Clinical Study Protocol

Protocol Title:	A Phase I/II Trial of Dabrafenib, Trametinib and Metformin Administered to Unresectable Stage IIIC and Stage IV $BRAF^{V600E}$+ Melanoma Patients
Protocol Number:	BCC-MEL-14-01
Products:	Dabrafenib, Trametinib and Metformin
Date of Protocol:	April 30, 2014
Sponsor:	James Graham Brown Cancer Center University of Louisville 529 South Jackson Street Louisville, KY 40202
Principal Investigator:	Jason Chesney, M.D., Ph.D.
Sub-Investigators:	Donald M. Miller, M.D., Ph.D. Kelly M. McMasters, M.D., Ph.D. Sucheta Telang, M.B.B.S.
Study Statistician:	Shesh N. Rai, Ph.D.

SYNOPSIS

Name of Sponsor:	**James Graham Brown Cancer Center**
Name of Active Ingredients:	**Dabrafenib, Trametinib and Metformin**
Title of Study:	A Phase I/II Trial of Dabrafenib, Trametinib and Metformin Administered to Unresectable Stage IIIC and Stage IV $BRAF^{V600E}$+ Melanoma Patients
Protocol No.:	BCC-MEL-14-01
Investigators:	Jason Chesney, Donald M. Miller, Kelly M. McMasters, Sucheta Telang, and Shesh N. Rai
Study centers:	James Graham Brown Cancer Center
Study duration: Approximately 36 months	

Objectives:

Primary

- To evaluate the clinical activity of the FDA-approved drugs Dabrafenib (150 mg PO BID) and Trametinib (2 mg PO QD) in combination with Metformin (500 mg PO BID x 2 weeks, then 850 mg PO BID) in patients with unresectable $BRAF^{V600E}$ positive Stage IIIC and Stage IV melanoma (Phase I).
- To evaluate the clinical activity of the combined Dabrafenib/Metformin regimen (Phase II).
- To monitor the safety profile of the combined regimen Dabrafenib/Metformin (Phase I/II)
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Secondary

- To estimate the overall survival of patients who have been treated with Dabrafenib, Trametinib and Metformin.
- To describe the toxicities.
- To explore the effect of other covariates (demographic, disease and treatment related) on objective response rate and toxicity and overall survival.

Number of patients:	**A total of 53 patients are planned for the study.**
Diagnosis and entry criteria:	**Inclusion Criteria** Patients may be entered in the study only if they meet all of the following criteria. 1. Male or female patients ≥18 years of age; 2. Patients with histologically confirmed BRAFV600E melanoma (Stage IIIC or Stage IV, American Joint Commission on Cancer); 3. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 to 2; 4. Life expectancy ≥3 months; 5. At least 1 site of radiographically measurable disease by RECIST 1.1 6. Adequate hematologic, renal, and liver function as defined by laboratory values performed within 42 days prior to initiation of dosing: • Absolute neutrophil count (ANC) ≥1.0 x 10^9/L; • Platelet count ≥50 x 10^9/L; • Hemoglobin ≥8 g/dL; • Serum creatinine ≤2 x upper limit of normal (ULN) • Total serum bilirubin ≤3 x ULN; • Serum aspartate transaminase (AST/SGOT) or serum alanine transaminase (ALT/SGPT) ≤3x ULN, and ≤4 x ULN if liver metastases are present.

	7. Fertile males should use an effective method of contraception during treatment and for at least 3 months after completion of treatment, as directed by their physician; 8. Pre-menopausal females and females <2 years after the onset of menopause should have a negative pregnancy test at Screening. Pre-menopausal females must agree to use an acceptable method of birth control from the time of the negative pregnancy test up to 90 days after the last dose of study drug. Females of non-childbearing potential may be included if they are either surgically sterile or have been postmenopausal for ≥1 year; 9. Before study entry, written informed consent must be obtained from the patient prior to performing any study-related procedures.
Diagnosis and entry criteria:	**Exclusion Criteria** Patients will not be entered in the study for any of the following: 1. Prior treatment with Vemurafenib or Dabrafenib 2. Known hypersensitivity to Metformin or any of its components; 3. Received radiotherapy for non CNS disease within the 2 weeks prior to commencing study treatment or have not recovered from side effects of all radiation-related toxicities to Grade ≤1, except for alopecia; 4. Pregnant, breast-feeding, or refusing double barrier contraception, oral contraceptives, or avoidance of pregnancy measures; 5. Have any other uncontrolled infection or medical condition that could interfere with the conduct of the study.
Test product, dose and mode of administration:	Dabrafenib (150 mg PO BID) and Trametinib (2 mg PO QD) in combination with Metformin (500 mg PO BID x 2 weeks, then 850 mg PO BID) until progression.
Reference therapy:	Dabrafenib and Trametinib without Metformin.
Duration of treatment:	• Pre-treatment phase: An up to 42-day Screening period for collection of Baseline assessments (scans prior to study enrollment may be used for baseline measurement); • Treatment phase: Treatment period of 28-day cycles until progression unless unacceptable toxicity; • Follow-up phase: Patients will be followed for survival for a period of up to 3 years.
Criteria for evaluation:	**Efficacy Assessments** Tumor response and disease progression will be determined by the Investigator using objective radiologic criteria (Investigator assessed review of CT scans). Disease response or progression will be determined according to RECIST 1.1. An MRI will be used only if CT scans are not appropriate or CT scan results are not conclusive. Primary efficacy endpoint: RECIST 1.1 objective response rates Secondary efficacy endpoint: Overall survival **Pharmacokinetic** Not applicable. **Pharmacodynamic**

Criteria for evaluation (continued):	Not applicable **Safety** Safety will be assessed by the monitoring and recording of all adverse events (AEs) and serious adverse events (SAEs), regular monitoring of hematology, blood chemistry, regular measurement of vital signs, and the performance of physical examinations.
Statistical Methods:	In phase I for the Dabrafenib, Trametinib and Metformin regimen, we will enroll 6 patients. We will allow at the most two CTCAE drug-related grade 4 toxicities in 6 patients in order to advance to Phase II. If we observe any drug-related deaths or more than two CTCAE grade 4 events, then we will halt the trial. In the published literature, the objective response rate to Dabrafenib/Trametinib using RECIST 1.1 Criteria is 76% (95% CI, 65% to 87%). We expect that the overall response rate should be between 60-80%. Therefore an objective response rate less than 64% should indicate the treatment is not sufficiently promising (P0 = 0.64); this is a bit lower than the lower limit of the 95% CI. We expect the therapy to increase the overall response rate at 80% (P1 = 0.80). Using Simon's two stage minimax design for phase II trials we plan to enroll a maximum of 53 patients.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADR	Adverse drug reaction
AE	Adverse event
AJCC	American Joint Commission on Cancer
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CI	Confidence interval
CNS	Central nervous system
CQA	Clinical Quality Assurance
CR	Complete response
CRO	Contract research organization
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	Curriculum vitae
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
ELISA	Enzyme-linked immunosorbent assay
ESA	Erythroid-stimulating agents
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GM-CSF	Granulocyte macrophage colony-stimulating factor
HIV	Human immunodeficiency virus
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFN-α	Interferon-α
IFPMA	International Federation of Pharmaceutical Manufacturers and Associations
IHC	Immunohistochemical
IL-2	Interleukin-2
IRT	Interactive Response Technology
IV	Intravenous
KM	Kaplan-Meier

LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified Intent-to-Treat
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NYHA	New York Heart Association
OR	Objective response
ORR	Overall response rate
PD	Progressive disease
PFS	Progression-free survival
PI	Principal Investigator
PR	Partial response
PS	Performance Status
RBC	Red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable disease
SOP	Standard Operating Procedure
SPD	Sum of the products of the two largest perpendicular diameters
STD	Standard deviation
TEAE	Treatment-emergent adverse event
TNM	Tumor, Node, Metastasis
TTPTreg	Time to progression Regulatory T cells
UICCTTP	International Union Against Cancer Time to progression
ULNUICC	Upper limit of normal International Union Against Cancer
USULN	United States Upper limit of normal
WBCUS	White blood cells United States
WHOWBC	World Health Organization White blood cells
WHO	World Health Organization

1. INTRODUCTION

1.1 Management of Unresectable and Metastatic Melanoma

Over 40,000 people die of metastatic melanoma each year worldwide and, in a recent review of 2,100 stage IV melanoma patients, the median overall survival was 6.2 months, with only 25.5% alive at one year[35]. These poor survival statistics are likely due to the lack of efficacy of the current U.S. F.D.A.-approved agents including : Dacarbazine (2.7% complete response [CR] rate)[1], high-dose Interleukin 2 (6% CR rate)[2] Ipilimumab (1.5% CR rate)[3] and the new B-Raf inhibitor, PLX4032 or Vemurafenib (2.3% CR rate but a 50% partial response (PR) rate)[4].

1.2 Rationale for Combined Dabrafenib, Trametinib, and Metformin Administration in Melanoma.

Receptor tyrosine kinases stimulate the Ras/Raf/MEK/ERK (MAPK) pathway which is required for the survival and growth of cancer cells[5]. Three *RAF* genes code for cytoplasmic serine/threonine kinases that are regulated by direct binding to Ras and in particular, the *BRAF* gene has been found to contain kinase-activating somatic missense mutations in up to 66% of malignant melanomas, the most common being V600E[6]. A recent phase 1, dose-escalation trial of a V600E B-Raf specific inhibitor PLX4032 (also termed, RG7204, RO5185426 and Vemurafenib) revealed that 10/16 stage IV V600E B-Raf^{+} melanoma patients who received 240 mg or more of PLX4032 twice daily experienced a partial response and 1/16 experienced a complete response[7]. In the extension cohort, 24/32 patients experienced a partial response and 2 experienced a complete response. Grade 3 toxicities predominantly included arthralgias, rashes, nausea and squamous cell carcinomas of unclear etiology. A pivotal phase II trial of PLX4032 in previously treated metastatic melanoma patients with the V600E B-Raf mutation then demonstrated that of 132 patients treated, 3 had complete responses, 66 had partial responses and 39 had stable disease (presented at the 7th annual International Melanoma Research Congress of the Society for Melanoma Research in November 2010). A randomized, open-label, controlled, multicentre, global study on OS in previously untreated patients with unresectable stage IIIC and stage IV melanoma with V600E *BRAF* mutation then compared this B-Raf inhibitor, now called **Vemurafenib**, to dacarbazine (the BRIM3 trial). Results at 6 months indicated that response rate and OS in the Vemurafenib cohort exceeded the dacarbazine cohort: 48% vs. 6% and 84% vs. 64%, respectively[8]. This is perhaps the most exciting new targeted therapy to be developed in oncology since the development of Imatinib and, after an interim analysis, the data and safety monitoring board recommended crossover from Dacarbazine to Vemurafenib. ***However, it is currently clear that B-Raf inhibitors will only yield durable (> 6 month) CRs or PRs in a small subset of stage IV melanoma patients (< 10%) due to the development of resistance (described***

below). <u>Despite this limitation, the FDA approved Vemurafenib for the treatment of unresectable stage IIIC and stage IV melanoma in August 2011.</u>

Although the mutant B-Raf inhibitors are demonstrating dramatic clinical activity and the Vemurafenib interim analysis demonstrated improved OS, resistance is to these agents is clearly developing (*reviewed in*[9, 10]). Nazarian *et al.* demonstrated that melanoma cells from 4/11 Vemurafenib resistant but mutant B-Raf positive melanoma patients developed upregulation of Platelet Derived Growth Factor Receptor β (PDGFRβ) which can activate alternative survival pathways[11]. They also identified a single melanoma patient who developed an activating mutation of the upstream N-Ras coincident with Vemurafenib resistance. They found that stable knock-down of N-Ras could confer sensitivity to Vemurafenib and that the N-Ras dependent MAPK pathway activation sensitizes Vemurafenib -resistant cells to MEK inhibitors[11]. In order to identify kinases capable of circumventing B-Raf inhibition, Johannessen *et al.* expressed 597 sequence-validated kinase open reading frames (ORFs) in A375 cells, a B-Raf^{V600E} melanoma cell line that is sensitive to the B-Raf inhibitor PLX4720 and examined the effects of the cytotoxicity of a B-Raf inhibitor, PLX4720[12]. Although they identified 9 candidate ORFs, both C-Raf and the proto-oncogene COT/Tpl2 (also known as MAP3K8) over-expression were confirmed to confer resistance to PLX4720 via MAP kinase reactivation. In independent studies, Villanueva *et al.* found that chronic exposure of a B-Raf^{V600E} melanoma line to a B-Raf inhibitor increased Insulin Growth Factor-1 Receptor (IGF-1R) expression and activation of AKT, and that combined treatment with IGF-1R/PI3K and Ras/Raf/mitogen-activated protein kinase kinase (MEK) inhibitors caused death of the B-Raf inhibitor resistant cells[13]. Recently, a new B-Raf inhibitor, Dabrafenib, was combined with a MEK inhibitor, Trametinib, and found to increase the response rate in melanoma patients to 76% (Flaherty et al. NEJM 367:1694, 2012), indicating that this combination should be considered the first line of therapy for melanoma patients. *Although inhibitors of the MAPK pathway may be able to overcome some of the resistance and improve the clinical efficacy of mutant B-Raf inhibitors, the sheer multiplicity and multi-level nature of the compensatory changes in the signalling pathways suggests that farther downstream effectors need to be targeted simultaneously.*

