disorders | Renal failure, acute renal failure | Uncommon |

| | | |
|---|---|---|
| | Tubulointerstitial nephritis | Rare |
| General disorders and administration site conditions | Asthenia, chills, fatigue, pyrexia | Very common |
| | Influenza-like illness | Common |

*frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000). Unknown - insufficient data to determine the frequency of the ADR. Information taken from the Dabrafenib Investigator's Brochure Edition 8, Dated 16 August 2016.

**Dabrafenib in combination with Trametinib**

| | **"Additional Adverse Events considered to be Expected for Reporting Purposes - observed in clinical development programs in Dabrafenib in combination with Trametinb"** | | |
|---|---|---|---|
| **MedDRA system organ class** | **Event** | **n/N (%)** | **Frequency Category*** |
| Hepatobiliary disorder | Liver disorders[1] | 41/5866 (0.69%) | Uncommon |

1. Liver disorders include Hepatotoxicity, Hepatitis, Hepatocellular injury, Liver disorder, Jaundice, Hepatomegaly, Hepatitis toxic, Hepatorenal syndrome, Hepatitis fulminant, Drug-induced liver injury and Liver injury.

### 7.3 Adverse Event Characteristics

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

- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.

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

## 7.4 Serious Adverse Events

A serious adverse event (SAE) is any adverse event during this study that results in one of the following outcomes:

- Death
- Hospitalization for greater than 24 hours
- Prolonging an existing inpatient hospitalization
- A life-threatening experience (that is, immediate risk of dying)
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Considered significant by the investigator for any other reason

- All events of possible drug-induced liver injury with hyperbilirubinaemia defined as ALT ≥3xULN **and** bilirubin ≥ 2xULN (>35% direct) (or ALT ≥ 3xULN and INR>1.5, if INR measured) or termed 'Hy's Law' events (INR measurement is not required and the threshold value stated will not apply to patients receiving anticoagulants).

NOTE: bilirubin fractionation is performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick indicating direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a subject meets the criterion of total bilirubin ≥ 2xULN, then the event is still reported as an SAE. If INR is obtained, include values on the SAE form. INR elevations >1.5 suggest severe liver injury.

- Any new primary cancers and treatment emergent malignancies (including squamous cell carcinoma and new primary melanoma) with the exception of basal cell carcinoma (BCC). BCC should be reported as an AE or SAE based on the discretion of the investigator.
- Symptomatic LVEF decrease that meets stopping criteria or asymptomatic LVEF decrease that does not recover.
- Retinal pigment epithelial detachment (RPED) or retinal vein occlusion (RVO)

Previously planned (prior to signing the informed consent form) surgeries, and non-disease related elective surgeries planned during the course of the study, should not be reported as SAEs unless the underlying medical condition has worsened or appeared during the course of the study.

Preplanned hospitalizations or procedures for preexisting conditions that are already recorded in the patient's medical history at the time of study enrollment should not be considered SAEs. Hospitalization or prolongation of hospitalization without a precipitating clinical AE (e.g., for the administration of study therapy or other protocol-required procedure) should not be considered SAEs.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the

outcomes listed in this definition.

Death due to disease progression should not be reported as an SAE unless the investigator deems it to be related to the use of study drug.

Study site personnel must alert Novartis of any SAE as soon as possible and no later than 24 hours of the investigator and/or institution receiving notification of the SAE experienced by a patient participating in the study. The SAE reports are to be sent to Novartis via fax at 1-**877-778-9739**.

**Pregnancies**

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be **reported to Novartis within 24 hours** of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis Drug Safety and Epidemiology Department (DS&E) by fax (877-778-9739). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother. If a pregnancy occurs while on study treatment, the newborn will be followed for at least 3 months.

### 7.5 Expedited Adverse Event Reporting

7.5.1 Investigators **must** report to the Overall PI any serious adverse event (SAE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form. Each serious adverse event must be reported by the investigator to **Novartis within 24 hours** of learning of its occurrence, even if it is not felt to be treatment-related. Follow-up information about a previously reported serious adverse event must also be reported to Novartis within 24 hours of receiving it. If the serious adverse event has not been previously documented (new occurrence) and it is thought to be related to study drug (or therapy), the Medical Safety Expert of the Drug Safety & Epidemiology (DS&E) Department may contact the investigator to obtain further information. If warranted, an investigator alert may be issued, to inform all investigators involved in any study with the same drug (or therapy) that this serious adverse event has been reported.

The investigator must complete the FDA MedWatch 3500a form and Novartis SAE coversheet in English, assess the relationship to study treatment and send the initial completed MedWatch form and Novartis SAE coversheet by fax 1.877.778.9739 **within 24 hours** to the local Novartis Drug Safety & Epidemiology (DS&E) Department. The investigator must then ensure that the form and coversheet are accurately and fully completed with follow-up information and fax those to Novartis DS&E Department within 2 to 3 calendar days for deaths or life-threatening events and 5 calendar days for other serious adverse events. The original and the duplicate copies of the FDA MedWatch form, Novartis SAE coversheet, and the fax confirmation sheet must be kept with the case report forms at the study site.

Follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or discontinued study participation. The MedWatch form, Novartis SAE coversheet, and fax confirmation sheet must be retained. Pregnancy follow-up should describe the outcome of the pregnancy, including any voluntary or spontaneous termination, details of the birth, and the presence or absence of any congenital abnormalities or birth defects.

7.5.2 DF/HCC Expedited Reporting Guidelines

Investigative sites within DF/HCC will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

### 7.6 Expedited Reporting to the Food and Drug Administration (FDA)

The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Overall PI will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

### 7.7 Expedited Reporting to Hospital Risk Management

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

### 7.8 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must <u>also</u> be reported in routine study data submissions.**

## 8. BIOMARKER, CORRELATIVE, SPECIAL STUDIES, AND PHARMACEUTICAL INFORMATION

### 8.1 Collection of Archival Tissue

Archival tumor tissue will be collected on all patients enrolling to the trial as described in Section 2.6 - Correlative Studies. Patients who do not have archival tissue available will be allowed to enroll at the discretion of the principal investigator.

Depending on availability, 10 - 20 unstained slides will be collected. Less than the goal amount of tissue is acceptable if archival tissue is limited. The slide collection should be labeled with the protocol number and study subject number. Slides should be mailed to the following address for analysis:

ATTN: CIO Laboratory Manager
Center for Immuno-Oncology Laboratory
Jimmy Fund Building Room 406
1 Jimmy Fund Way
Boston, MA 02115

### 8.2 Exploratory Fresh Tumor Biopsies

Optional fresh tumor biopsies will be obtained from patients enrolled during either phase of the trial, as described in Section 2.6 – Correlative Studies. The biopsies will only be obtained if the treating investigator believes the biopsy to be clinically feasible and if the patient is willing to undergo the biopsy procedures.

The optional on-treatment biopsy can be collected anytime between Cycle 1 Day 15 and Cycle 2 Day 7. An additional optional biopsy at the time of disease progression will also be offered to patients if deemed clinically feasible. Preferably, time of progression biopsies should be obtained prior to the initiation of another cancer treatment. However, in the event that it is not possible to perform the biopsy before another treatment is begun, the biopsy can be obtained up to 30 days after the last dose of MCS110.

Core biopsy samples should be obtained for analysis. Three-to-four biopsy passes utilizing a 16-18 gauge needle are preferable, but a 20 gauge core needle biopsy is also acceptable. Less than the goal amount of tissue is acceptable for the biopsy procedures, and should be based upon the clinical judgment of the treating investigator and the clinician performing the procedure.

Biopsy samples should be formalin-fixed and paraffin embedded per institutional standards.

Both the pre and on-treatment tumor biopsy samples should be labeled with the protocol number and study subject number, and should be sent to the CIO lab for analysis:

ATTN: CIO Laboratory Manager
Center for Immuno-Oncology Laboratory
Jimmy Fund Building Room 406
1 Jimmy Fund Way
Boston, MA 02115

## 8.3 Laboratory Correlative Studies

A cell-free DNA (cfDNA) plasma sample and a circulating immune cell (CIC) sample will be collected at baseline (prior to the first dose of MCS110, dabrafenib, and trametinib), at visits immediately following restaging scans (i.e., cycle 3 day 1, cycle 5 day 1, cycle 7 day 1, etc.), and at the off study visit. Samples collected on days where study medication dosing will occur can be collected anytime pre-dosing.

### 8.3.1 Cell-free DNA (cfDNA) and Circulating Immune Cell (CIC) Sample Collection Procedure:

1. Blood samples should be labeled with the protocol number, study subject number, date of the draw, and the label, "cfDNA/CIC."
2. Draw venous blood into three 10 mL EDTA tubes, immediately gently invert the tube 3-4 times.
3. Send tubes to the CIO lab for processing within 6 hours of blood draw (tubes sent outside of this window due to shipping or scheduling difficulties will not be considered protocol violations):

   ATTN: CIO Laboratory Manager
   Center for Immuno-Oncology Laboratory
   Jimmy Fund Building Room 406
   1 Jimmy Fund Way
   Boston, MA 02115

## 8.4 MCS110

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

### 8.4.1 **Description**

**Molecular Structure:** MCS110 is a IgG1/κ high affinity, humanized monoclonal antibody directed against human macrophage colony stimulating factor (M-CSF; also known as colony-stimulating factor-1 [CSF-1]). It is a polypeptide composed of 1324 amino acid residues with two heavy chains and two light chains in heterodimeric arrangement.

**Molecular mass:** MCS110 has a non-glycosylated molecular mass of 144.9 kDa.

**pH:** 5.5- 6.5

8.4.2 **Form**

The MCS110 150 mg/7.5 mL solution for infusion is formulated as a sterile solution intended for intravenous (IV) administration. Each vial of MCS110 150 mg/7.5 mL solution for infusion contains 150 mg MCS110 drug substance and the following excipients: L-histidine, NaCl, Polysorbate 80, HCl, and water for injection.

8.4.3 **Storage**

Drug product should be stored at 2-8°C. Only qualified individuals should be responsible for drug access and storage.

If not used immediately, the MCS110 20mg/mL Concentrate for Solution for Infusion and MCS110 Solution for Infusion might be stored at 2- 8°C for not longer than 24 hours. The standing time of 24 hours is defined as the time from the first vial has been pierced until the end of administration. Upon storage, allow the Solution for Infusion to come to room temperature for 5-10 minutes but not more than 15 minutes before administration

8.4.4 **Compatibility**

Drug product should be diluted with a 0.9% NaCl solution before administration to patients. Compatible materials for infusion and dilution instructions are listed in the pharmacy manual for CMCS110ZUS01T.

8.4.5 **Handling**

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

8.4.6 **Availability**

MCS110 is provided by Novartis for use in this clinical trial.

8.4.7 **Preparation**

Instructions for preparation are listed in the pharmacy manual for CMCS110ZUS01T. Drug product should be diluted with a 0.9% NaCl solution before administration to patients.

8.4.8 **Administration**

MCS110 will be given once on day 1 of the 21 day cycle via IV infusion. MCS110 should be

administered in a 1 hour (±5 min) infusion. On days where MCS110, dabrafenib, and trametinib are all to be given, order of administration does not matter.

Only 0.9% normal saline should be used for dilution and post-infusion flushing of the infusion line. Post-infusion, the infusion line must be flushed with 0.9% normal saline, with a volume equal to or greater than the hold-up volume of the infusion line.

Further instructions for administration are listed in the pharmacy manual for CMCS110ZUS01T.

8.4.9 **Ordering**

Drug product will be ordered from Novartis by site pharmacy personnel.

8.4.10 **Accountability**

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

8.4.10 **Destruction and Return**

The disposal or return transport of MCS110 will comply with DFCI institutional policies on handling and documentation.

## 8.5 Dabrafenib

8.5.1 **Description**

Dabrafenib mesylate is a kinase inhibitor.

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

**Molecular Formula:** $C_{23}H_{20}F_3N_5O_2S_2 \cdot CH_4O_3S$

**Molecular Weight:** 615.68

Dabrafenib mesylate is a white to slightly colored solid with three pKas: 6.6, 2.2, and -1.5. It is very slightly soluble at pH 1 and practically insoluble above pH 4 in aqueous media.

8.5.2 **Form**

TAFINLAR (dabrafenib) capsules are supplied as 50 mg and 75 mg capsules for oral administration. Each 50 mg capsule contains 59.25 mg dabrafenib mesylate equivalent to 50 mg of dabrafenib free base. Each 75 mg capsule contains 88.88 mg dabrafenib mesylate equivalent to 75 mg of dabrafenib free base.

8.5.3 **Storage**

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Only qualified individuals should be responsible for drug access and storage.