For millennia, the herb *Galega officinalis* (French Lilac, Italian Fitch or Goat's Rue) has been used to produce tea to relieve frequent urination and sweet-smelling breath. This herbal remedy for what was eventually found to be caused by the hyperglycemia of Diabetes Mellitus (DM) led several investigators during the 20th century to purify the active components of the herb, biguanides, including Phenformin, Buformin and Metformin (*i.e. N',N'*-dimethylbiguanide). Although Phenformin and Buformin were limited by toxicity related to lactic acidosis, Metformin is currently FDA-approved and widely used for the treatment of DM. The precise mechanism of action of metformin is not well defined but the agent does inhibit complex I of the electron transport chain, oxygen consumption and ATP in hepatocytes[14, 15] and in myocytes (http://www.seahorsebio.com/ resources/posters/2007-06-17_wu_metformin-induced.pdf). Such a decrease in the intracellular concentration of ATP will cause an allosteric

activation of 6-phosphofructo-1-kinase and resultant increased glucose uptake and glycolytic flux[16] as well as activation of AMP kinase (AMPK) which increases glucose transporter (GLUT4) expression and translocation in myocytes[17] which may in part explain the anti-diabetic effects of Metformin.

Several retrospective epidemiological studies of diabetic patients who were treated with Metformin have found that these patients had a lower risk of developing all types of cancer and of cancer-related deaths relative to diabetic patients who received other oral glucose-lowering agents[18-21]. Additionally, diabetic breast cancer patients on Metformin were found after resection to experience a higher rate of microscopic complete responses after neoadjuvant chemotherapy than diabetic patients not being treated with Metformin or non-diabetic patients[22]. The mechanism for these statistically significant effects is an area of active investigation and several pre-clinical and clinical investigators are now attempting to improve outcomes of standard anti-neoplastic agents with Metformin.

Signaling though the B-Raf oncogene in melanoma cells blocks the activation of AMPK by the kinase LKB1 and inhibition of B-Raf, like Metformin, caused activation of AMPK[23, 24]. Perhaps not surprisingly, Metformin has been found to have significant pre-clinical activity in melanoma cells *in vitro* and *in vivo*, including: (i) causing a G2/M cell cycle arrest and apoptosis; (ii) mitochondrial membrane depolarization; (iii) induction of the p53 tumor suppressor; (iv) induction of autophagy; and (v) anti-tumor activity against the B16 syngeneic mouse model of melanoma[25]. Additionally, the combination of the B-Raf inhibitor, Vemurafenib, with Metformin has been found to synergistically kill $BRAF^{V600E}$-positive melanoma cells *in vitro* (although certain highly resistant lines are marginally promoted by the combination)[26]. Last, a phase I trial of the combination of a mTOR inhibitor, Temsirolimus (which has no efficacy against melanoma) with Metformin in 8 solid tumor patients, revealed a partial response in a single metastatic squamous cell carcinoma patient and stable disease in four patients, including a stage IV melanoma patient who experienced no progression for 22 months while on therapy (median overall survival is < 1 year)[27]. **Based on these pre-clinical studies and phase I trial, we hypothesize that the combination of an FDA-approved non-toxic dose of oral Metformin with the B-Raf inhibitor, Dabrafenib, and the MEK inhibitor, Trametinib, will yield little toxicity and improve clinical outcomes in terms of objective response rates and survival in metastatic melanoma patients.** An important consideration for such a combination trial is the possibly that Metformin will decrease blood glucose concentration in non-diabetic patients and thus cause hypoglycemia and associated symptoms. *However, in a randomized trial of 166* ***non-diabetic*** *men with hypertension, the fasting blood glucose (5.6 ± 0.74 mM) only dropped by 3% after three months of treatment with 850 mg PO BID of metformin (to 5.44 mM ± 0.83)*[28].

2. STUDY OBJECTIVE(S)

2.1 Primary

- To evaluate the clinical activity of the FDA-approved drugs Dabrafenib (150 mg PO BID) and Trametinib (2 mg PO QD) in combination with Metformin (500 mg PO BID x 2 weeks, then 850 mg PO BID) in patients with unresectable BRAFV600E positive Stage IIIC and Stage IV melanoma (Phase I).
- To evaluate the clinical activity of the combined Dabrafenib/Trametinib/Metformin regimen (Phase II).
- To monitor the safety profile of the combined regimen Dabrafenib/Trametinib/Metformin (Phase I/II).

2.1 Secondary Objective:

- To estimate the overall survival of patients who have been treated with Dabrafenib, Trametinib and Metformin.
- To describe the toxicities.
- To explore the effect of other covariates (demographic, disease and treatment related) on objective response rate and toxicity and overall survival.

3. INVESTIGATIONAL PLAN

3.1 Summary of Study Design

This will be an open-label, clinical efficacy study of Dabrafenib, Trametinib and Metformin in patients with unresectable Stage IIIC and Stage IV melanoma. 53 patients with radiographically measurable melanoma will be enrolled and treated in the study. One cycle of therapy will last 28 days, and will continue until progression. Radiologic examinations including a computed tomography (CT) scan of the head, chest, abdomen, pelvis, and other sites of disease, as appropriate, will be performed during Screening, every 2 months during treatment, and at 4 weeks (+/- 1 week) following the final treatment administration of the combination therapy. Magnetic resonance imaging (MRI) may be performed for brain imaging and/or if CT scans are not appropriate or CT scan results are not conclusive. Although not preferred, CT scans may be performed without contrast. Therapeutic response will be determined using RECIST 1.1.

3.1.1 Dose-Schedules

Patients will receive Dabrafenib (150 mg PO BID), Trametinib (2 mg PO QD) and Metformin (500 mg PO BID x 2 weeks, then 850 mg PO BID). Treatment will continue until progression, unless the patient experiences unacceptable toxicity. Patients will be evaluated for (1) clinical response, (2) safety, and (3) survival.

3.2 Study Periods

Study periods are 28-day cycles.

3.2.1 Screening

The patient must sign an Informed Consent Form (ICF) before any study procedures are performed. Screening procedures must be performed within 42 days of the first dose of study drug.

- Eligibility evaluation (review of inclusion/exclusion criteria);
- History of prior systemic treatment, including drug therapy and any other anti-cancer therapies such as radiation therapy;
- Demographic information (date of birth, gender, race, ethnicity);
- Determination of Stage IIIC or Stage IV disease; if Stage IV disease, document M1a/b/c;
- Relevant medical history and surgical history, including treatment history for melanoma and BRAF status;
- Vital signs (body temperature, respiratory rate, blood pressure, heart rate, height, and weight [kg]);
- Physical examination;
- Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) (see Appendix);
- Clinical laboratory assessment (hematology and serum chemistry);
- Serum pregnancy test for female patients of childbearing potential;
- Tumor assessment (imaging), unless results are available from appropriate CT scans performed within 42 days prior to the initiation of Dabrafenib/Trametinib/Metformin. CT scans with contrast are preferred; the Investigator may authorize CT scans without contrast;
- Radiological assessment of the brain: All patients are required to have a CT scan with contrast or MRI scan of the brain, unless results from appropriate scans performed within 42 days are available;
- 2D-Echo or MUGA (in accordance with the manufacturer's package insert for Trametinib).
- Collection of AEs.