8.4.4 **Compatibility**

Review the full FDA Tafinlar (dabrafenib) Label for drug information.

8.4.5 **Handling**

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

8.4.6 **Availability**

Dabrafenib is commercially available.

8.4.7 **Preparation**

Instructions for preparation are listed in the full FDA Tafinlar (dabrafenib) Label.

8.4.8 **Administration**

Dabrafenib will be given as per package instructions. Dabrafenib should be taken orally every 12 hours. A missed dose can be taken up to 6 hours prior to the next dose. Doses that would be administered outside of that timeframe should be considered missed and should not be taken. Tablets should not be crushed or chewed. A vomited dose should not be retaken, patients should continue with the next scheduled dose. Dabrafenib should be taken orally with approximately 200 mL of water under fasted conditions. On days where MCS110, dabrafenib, and trametinib are all to be given, order of administration does not matter.

8.4.9 **Ordering**

Dabrafenib is commercially available. The investigator or designated study personnel are responsible for maintaining dispensing records of dabrafenib per institutional standards.

8.4.10 **Accountability**

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

8.4.10 **Destruction and Return**

The disposal or return transport of dabrafenib will comply with DFCI institutional policies on handling and documentation.

## 8.6 Trametinib

8.5.1 **Description**

Trametinib dimethyl sulfoxide is a kinase inhibitor.

**Chemical Name:** acetamide, N-[3-[3454 cyclopropyl-5-[(2-fluoro-4- iodophenyl)amino]-3,4,6,7-tetrahydro-6,8-dimethyl- 2,4,7455 trioxopyrido[4,3-d]pyrimidin-1(2H)-yl]phenyl]-, compound with 1,1'-sulfinylbis[methane] (1:1)

**Molecular Formula:** $C_{26}H_{23}FIN_5O_4 \cdot C_2H_6OS$

**Molecular Weight:** 693.53

Trametinib dimethyl sulfoxide is a white to almost white powder. It is practically insoluble in the pH range of 2 to 8 in aqueous media.

8.5.2 **Form**

MEKINIST (trametinib) tablets are supplied as 0.5 mg and 2 mg tablets for oral administration. Each 0.5 mg tablet contains 0.5635 mg trametinib dimethyl sulfoxide equivalent to 0.5 mg of trametinib non-solvated parent. Each 2 mg tablet contains 2.254 mg trametinib dimethyl sulfoxide equivalent to 2 mg of trametinib non-solvated parent.

8.5.3 **Storage**

Store refrigerated at 2° to 8°C (36° to 46°F). Do not freeze. Dispense in original bottle. Do not remove desiccant. Protect from moisture and light. Do not place medication in pill boxes. Only qualified individuals should be responsible for drug access and storage.

8.4.4 **Compatibility**

Review the full FDA Mekinist (trametinib) Label for drug information.

### 8.4.5 **Handling**

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

### 8.4.6 **Availability**

Trametinib is commercially available.

### 8.4.7 **Preparation**

Instructions for preparation are listed in the FDA Mekinist (trametinib) Label.

### 8.4.8 **Administration**

Trametinib will be given as per package instructions. Trametinib should be taken orally daily. A missed dose can be taken up to 12 hours prior to the next dose. Doses that would occur outside of this timeframe should be considered missed and should not be taken. Tablets should not be crushed or chewed. A vomited dose should not be retaken, patients should continue with the next scheduled dose. Trametinib can be taken with or without food. On days where MCS110, dabrafenib, and trametinib are all to be given, order of administration does not matter.

### 8.4.9 **Ordering**

Trametinib is commercially available. The investigator or designated study personnel are responsible for maintaining dispensing records of dabrafenib per institutional standards.

### 8.4.10 **Accountability**

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

### 8.4.10 **Destruction and Return**

The disposal or return transport of trametinib will comply with DFCI institutional policies on handling and documentation.

## 9. STUDY CALENDAR

Baseline evaluations are to be conducted within 14 days prior to start of protocol therapy, with the exception of the informed consent, echocardiogram, ophthalmologic exam, and baseline

tumor imaging which may be obtained up to 28 days prior to the start of protocol therapy.

Assessments must be performed prior to administration of any study agent.

| | **Table 2: Study Calendar** | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **Pre-Study[L]** | **Cycle 1 Day 1** | **Cycle 1 Day 8[M]** | **Cycle 1 Day 15[M]** | **Cycle 2 Day 1[M]** | **Cycle 3+ Day 1[N,M]** | **Off Study[O]** | **Every 3 Months after Discontinuing** |
| Informed Consent | X | | | | | | | |
| Archival Tumor Tissue Collection[A] | X | | | | | | | |
| Demographics | X | | | | | | | |
| Medical history | X | | | | | | | |
| Concurrent meds | X | X----------X | | | | | X | |
| Physical exam | X | X | X | X | X | X | X | |
| Vital signs[B] | X | X | X | X | X | X | X | |
| Height | X | | | | | | | |
| Weight | X | X | X | X | X | X | X | |
| ECOG Performance Status | X | X | | X | | X | X | |
| CBC w/diff, plts | X | X | X | X | X | X | X | |
| C-Reactive Protein (CRP) | X | *Repeat as clinically indicated.* | | | | | | |
| PT-INR, PTT | X | *Repeat as clinically indicated.* | | | | | | |
| Serum chemistry[C] | X | X | X | X | X | X | X | |
| EKG[D] | X | X | | | X | X[D] | | |
| Echocardiogram[E] | X | | | | X | X[E] | | |
| Dermatologic Evaluation | X | *Dermatologic evaluations to be performed to assess for suspicious skin lesions every 9 weeks (± 1 week) while on dabrafenib/trametinib therapy or as per institutional standards. Evaluation can be performed and documented by treating investigator or by dermatologist.* | | | | | X | |
| Adverse event evaluation | | X----------X | | | | | X | |