3.2.2 Treatment Cycles

3.2.2.1 Day 1 of Each Cycle

On Day 1 of each 28-day treatment cycle until PD, the following assessments/treatment administrations will occur:

- Vital signs (prior to treatment, including: body temperature, respiratory rate, blood pressure, heart rate, weight [kg]);
- Physical examination
- ECOG PS;

- Clinical laboratory assessment (obtained and reviewed prior to treatment: hematology and serum chemistry);
- Collection of AEs.
- Every two-three months while on study treatment, 2D-Echo or MUGA,

3.2.2.2 Day 15 of First Cycle

On Day 15 of the first 28-day treatment cycle, the following assessments will occur:

- Vital signs (prior to treatment, including: body temperature, respiratory rate, blood pressure, heart rate, weight [kg]);
- Physical examination
- ECOG PS;
- Clinical laboratory assessment (obtained and reviewed prior to treatment: hematology and serum chemistry);
- Collection of AEs.

3.2.3 Radiological Examinations During Study Treatment, at End of Treatment, and in Follow-Up

Radiologic examinations, including a CT scan of the head, chest, abdomen, and pelvis (or MRI for brain imaging when CT scans are not appropriate or CT scan results are not conclusive) will be performed 1 day (±1 week) after the final treatment administration during cycle 2, and then every two months while continuing study treatment. Radiologic examinations may be performed at the end of treatment. If PD, radiologic assessments performed subsequent to the end of treatment scans shall be at the discretion of the investigator.

3.2.4 Follow-Up for Survival

Patients will be followed for up to three years following the last treatment administration. The Investigator or designees will make every possible attempt at least every 3 months (±7 days), for up to three years after the last treatment to contact the patient or family to obtain the survival information of the patient and, if applicable, the start date of additional anti-cancer treatment.

3.3 Selection of Study Population

3.3.1 Inclusion and Exclusion Criteria

Inclusion Criteria

Patients may be entered in the study only if they meet all of the following criteria.

1. Male or female patients ≥18 years of age;
2. Patients with histological confirmed BRAFV600E mutation+ melanoma (Stage IIIC or Stage IV, American Joint Commission on Cancer);
3. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 to 2;
4. Life expectancy ≥3 months;
5. At least 1 site of radiographically measurable disease by RECIST 1.1
6. Adequate hematologic, renal, and liver function as defined by laboratory values performed within 42 days prior to initiation of dosing:
   - Absolute neutrophil count (ANC) ≥1.0 x 10^9/L;
   - Platelet count ≥50 x 10^9/L;
   - Hemoglobin ≥8 g/dL;
   - Serum creatinine ≤2 x upper limit of normal (ULN)
   - Total serum bilirubin ≤3 x ULN;
   - Serum aspartate transaminase (AST/SGOT) or serum alanine transaminase (ALT/SGPT) ≤3x ULN, and ≤4 x ULN if liver metastases are present.
7. Fertile males should use an effective method of contraception during treatment and for at least 3 months after completion of treatment, as directed by their physician;
8. Pre-menopausal females and females <2 years after the onset of menopause should have a negative pregnancy test at Screening. Pre-menopausal females must agree to use an acceptable method of birth control from the time of the negative pregnancy test up to 90 days after the last dose of study drug. Females of non-childbearing potential may be included if they are either surgically sterile or have been postmenopausal for ≥1 year;
9. Before study entry, written informed consent must be obtained from the patient prior to performing any study-related procedures.

Exclusion Criteria

Patients will not be entered in the study for any of the following:

1. Prior treatment with Vemurafenib or Dabrafenib;
2. Known hypersensitivity to Metformin or any of its components
3. Received radiotherapy for non CNS disease within the 2 weeks prior to commencing study treatment or have not recovered from side effects of all radiation-related toxicities to Grade ≤1, except for alopecia;
4. Pregnant, breast-feeding, or refusing double barrier contraception, oral contraceptives, or avoidance of pregnancy measures;
5. Have any other uncontrolled infection or medical condition that could interfere with the conduct of the study.

3.3.2 Patient Withdrawal

All patients are free to withdraw from participation in the study at any time, for any reason, specified or unspecified, and without prejudice to further treatment. The Investigator may end this study at any time, for any reason.

4. STUDY TREATMENTS

4.1 Treatments Administered

Patients will receive Dabrafenib (150 mg PO BID), Trametinib (2 mg PO QD) and Metformin (500 mg PO BID x 2 weeks, then 850 mg PO BID). Treatment will continue until progression, unless the patient experiences unacceptable toxicity. Patients will be evaluated for (1) clinical response, (2) safety, and (3) survival.

4.2 Description of Dabrafenib

Dabrafenib is an inhibitor of some mutated forms of BRAF kinases with in vitro IC50 values of 0.65, 0.5, and 1.84 nM for BRAF V600E, BRAF V600K, and BRAF V600D enzymes, respectively. Dabrafenib also inhibits wild-type BRAF and CRAF kinases with IC50 values of 3.2 and 5.0 nM, respectively, and other kinases such as SIK1, NEK11, and LIMK1 at higher concentrations. Some mutations in the BRAF gene, including those that result in BRAF V600E, can result in constitutively activated BRAF kinases that may stimulate tumor cell growth. Dabrafenib inhibits BRAF V600 mutation-positive melanoma cell growth in vitro and in vivo.

4.3 Side Effects, Warnings and Precautions of Dabrafenib.

As stated in the manufacturer's package insert for the FDA-approved Dabrafenib:

New Primary Cutaneous Malignancies: Across clinical trials of Dabrafenib (n = 586), the incidence of cutaneous Squamous Cell Carcinoma was 11%.

Serious Febrile Drug Reactions: The incidence of fever (serious and non-serious) was 28% in patients treated with dabrafenib. Withhold Trametinib for fever of 101.3°F or greater or for any serious febrile drug reaction and evaluate for signs and symptoms of infection.

Hyperglycemia: The incidence of Grade 3 hyperglycemia based on laboratory values was 6% (12/187) in patients treated with dabrafenib.

Ophthalmologic Reactions: Uveitis and Iritis occurred in 1% (6/586) of patients treated with dabrafenib across clinical trials.

Hemolytic Anemia: Dabrafenib, which contains a sulfonamide moiety, confers a potential risk of hemolytic anemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.