| | **Table 2: Study Calendar** | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **Pre-Study[L]** | **Cycle 1 Day 1** | **Cycle 1 Day 8[M]** | **Cycle 1 Day 15[M]** | **Cycle 2 Day 1[M]** | **Cycle 3+ Day 1[N,M]** | **Off Study[O]** | **Every 3 Months after Discontinuing** |
| Radiologic evaluation | X | *CT or MRI imaging of any disease-involved site. Radiologic measurements should be performed at the end of cycle 2 (Cycle 2 Day 21) and at the end of every 2 cycles of treatment thereafter (i.e., Cycle 4 Day 21, Cycle 6 Day 21, and so on). There is a +/- 7 day scheduling window on imaging evaluations.* | | | | | X | |
| Serum β-HCG[F] | X | | | | | | | |
| Urine Pregnancy Test[P] | | X | | | X | X | X | |
| Ophthalmologic examination | X | | | | X | *To be conducted at baseline, on cycle 2 day 1, and as clinically indicated – to be done at the treating investigator's discretion based on institutional standards and the presence of symptoms.* | | |
| cfDNA Sample[G] | | X | *Samples to be collected at visits immediately following restaging scan visits (i.e., cycle 3 day 1, cycle 5 day 1, cycle 7 day 1, etc.)* | | | | X | |
| Plasma CIC Sample[H] | | X | *Samples to be collected at visits immediately following restaging scan visits (i.e., cycle 3 day 1, cycle 5 day 1, cycle 7 day 1, etc.)* | | | | X | |
| Fresh Tumor Tissue Biopsy[I] | | | | X | | | | |
| MCS110 Administration | | X | *MCS110 to be administered as described in Section 5.* | | | | | |
| Dabrafenib Administration[J] | | X | *Dabrafenib to be administered as described in Section 5 and as per institutional standards.* | | | | | |
| Trametinib Administration[J] | | X | *Trametinib to be administered as described in Section 5 and as per institutional standards.* | | | | | |
| Telephone or Care Provider Contact[K] | | | | | | | | X |

A. Participants must have archival tumor tissue available for enrollment. Participants without archival tissue may be enrolled at the discretion of the principal investigator. See Section 9 for further detail.
B. Vital signs to include heart rate, blood pressure, temperature, respiratory rate, and oxygen saturation ($O_2$ sat).
C. Serum chemistry to include: sodium, potassium, chloride, $CO_2$, blood urea nitrogen (BUN), creatinine, glucose, albumin, total protein, alkaline phosphatase, total bilirubin, SGOT [AST], SGPT [ALT], globulin, phosphorus, magnesium, calcium, and creatinine phosphokinase (CPK). Other tests may be ordered as clinically indicated. If a patient experiences a new grade 2 or greater increase in CPK, a CK-MB, troponin (I or T), urine and serum myoglobin and aldolase or other skeletal marker should also be obtained.
D. EKG (single) to be performed during screening, at anytime pre-dose on Cycle 1 Day 1, Cycle 2 Day 1, and Cycle 3 day 1. EKGs to be collected every 3 months thereafter . EKGs can be performed more frequently as clinically indicated or as per institutional standards.
E. Echocardiogram to be performed during screening, on Cycle 2 day 1, and then every 3 months thereafter. Echo can be performed more frequently if clinically indicated.
F. Serum pregnancy test only required for women of childbearing potential. Childbearing potential defined as any female who has experienced menarche and who has not undergone

| | **Table 2: Study Calendar** | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **Pre-Study[L]** | **Cycle 1 Day 1** | **Cycle 1 Day 8[M]** | **Cycle 1 Day 15[M]** | **Cycle 2 Day 1[M]** | **Cycle 3+ Day 1[N,M]** | **Off Study[O]** | **Every 3 Months after Discontinuing** |

successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea >12 consecutive months; or women with a documented plasma follicle-stimulating hormone level >35µlU/mL).

G. cfDNA plasma genotyping sample to be obtained anytime pre-dose on Cycle 1 Day 1. The exact time of the sample should be recorded. Additional samples to be collected at visits immediately following restaging scans (i.e., cycle 3 day 1, cycle 5 day 1, cycle 7 day 1, etc.), and at the off study visit. Please see Section 9 for more detail.

H. Plasma CIC sample to be obtained anytime pre-dose on Cycle 1 Day 1. The exact time of the sample should be recorded. Additional samples to be collected at visits immediately following restaging scans (i.e., cycle 3 day 1, cycle 5 day 1, cycle 7 day 1, etc.), and at the off study visit. Please see Section 9 for more detail.

I. Optional fresh tumor tissue biopsy to be obtained anytime between cycle 1 day 15 and cycle 2 day 7. An additional optional biopsy at the time of disease progression may be obtained up to 30 days after the last dose of MCS110. Please see Section 9 for more detail.

J. Dabrafenib and trametinib to be dispensed and administered as described in Section 5 and as per institutional standards.

K. Participants will be followed until death or withdrawal of consent after removal from protocol therapy. This follow up will be performed by review of the medical record, contact with care providers, and/or telephone contact as needed every 3-4 months.

L. Baseline evaluations are to be conducted within 14 days prior to start of protocol therapy, with the exception of the informed consent, echocardiogram, ophthalmologic exam, and baseline tumor imaging which may be obtained up to 28 days prior to the start of protocol therapy.

M. A +/- 3 day scheduling window exists to accommodate holidays, adverse weather, vacations, or other scheduling requests.

N. The start of a subsequent cycle may be delayed by up to 7 days to allow for vacations or other scheduling requests.

O. Off-study evaluation to be completed within 30 days of the last dose of MCS110. Note: Follow up visits or other contact is required in order to identify SAEs during the 30 days following the end of study treatment.

P. Urine pregnancy test only required for women of childbearing potential. Childbearing potential defined as any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea >12 consecutive months; or women with a documented plasma follicle-stimulating hormone level >35µlU/mL).

## 10. MEASUREMENT OF EFFECT

Although response is not the primary endpoint of the phase I portion of this trial, participants with measurable disease will be assessed by standard criteria. For the purposes of this study, participants should be re-evaluated every eight weeks. In addition to a baseline scan, confirmatory scans will also be obtained not less than four weeks following initial documentation of an objective response.

### 10.1 Antitumor Effect – Solid Tumors

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:221-247, 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 the RECIST criteria.

#### 10.1.1 Definitions

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

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

#### 10.1.2 Disease Parameters

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

Note: Tumor lesions that are situated in a previously irradiated area will not be considered measurable.

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, abdominal masses (not followed by CT or MRI), and cystic lesions are all considered non-measurable.

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

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

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

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

### 10.1.3 Methods for Evaluation of Disease

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

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

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

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

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

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

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

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

(c) FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical

literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

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

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.

MIBG (meta-iodobenzylguanidine).The following is recommended, to assure high quality images are obtained.