4.4 Description of Trametinib

Reversibly and selectively inhibits mitogen-activated extracellular kinase (MEK) 1 and 2 activation and kinase activity. MEK is a downstream effector of the protein kinase B-raf (BRAF); BRAF V600 mutations result in constitutive activation of the BRAF pathway (including MEK1 and MEK2). Through inhibition of MEK 1 and 2 kinase activity, trametinib causes decreased cellular proliferation, cell cycle arrest, and increased apoptosis. The combination of trametinib and dabrafenib allows for greater inhibition of the MAPK pathway, resulting in BRAF V600 melanoma cell death.

4.5 Side Effects, Warnings and Precautions of Trametinib.

As stated in the manufacturer's insert for the FDA-approved Trametinib:

Cardiovascular: Hypertension (15%) and Cardiomyopathy

Dermatologic: Skin rash (57%)

Endocrine & metabolic: Hypoalbuminemia (42%)

Gastrointestinal: Diarrhea (43%)

Hematologic & oncologic: Anemia (38%)

Hepatic: Increased serum AST (60%)

4.6 Description of Metformin

A complex I inhibitor that decreases hepatic glucose production, decreasing intestinal absorption of glucose and improves insulin sensitivity (increases peripheral glucose uptake and utilization).

4.7 Side Effects, Warnings and Precautions of Metformin.

Gastrointestinal: Diarrhea (12% to 53%); nausea/vomiting (7% to 26%; 7% to 9%); flatulence (12%)

Neuromuscular & skeletal: Weakness (9%)

4.8 Dose Delays and Modifications

Dose delays and modifications of each of the three drugs in this combination regimen will be at the Investigator's discretion. Investigators will refer to the dosing guidelines in the package inserts for guidance on dosing decisions.

4.9 Concomitant Medications

Concomitant medications and treatment (for example, palliative radiotherapy) during the study will be allowed at the Principal Investigator's discretion.

5. EFFICACY AND SAFETY MEASURES

5.1 Schedule of Events

A schedule of events is presented in Appendix 1.

5.2 Efficacy Measures

This study includes assessments of safety and efficacy as outlined in the sections below. Disease progression and efficacy response will be determined using RECIST 1.1.

5.2.1 Primary Efficacy Endpoints

The primary efficacy endpoints are RECIST 1.1 and safety. Efficacy responses will be assessed following the last administration of the test agents.

5.2.2 Secondary Endpoint

Secondary endpoint is overall survival.

5.2.3 Tumor Assessments

Tumor measurements will be performed using RECIST 1.1. At a minimum, CT scans of the head, chest, abdomen, and pelvis will be performed at study entry, every 2 months while on treatment, following the last administration of the test agents, or at any time there is clinical evidence of disease progression, to evaluate disease status.

This section provides the definitions of the criteria used to determine objective tumor response for target lesions using RECIST 1.1.

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 diameters of target lesions.

Progressive Disease (PD): At least a 20% increase in the sum of 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 unequivocal new metastatic lesions is also considered progression).

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

5.3 Safety Measures

5.3.1 Adverse Events

The investigator is responsible for recording all AEs observed during the study period. Definition of AE: An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

Definition of Serious Adverse Event (SAE) or serious suspected adverse reaction: A SAE, experience or reaction, is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Results in death;
- Is life-threatening (the patient is at a risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe);
- Requires inpatient hospitalization or prolongation of existing hospitalization: Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study;
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions;
- Is a congenital abnormality/birth defect;
- Other: as determined by the Investigator, medically significant events that do not meet any of the criteria above, but may jeopardize the patient and may require medical or surgical intervention to prevent one of the other serious outcomes listed in the definition above.

Clinical laboratory tests will be reviewed for results of potential clinical significance at all timepoints throughout the study. The Investigator will evaluate any change in laboratory values. If the Investigator determines a laboratory abnormality to be clinically significant, it is considered a laboratory AE; however, if the laboratory value abnormality is consistent with a current diagnosis, it may be documented accordingly.

An Adverse Drug Reaction (ADR) is defined as all noxious and unintended responses to a medicinal product related to any dose. An Unexpected Adverse Drug Reaction is defined as any adverse reaction, the nature of which is not consistent with the applicable product information.

Each AE is to be evaluated for duration, severity according to NCI CTCAE v. 4.0, seriousness, and causal relationship to the investigational drug. The action taken and the outcome must also be recorded.

Relationship

The causal relationship between the study drug and the AE has to be characterized as not related, possibly related, or probably related. Events can be classified as "not related" if there is not a reasonable possibility that the study drug caused the AE. A "possible" relationship suggests that the association of the AE with the study drug is unknown; however, the AE is not reasonably supported by other conditions. A "probable" relationship suggests that a reasonable temporal sequence of the AE with the study drug administration exists and, in the Investigator's clinical judgment, it is likely that a causal relationship exists between the study drug administration and the AE, and other conditions (concurrent illness, progression or expression of disease state, or concomitant medication reactions) do not appear to explain the AE.

5.3.1.1 Reporting of Adverse Events

All AEs, regardless of severity and whether or not they occurred during the study treatment or within 21 days following the last treatment, are to be documented by the Investigator appropriately, including date of onset, severity, action taken, outcome, and relationship to study drug. Adverse events occurring between the time of signing informed consent to the time of the first dose will NOT be captured as AEs unless the AE is a direct result of a study-specific procedure or results in death from an event other than PD.

The Data and Safety Monitoring Plan of the Brown Cancer Center will be used for this phase I/II protocol. The investigators will conduct continuous review of data and patient safety at weekly meetings where the results of each patient's treatment are discussed. The discussion will include the number of patients, significant toxicities as described in the protocol, dose adjustments, and responses observed. Quarterly summaries of SAEs will be submitted through the CTO to the DSMC for review.

In the case of an SAE, the Investigator must notify the Co-Chairman of the Data Safety Monitoring Committee within 24 hours of becoming aware of the event, and will notify the Institutional Review Board in accordance with its guidelines.

5.3.2 **Laboratory Assessments.** At Day 1 of each cycle, a CBC with a 3-part differential and a CMP will be ordered and assessed by the Investigator.

6. STATISTICS

6.1 Study Design:

The study will be a single-arm, single center, uncontrolled phase I/II trial to estimate the safety of the combined treatments and then estimate the efficacy in terms of objective response (CR+PR) rate in patients with stage IIIC and Stage IV melanoma treated with dabrafenib/trametinib and metformin.

6.2 End-Point Definitions:

We will use two main end points. The primary endpoint of interest is the clinical response as defined in Section 5. The second end point will be tolerability to treatment. Secondary end points to be considered are the overall survival, OS, which is the time to first event or death due to any reason.

6.3 Sample Size:

The study is conducted in 2 phases.

Phase I:

In phase I, we will enroll 6 patients for the combination regimen of Dabrafenib/Trametinib/Metformin. We will allow at the most two drug-related CTCAE grade 4 toxicities in 6 patients in order to advance to Phase II. If we observe any drug-related deaths or more than two drug-related CTCAE grade 4 events, then we will halt the trial.

The Data and Safety Monitoring Plan of the Brown Cancer Center will be used for this phase I/II protocol. The investigators will conduct continuous review of data and patient safety at weekly meetings where the results of each patient's treatment are discussed. The discussion will include the number of patients, significant toxicities as described in the protocol, dose adjustments, and responses observed. Quarterly summaries of SAEs will be submitted through the CTO to the DSMC for review.

Phase II:

There is no data available at the institution to support the sample size justification based on efficacy of this treatment combination. **In the published literature, the objective response rate to Dabrafenib and Trametinib using RECIST 1.1 Criteria is 76% (N=54, 95% CI, 65% to 87%) (Flaherty et al, NEJM, 367:1694, 2012).** We expect that the overall response rate should be between 60-80%. Therefore an objective response rate less than 64% should indicate the treatment is not sufficiently promising (P0 = 0.64); this is a bit lower than the lower limit of the 95% CI. We expect the therapy to increase the overall response rate at 80% (P1 = 0.80). Using Simon's two stage minimax design for phase II trials we plan to enroll a maximum of 53 patients. In first stage, 20 patients will be enrolled. Table S1 gives the details of the justification of this sample size. Note that if the treatment is not altered in Phase I, patients enrolled on Phase I will be included in Phase II in the efficacy estimation.

Table S1. Sample size justification P0 =0.64, P1=0.80, alpha=0.05 and power =80%

MiniMax Two Stage Design	MiniMax Design
First Stage Sample Size (n1)	20
Upper Limit For 1st Stage Rejection of Drug (# of OR)	13
Maximum Sample Size (n)	53
Upper Limit for 2nd Stage Rejection of Drug (# of OR)	39
Expected Sample Size If Response Probability = 0.64	33
Probability of Early Termination at If RP=0.64	0.62

6.4 Accrual Rate:

Based on our experience we plan to enroll 30 patients per year. It will take approximately 2.0 years to complete the enrollment of 53 patients. Depending on the treatment's performance we may not need to enroll all 53 participants. Given the relatively short overall survival times, all patients will be followed for up to 3 years once enrolled and after the end of treatment with Dabrafenib/Trametinib/Metformin.

6.5 Statistical Analysis:

General Approach:

Patients receiving treatment will be presented. Patients receiving treatment who are found not to have fully met the eligibility criteria will be presented. On-study protocol violations will also be presented. Patients who do not complete the required observations will be listed and evaluated separately as necessary. Reasons for study discontinuation and date of withdrawal from study will be presented.

Descriptive statistics related to the participant characteristics, treatment, and prognostic factors will be reported. Clinical response rates (complete, partial, and sustained) along with 95% confidence intervals will be estimated. The overall survival will be estimated by the Kaplan-Meier method[29]. Differences in survival will be evaluated through the estimated hazard rates using the un-weighted log-rank tests. The OS time will be determined as the time from enrollment until death or last follow-up evaluation. In order to examine the significant prognostic factors, we will use the Cox proportional hazards regression models in both uni-variable and multi-variable setting[30]. Descriptive statistics associated with the toxic events will be reported. The factors to be analyzed are ethnicity, gender, age, and pathological subtype. The various factors will be placed into categorical variables.

All calculations will be performed with SAS statistical software (SAS Institute Inc., Cary, NC). Analyses for specific aims are outlined below.

Statistical Analysis for specific aims:

Primary Objectives:

- *To evaluate the safety of the FDA-approved Dabrafenib and Trametinib in combination with Metformin in patients with unresectable Stage IIIC and Stage IV melanoma (Phase I).*

  A total of 6 consecutive patients will be evaluated on this combination treatment. If any drug-related death occurs in this early stage, the study will be suspended. To continue on Phase II, at the most two drug-related CTCAE grade 4 events are allowed, which is in line with a Typical Phase I study with only one dose.

- *To estimate the efficacy of the Trametinib/Dabrafenib/Metformin regimen (Phase II).*

The efficacy will be estimated based on objective response (OR) rate, which is PR+ CR. We will estimate the OR rate along with its 95% confidence interval. We will also estimate CR and PR rates along with 95% confidence intervals. We will also compare these rates with published rates NEJM (2011)[8] by comparing the confidence intervals.

- *To monitor the safety the combined regimens (Phase I/II).*
  The monitoring rule is outlined in the next subsection.

Secondary Objective:

- *To estimate the overall survival rate on the combined regimes.*
  We will estimate the overall survival (OS) rates using the method of Kaplan-Meier. To compare the results with historical controls (results published in NEJM, 2011 and others), we need to estimate fixed term (such as 1-year, 2-year) OS rate along with 95% confidence interval precisely, that we plan to do using the method or Yuan and Rai (2011)[31]

- *To describe the toxicities.*
  We will produce frequency and percentages of different CTCAE.

- *To explore the effect of other covariates (demographic, disease and treatment related) on objective response rate and toxicity and overall survival.*
  We will identify the covariates and define specific groups, using some cut-offs, that are meaningful in a regression analysis. The effect of the covariates on a dichotomous outcome (OR or Toxicity) and time-to-event (OS) will be explored using a logistic regression and Cox proportional Hazards model, respectively.

6.6 Monitoring Rule for Phase II:

Safety monitoring of the accumulated outcomes data is designed to ensure the continuing safety of the currently enrolled participants and participants not yet enrolled. This is achieved by stopping the trial early to reduce the number of participants exposed to a harmful or ineffective treatment.

6.7 Non-efficacious Treatment (Futility):

In the combined regimen Dabrafenib/Trametinib/Metformin: in the first stage we will enroll 28 participants and if we observe at most 12 objective responses we will not enroll any new participants. If we observe 13 or more objective responses in the first stage, then we plan to enroll an additional 25 patients. In order for the treatment to be declared effective there has to be objective responses in at least 29 patients. If the objective response rate is only 41%, we will have 66% chance of stopping the study early and, at most, 37 patients will be treated on the potentially ineffective therapy.

6.8 Toxic Treatment (Safety) for Combined Phase I/II Trial:

The cumulative number of grade 3 or 4 toxic events will be monitored after each person is enrolled[32, 33]. If the cumulative number of toxic events produces enough evidence to conclude that the true toxicity rate is greater than or equal to 33% (Pt0 = 0.33) then the trial will be stopped early for safety reasons. The cumulative number of toxic events after each is person is treated will be compared to the boundary values in Table S2. If the cumulative number of toxic events after person is treated is greater than or equal to the associated boundary value bi then the combination treatment is rejected for safety considerations. With this rule, there is only a 5% chance of stopping the trial early for lack of safety if the true toxicity rate is less than 33%. Continual assessment of the toxic events ensures we do not expose an undue number of patients to a harmful treatment.