Patient preparation: Iodides, usually SSKI (saturated solution of potassium iodide), are administered to reduce thyroidal accumulation of free radioiodine, preferably beginning the day prior to injection and continuing for 3 additional days (4 days total). For infants and children, one drop t.i.d. is sufficient, for adolescents 2 drops t.i.d., and for adults 3 drops t.i.d. Participants and/or parents are asked about exposure to potential interfering agents. If none is noted, an indwelling intravenous line is established. The dose of MIBG is administered by slow intravenous injection over 90 seconds.

Images from the head to the distal lower extremities should be obtained.

I-123MIBG scintigraphy is performed to obtain both planar and tomographic images.

Planar: Anterior and posterior views from the top of the head to the proximal lower extremities are obtained for 10 minutes at 24 hours and occasionally at 48 hours following injection of 10 mCi/1.7 square meters of body surface area (~150 μCi/kg, maximum 10 mCi). Anterior views of the distal lower extremities are adequate. A large field of view dual head gamma camera with low energy collimators is preferred.

SPECT: Most participants receiving I-123 MIBG also undergo SPECT at 24 hours, using a single or multi-headed camera with a low energy collimator. The camera is rotated through 360 degrees, 120 projections at 25 seconds per stop. Data are reconstructed using filtered back projections with a Butterworth filter and a cut off frequency of 0.2-0.5. SPECT/CT may be performed at institutions with this capacity.

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 data 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 from 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 participant 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.

#### 10.1.3.1 Evaluation of Target Lesions

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

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

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

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient

increase to qualify for PD, taking as reference the smallest sum diameters while on study.

10.1.3.2 Evaluation of Non-Target Lesions

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

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

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

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

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

10.1.3.3 Evaluation of New Lesions

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

10.1.3.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (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 Participants with Measurable Disease (*i.e.*, Target Disease)**

| Target Lesions | Non-Target Lesions | New Lesions | Overall Response | Best Overall Response when Confirmation is Required* |
|---|---|---|---|---|
| CR | CR | No | CR | ≥4 wks Confirmation** |
| CR | Non-CR/Non-PD | No | PR | ≥4 wks Confirmation** |
| CR | Not evaluated | No | PR | |
| PR | Non-CR/Non-PD/not evaluated | No | PR | |
| SD | Non-CR/Non-PD/not evaluated | No | SD | Documented at least once ≥4 wks from baseline** |
| PD | Any | Yes or No | PD | no prior SD, PR or CR |
| Any | PD*** | Yes or No | PD | |
| Any | Any | Yes | PD | |

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

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

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

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

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

10.1.4 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started, or death due to any cause. Participants without events reported are censored at the last disease evaluation).

Duration of overall complete response: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

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.

#### 10.1.5 Progression-Free Survival

Overall Survival: Overall Survival (OS) is defined as the time from randomization (or registration) to death due to any cause, or censored at date last known alive.

Progression-Free Survival: Progression-Free Survival (PFS) is defined as the time from randomization (or registration) to the earlier of progression or death due to any cause. Participants alive without disease progression are censored at date of last disease evaluation.

Time to Progression: Time to Progression (TTP) is defined as the time from randomization (or registration) to progression, or censored at date of last disease evaluation for those without progression reported.

#### 10.1.6 Response Review

Evaluation of scans will be done centrally at the DFCI using the Tumor Metrics Core.

## 11. DATA REPORTING / REGULATORY REQUIREMENTS

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

### 11.1 Data Reporting

#### 11.1.1 Method

The ODQ will collect, manage, and perform quality checks on the data for this study.

#### 11.1.2 Responsibility for Data Submission

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to the ODQ according to the schedule set by the ODQ.

### 11.2 Data Safety Monitoring

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

The DSMC will review each protocol up to four times a year or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring with 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

### 11.3 Multicenter Guidelines

Not Applicable.

### 11.4 Collaborative Agreements Language

Not Applicable.

## 12. STATISTICAL CONSIDERATIONS

A standard 3+3 design is planned for the dose finding phase I portion of the trial. The phase I portion of the trial will require a minimum of six and a maximum of 18 patients to determine the MTD and RP2D. Following identification of the MTD and RP2D, a single-arm phase II trial will commence. A total of 25 patients with metastatic melanoma harboring a *BRAF* V600E or V600K mutation will be enrolled to the phase II portion of the trial.

### 12.1 Study Design/Endpoints

**Endpoints:**

**Primary**

*Phase I*

Dose-limiting toxicity of the combination of MCS110 with BRAF/MEK inhibition.

*Phase II*

Overall response (CR or PR as best overall response) according to RECIST criteria (Version 1.1). At the time of each restaging, patients will be classified as achieving complete response (CR), partial response (PR), stable disease (SD), progressive Overall response will be determined by the best overall confirmed response designation recorded between the date of first dose of trial therapy and the date of objectively documented disease progression or cessation of trial therapy, whichever occurs first. For patients without documented progression or cessation of trial

therapy, all available response designations contributed to the objective response determination.

**Secondary Endpoints:**

Progression-free and overall survival are defined in Section 10.1.5.

Toxicity will be assessed using the CTCAE version 4.0.

**Design:**

*Phase I*
A conventional algorithm (3+3 design) will be used to identify the MTD, escalating on 0/3 or 1/6 DLTs, and de-escalating if two DLTs are encountered. The MTD will be the highest dose level at which 0/3 or 1/6 subjects experience a DLT. If dose level 1 is discovered to be intolerable (with 2/3 or ≥ 2/6 subjects experiencing a DLT), the trial will proceed with enrollment to the fallback dose level of -1. If the fallback dose level is also found to be intolerable, the trial will be discontinued. The probabilities of escalation if the true but unknown DLT rates are 10, 20, 30, 40, and 50% are 91, 71, 49, 31, and 17%, respectively.

*Phase II*
The design of the phase II trial will be based on the endpoint of ORR.

A Simon, two-stage design with a total of 25 patients will be used. For this we assume a desirable response rate of 20% and a null rate of 1%. We will enroll 15 patients in the first stage. If no responses are observed then the trial will stop. If one or more responses are observed, then 10 additional patients will be enrolled. If two or more of the 25 patients have response, then we will conclude that there is evidence of adequate response in this cohort. If the true response rate is 1%, the probability is 0.86 that the study will stop at the end of the first stage. The power of this design is 95% with a type-I error of 0.02 (target 0.1).