Table S2. Toxicity Boundaries, N = 53, Pt0 = 0.33, and alpha=0.05

Minimum Number of Subjects	Maximum Number of Subjects	Number of Toxicities
4	4	4
5	6	5
7	7	6
8	9	7
10	11	8
12	14	9
15	16	10
17	18	11
19	19	12
20	22	13
23	23	14
24	27	15
28	28	16
29	30	17
31	32	18
33	34	19
35	37	20
36	40	21
41	42	22
43	45	23
46	47	24
48	50	25
51	52	26
53	54	27

7. ETHICS

7.1 Ethical Conduct of the Study

This study will be conducted and the informed consent will be obtained according to the ethical principles stated in the Declaration of Helsinki (2008), the applicable guidelines for GCP, or the applicable drug and data protection laws and regulations of the countries where the study will be conducted.

7.2 Patient Information and Informed Consent

The ICF will be used to explain the risks and benefits of study participation to the patient in simple terms before the patient will be entered into the study. The ICF contains a statement that the consent is freely given, that the patient is aware of the risks and benefits of entering the study, and that the patient is free to withdraw from the study at any time. Written consent must be given by the patient and/or legal representative, after the receipt of detailed information on the study.

The Investigator is responsible for ensuring that informed consent is obtained from each patient or legal representative and for obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of study drug. The Investigator will provide each patient with a copy of the signed and dated ICF and will document in the patient's source notes that informed consent was given.

REFERENCES

1. Middleton MR, Grob JJ, Aaronson N, Fierlbeck G, Tilgen W, Seiter S, Gore M, Aamdal S, Cebon J, Coates A, Dreno B, Henz M, Schadendorf D, Kapp A, Weiss J, Fraass U, Statkevich P, Muller M, Thatcher N: Randomized phase III study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. J Clin Oncol 2000, 18:158-66

2. Atkins MB, Lotze MT, Dutcher JP, Fisher RI, Weiss G, Margolin K, Abrams J, Sznol M, Parkinson D, Hawkins M, Paradise C, Kunkel L, Rosenberg SA: High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: analysis of 270 patients treated between 1985 and 1993. J Clin Oncol 1999, 17:2105-16

3. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, Gonzalez R, Robert C, Schadendorf D, Hassel JC, Akerley W, van den Eertwegh AJ, Lutzky J, Lorigan P, Vaubel JM, Linette GP, Hogg D, Ottensmeier CH, Lebbe C, Peschel C, Quirt I, Clark JI, Wolchok JD, Weber JS, Tian J, Yellin MJ, Nichol GM, Hoos A, Urba WJ: Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 363:711-23

4. Ribas A, Kim KB, Schuchter LM, Gonzalez R, Pavlick AC, Weber JS, McArthur GA, Hutson TE, Flaherty KT, Moschos SJ, Joe JA, Sosman JA: BRIM-2 An open-label, multicenter phase II study of vemurafenib in previously treated patients with BRAF V600E mutation-positive metastatic melanoma. J Clin Oncol 2011, 29 Supplement (Abstract 8509)

5. Avruch J, Khokhlatchev A, Kyriakis JM, Luo Z, Tzivion G, Vavvas D, Zhang XF: Ras activation of the Raf kinase: tyrosine kinase recruitment of the MAP kinase cascade. Recent Prog Horm Res 2001, 56:127-55

6. Davies H, Bignell GR, Cox C, Stephens P, Edkins S, Clegg S, Teague J, Woffendin H, Garnett MJ, Bottomley W, Davis N, Dicks E, Ewing R, Floyd Y, Gray K, Hall S, Hawes R, Hughes J, Kosmidou V, Menzies A, Mould C, Parker A, Stevens C, Watt S, Hooper S, Wilson R, Jayatilake H, Gusterson BA, Cooper C, Shipley J, Hargrave D, Pritchard-Jones K, Maitland N, Chenevix-Trench G, Riggins GJ, Bigner DD, Palmieri G, Cossu A, Flanagan A, Nicholson A, Ho JW, Leung SY, Yuen ST, Weber BL, Seigler HF, Darrow TL, Paterson H, Marais R, Marshall CJ, Wooster R, Stratton MR, Futreal PA: Mutations of the BRAF gene in human cancer. Nature 2002, 417:949-54

7. Flaherty KT, Puzanov I, Kim KB, Ribas A, McArthur GA, Sosman JA, O'Dwyer PJ, Lee RJ, Grippo JF, Nolop K, Chapman PB: Inhibition of mutated, activated BRAF in metastatic melanoma. N Engl J Med 363:809-19

8. Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, Dummer R, Garbe C, Testori A, Maio M, Hogg D, Lorigan P, Lebbe C, Jouary T, Schadendorf D, Ribas A, O'Day SJ, Sosman JA, Kirkwood JM, Eggermont AM, Dreno B, Nolop K, Li J, Nelson B, Hou J, Lee RJ, Flaherty KT, McArthur GA: Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med 364:2507-16

9. Poulikakos PI, Rosen N: Mutant BRAF melanomas--dependence and resistance. Cancer Cell 19:11-5

10. Solit DB, Rosen N: Resistance to BRAF inhibition in melanomas. N Engl J Med 364:772-4

11. Nazarian R, Shi H, Wang Q, Kong X, Koya RC, Lee H, Chen Z, Lee MK, Attar N, Sazegar H, Chodon T, Nelson SF, McArthur G, Sosman JA, Ribas A, Lo RS: Melanomas acquire resistance to B-RAF(V600E) inhibition by RTK or N-RAS upregulation. Nature 468:973-7

12. Johannessen CM, Boehm JS, Kim SY, Thomas SR, Wardwell L, Johnson LA, Emery CM, Stransky N, Cogdill AP, Barretina J, Caponigro G, Hieronymus H, Murray RR, Salehi-Ashtiani K, Hill DE, Vidal M, Zhao JJ, Yang X, Alkan O, Kim S, Harris JL, Wilson CJ, Myer VE, Finan PM, Root DE, Roberts TM, Golub T, Flaherty KT, Dummer

R, Weber BL, Sellers WR, Schlegel R, Wargo JA, Hahn WC, Garraway LA: COT drives resistance to RAF inhibition through MAP kinase pathway reactivation. Nature 468:968-72

13. Villanueva J, Vultur A, Lee JT, Somasundaram R, Fukunaga-Kalabis M, Cipolla AK, Wubbenhorst B, Xu X, Gimotty PA, Kee D, Santiago-Walker AE, Letrero R, D'Andrea K, Pushparajan A, Hayden JE, Brown KD, Laquerre S, McArthur GA, Sosman JA, Nathanson KL, Herlyn M: Acquired resistance to BRAF inhibitors mediated by a RAF kinase switch in melanoma can be overcome by cotargeting MEK and IGF-1R/PI3K. Cancer Cell 18:683-95

14. El-Mir MY, Nogueira V, Fontaine E, Averet N, Rigoulet M, Leverve X: Dimethylbiguanide inhibits cell respiration via an indirect effect targeted on the respiratory chain complex I. J Biol Chem 2000, 275:223-8

15. Owen MR, Doran E, Halestrap AP: Evidence that metformin exerts its anti-diabetic effects through inhibition of complex 1 of the mitochondrial respiratory chain. Biochem J 2000, 348 Pt 3:607-14

16. Beatty CH, Young MK, Bocek RM: Control of glycolysis in skeletal muscle from fetal rhesus monkeys. Pediatr Res 1976, 10:149-53

17. Towler MC, Hardie DG: AMP-activated protein kinase in metabolic control and insulin signaling. Circ Res 2007, 100:328-41

18. Decensi A, Puntoni M, Goodwin P, Cazzaniga M, Gennari A, Bonanni B, Gandini S: Metformin and cancer risk in diabetic patients: a systematic review and meta-analysis. Cancer Prev Res (Phila) 3:1451-61

19. Evans JM, Donnelly LA, Emslie-Smith AM, Alessi DR, Morris AD: Metformin and reduced risk of cancer in diabetic patients. BMJ 2005, 330:1304-5

20. Landman GW, Kleefstra N, van Hateren KJ, Groenier KH, Gans RO, Bilo HJ: Metformin associated with lower cancer mortality in type 2 diabetes: ZODIAC-16. Diabetes Care 33:322-6

21. Libby G, Donnelly LA, Donnan PT, Alessi DR, Morris AD, Evans JM: New users of metformin are at low risk of incident cancer: a cohort study among people with type 2 diabetes. Diabetes Care 2009, 32:1620-5

22. Jiralerspong S, Palla SL, Giordano SH, Meric-Bernstam F, Liedtke C, Barnett CM, Hsu L, Hung MC, Hortobagyi GN, Gonzalez-Angulo AM: Metformin and pathologic complete responses to neoadjuvant chemotherapy in diabetic patients with breast cancer. J Clin Oncol 2009, 27:3297-302

23. Esteve-Puig R, Canals F, Colome N, Merlino G, Recio JA: Uncoupling of the LKB1-AMPKalpha energy sensor pathway by growth factors and oncogenic BRAF. PLoS One 2009, 4:e4771

24. Zheng B, Jeong JH, Asara JM, Yuan YY, Granter SR, Chin L, Cantley LC: Oncogenic B-RAF negatively regulates the tumor suppressor LKB1 to promote melanoma cell proliferation. Mol Cell 2009, 33:237-47

25. Janjetovic K, Harhaji-Trajkovic L, Misirkic-Marjanovic M, Vucicevic L, Stevanovic D, Zogovic N, Sumarac-Dumanovic M, Micic D, Trajkovic V: In vitro and in vivo anti-melanoma action of metformin. Eur J Pharmacol 668:373-82

26. Niehr F, von Euw E, Attar N, Guo D, Matsunaga D, Sazegar H, Ng C, Glaspy JA, Recio JA, Lo RS, Mischel PS, Comin-Anduix B, Ribas A: Combination therapy with vemurafenib (PLX4032/RG7204) and metformin in melanoma cell lines with distinct driver mutations. J Transl Med 9:76

27. Mackenzie MJ, Ernst S, Johnson C, Winquist E: A phase I study of temsirolimus and metformin in advanced solid tumours. Invest New Drugs

28. Charles MA, Eschwege E, Grandmottet P, Isnard F, Cohen JM, Bensoussan JL, Berche H, Chapiro O, Andre P, Vague P, Juhan-Vague I, Bard JM, Safar M: Treatment with metformin of non-diabetic men with hypertension, hypertriglyceridaemia and central fat distribution: the BIGPRO 1.2 trial. Diabetes Metab Res Rev 2000, 16:2-7

29. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. Journal of American Association, 53:457-481, 1958.

30. Cox DR. Regression models and life tables. Journal of the Royal Statistical Society, 34:187-220, 1972.

31. Yuan, X and Rai, SN. Confidence Intervals for Survival Probabilities: A Comparison Study. Communications in Statistics – Simulation and Computation, 40(7): 978-991, 2011.)

32. Ray HE and Rai SN. An Evaluation of a Simon 2-Stage phase II clinical trial desing incorporating toxicity monitoring. Contemporary Clinical Trials, 32:428-436, 2011.

33. Ivanova A, Qaqish BF, and Schell MJ. Continuous toxicity monitoring in phase II trials in oncology. Biometrics, 61:540-545, 2005.

34. Simon R. Optimal two stage designs for phase II clinical trials. Controlled Clinical Trials, 10: 1-10, 1989.

35. Korn EL, Liu PY, Lee SJ, Chapman JA, Niedzwiecki D, Suman VJ, Moon J, Sondak VK, Atkins MB, Eisenhauer EA, Parulekar W, Markovic SN, Saxman S, Kirkwood JM: Meta-analysis of phase II cooperative group trials in metastatic stage IV melanoma to determine progression-free and overall survival benchmarks for future phase II trials. J Clin Oncol 2008, 26:527-34.

APPENDIX 1: SCHEDULE OF EVENTS

Period	Screening	Day 1 each cycle and End of Treatment	Day 15	Day 1 Cycle 2 then Q2-3 months	Day 1 Cycle 3 (or End of Treatment if PD)	Follow-up for Survival
Assessments	0 to 42 days Pre-treatment	Every 28 days Until PD (±3 days)	First Cycle Only (±3 Days)	1 Day (±7 days) After Cycle 2, and Continue q2-3 Months while on treatment.	1 Day (±7 days) After final dose in Cycle 2 (and Continue Q2 months Until PD)	Every 3 Months (±7 days) , up to 3 years after last dose
Informed consent	X					
Inclusion/exclusion criteria	X					
Demographic information	X					
TNM staging (AJCC)	X					
Medical history	X					
Vital signs	X	X	X			
Physical exam	X	X	X			
ECOG PS	X	X	X			
Hematology	X	X	X			
Serum chemistry	X	X	X			
2D-Echo	X			X		
Pregnancy test (if applicable)	X					
Dabrafenib/Trametinib & Metformin Initiation		X				
Radiological assessments[a]	X				X	
Adverse events	X	X	X			
Survival information via telephone interview or in-person contact at SOC clinic visit						X

[a]CTs of the head, chest, abdomen, pelvis, and other sites of disease will be performed every 2 months, +/- 7 days of Day 1 of the subsequent cycle.

APPENDIX 2: ECOG PERFORMANCE CRITERIA

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