## 12.2 Sample Size, Accrual Rate and Study Duration

The planned sample size is between six and 18 patients in the phase I portion of the trial, and 25 patients in the phase II portion of the trial, for a total of six to 43 patients. The planned accrual rate is approximately 5 patients per quarter. Up to an additional one year of follow-up will be required for the last participant accrued to observe the patient's response and survival following therapy, for a total study length of about four years. Participants will be identified via targeted NextGen sequencing using the DFCI/BWH OncoPanel or another CLIA-certified method for genotyping.

| Accrual Targets | | | | | |
|---|---|---|---|---|---|
| **Ethnic Category** | **Sex/Gender** | | | | |
| | **Females** | | **Males** | | **Total** |
| Hispanic or Latino | 0 | + | 1 | = | 1 |
| Not Hispanic or Latino | 12 | + | 24 | = | 36 |
| **Ethnic Category: Total of all subjects** | 12 | + | 25 | = | 37 |
| **Racial Category** | | | | | |
| American Indian or Alaskan Native | 0 | + | 1 | = | 1 |
| Asian | 0 | + | 0 | = | 0 |
| Black or African American | 0 | + | 0 | = | 0 |
| Native Hawaiian or other Pacific Islander | 0 | + | 0 | = | 0 |
| White | 12 | + | 24 | = | 36 |
| **Racial Category: Total of all subjects** | 12 | + | 25 | = | 37 |

### 12.3 Analysis of Primary and Secondary Endpoints

The primary and secondary analyses will include all eligible patients who started assigned therapy. The phase II evaluations will not include the patients enrolled in the phase I portion of this trial (see above for statistical analysis plan). The exception to this includes the planned analysis of toxicity data, which will include all patients who received study drug regardless of eligibility.

Phase I: The proportion of patients with DLTs will be summarized by dose cohort.

Phase II: The primary endpoint of ORR will be summarized and presented with a 95% confidence interval estimated using the method of Atkinson and Brown, which allows for the two-stage design. PFS and OS will be summarized using the method of Kaplan-Meier. Medians and PFS/OS estimates at pre-specified time points will be summarized and presented with 95% confidence intervals based on log(-log(endpoint)) methods.

Exploratory Endpoints:
Data from correlative studies will be summarized using descriptive statistics. Associations to clinical outcome between MAPK signaling, TAMs, and immune infiltrates will be compared and summarized by descriptive methods and may be explored graphically.

Additionally, tumor DNA levels obtained from the serial collection of cfDNA samples will be examined to explore whether clinical outcome correlates to fluctuations following the administration of MCS110 combination therapy.

### 12.4 Reporting and Exclusions

#### 12.4.1 Evaluation of Toxicity

All participants will be evaluable for toxicity from the time of their first dose of study medication.

#### 12.4.2 Evaluation of the Primary Efficacy Endpoint

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

## 13. ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES

### 13.1 Ethics and good clinical practice

This study must be carried out in compliance with the protocol and Good Clinical Practice, as described in:

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996.
2. Directive 91/507/EEC, The Rules Governing Medicinal Products in the European Community.
3. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).
4. Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996).

The investigator agrees, when signing the protocol, to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

### 13.2 Institutional Review Board/Independent Ethics Committee

Before implementing this study, the protocol, the proposed informed consent form and other information to subjects, must be reviewed by a properly constituted Institutional Review Board/Independent Ethics Committee (IRB/IEC). A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC must be given to Novartis before study initiation. The name and occupation of the chairman and the members of the IRB/IEC will be supplied to Novartis. Any amendments to the protocol, other than administrative ones, must be approved by this committee.

### 13.3 Informed consent

The investigator must explain to each subject (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and

benefits involved and any discomfort it may entail. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it, and should be given a copy of the signed document. If the subject cannot read or sign the documents, oral presentation may be made or signature given by the subject's legally appointed representative, if witnessed by a person not involved in the study, mentioning that the patient could not read or sign the documents. No patient can enter the study before his/her informed consent has been obtained.
The informed consent form is considered to be part of the protocol, and must be submitted by the investigator with it for IRB/IEC approval.

Women of child bearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

### 13.4 Discontinuation of the study

Novartis reserves the right to discontinue support for any study under the conditions specified in the clinical trial agreement.

### 13.5 Changes to the protocol

Any change or addition to this protocol requires a written protocol amendment that must be approved by Novartis and the investigator before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation or the scientific quality of the study, require additional approval by the IRB/IEC. A copy of the written approval of the IRB/IEC must be sent to Novartis.

Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB/IEC approval but the IRB/IEC of each center must be kept informed of such administrative changes.

### 13.7 Disclosure and confidentiality

The investigator agrees to keep all information provided by Novartis in strict confidence and to request similar confidentiality from his/her staff and the IRB/IEC. Study documents provided by Novartis (investigators' brochures and other material) will be stored appropriately to ensure their confidentiality. The information provided by Novartis to the investigator may not be disclosed to others without direct written authorization from Novartis, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial.

### 13.8 Declaration of Helsinki

The investigator must conduct the trial in accordance with the principles of the Declaration of

Helsinki. Copies of the Declaration of Helsinki and amendments will be provided upon request or can be accessed via the website of the World Medical Association at http://www.wma.net/en/10home/index.html

## 14. PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

Any formal presentation or publication of data from this trial may be published after review and comment by Novartis and prior to any outside submission. Novartis must receive copies of any intended communication in advance of publication (at least twenty-one working days for presentational materials and abstracts and thirty working days for manuscripts). These requirements acknowledge Novartis' responsibility to provide peer input regarding the scientific content and conclusions of such publications or presentations. The Principal Investigator/Institution shall have the final authority to determine the scope and content of its publications, provided such authority shall be exercised with reasonable regard for the interests of Novartis and, in accord with the trial contract and shall not permit disclosure of Novartis confidential or proprietary information.

**REFERENCES**

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin.* 2016;66(1):7-30.
2. Chapman PB, Hauschild A, Robert C, et al. Improved survival with dabrafenib in melanoma with BRAF V600E mutation. *N Engl J Med.* 2011;364(26):2507-2516.
3. Long GV, Menzies AM, Nagrial AM, et al. Prognostic and clinicopathologic associations of oncogenic BRAF in metastatic melanoma. *J Clin Oncol.* 2011;29(10):1239-1246.
4. Robert C, Karaszewska B, Schachter J, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. *N Engl J Med.* 2015;372(1):30-39.
5. Larkin J, Ascierto PA, Dréno B, et al. Combined dabrafenib and trametinib in BRAF-mutated melanoma. *N Engl J Med.* 2014;371(20):1867-1876.
6. Kacinski BM. CSF-1 and its receptor in ovarian, endometrial and breast cancer. *Ann Med.* 1995;27(1):79-85.
7. Sasmono RT, Oceandy D, Pollard JW, et al. A macrophage colony-stimulating factor receptor-green fluorescent protein transgene is expressed throughout the mononuclear phagocyte system of the mouse. *Blood.* 2003;101(3):1155-1163.
8. Bourette RP, Rohrschneider LR. Early events in M-CSF receptor signaling. *Growth Factors.* 2000;17(3):155-166.
9. Pixley FJ, Stanley ER. CSF-1 regulation of the wandering macrophage: complexity in action. *Trends Cell Biol.* 2004;14(11):621-638.
10. Lin H, Lee E, Hestir K, et al. Discovery of a cytokine and its receptor by functional screening of the extracellular proteome. *Science.* 2008;320(5877):807-811.
11. Nowicki A, Szenajch J, Ostrowska G, et al. Impaired tumor growth in colony-stimulating factor 1 (CSF-1)-deficient, macrophage-deficient op/op mouse: evidence for a role of CSF-1-dependent macrophages in formation of tumor stroma. *Int J Cancer.* 1996;65(1):112-119.
12. Lewis CE, Pollard JW. Distinct role of macrophages in different tumor microenvironments. *Cancer Res.* 2006;66(2):605-612.
13. Bingle L, Brown NJ, Lewis CE. The role of tumour-associated macrophages in tumour progression: implications for new anticancer therapies. *J Pathol.* 2002;196(3):254-265.
14. Lin EY, Nguyen AV, Russell RG, Pollard JW. Colony-stimulating factor 1 promotes progression of mammary tumors to malignancy. *J Exp Med.* 2001;193(6):727-740.
15. Dubreuil P, Torrès H, Courcoul MA, Birg F, Mannoni P. c-fms expression is a molecular marker of human acute myeloid leukemias. *Blood.* 1988;72(3):1081-1085.
16. Kacinski BM, Scata KA, Carter D, et al. FMS (CSF-1 receptor) and CSF-1 transcripts and protein are expressed by human breast carcinomas in vivo and in vitro. *Oncogene.* 1991;6(6):941-952.
17. Tang R, Beuvon F, Ojeda M, Mosseri V, Pouillart P, Scholl S. M-CSF (monocyte colony stimulating factor) and M-CSF receptor expression by breast tumour cells: M-CSF mediated recruitment of tumour infiltrating monocytes? *J Cell Biochem.* 1992;50(4):350-356.
18. Kacinski BM. CSF-1 and its receptor in breast carcinomas and neoplasms of the female reproductive tract. *Mol Reprod Dev.* 1997;46(1):71-74.
19. Mroczko B, Groblewska M, Wereszczyńska-Siemiatkowska U, et al. Serum macrophage-colony stimulating factor levels in colorectal cancer patients correlate with lymph node metastasis and poor prognosis. *Clin Chim Acta.* 2007;380(1-2):208-212.

20. Zhu XD, Zhang JB, Zhuang PY, et al. High expression of macrophage colony-stimulating factor in peritumoral liver tissue is associated with poor survival after curative resection of hepatocellular carcinoma. *J Clin Oncol.* 2008;26(16):2707-2716.
21. Scholl SM, Pallud C, Beuvon F, et al. Anti-colony-stimulating factor-1 antibody staining in primary breast adenocarcinomas correlates with marked inflammatory cell infiltrates and prognosis. *J Natl Cancer Inst.* 1994;86(2):120-126.
22. Pollard JW. Tumour-educated macrophages promote tumour progression and metastasis. *Nat Rev Cancer.* 2004;4(1):71-78.
23. Guo JK, Cantley LG. Cellular maintenance and repair of the kidney. *Annu Rev Physiol.* 2010;72:357-376.
24. Hume DA. The mononuclear phagocyte system. *Curr Opin Immunol.* 2006;18(1):49-53.
25. Watanabe S, Yoshimura A, Inui K, et al. Acquisition of the monocyte/macrophage phenotype in human mesangial cells. *J Lab Clin Med.* 2001;138(3):193-199.
26. Wang T, Papoutsi M, Wiesmann M, et al. Investigation of correlation among safety biomarkers in serum, histopathological examination, and toxicogenomics. *Int J Toxicol.* 2011;30(3):300-312.
27. Radi ZA, Koza-Taylor PH, Bell RR, et al. Increased serum enzyme levels associated with kupffer cell reduction with no signs of hepatic or skeletal muscle injury. *Am J Pathol.* 2011;179(1):240-247.
28. Leek RD, Harris AL. Tumor-associated macrophages in breast cancer. *J Mammary Gland Biol Neoplasia.* 2002;7(2):177-189.
29. Straussman R, Morikawa T, Shee K, et al. Tumour micro-environment elicits innate resistance to RAF inhibitors through HGF secretion. *Nature.* 2012;487(7408):500-504.
30. Wilson TR, Fridlyand J, Yan Y, et al. Widespread potential for growth-factor-driven resistance to anticancer kinase inhibitors. *Nature.* 2012;487(7408):505-509.
31. Mok S, Tsoi J, Koya RC, et al. Inhibition of colony stimulating factor-1 receptor improves antitumor efficacy of BRAF inhibition. *BMC Cancer.* 2015;15:356.
32. Noy R, Pollard JW. Tumor-associated macrophages: from mechanisms to therapy. *Immunity.* 2014;41(1):49-61.
33. Wang T, Xiao M, Ge Y, et al. BRAF Inhibition Stimulates Melanoma-Associated Macrophages to Drive Tumor Growth. *Clin Cancer Res.* 2015;21(7):1652-1664.
34. Hu-Lieskovan S, Mok S, Homet Moreno B, et al. Improved antitumor activity of immunotherapy with BRAF and MEK inhibitors in BRAF(V600E) melanoma. *Sci Transl Med.* 2015;7(279):279ra241.
35. Ng CM, Lum BL, Gimenez V, Kelsey S, Allison D. Rationale for fixed dosing of pertuzumab in cancer patients based on population pharmacokinetic analysis. *Pharm Res.* 2006;23(6):1275-1284.
36. Wang DD, Zhang S, Zhao H, Men AY, Parivar K. Fixed dosing versus body size-based dosing of monoclonal antibodies in adult clinical trials. *J Clin Pharmacol.* 2009;49(9):1012-1024.
37. Zhang S, Shi R, Li C, Parivar K, Wang DD. Fixed dosing versus body size-based dosing of therapeutic peptides and proteins in adults. *J Clin Pharmacol.* 2012;52(1):18-28.
38. Narwal R, Roskos LK, Robbie GJ. Population pharmacokinetics of sifalimumab, an investigational anti-interferon-α monoclonal antibody, in systemic lupus erythematosus. *Clin Pharmacokinet.* 2013;52(11):1017-1027.
39. Garraway LA, Lander ES. Lessons from the cancer genome. *Cell.* 2013;153(1):17-37.

40. Gros A, Turcotte S, Wunderlich JR, Ahmadzadeh M, Dudley ME, Rosenberg SA. Myeloid cells obtained from the blood but not from the tumor can suppress T-cell proliferation in patients with melanoma. *Clin Cancer Res.* 2012;18(19):5212-5223.

**APPENDIX A PERFORMANCE STATUS CRITERIA**

| **ECOG Performance Status Scale** | | **Karnofsky Performance Scale** | |
|---|---|---|---|
| Grade | Descriptions | Percent | Description |
| 0 | Normal activity. Fully active, able to carry on all pre-disease performance without restriction. | 100 | Normal, no complaints, no evidence of disease. |
| | | 90 | Able to carry on normal activity; minor signs or symptoms of disease. |
| 1 | Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work). | 80 | Normal activity with effort; some signs or symptoms of disease. |
| | | 70 | Cares for self, unable to carry on normal activity or to do active work. |
| 2 | In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours. | 60 | Requires occasional assistance, but is able to care for most of his/her needs. |
| | | 50 | Requires considerable assistance and frequent medical care. |
| 3 | In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. | 40 | Disabled, requires special care and assistance. |
| | | 30 | Severely disabled, hospitalization indicated. Death not imminent. |
| 4 | 100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. | 20 | Very sick, hospitalization indicated. Death not imminent. |
| | | 10 | Moribund, fatal processes progressing rapidly. |
| 5 | Dead. | 0 | Dead. |

**APPENDIX B**

# BRAF/MEK Ophthalmic Exam Source Worksheet

Subject Name: _____**Note to examiner:** Please assess particularly for visible retinal pathology.

*** Optical coherence tomography is highly recommended** For patients in whom retinal abnormalities are noted, **color fundus photos, and fluorescein angiography if clinically indicated, are recommended.**

| ***OPHTHALMIC EXAMINATION*** | | |
|---|---|---|
| 1. Date of Examination: | _ _/_ _ _/_ _ _ _<br>dd / mmm / yyyy | |
| **VISUAL ACUITY** | | |
| Enter corrected visual acuity | OD: | OS: |
| **TONOMETRY** | | |
| Enter IOP (mmHg) | OD: | OS: |
| **INDIRECT FUNDOSCOPY** | | |
| **Indirect Exam:** Indicate normal or specify abnormalities | OD: | OS: |
| **CONFRONTATION VISUAL FIELD EXAM OR AUTOMATED PERIMETRY (e.g., Humphrey 24-2 or 30-2 or equivalent if using a non-Humphrey instrument)** | | |
| Indicate normal or specify any abnormalities | OD: | OS: |
| **OPTICAL COHERENCE TOMOGRAPHY (strongly recommended)** | | |
| Indicate normal or specify any abnormalities | OD: | OS: |
| **COLOR FUNDUS PHOTOS (recommended if retinal abnormalities are noted)*** | | |
| Indicate normal or specify any abnormalities | OD: | OS: |
| **FLORESCEIN ANGIOGRAPHY (suggested if retinal abnormalities are noted and test clinically indicated)*** | | |
| Indicate normal or specify any abnormalities | OD: | OS: |

| Were any of the following noted on ocular history or exam? | Yes | No |
|---|---|---|
| • History of CSR? | | |
| • Evidence of new optic disc cupping? | | |
| • Evidence of new visual field defects? | | |
| **EXCLUSION CRITERIA** | Yes | No |
| • History of RVO?<br>o *If yes, patient is not eligible for the study.* | | |

**Signature of Examiner: _____**

**Printed Name: _____ Date: _____**

Dabrafenib, Trametinib, or Dabrafenib-Trametinib **Treatment Modification for Visual Changes**

**Visual Changes**

| CTCAE Grade | Management Guideline | Action and Dose Modification |
|---|---|---|
| **Grade 1*** | • Consult ophthalmologist within 7 days of onset. | • If dilated fundus examination cannot be performed within 7 days of onset, hold trametinib until RPED and RVO can be excluded by retina specialist/ ophthalmologist. Dabrafenib may be continued.<br>• If RPED and RVO excluded, continue (or restart) trametinib at same dose level<br>•<br>• If Uveitis/Iritis, refer to table below for Iritis/Uveitis<br>• If RPED suspected or diagnosed, refer to RPED dose modification table below; **report as SAE if diagnosed**.<br>• If RVO diagnosed: **Permanently discontinue trametinib and report as SAE**. |
| **Grade 2 and Grade 3** | • Consult ophthalmologist immediately. | • Hold trametinib. Dabrafenib may be continued.<br>• If RPED and RVO excluded, restart trametinib at same dose level<br>• If Uveitis/Iritis, refer to table below for Uveitis/Iritis<br>• If RPED diagnosed, see RPED dose modification table below; **report as SAE**.<br>• If RVO diagnosed: **Permanently discontinue trametinib and report as SAE**. |

**Visual Changes**

| CTCAE Grade | Management Guideline | Action and Dose Modification |
|---|---|---|
| **Grade 4** | • Consult ophthalmologist immediately. | • Interrupt trametinib. Dabrafenib may be continued.<br>• If RPED and RVO excluded, may consider restarting trametinib at same or reduced dose after discussion with study medical monitor.<br>• If Uveitis/Iritis, refer to table below<br>• **If RVO or RPED diagnosed, permanently discontinue trametinib** and report as SAE. |
| Abbreviations: RPED = retinal pigment epithelial detachments; RVO = retinal vein occlusion; SAE = serious adverse event<br>*If visual changes are clearly unrelated to study treatment (e.g., allergic conjunctivitis), monitor closely but ophthalmic examination is not required. | | |